DOCTORAL THESIS

Selectivity control in Pd-catalyzed C-H functionalization reactions

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Dr. Rubén Martín Romo, Group Leader of Research Group,

CERTIFIES, that the present Doctoral Thesis entitled: "**Selectivity control in Pd-catalyzed C-H functionalization reactions**", presented by Areli Flores-Gaspar to receive the degree of Doctor, has been carried out under his supervision at the Institute of Chemical Research of Catalonia (ICIQ).

Tarragona, 22th February 2013.

PhD Thesis Supervisor

_____

Rubén Martín Romo

Hace cuatro años comencé con mucha ilusión una aventura llamada "Doctorado". El trabajo realizado estos años se ve reflejado en esta tesis sin embargo no es algo que haya hecho sola. En este espacio me gustaría agradecer a todos los que formaron parte de este proceso tanto en el ámbito académico como en el aspecto personal.

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List of publications

The results of this PhD thesis have delivered the following publications:

1. *"Recent advances in the synthesis and application of Benzocyclobutenones and related compounds"* **A. Flores-Gaspar**, R. Martin, *Synthesis,* **2013**, 45, 563.

2. *"N-Heterocyclic Carbene Dichotomy in Pd-Catalyzed Acylation of Aryl Chlorides via C-H Bond Functionalization"* **A. Flores-Gaspar**, A. Gutierrez-Bonet, R. Martin, *Org. Lett.,* **2012**, 14, 5234.

3. *"Synthesis of 8,8-Dipropylbicyclo[4.2.0]octa-1,3,5-trien-7-one via Pd-catalyzed Intramolecular C-H Bond-Acylation"* **A. Flores-Gaspar**, R. Martin*, Org. Synth*., **2012**, 89, 159-169.

4. *"Mechanistic Switch via Subtle Ligand Modulation: Pd-catalyzed Synthesis of α,β-Substituted Styrenes via C-H Bond-Functionalization"* **A. Flores-Gaspar**, R. Martin, *Adv. Synth. Catal*., **2011**, 353, 1223-1228.

5. *"Pd-catalyzed intramolecular acylation of aryl bromides via C-H functionalization: A highly efficient synthesis of benzocyclobutenones*" P. Álvarez-Bercedo, **A. Flores-Gaspar**, A. Correa, R. Martin, *J. Am. Chem. Soc*., **2010**, 132, 466-467.

The following publications are in preparation:

6. *"Towards an understanding of the mechanism switch in Pd-catalyzed C-H functionalization of aryl bromides: A combined experimental and theoretical perspective"* **A. Flores-Gaspar**, A. Hamilton, C. Bo, R. Martin*, to be submitted.*

7. *"Fe-catalyzed aldehyde-ketone rearrangement: divergence in product selectivity by substrate modulation"* A. Gutiérrez-Bonet; **A. Flores-Gaspar**; R. Martin, *to be submitted*.

Abbreviations

BCB	Benzocyclobutenone
δ	Chemical shift
CDCl3	Deuterated chloroform
J	Coupling constant
conv	Conversion
DCM	Dichloromethane
DIBALH	Diisobutylaluminium hydride
DMF	Dimethylformamide
dd	Double doublet
d	Doublet
equiv.	Equivalent
et. al.	*et. alli. ("and others")*
h	hours
LDA	Lithium diisopropylamide
Me	Methyl
mp	Melting point
m	Multiplet
NMR	Nuclear Magnetic Resonance
ppm	Parts per million
PCC	Pyridinium chlorochromate
s	Singlet
NaHMDS	Sodium bis(trimethylsilyl)amide
TBDMS	Tert-Butyldimethylsilyl ether
THF	Tetrahydrofurane
OTf	Trifluoromethanesulfonate
TMS	Trimethyl silyl ether
t	Triplet

The rest of abbreviations and acronyms:
'Guidelines for authors' *J. Org. Chem* **2008**, 73, 23A-24A.

Chapter 1
General Introduction

1.1

General Background of catalysis

Human beings have been familiar with the term catalysis long before they assumed how it does take place. Indeed, there are countless number of examples in nature in which chemical reactions only occur in the presence of an entity that drastically accelerates a reaction that otherwise does not take place, or at least at a slower rate.[1]

The term ***catalysis*** coming from the Greek words *kata* meaning down and *lyein* meaning loosen was proposed in 1836 by the Swedish chemist Jöns Jacob Berzelius (1779-1848) in order to explain various decomposition and transformation reactions. He assumed that catalysts possessed special powers that could influence the affinity of chemical substances and he described the phenomena of catalysis as follow:[2,3]

"Many bodies have the property of exerting on other bodies an action which is very different from chemical affinity. By means of this action they produce decomposition in bodies, and form new compounds into the composition of which they do not enter. This new power, hitherto unknown, is common both in organic and inorganic nature; I shall call it catalytic power; I shall also call Catalysis the decomposition of bodies by this force."

Anselme Payen and Jean François Persoz were the first chemists to recognize the role of catalysts in living systems by isolating a material from malt that

[1] Webb, M. E.; Marquet, A.; Mendel, R. R.; Rébeillé, F.; Smith, A. G., *Nat. Prod. Rep.,* **2007**, *24*, 988.
[2] Berzelius, J. J. *Edinburgh New Philosophical Journal,* **1936**, 223.
[3] Wisniak, J., *Educ. Quím.,* **2010**, *21*, 60.

drastically accelerated the conversion of starch into sugar.[4] Payen called the substance *diastase*, and a half century later, the German physiologist Willy Kahne suggested the name *enzyme* for catalysts that occur in living systems. However, it was not until 1895 when the Nobel Prize winner Wilhelm Ostwald introduced the concept ***"rate of chemical reaction"*** that mathematically is defined as the differential quotient of the amount of substance with respect to time.[5] Such new concept re-defined the meaning of catalyst as the following:

"A catalyst is a substance which increases the rate at which a chemical reaction approaches equilibrium without becoming itself permanently involved."

By the end of the 19th century, catalysts rapidly became important in a variety of industrial applications. A very nice example is the synthesis of Indigo. Initially, the dye was obtained by extraction of the plant (*Indigofera tinctoria*) mainly grown in India. In 1878 the German chemist Adolf Baeyer succeeded in formulating its preparation in the laboratory.[6] Three decades later, Karl Heumann found a procedure for preparing Indigo from aniline.[6] As for many other cases, serendipity and good fortune was a key factor when making a scientific innovation. Thus, a broken thermometer revealed that mercury was indeed catalyzing the preparation of Indigo. Such discovery set up the stage for the implementation of a large-scale process at BASF in Zürich (Figure 1.1).

[4] Adlercreutz, P.; Straathof, A. J. J., "Applied biocatalysis", 2nd ed. CRC Press. **1994**.
[5] www.nobelprize.org
[6] Elmar Steingruber "Indigo and Indigo Colorants", Weinheim, Ullmann's Encyclopedia of Industrial Chemistry, Wiley-VCH, **2004**.

Figure 1.1[7]

For more than 100 years, catalysis has been a key contributory factor for producing daily used chemicals at large scale. A selection of important industrial processes involving the presence of a catalyst is the following: [8]

- Preparation of sulfuric acid from sulfur oxides (the Contact process catalyzed by Pt, V_2O_5; 1888);[8]
- Synthesis of nitric acid from ammonia (the Ostwald process catalyzed by Pt/Rh nets; 1906);[8]
- Production of ammonia from its elements (the Haber-Bosch uses iron-based catalyst; 1908);[8]
- Synthesis of methanol from CO/H_2 (catalyzed by ZnO/Cr_2O_3; 1923);8
- Ethylene polymerization at low-pressure (Ziegler-Natta process catalyzed by Ti compounds; 1954);[8]
- Hydrogenation, isomerization and hydroformylation reactions (Wilkinson catalyst and Rh/phosphine ligands; 1964 and 1983);[8]
- Synthesis of α-olefies from ethylene (SHOP process catalyzed by Ni/phosphines; 1977);[8]
- Production of acetic acid (Cativa process: Rh-catalysed methanol carbonylation; 1970)[8]

[7] http://agro.basf.co.cr/empresa.php
[8] Hagen, J. *Industrial Catalysis: Apractical Approach, 2nd ed.* **2006**, Wiley-VCH GmbH & Co.

Catalytic processes are present in the manufacture of a large number of organic intermediate products that are required for the production of plastics, synthetic fibers, pharmaceuticals, dyes, crop-protection agents, resins, and pigments. In fact, the economic importance of catalysis is reflected in the following numbers:

- More than 85% of all chemical products are manufactured with the help of catalysts.[9]
- 15-20% of the economic activities in industrialized countries depend directly on catalysis.[10]
- The commercial value of the catalysts produced annually amounts to approx. 14 billion US$.[10]

An analysis of the catalysts manipulation in the industry sectors denotes that there is an almost even distribution across four different sectors being the most important the environmental applications followed by the manufacturing of chemicals (Figure 1.2).[11]

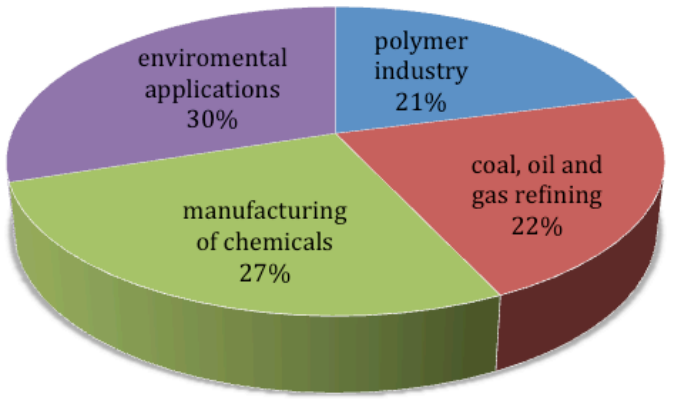


Figure 1.2

[9]German Catalysis Society. "Roadmap for catalysis research in Germany", 3rd ed.; Dechema, **2010**. (www.gecats.de)
[10] Behr, A.; Neubert, P. "Applied Homogeneous Catalysis"; Wiley-VCH: Weinheim, **2012**.
[11] Heveling, J. *J. Chem. Educ.*, **2012**, *89*, 1530.

While there are a myriad of compounds capable to drastically accelerate reactions, the suitability of a catalyst for an industrial process depends mainly on the following three properties:[8]

1. **Activity.** This is a measure of how fast one or more reactions proceed in the presence of the catalyst. An active catalyst will pass a large number of times for the cycle remaining unaltered; thus, the activity can be measured by the total number of substrate molecules that the catalyst convert into product molecules (TON) or in the number of substrate molecules converted in a certain period of time (TOF).[8]
2. **Selectivity**. The selectivity is the fraction of the starting material that is converted to the desired product. Good selectivity means more effective use of the feedstock as well as the reduction of waste, minimizing the work-up treatment, a matter of great importance, particularly in Industry.[8]
3. **Stability** (deactivation behavior). The chemical, thermal, and mechanical stability of a catalyst determines its lifetime in the cycle. Catalyst stability is influenced by numerous factors, including decomposition or poisoning, among others. Catalyst deactivation can be followed by measuring activity or selectivity as a function of time. Catalysts that lose activity during a process can often be regenerated before they ultimately have to be replaced. Not surprisingly, the total catalyst lifetime is of crucial importance for the economics of a process.[12]

It is rather difficult to determine which of these properties is the most important. Today, the efficient use of raw materials and energy is of major importance, and sometimes is preferable to optimize existing processes than to develop new ones.[8] In most instances, reactions should follow this priority rule:

Selectivity >Stability >Activity.

[12] van Leeuwen, P. W. N. M. "*Homogeneous Catalysis" Undestanding the art*. Klue Academic Publications, **2004**.

In a general context, the large number of existing catalysts can be classified according to different criteria: their physical state, their chemical nature, the nature of the reactions that they catalyze, or the state of aggregation.[8] Following the state of aggregation criteria, the phenomena of catalysis can be divided as shown in Figure 1.3.

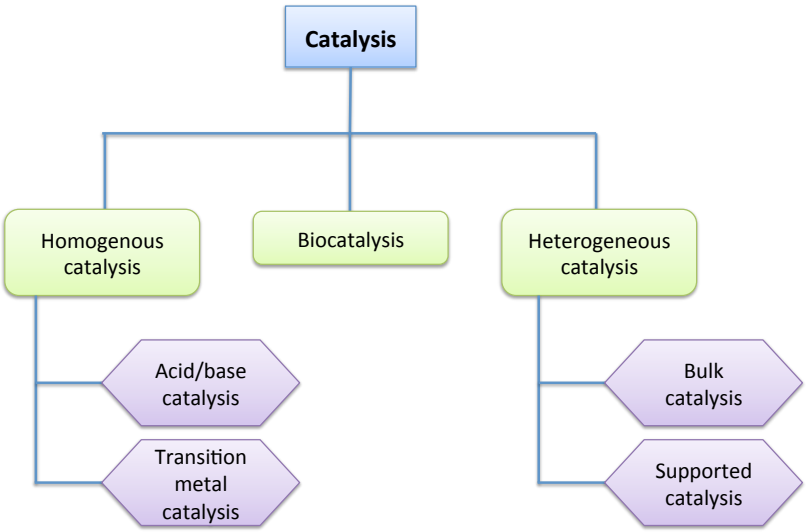


Figure 1.3

In recent years, the employment of soluble transition metal complexes as catalysts for organic transformations has grown exponentially. In homogeneous catalysis, the use of metal complexes in catalytic amounts for the activation and functionalization of inert bonds has a considerable interest in the area of sustainability and atom economy. The Organization for Economic Cooperation and Development (OECD) defines sustainable chemistry as:

"Sustainable chemistry seeks to improve the efficiency with which natural resources are used to meet human needs for chemical products and services. Sustainable chemistry encompasses the design, manufacture and use of efficient, effective, safe and more environmentally benign chemical products and processes. Sustainable chemistry stimulates innovation across all sectors to design and discover new chemicals, production processes, and product

stewardship practices that will provide increased performance and increased value while meeting the goals of protecting and enhancing human health and the environment."[13]

According to SusChem (European technology Platform For Sustainable chemistry) "the chemical industry has a long track record of 'doing more with less' by developing an integrated resource efficiency strategy throughout the process industries, input resources (including raw materials, renewable feedstock, energy, water), all output materials (including products, by-products, waste streams) and recycle options can be significantly optimized".[14]

[13] "Sustainable Chemistry Strategic Research"
http://www.suschem.org/aboutsuschem/sustainable-chemistry.aspx
[14] "Sustainable Chemistry Strategic Research" http://www.suschem.org/priorities.aspx

1.2

C-H Activation reactions

The ability to use cheap, abundant, non-toxic and attractive raw materials for the preparation of functional organic molecules is becoming a necessary goal for achieving societal, economic and environmental objectives.[15] A major issue of this endeavor is not only the design of better methodologies to produce bulk chemicals, but also to synthesize new materials for industry, medicine and research. The activation of ubiquitous, and widespread inert chemical entities such as carbon-hydrogen (C-H),[16] carbon-carbon (C-C) bonds[17] and carbon dioxide (CO_2),[18] would definitely fill this gap; unfortunately, the robustness and high bond energies associated with these rather inert molecules pose fundamental challenges for chemists from both thermodynamic and kinetic point of view. Beyond any doubt, the key for success has been the utilization of metal-catalyzed reactions, thus undoubtedly changing the landscape of organic synthesis providing new synthetic tools that facilitate further manipulation. Not

[15] Taniewski, M. *Chem. Eng. Technol.* **2006**, *29*, 1397.

[16] For reviews on C-H activation chemistry, see: a) Hartwig, J. F. *Chem. Soc. Rev.* **2011**, *40*, 1992. b) Gutekunst, W. R.; Baran, P. S., *Chem. Soc. Rev.* **2011**, *40*, 1976. c) Gutekunst, W. R.; Baran, P. S., *Chem. Soc. Rev.* **2011**, *40*, 1976. d) McMurry, L.; O´Hara, F.; Gaunt, M. *Chem. Soc. Rev.* **2011**, *40*, 1885. e) Lyons, T. W.; Sanford, M. *Chem. Rev.* **2010**, *110*, 1147. f) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem. Eur. J.* **2010**, *16*, 2654. g) Chen, X.; Engle, K. M.; Wang, D. H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. h) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. i) Bergman, R. G., *Nature* **2007**, *446*, 391.

[17] For selected reviews, see: (a) Murakami, M.; Matsuda, T. *Chem. Commun.* **2011**, *47*, 1100. (b) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117. (c) Necas, D.; Kotora, M. *Curr. Org. Chem.* **2007**, *11*, 1566. (d) Jun, C.-H. *Chem. Soc. Rev.* **2004,** *33*, 610. (e) Nishimura, T.; Uemura, S. *Synlett* **2004**, 201. (f) van der Boom, M. E.; Milstein, D. *Chem. Rev.* **2003**, *103*, 1759 and citations therein.

[18] For selected reviews, see: (a) Huang, K.; Sun, C.-L.; Shi, Z.-J. *Chem. Soc. Rev.* **2011**, *40*, 2435. (b) Sakakura, T.; Kohno, K. *Chem. Commun.* **2009**, 1312. (c) Correa, A.; Martin, R. *Angew. Chem., Int. Ed.* **2009**, *48*, 6201. (d) Yu, K. M. K.; Curcic, I.; Gabriel, J.; Tsang, S. C. E. *ChemSusChem* **2008**, *1*, 893. (e) Sakakura, T.; Choi, J.-C.; Yasuda, H. *Chem. Rev.* **2007**, *107*, 2365. (f) Kleij, A.; Martin, R. *ChemSusChem* **2011**, *4*, 1259.

surprisingly, the potential of these processes has been illustrated recently by Ru- or Mo-catalyzed metathesis reactions and Pd-catalyzed cross-coupling reactions, recently awarded with the Nobel Prize in chemistry 2005 and 2010, respectively.[19]

Despite the tremendous success in metal-catalyzed cross-coupling reactions aimed at forming C-C bonds[20], there are still several issues that need to be taken into account: 1) inherent instability of organometallic reagents (for instance decomposition *via* β-elimination or proto-demetalation when alkyl organometallic compounds are used), 2) the need for stoichiometric amounts of organometallic species, 3) prefunctionalization is required for both coupling counterparts, and 4) a considerable amount of waste is generated (Figure 1.4).

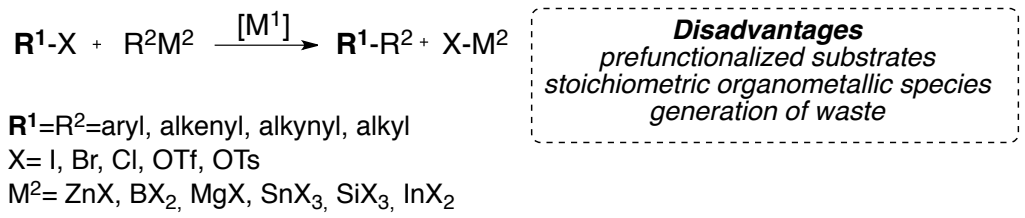


Figure 1.4

In recent years we have witnessed a renaissance in the area of inert bond-cleavage, particularly in the field of C-H bond-functionalization reactions.[16] The utilization of these processes drastically reduces the amount of waste and the problems associated when dealing with stoichiometric amounts of metal reagents (Figure 1.5).[21] However, the need for prefunctionalization of the electrophilic

[19] "The Nobel Prize in Chemistry". Nobelprize.org. 16 Feb 2013. http://www.nobelprize.org/nobel_prizes/chemistry

[20] Negishi, E.-I.; Zeng, X.; Tan, Z.; Qian, M.; Hu, Q.; Huang, Z. *"Metal-catalyzed Cross-coupling Reactions",* 2nd Ed Wiley-VCH, New York, **2004**.

[21] a) Ackermann, L.; Althammer, A.; Born, R. *Angew. Chem., Int. Ed.,* **2006**, *45*, 2619. b) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K., *J. Am. Chem. Soc.,* **2006**, *128*, 581. c) Ferraccioli, R.; Carenzi, D.; Motti, E.; Catellani, M., *J. Am. Chem. Soc.,* **2006**, *128*, 722. d) Alberico, D.; Scott, M. E.; Lautens, M., *Chem. Rev*., **2007**, *107*, 174.

counterpart still constitutes a problem to be overcome, particularly from the standpoint of sustainability.

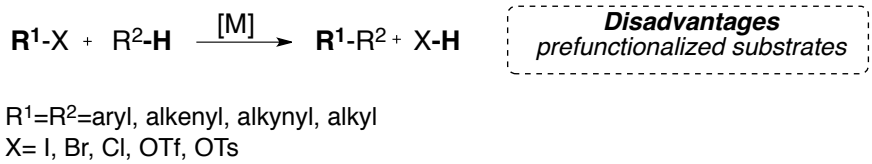


Figure 1.5

Alternatively, the cross coupling reaction of two coupling partners possessing C-H bonds would be the most atom step-economical transformation with minimum generation of waste (Figure 1.6).[22] However, while very attractive this approach might suffer from site-selectivity due to the ability of many C-H bonds to participate across the cross-coupling event, thus representing a considerable challenge. Additionally, one should take into account that the transformation requires stoichiometric amounts of oxidant.

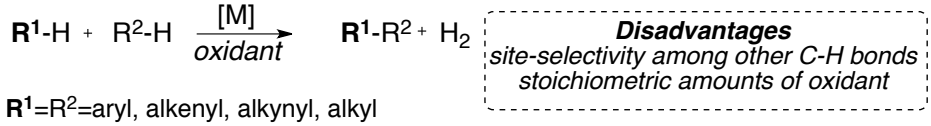


Figure 1.6

[22] a) Yeung, C. S.; Dong, V. M.; *Chem. Rev.* **2011**, *111*, 1215. b) Li, C. –J. *Acc. Chem. Res.,* **2009**, *42*, 335. c) Hull, K. L.; Sanford, M. S., *J. Am. Chem. Soc*., **2009**, *131*, 9651. d) Brasche, G.; García-Fortanet, J.; Buchwald, S. L., *Org. Lett*., **2008**, *10*, 2207. e) Cho, S. H.; Hwang, S. J.; Chang, S., J. *Am. Chem. Soc.,* **2008**, *130*, 9254. f) Stuart, D. R.; Fagnou, K., *Science*, **2007**, 316, 1172. g) Stuart, D. R.; Villemure E.; Fagnou, K. *J. Am. Chem. Soc.,* **2007**, *129*, 12072. h) Hull, K. L.; Sanford, M. S.; *J. Am. Chem. Soc.,* **2007**, *129*, 11904. i) Li, B. –J. ; Tian, S. –L.; Fang, Z.; Shi, Z. –J., *Angew. Chem., Int. Ed.,* **2008**, *47*, 1115. j) Dwight, T. A.; Rue, N. R.; Charyk, D.; Josselyn, R.; DeBoef, B., *Org. Lett*., **2007**, *9*, 3137. k) Potavathri, S.; Dumas, A. S.; Dwight, T. A.; Naumiec, G. R.; Hammann, J. M.; DeBoef, B., *Tetrahedron Lett.,* **2008**, *49*, 4050. l) Xia, J.-B.; You, S.-L., *Organometallics,* **2007**, *26*, 4869. m) Hull, K. L.; Sanford, M. S., *J. Am. Chem. Soc.*, **2007**, *129*, 11904. n) Hull, K. L.; Lanni, E. L.; Sanford, M. S., *J. Am. Chem. Soc*., **2006**, *128*, 14047.

Despite many advances, there are still significant challenges posed in the C-H bond functionalization event: a) Overcoming the low reactivity of the C-H bond and b) the selective activation of only one C–H bond among many similar entities in the same molecule (site-selectivity). According to recent there have been different techniques to overcome all these limitations:

a) Overcoming the low reactivity of the C-H bond.

C-H bonds are considerably stronger than C-X bonds (CH_3-H, 105 kcal mol^{-1}; Ph-H, 110 kcal mol^{-1}; Ph-I, 65 kcal mol^{-1}),[23] reinforcing the notion that C-H bonds are "inert". However the corresponding metalated product (M-C) is much more reactive than the corresponding C-H counterparts (Pd-C(CH_3), 41.6 kcal mol^{-1}; Pd-C(Ph), 38.6 kcal mol^{-1}), thus facilitating the subsequent functionalization.[24]

It is important to make a distinction between two concepts: ***Activation of C-H bonds*** involves coordination of a C-H bond to a metal complex followed by oxidative addition, thus forming a ***M-H bond*** and increasing the oxidation state by two units. Historically, the term "C-H bond activation" carries out considerable mechanistic claim[25] while *"**C-H bond functionalization**"* simply describes a ***formal process*** where a new functionality is replacing the H atom. From a mechanistic point of view, the C-H bond metalation step can proceed *via* distinct reaction pathways depending on the nature of the metal fragment. Usually, the different mechanism are classified as follows:

1. ***Oxidative addition***.[26] The mechanism proceeds with electron-rich and low-valent late transition metals *via* a formal C-H activation where compounds of the type **(1)** are formed in which a M-H bond is present (Figure 1.7). This

[23] Siegbahn, P. E. M. *J. Phys. Chem.* **1995**, *99*, 12723.
[24] For select reviews on mechanistic aspects of C-H bond functionalizations, see: (a) Balcells, D.; Clot, E.; Eisenstein, O., *Chem. Rev*. **2010**, *110*, 749. (b) Lersch, M.; Tilset, M. Chem. Rev. **2005**, *105*, 2471. (c) Ritleng, V.; Sirlin, C.; Pfeffer, M. Chem. Rev. **2002**, *102*, 1731.
[25] Bergman, R. G. *Nature,* **2007**, *446*, 391.
[26] a) Labinger, J. A.; Bercaw, J. E. *Nature*, **2002**, 417, 507. b) Goldman, A. S.; Goldberg, K. I. ACS Symposium Series 885, *Activation and Functionalization of C-H Bonds*, **2004**.

activation is not only affected by the nature of the metal species; ligands have also a pronounced electronic effect in the metalation reaction. While σ-donor ligands favor metal complexes in high oxidation states, π-acceptor ligands reduce the electron density on the metal center making the oxidative addition less favorable.

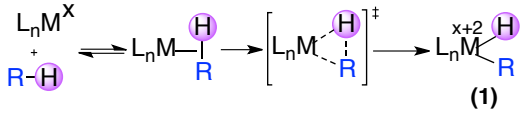


Figure 1.7

*2. **σ-bond metathesis**.*[26] Early transition metals with d^0 configuration undergo a concerted process by forming easily electron deficient centers that facilitate the required four-center σ-bond metathesis transition state to yield compound **(2)** (Figure 1.8).

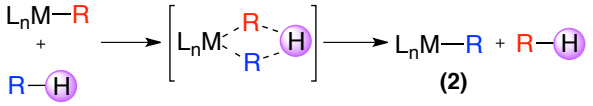


Figure 1.8

*3. **Electrophilic substitution**.*[26] Reactions classified as such result in functionalized products without any observance of intermediate organometallic species. This type of reaction is illustrated in Figure 1.9, where $[M^{x+2}]$ **(3)** is a later or post-transition metal usually in a strong polar medium such ether. The presumed organometallic intermediate $[L_nM^{x+2}(R)(X)]$ **(4)** involved in the transformation is formed trough substitution of the metal for a proton.

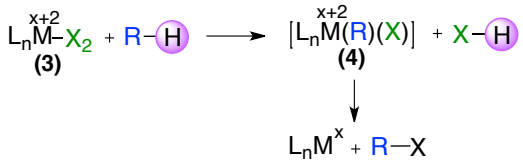
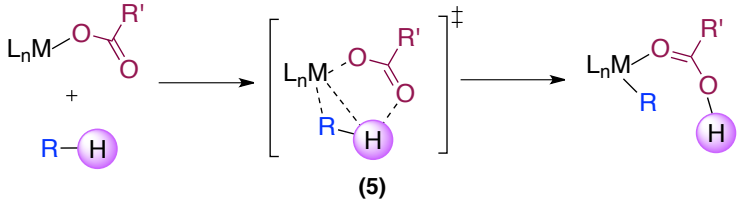


Figure 1.9

4. ***Base-assisted metalation-*** **CMD (concerted-metalation-deprotonation).**[27] Reactions that take place using bifunctional ligands as carboxylate or acetate groups are mostly proposed to proceed *via* a mechanism in which the metallation takes place *via* a concerted base-assisted deprotonation (intermediate **(5)**) (Figure 1.10). The first experimental and theoretical mechanistic studies on the catalytic direct functionalization of simple arenes through CMD mechanism were mainly carried out by the groups of Echavarren[28] and Fagnou.[29] Additionally, CMD have been also established as a mechanistic pathway for the direct activation of C-H(sp^3) bonds.[30]



(5)

Figure 1.10

b) The selective activation of only one C–H bond among many similar entities in the same molecule. The use of directing groups (DG), such as amides, pyridines, or acetanilides, has become the strategy of choice to allow site-

[27] a) Ackermann, L. *Chem. Rev.* **2011**, 111, 1315. b) Lapointe, D.; Fagnou, K., *Chem. Lett.,* **2010**, *39*, 1118.

[28] a) González, J. J.; García, N.; Gómez-Lor, B.; Echavarren, A. M., *J. Org. Chem.* **1997**, *62*, 1286. b) García-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066. c) García-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren A. M. *J. Am. Chem. Soc.* **2007**, *129*, 6880. d) Pascual, S.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *Tetrahedron*, **2008**, 6021.

[29] a) Campeau, L.-C.; Parisien, M.; Leblanc, M.; Fagnou, K., *J. Am. Chem. Soc.* **2004**, *126*, 9186. b) Lafrance, M.; Blaquière, N.; Fagnou, K., *Chem. Commun.* **2004**, 2874. c) Parisien, M.; Valette, D.; Fagnou, K., *J. Org. Chem.* **2005**, *70*, 7578. d) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K., *J. Am. Chem. Soc.* **2006**, *128*, 581. e) Lafrance, M.; Rowley, C. N.; Woo, T. K., Fagnou, K. *J. Am. Chem. Soc*. **2006**, *128*, 8754. f) Gorelsky, S. I.; Lapointe, D.; Fangou, K. *J. Am. Chem. Soc*. **2008**, *130*, 10848.

[30] a) Baudoin, O.; Herrbach, A.; Guéritte, F., *Angew. Chem. Int. Ed*. **2003**, *42*, 5736. b) Hitce, J.; Retailleau, P.; Baudoin, O., *Chem. Eur. J.* **2007**, *13*, 792. c) Kefalidis, C. E.; Baudoin, O.; Clot, E., *Dalton Trans.* **2010**, 39, 10528. d) M. Chaumontet, R. Piccardi, N. Audic, J. Hitce, J.-L. Peglion, E. Clot, O. Baudoin, *J. Am. Chem. Soc*. **2008**, *130*, 15157.

selective functionalization.[31] The role of a DG is to direct the transition metal into close proximity of to the C-H bond to be functionalized thus, resulting in high regioselectivity and increased reactivity (Figure 1.12). In recent years, a large number of C-C and C-heteroatom bond-forming processes have been reported using this approach.[32] However the use of DG's have undeniable limitations: a) most of the times only *ortho* C-H bonds are activated,[33] b) additional synthetic steps are often required to both install the DG into the starting material and to manipulate it after C-H functionalization. Not surprisingly, considerable efforts are currently focused on the development of easily modifiable or removable DG.[34]

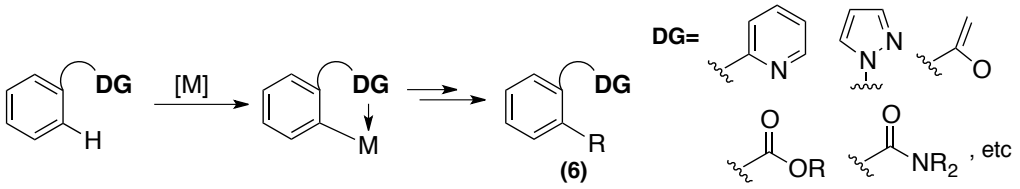


Figure 1.12

Despite all the setbacks mentioned, the fact that chemists are capable of cleavage C-H bonds has changed the manner in which complex molecules can be

[31] Neufeldt, S. R.; Sanford, M. S., *Acc. Chem. Res.,* **2012**, *45*, 936.

[32] For directing groups in transition-metal-catalyzed C-H activations see: a) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H., *Chem. Rev.,* **2012**, *112,* 5879. b) Kuhl, N.; Hopkinson, N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem. Int. Ed.* **2012**, *51*, 10236. c) Colby, D. A.; Bergman, R. G.; Ellman, J. A., *Chem. Rev.*, **2010**, 110, 624. d) Daugulis, O., *Top. Curr. Chem.,* **2010**, *292*, 57. e) Ackermann, L.; Vicente, R., *Top. Curr. Chem.,* **2010**, *292*, 211. f) Daugulis, O.; Do. H. –H.; Shabashov, D., *Acc. Chem. Res.*, **2009**, *42*, 1074. g) Ritleng, V.; Sirlin, C.; Pfeffer, M., *Chem. Rev.*, **2002**, *102*, 1731.

[33] For examples of meta-selective C-H functionalization see: a) Leow, D.; Li, G.; Mei, T. –S.; Yu, J. –Q., *Nature*, **2012**, *486*, 518. b) Truong, T.; Daugulis, O., *Angew. Chem. Int. Ed.* **2012**, 51, 11677. c) Wang, D.-H.; Engle, K. M.; Shi, B.-F.; Yu, J.-Q., *Science* **2010**, *327*, 315. d) Duong, H. A.; Gilligan, R. E.; Cooke, M. L.; Phipps, R. J.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2011**, *50*, 463. e) Cho, J. Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E.; Smith, M. R., *Science* **2002**, *295*, 305. f) Chotana, G. A.; Rak, M. A.; Smith, M. R., *J. Am. Chem. Soc.* **2005**, *127*, 10539. g) Murphy, J. M.; Liao, X.; Hartwig, J. F., *J. Am. Chem. Soc.* **2007**, *129*, 15434. h) Boebel, T. A.; Hartwig, J. F., *Organometallics* **2008**, *27*, 6013. i) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593.

[34] For removable directing groups see: a) Rousseau, G.; Breit, B. *Angew. Chem. Int. Ed.* **2011**, *50*, 2450.; b) Wang, C.; Chen, H.; Wang, Z.; Chen, J.; Huang, Y. *Angew. Chem. Int. Ed.* **2012**, *51*, 7242. c) Cornella, J.; Righi, M.; Larrosa, I. *Angew. Chem. Int. Ed*. **2011**, *50*, 9429.

synthesized. In this sense C-H bond functionalization has found application in the field of total syntheses of natural products of great complexity, for instance the synthesis of molecules **(7)-(10)** shows the high importance of this subject in further transformations (Figure 1.13).[35]

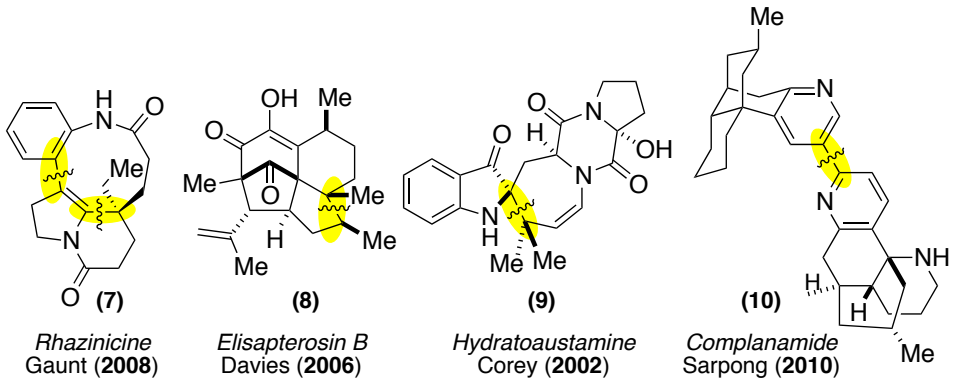


Figure 1.13

The vast majority of C-H bond functionalization processes are focused on aromatic C_{sp2}-H bonds. From a synthetic point of view, the C-H bond functionalization of aldehydic fragments **(11)** has a great potential because aldehydes are probably the best synthons in organic synthesis. Thus, C-H bond functionalization of aldehydic bonds represents a straightforward alternative in route to ketones derivatives **(12)** with zero waste generation and without the need of directing groups (Figure 1.14).

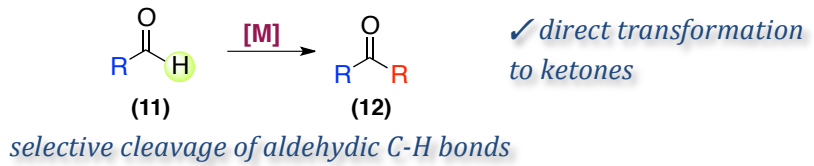


Figure 1.14

[35] a) Beck, E. M.; Grimster, N. P.; Hatley, R.; Gaunt, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 2528. b) Davies, H. M. L.; Dai, X.; Long, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 2485. c) Baran, P. S.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 7904. d) Fischer, D. F.; Sarpong, R. *J. Am. Chem. Soc.* **2010**, *132*, 5926.

1.2.1 Hydroacylation reactions

The transition metal-catalyzed hydroacylation of aldehydes with alkenes and alkynes constitutes an elegant example that results from combining a C-H activation event with a subsequent C-C bond formation.[36] The hydroacylation reaction formally involves the addition of an acyl unit and a hydrogen atom across the C-C multiple bond to form compounds of the type **(16)**. The drawbacks associated to this reaction are the limited set of substrates that can be used, as well as the irreversible *decarbonylation* event that results in decomposition of the starting material and the catalyst poisoning forming compound **(17)**.

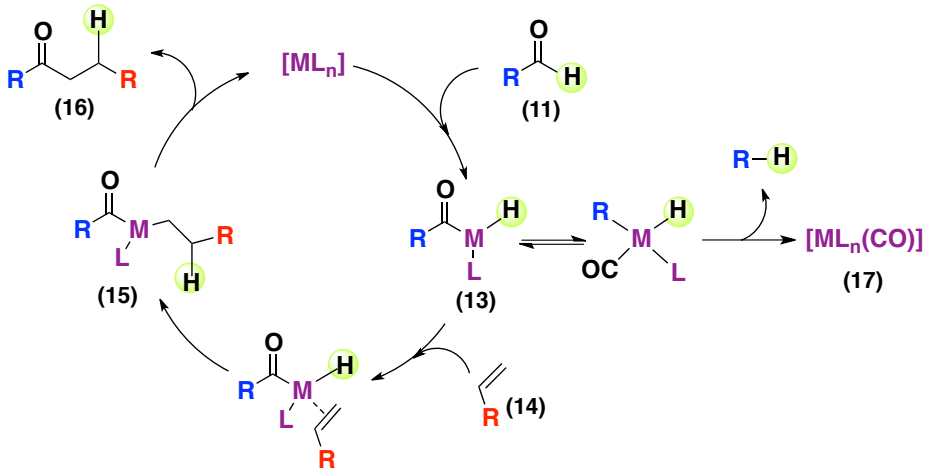


Figure 1.15

The accepted mechanism for hydroacylation reactions is depicted in Figure 1.15. The sequence is initiated by an oxidative addition of the metal to the aldehydic C-H bond forming acyl-metal hydride species (RCO-M-H). These species can follow two different pathways: 1) coordination to a π-system followed by migratory insertion and reductive elimination, thus forming the new C-C bond

[36] For recent review of transition metal catalyzed hydroacylation reactions see: a) Leung, J. C., Krische, M. J. *Chem Sci.* **2012**, *3*, 2202. b)Willis, M. C. *Chem. Rev.* **2010**, 110, 725. c) Jun, C. –H.; Jo. E. –A.; Park, J. –W.; *Eur. J. Org. Chem.* **2007**, 1869.

and recovering the active metal species or 2) decarbonylation from the acyl metal hydride, and subsequent reductive elimination, thus delivering the corresponding reduced compound.

Although decarbonylation processes have turned out to be useful synthetic methodologies,[37] such step constitutes a serious drawback that need to be overcome in hydroacylation reactions. Mechanistic studies recently demonstrated that decarbonylation can be easily modulated depending on the reaction conditions, in which the nature of the solvent and substrate plays a crucial role.[38] Related stoichiometric studies also indicated that reductive elimination, toward the reduced product, is often times the turnover-limiting step.[39]

Prompted by studies reported by Miller[40] and Larock,[41] Bosnich described in 1988 the first catalytic example of intramolecular rhodium hydroacylation reaction of 4-pentanals **(18)** to yield cyclopentanone derivatives using the cationic complex $[Rh(dppe)]_2(ClO_4)_2$ as catalyst (Figure 1.16). The decarbonylation process was avoided by stabilizing the acyl-metal-hydride intermediate making stable six-metallacyclic complexes **(20)**.[42] The maturity of this reaction was illustrated by the success when performing enantioselective transformations.[43]

[37] For application of decarbonylation in synthesis see: a) Kreis, M.; Palmelund, A.; Bunch, L.; Madsen, R. *Adv. Synth. Catal.* **2006**, *348*, 2148. b) Fristrup, P.; Kreis, M.; Palmelund, A.; Norrby. P. O.; Madsen, R. *J. Am. Chem. Soc.* **2008**, *130*, 5206. c)Iwai, T.; Fujihara, T.; Tsuji, Y. *Chem. Commun.* **2008**, 6215.
[38] a) Hyatt, I. F. D.; Anderson H. K.; Morehead, A. T.; Sargent, A. L. *Organometallics,* **2008**, *27*, 135. b) Y.-T. Hong, A. Barchuk, M. J. Krische, *Angew. Chem., Int. Ed.,* **2006**, *45*, 6885.
[39] a) Fairlie, D. P.; Bosnich, B. *Organometallics,* **1988**, *7*, 946. b) Lenges, C. P.; White, P. S; Brookhart, M. *J. Am Chem. Soc.* **1998**, *120*, 6965. c) Roy, A. H.; Lenges, C. P.; Brookhart, M. *J. Am Chem. Soc.* **2007**, *129*, 2082.
[40] Campbell, R. E.; Lochow, C. F.; Vora, K. P.; Miller, R. G. *J. Am Chem. Soc.* **1980**, *102*, 5824.
[41] Larock, R. C.; Oertle, K.; Potter, G. F. *J. Am Chem. Soc.* **1980**, *186*, 627.
[42] a) Fairlie, D. P.; Bosnich, B.; *Organometallics* **1988**, *7*, 936. b) Fairlie, D. P.; Bosnich, B.; *Organometallics* **1988**, *7*, 946.
[43] Bosnich, B. *Acc. Chem. Res.* **1998**, *31*, 667.

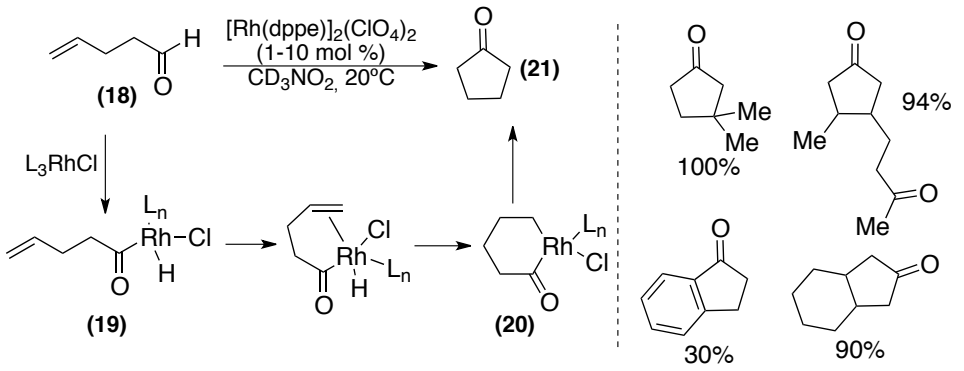


Figure 1.16

Formation of ring systems larger than cyclopentanones using intramolecular hydroacylation is much more challenging because the metallacycle formed is less stable than the corresponding five-membered metallacycle. Additionally, reductive elimination when forming larger rings is much slower and therefore decarbonylation become dominant. Mori and co-workers demonstrated that the synthesis of cycloheptanone products **(23)** is possible starting from dienal substrates **(22)** (Figure 1.17)[44]. It is noteworthy that the initial geometry of the dienal substrate plays an important role in the reaction; thus, while *Z* alkene at C6 position produced the cyclopentanone product, the diene containing an *E* alkene in the same position gives the desired heptanone product.

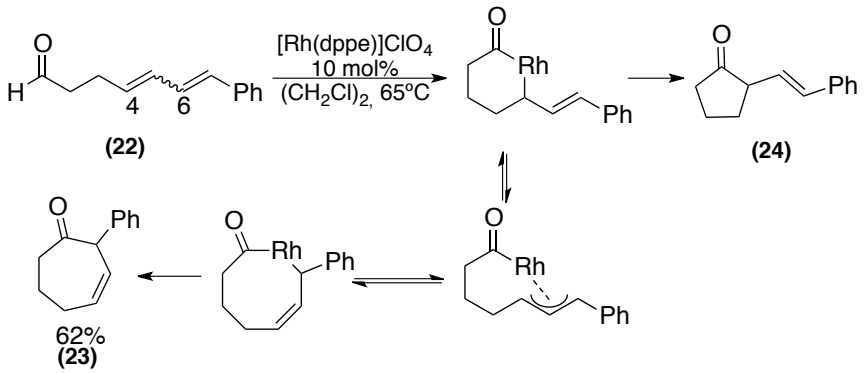


Figure 1.17

[44] a) Sato, Y.; Oonishi, T.; Mori, M. *Angew. Chem. Int. Ed.* **2002**, *41*, 1218. b) Oonishi, T.; Mori, M; Sato, Y. *Synthesis*, **2007**, 2323.

Other larger rings can be also synthesized by hydroacylation reactions, Figure 1.18. Shair and co-workers demonstrated that eight-membered rings are within reach using intramolecular hydroacylation by incorporating a cyclopropane fragment in the substrate, triggering a ring expansion in the rhodacycle yielding the corresponding cyclooctanone derivative **(25)**.[45] Benford also reported the synthesis of seven-membered rings containing an heteroatom **(26)**. [46] Subsequently, Dong reported the enantioselective version using cationic Rh complexes and (*R,R*)-Me-DuPhos as the chiral ligand.[47]

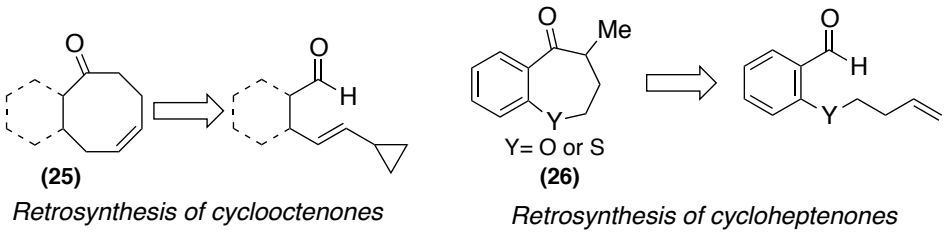


Figure 1.18

Although intermolecular reactions using alkenes as substrates have been largely examined, the alkyne fragment has been less studied. Recently, Willis and co-workers reported a system that provides control over regioselectivity in the hydroacylation of alkynes, especially in electron-poor derivatives, in which a bulky *ortho*-^{i}Pr-dppe-Rh catalyst promotes the formation of branched adducts **(28)** (Figure 1.19-right). In contrast dppe-Rh and DPE-Rh catalysts favor the formation of the linear product **(27)** (Figure 1.19-left).[48]

[45] Aloise, A. D.; Layton, M. E.; Shair, M. D. *J. Am. Chem. Soc.* **2000**, *122*, 12610.
[46] Bendoford, H. D.; Colella, C. M.; Dixon, E. C.; Marchetti, M.; Matukonis, A. N.; Musselman, J. D.; Tiley, T. A. *Tetrahedron Lett.* **2002**, *43*, 7031.
[47] a) Coulter, M.M.; Dornan, P. K.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 6932. b) Zengming, S.; Dornan, P. K.; Khan, H. A.; Woo, T. K.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 1077.
[48] González-Rodríguez, C.; Pawley, R. J.; Chaplin, A. B.; Thompson, A. L.; Weller, A. S. W.; Willis, A. C. *Angew. Chem. Int, Ed.* **2011**, *22*, 5134.

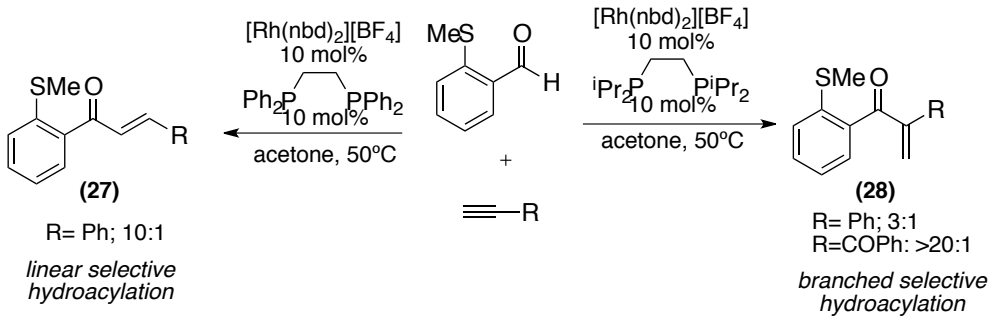


Figure 1.19

1.2.1.1 Hydroacylation with aldimine derivatives

Although chelation control greatly contributed to the success of hydroacylation reactions, the need for introducing N, P, S, or O motifs in ortho-position for preventing decarbonylation drastically restricts the scope of these processes. [49] A different way to successfully achieve metal-catalyzed hydroacylation reactions is the utilization of a masked aldehyde.[50] The use of picolyl imines as masking aldehydes forming aldimine derivatives **(29)** has been extensively used in hydroacylation reactions. However, in efforts to expand the utility of the process, Ju has reported the *in situ* generation of aldimide derivatives from aldehydes and alcohols. In these systems, the presence of $Rh(PPh_3)_3Cl$ (Wilkinson's catalyst) allowed the formation of propiophenone derivatives in high yields, Figure 1. 20.[51]

[49] a) González-Rodríguez, C., Parsons, S. R.; Thompson, A. L.; Willis, M. C. *Chem. Eur.* **2010**, *16*, 10950. b) Coulter, M. M.; Dornan, P. K.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 6932.
[50] Suggs, J. W. *J. Am. Chem. Soc.* **1979**, *101*, 489.
[51] a) Jun, C. H.; Lee, D.-Y; Lee, H.; Hong. J.-B. *Angew. Chem., Int. Ed.* **2000**, *39*, 3070. b) Jun, C. –H.; Lee, D. –Y.; Lee, H.; Hong, J. –B.; *Angew. Chem. Int. Ed.* **2000**, *39*, 3070.

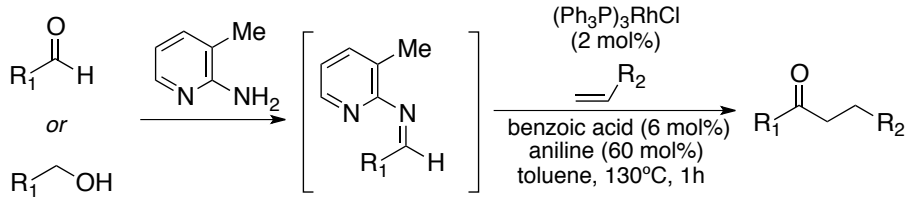


Figure 1.20

In summary, hydroacylation reaction is an useful methodology for the synthesis of ketones. Unfortunately, this protocol is mostly limited to the utilization of π-systems as coupling counterpart, resulting in regioselectivity issues depending on the substrate used (Figure 1.21). Additionally, the need for directing groups for preventing decarbonylation lowers down the application profile of this methodology, although the use of masked aldehydes minimize this side reaction. Therefore, the development of new catalytic methodologies in route to ketone derivatives without the need of π-systems would constitute an attractive alternative in the area of aldehyde C-H bond functionalization.

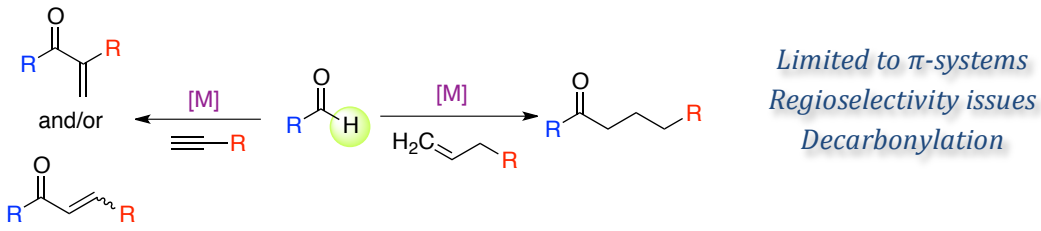


Figure 1.21

1.2.2 Metal catalyzed arylation *via* functionalization of aldehydic C-H bonds.

The direct introduction of carbonyl functional groups into aromatic motifs *via* aldehyde C-H bond functionalization potentially provides a complementary approach to classical Friedel-Crafts acylation (Figure 1.22 top right using Ar-H).[52] Additionally, such C-H bond functionalization reaction represents an alternative to the nucleophilic addition of organometallic compounds to carboxylic acid derivatives (Figure 1.22-**a**)[53] and the oxidation of secondary alcohols (Figure 1.22-**b**).[54]. However, significant chemoselectivity issues of classical methods, drastic reaction conditions, need of stoichiometric amounts of organometallic reagents and a large amount of by-products represent a limitation of these methods.

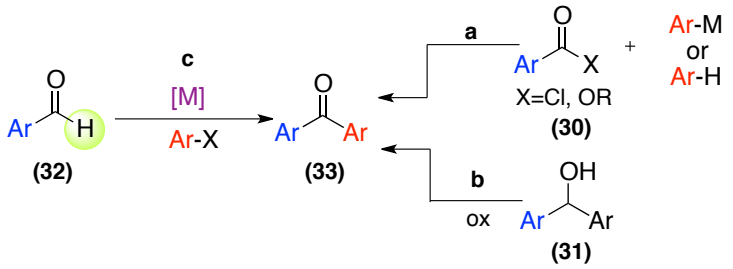


Figure 1.22

The first report concerning the C-H functionalization of an aldehyde by a metal complex and its further transformation to diarylketones was published in 1985 using organovanadium reagents that reacted with aryl and aliphatic aldehydes resulting in the oxidative C-C bond formation leading the corresponding diaryl

[52] a) Furstner, A.; Voigtlander, D.; Schrader, W.; Giebel, D.; Reetz, *Org. Lett.* **2001**, *3*, 417. b) Gmouth, S.; Yang, H.L.; Vaultier, M. *Org. Lett.* **2003**, *5*, 2219. c) Fillion, E.; Fishlock, D.; Wilsily, A.; Goll, J.M. *J. Org. Chem.* **2005**, *70*, 1316.
[53] a) Reddy, C.K.; Knochel, P. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1700. b) Wu, T.C.; Xiong, H.P.; Rieke, R.D. *J. Org. Chem.* **1990**, *55*, 5045. c) Tatamidani, H.; Kakiuchi, F.; Chatani, N. *Org. Lett.* **2004**, *6*, 3597.
[54] March, J. *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*; (4th ed.) John Wiley and Sons, New York, 1992.

ketone (Figure 1.23).[55] The organovanadium reagents used in this methodology are formed *in situ* from equimolar amounts of vanadium trichloride and organolithium or magnesium compounds at low temperature (-78ºC). The mechanism of the reaction suggested the formation of $RVCl_2$ **(34)** species after transmetallation with the organolithium or organomagnesium species followed by β-hydride elimination.

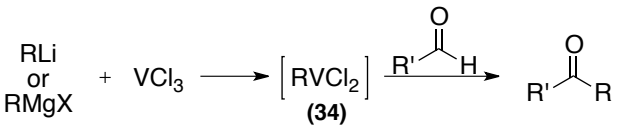


Figure 1.23

Nomura reported in 1996, the first example of the direct catalytic arylation of aldehydic C-H bonds in compounds of the type **(35)** with aryl iodides **(36)** to yield unsymmetrical diaryl ketones **(37)**.[56] It was found that the best results were achieved in the presence of $PdCl_2$ (5 mol%), Na_2CO_3 as base (2 equiv.) and LiCl or $BzEt_3NCl$ as additive in DMF at 100ºC for 10 h. Although the scope of the reaction included functionalities such as alkoxy, nitro, chloro and methoxy groups, the need for the hydroxyl group in *ortho*-position as well as the use of Ar-I as coupling counterpart limited the methodology for the use of these type of substrates (Figure 1.24).

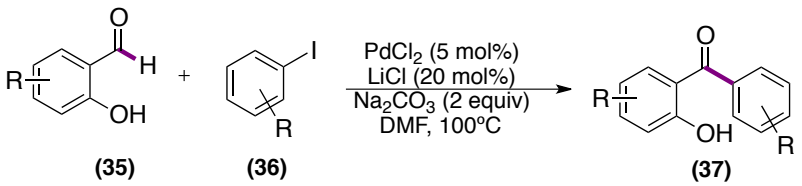


Figure 1.24

[55] Hirao, T.; Misu, D.; Agawa. T. *J. Am. Chem. Soc.* **1985**, 107, 7179.
[56] Satoh, T.; Itaya, T.; Miura, M.; Nomura, M. *Chem. Lett.* **1996**, 823.

In Figure 1.25 is shown the proposed mechanism of the reaction. The sequence commenced with an oxidative addition of the aryl iodide **(38)** to the *in situ* formed Pd(0) species, then a ligand exchange produced aryl(aryloxy)palladium **(39)** intermediates which evolved to a short-live Pd(IV) species **(40)** after C-H activation of the aldehydic C-H bond. After two-fold reductive eliminations the corresponding diaryl ketone was formed while recovering the Pd(0) active species.

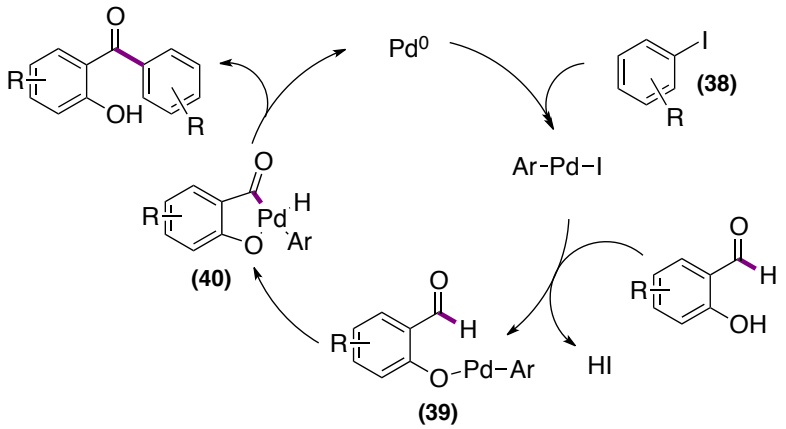


Figure 1.25

On the other hand, Hartwig reported a Rh-catalyzed intermolecular reaction of aryl iodides and *N*-heterocyclic aldimines **(41)** as masked aldehydes. Thus, the final ketimines **(42)** delivered the corresponding ketone **(43)** upon hydrolysis (Figure 1.26).[57,58]

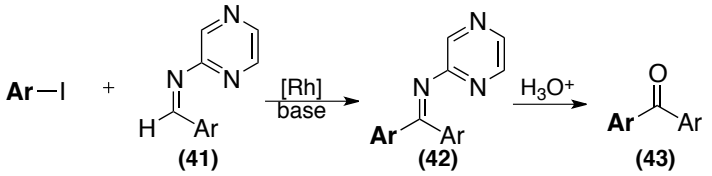


Figure 1.26

[57] Ishiyama, T.; Hartwig J. *J. Am. Chem. Soc.* **2000,** *122,* 12043.

[58] For a recent Heck-type synthesis of arylketones with aliphatic aldehydes via enamine intermediates see: a) Liu, Y.; Deng, C. –L.; Tang, R. –Y., Zhang, C. –G, Li, J. –H-. *Org. Lett.*, **2011**, *13*, 2184. b) Colbon, P.; Ruan.; Purdie, M.; Xiao, J. *Org. Lett.*, **2010**, *12*, 3670. c) Adak, L.; Bhadra, S.; Ranu. B. C.; *Tetrahedron Lett.,* **2010**, *51*, 3811. d) Ruan, J.; Saidi, O.; Iggo, J. A.; Xiao, J. *J. Am. Chem. Soc.* **2008**, *130*, 10510.

Cheng and co-workers reported the first nickel-catalyzed coupling of aryl iodides **(38)** with aldehydes **(44)** to give ketones **(45)** without the use of preformed precursors as aldimides and without requiring directing groups, Figure 1.27. The best reaction conditions where found when $NiLBr_2$ (10mol%) was used as precatalyst in the presence of Zn dust at 110ºC. The reaction showed a strong ligand effect; while bidentate phosphines such as dppm, dppe, dppp and dppb clearly afforded the desired product, the use of monodentate phosphines shutted down the reactivity. Mechanistically, such process involved an addition of the aryl group to the aldehyde motif followed by β-hydride elimination of the resulted metal alkoxide.[59]

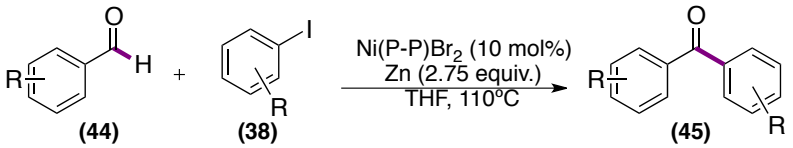


Figure 1.27

The use of different coupling counterparts other than aryl iodides was achieved by Jean-Pierre Genet and co-workers.[60] This new methodology involved the use of aryltrifluoroborates compounds **(46)** in a stoichiometric fashion (Figure 1.28). The scope of the reaction includes acidic hydroxyl substituents, heterocyclic aldehydes, as well as mono- and di-*ortho* substitution; gratifyingly under the same reaction conditions, other organometallic reagents such as organostannanes and organoboronic acids could be used as well.

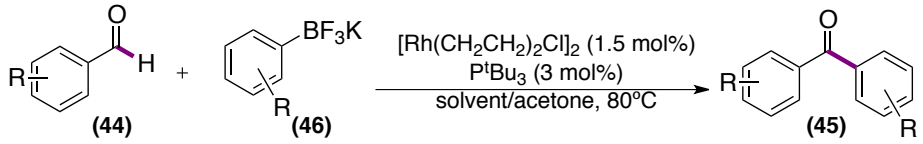


Figure 1.28

[59] Huang, Y. –C.; Majumdar, K. K.; Cheng, C. –H. *J. Org. Chem.* **2002**, *67*, 1682.
[60] Pucheault, M.; Darses, S.; Genet, J. –P. *J. Am. Chem. Soc.* **2004**, *126*, 15356.

The mechanism of the reaction is still under debate but likely involves transmetallation of the organotrifluoroborate reagent **(46)** to a Rh(I) intermediate **(47)**, insertion of the Ar-Rh across the adehydic C=O bond and final β-hydride elimination from the alkoxorhodium (I) complex **(47)** to form the diaryl ketone **(45)** and Rh-H specie, that ultimately reacted with acetone to regenerate the catalytic Rh(I) species **(48)**.

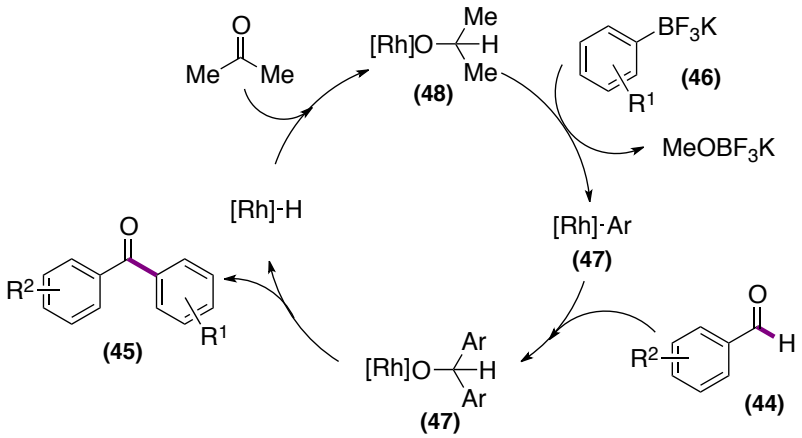


Figure 1.29

1.2.3 Arylation via functionalization of aldehydic C-H bonds by cross-dehydrogenative coupling reactions

The dehydrogenative acylation of aldehydic C-H bonds with arenes in the presence of a directing group represents an alternative route to diaryl ketones **(55)**.[61] In recent years a number of publications using 2-pyridine **(49)**,[62] oximes

[61] For a recent review on catalytic acylation of sp^2 C-H bonds, see: C. Pan, X. Jia, J. Cheng, *Synthesis* **2012**, 44, 677.

[62] a) Jia, X.; Zhang, S.; Wang, W.; Luo, F.; Cheng, J. *Org. Lett.* **2009**, *11*, 3120. b) Baslé, O.; Bidange, J.; Shuai, Q.; Li, C. –J. *Adv. Synth. Catal.* **2010**, *352*, 1145. c) Xiao, F.; Shuai, Q.; Zhao, F.; Baslé, O.; Deng, G.; Li, C. –J. *Org. Lett.* **2011**, *13*, 1614.

(50),[63] acetanilides **(51)**,[64] amides **(52)**,[65] indoles **(53)**,[66] and benzoxazoles **(54)**[67] as directing groups and Pd-complexes have been published (Figure 1.30).

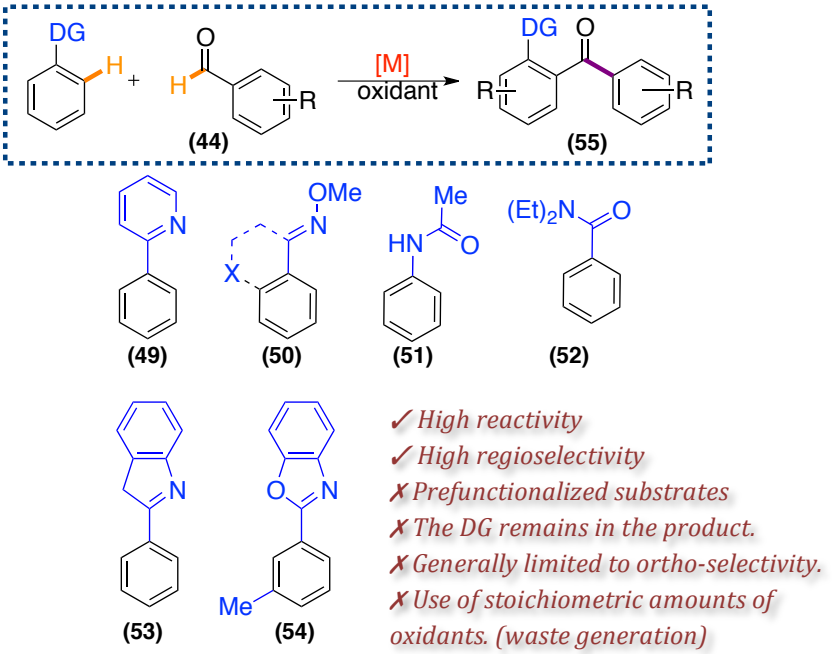


Figure 1.30

Recently, it was demonstrated that Rh-complexes could catalyze dehydrogenative acylations of aldehydic C-H bonds. For example, using *ortho*-methyl oximes **(56)** as directing groups, the best reaction conditions were found using [Cp*$RhCl_2$] (5 mol%), Ag_2CO_3 (2.5 equiv.) $AgSbF_6$ (0.2 equiv.) and DCM at 85ºC.[68] Mechanistically (Figure 1.31), the first step is the C-H functionalization of

[63] Chan, Ch. –W; Zhou, Z.; Chan, A. S. C.; Yu, W. –Y. *Org. Lett.* **2010**, *12*, 3926.
[64] a) Li, Ch.; Wang. L.; Li. P.; Zhou, W. *Chem. Eur, J.* **2011**, *17*, 10208. b) Wu, Y.; Li, B.; Mao, F.; Li, X.; Kwong, F. Y. *Org. Lett.* **2011**, *13*, 3258. c) C.-W. Chan, Z. Zhou, W.-Y. Yu, *Adv. Synth. Catal*. **2011**, *353*, 2999.
[65] a) Park. J.; Park, E.; Kim, A.; Lee, Y.; Chi, K. –W.; Kwak, J. H.; Jung, Y. H.; Kim, I. S. *Org. Lett.* **2011**, *13*, 4390. b) S. Sharma, E. Park, J. Park, I. S. Kim, *Org. Lett.* **2012**, *14*, 906. c) Sharma, S.; Park. J.; Park. E.; Kim, A.; Kim, M.; Kwak, J. H.; Jung, Y. H.; Kim, I. S. *Adv. Synth. Catal.,* **2013**, *355*, 332.
[66] Zhou, B.; Yang, Y.; Li, Y., *Chem. Commun*. **2012**, *48*, 5163.
[67] Zhang, Q.; Li, Ch.; Li, J.; Wu, Y. *Tetrahedron* **2013**, *69*, 320.
[68] Yaxi, Y.; Zhou, B.; Yuanchao, L. *Adv. Synth. Catal.* **2012**, *354*, 2916.

the arene fragment forming a 5-membered metallacycle **(57)**. Then, migratory insertion over the C=O bond of the aldehyde gave the intermediate **(58)** which after β-hydride elimination releases the product **(59)** and the resulting Rh(I) complex is reoxidized to recover the active Rh(III) species.

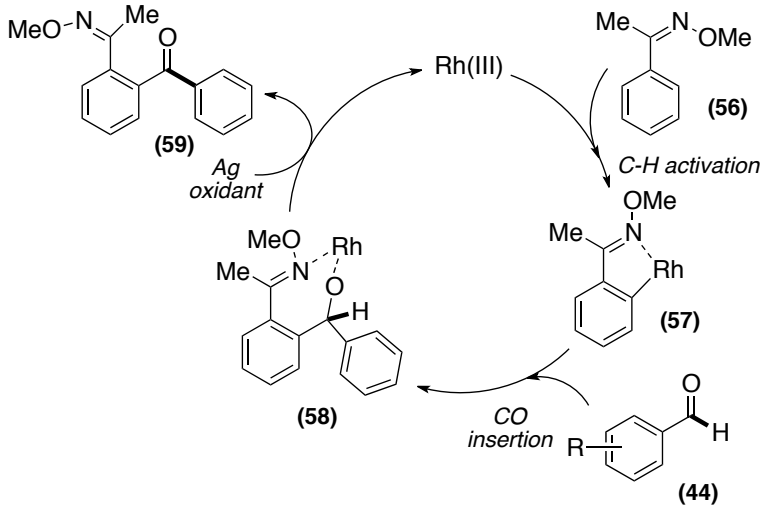


Figure 1.31

Despite the tremendous progress in dehydrogenative acylation processes, the scope of these reactions still remains limited to the presence of *ortho*-directing groups, thus lowering down the application profile of these methodologies. In order to overcome these limitations alternative methodologies for arylation *via* functionalization of aldehydic C-H bonds would be needed. In the present thesis, we aim at facing this challenge, providing an unique tool for preparing benzocyclobutenones *via* Pd-catalyzed intramolecular functionalization of aldehydic C-H bonds.

1.3

General Objectives

The general objectives of the present thesis are the following:

- To develop a new Pd-catalyzed methodology *via* functionalization of aldehydic C-H bonds to form rather elusive four-membered ring ketones from readily available aryl bromides.

- To explore the generality of the functionalization of aldehydic C-H bonds to other coupling counterparts.

- To elucidate the mechanistic pathway from which the Pd-catalyzed C-H functionalization of aldehyde operates.

Chapter 2

Pd-catalyzed intramolecular acylation *via* functionalization of aldehydic C-H bonds with aryl bromides

2.1

Objectives

The objectives of this chapter are the following:

❖ Design of a new route to benzocyclobutenones (BCBs) that overcome the limitations of the classical methods by an unprecedented intramolecular acylation of aryl bromides *via* functionalization of aldehydic C-H bonds.

❖ Study the effect of the ligand backbone for controlling selectivity issues.

2.2

Introduction to the preparation and application of Benzocyclobutenones

The interest of organic chemists in strained molecules has gained a considerable momentum in recent years. While the ring strain might be seen as a rather difficult problem to deal with, others have seen opportunities to devise new methods for their synthesis and the discovery of new reactivity within this area of expertise. The preparation and utilization of strain molecules has undoubtedly opened up new perspectives and horizons in preparative chemistry, changing the landscape of organic synthesis for new creative thinking and for devising new carbon-carbon or carbon-heteroatom bond-forming reactions.[69]

Benzocyclobutenones **(60)** are an intriguing class of four-membered ring ketones with a particularly high ring strain (Figre 2.1). While esthetically beautiful, these organic compounds have distinctive reactivity patterns that have inspired chemists to study in more detail such strain structures. The use of benzocyclobutenones in organic synthesis has evolved from mere curiosity to indispensable tools for building up a high degree of molecular complexity. The observed reactivity is primarily associated to the torsional and angle strain of the corresponding C-C bonds, allowing for the development of C-C bond-cleavage reactions, in some cases even in a regioselective manner Figure 2.1.[70, 71]

[69] a) *Small Ring Compounds in Organic Synthesis;* de Meijere, A. Springer: Berlin, *Top. Curr. Chem*., **2000**, 1- 230. (b) *Strained Organic Molecules* (Eds.: A. Greenberg, J. F. Liebman), Academic Press, New York, **1978**

[70] For a review see: Flores-Gaspar, A.; Martin, R., *Synthesis*, **2013**, *45*, 563.

[71] For reviews dealing with other four-membered rings, see: (a) Seiser, T.; Saget, T.; Tran, D. N.; Cramer, N. *Angew. Chem. Int. Ed.* **2011**, *50*, 7740. (b) Sadana, A. K.; Saini, R. K.; Billups, W. E. *Chem. Rev.*, **2003**, 103, 1539.

On the other hand, such ring strain has a remarkable influence on the carbonyl group electrophilicity; indeed, these compounds are much more susceptible to nucleophilic attack than regular aliphatic or cyclic ketones. Not surprisingly, the high ring strain of the four-membered ring allows for a thermal conrotatory retro-4π cyclization, leading to vinyl-ketene type intermediates **(61)** that can participate in a multiple number of synthetic transformations, mainly cycloaddition approaches, Figure 2.1.

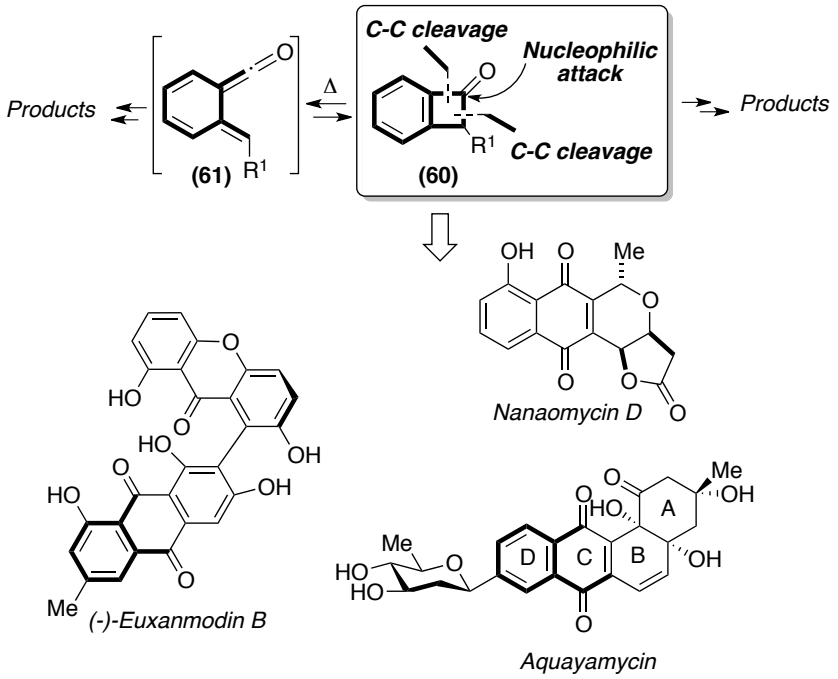


Figure 2.1

The exceptional scope of the reactions based upon the use of benzocyclobutenones or their derivatives as well as the high yields achieved in these processes makes them exceptionally practical when dealing with complex synthetic sequences. Some illustrative examples are shown in Figure 2.1, thus highlighting the tremendous synthetic potential of these rather unique backbones. The scope of these reactions is certainly wide, ranging from ring-expansion or ring-opening reactions to the preparation of synthetically attractive

heterocyclic scaffolds. Not surprisingly, these unique compounds have successfully been employed as a platform for natural product synthesis, Figure 2.1.

In recent years, the preparation and utilization of benzocyclobutenones has recently gained a considerable attention by the scientific community. Indeed, these methodologies have been recognized as powerful attractive transformations in both academia and pharmaceutical laboratories. This is particularly true when taking a closer look into the recent developments in this area of expertise, allowing levels of sophistication, efficiency and applicability that were beyond reach by traditional and classical methods in which benzocyclobutenones or their derivatives were used.

2.3

Synthetic methods for preparing benzocyclobutenones

At first sight, one might assume that the synthetic pathways to benzocyclobutenones **(60)** would not differ that much to those known in the literature for preparing much simpler cyclobutenone motifs **(62)**. A close literature survey indicates that this is clearly not the case. While there are a myriad of methods to prepare cyclobutenone derivatives,[71] our chemist's arsenal does not have yet a general and robust method for preparing benzocyclobutenones with high chemoselectivity and with a diverse set of substitution patterns. Most likely, the high ring-strain of the four-membered ring as well as the presence of the fused aromatic ring in the benzocyclobutenone core makes the development of a universal method for their synthesis a rather challenging task (Figure 2.2).

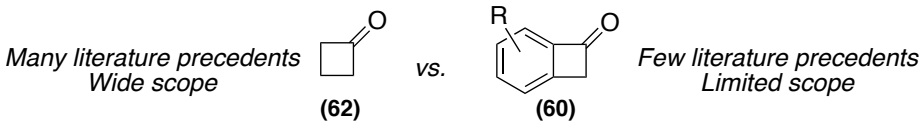


Figure 2.2

2.3.1 [2+2]-type cycloadditions

The [2+2]-cycloaddition of *in situ* generated benzynes **(64)** and olefins **(65)** is probably the most direct and utilized synthetic route to benzocyclobutenones.[72]

[72] For reviews on [2+2]-cycloaddition of benzynes and olefins, see: (a) Thummel, R. P. *Acc. Chem. Res.* **1980**, *13*, 70. (b) Klundt, I. L. *Chem. Rev.* **1970**, *70*, 471

The high reactivity of benzyne **(64)** makes such route thermodynamically feasible; [73] however, the natural tendency for retro-4π cyclization of benzocyclobutenones to form **(61)** advocates the notion that these cycloaddition approaches must be conducted at low temperatures (Figure 2.3).

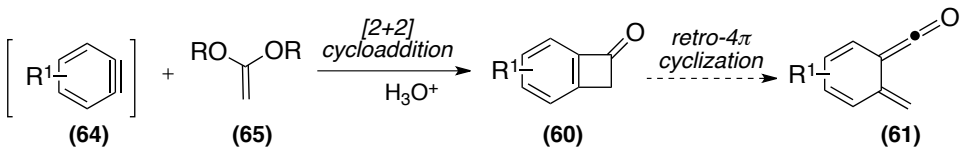


Figure 2.3

In 1982, Bisacchi developed a procedure for preparing the rather elusive benzocyclobutenones **(60)** from readily available aryl bromides **(66)**. [74] Deprotonation of the *ortho* C-H bond upon treatment with $NaNH_2$ triggers the formation of the benzyne derivative **(64)** that reacts with the olefin through a thermal [2+2] cycloaddition. A final hydrolysis ultimately affords the corresponding benzozyclobutenone (Figure 2.4). In general, good selectivities were found with *o*-methoxy or *o*-chloro substituents. However, low selectivies were obtained for *o*-methyl derivatives or with substituents in *meta* or *para* position. Santelli found that a high regioselectivity could be achieved when coupling 2-methylene-1,3-dioxepane and aryl bromides bearing *p*-fluoro or *p*-*tert*-butoxy substituents, although in low yields.[75] Additionally, it was discovered that benzocyclobutenones fused to heteroarynes proceeded equally well.[76] More

[73] For references dealing with the generation and utilization of arynes in synthesis, see: (a) Tadross, P. M.; Stolz, B. M. *Chem. Rev.* **2012**, *112*, 3550. (b) Chen, Y.; Larock, R. C. *Arylation Reactions involving the formation of arynes*. In Modern Arylation Methods; Ackermann, L., Ed.; Wiley-VCH: Weinheim, **2009**: pp 401-473.
[74] Stevens, R. V.; Bisacchi, G. S. *J. Org. Chem.* **1982**, *47*, 2393
[75] (a) Maurin, P.; Ibrahim-Ouali, M.; Santelli, M. *Eur J. Org. Chem.* **2002**, 151. (b) Maurin, P.; Ibrahim-Ouali, M.; Santelli, M. *Tetrahedron Lett.* **2001**, *42*, 8147
[76] Mariet, N.; Ibrahim-Ouali, M.; Santelli, M. *Tetrahedron Lett.* **2002**, *43*, 5789.

recently, Garg has reported that an otherwise analogous [2+2]-cycloaddition can be performed utilizing indolyne precursors with good regioselectivities as well.[77]

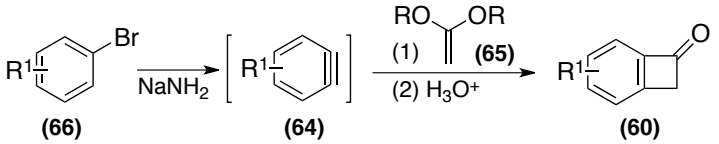


Figure 2.4

Convinced of the relevance of the [2+2]-cycloaddition approach, Suzuki and co-workers turned their attention to the development of a new procedure for generating the corresponding arynes *via* halogen-metal exchange in compounds of the type **(67)** and the use of ketene silyl acetals **(68)** as the olefin coupling partner (Figure 2.5). A final treatment with HF in MeCN at 0ºC delivered the final benzocyclobutenones **(69)**.[78] The scope of the reaction included different α,α'-substituents on the four-membered ring. However the presence of an *o*-alkoxy group was required for obtaining good regioselectivities.

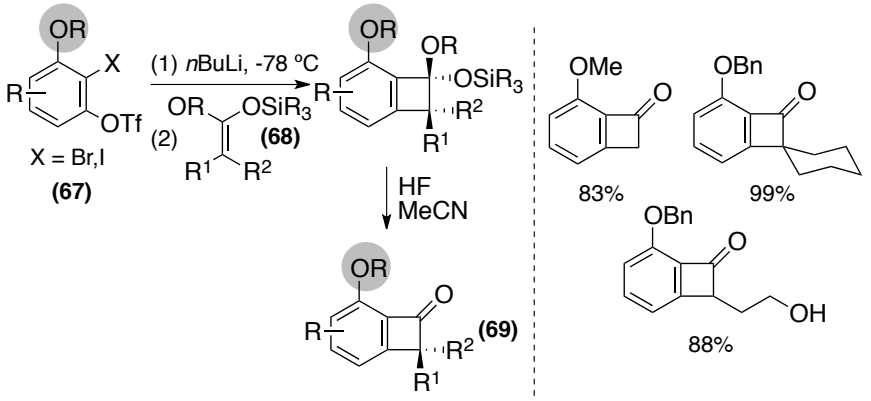


Figure 2.5

[77] a) Im, G. Y. J.; Bronner, S. M.; Goetz, A. E.; Paton, R. S.; Cheong, P. H. Y.; Houk, K. N.; Garg, N. K. *J. Am. Chem. Soc.* **2010**, *132*, 17933. b) Bronner, S. M.; Bahnck, K. B.; Garg, N. K. *Org. Lett.* **2009**, *11*, 1007.

[78] (a) Hosoya, T.; Kuriyama, Y.; Suzuki, K. *Synlett* **1995**, 177. (b) Hamura, T.; Hosoya, T.; Yamaguchi, H.; Kuriyama, Y.; Tanabe, M.; Miyamoto, M.; Yasui, Y.; Matsumoto, T.; Suzuki, K. *Helv. Chim. Acta* **2002**, *85*, 3589.

The rationale behind the observed regioselectivity could be attributed to the inductive effect of the *o*-methoxy group in **(70)** (Figure 2.6). Thus, the polarization of the *in situ* generated benzyne directs the nucleophilic attack of the β-carbon of the ketene silyl acetal **(71)** at the *meta* position triggering an intramolecular attack that ultimately affords the final four-membered ring **(72)**.[79] The preference for the β-carbon of the ketene silyl acetal is likely due to the greater stabilization of the canonical form **(73)**, in which the carbocation is further stabilized by the two contiguous oxygen moieties.

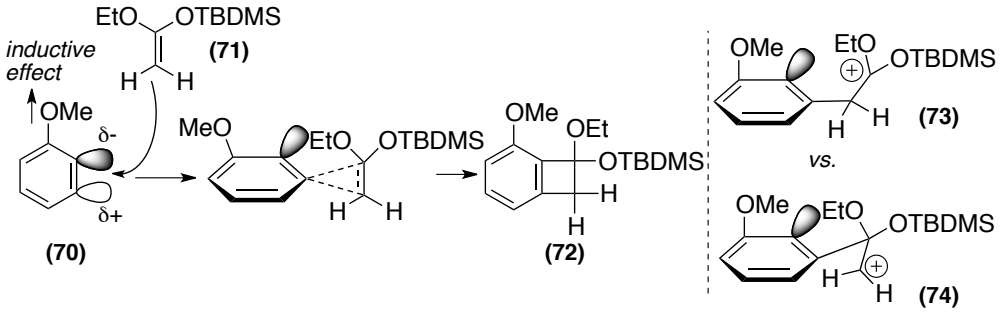


Figure 2.6

The results shown in Figure 2.5 demonstrated that an *o*-alkoxy group played an important, if not critical, role in the [2+2]-cycloaddition reaction for obtaining good regioselectivities. Suzuki and co-workers studied in more detail whether other substituents might exert a similar effect. Interestingly, their investigations showed that the presence of fused-strain rings **(75)** gave comparable regioselectivities.[80] The striking influence of the contiguous four-membered ring in **(77)** was demonstrated by the fact that low regioselectivities were obtained with larger rings in the *ortho* position. Thus, the authors hypothesized that the key for success was the high ring-strain associated to the four-membered ring in the vicinity. This assumption was supported by theoretical calculations in which it

[79] Hosoya, T.; Hamura, T.; Kuriyama, Y.; Miyamoto, M.; Matosumoto, T.; Suzuki, K. *Synlett*, **2000**, *4*, 520
[80] Hamura, T.; Ibusuki, Y.; Sato, K.; Matsumoto, T.; Osamura, Y.; Suzuki, K. *Org. Lett.* **2003**, *5*, 3551.

was found that C_2 was bound to an orbital of higher electronegativity, thus rendering C_1 more electron deficient and therefore more susceptible for nucleophilic attack. As shown in Figure 2.7, the electronic properties were much less pronounced when five-**(78)** or six-**(79)** membered rings were used as coupling counterparts, thus explaining the lower regioselectivities for these cases.

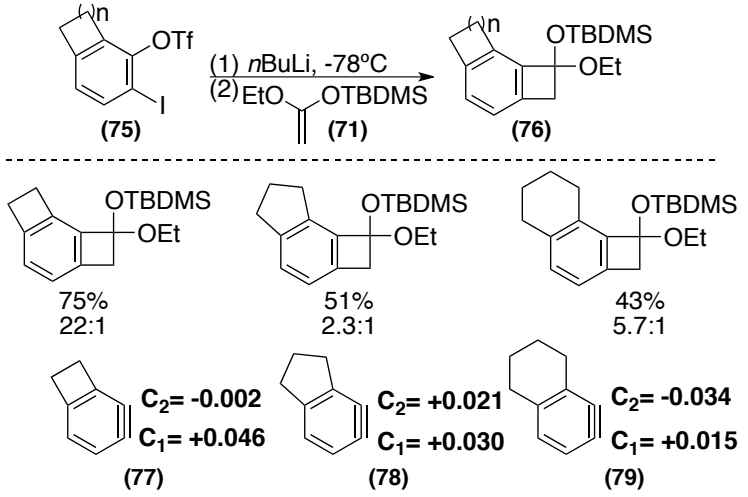


Figure 2.7

The alkoxy-directed ability and the strain-controlled nucleophilic attack could be combined in a synergistic manner. Indeed, Suzuki shown that poly-oxygenated tricyclobutabenzenes **(84)** are within reach by using an iterative [2+2] cycloaddition approach based on the use of *in situ* generated benzynes and subsequent reaction with ketene silyl acetals **(65)** (Figure 2.8).[81] Interestingly, the regioselectivity was perfectly controlled by the proximal four-membered ring, thus giving access to poly-fused aromatic compounds with exceptional ring strain.

[81] Hamura, T.; Ibusuki, Y.; Uekusa, H.; Matsumoto, T.; Suzuki, K. *J. Am. Chem. Soc.* **2006**, *128*, 3534.

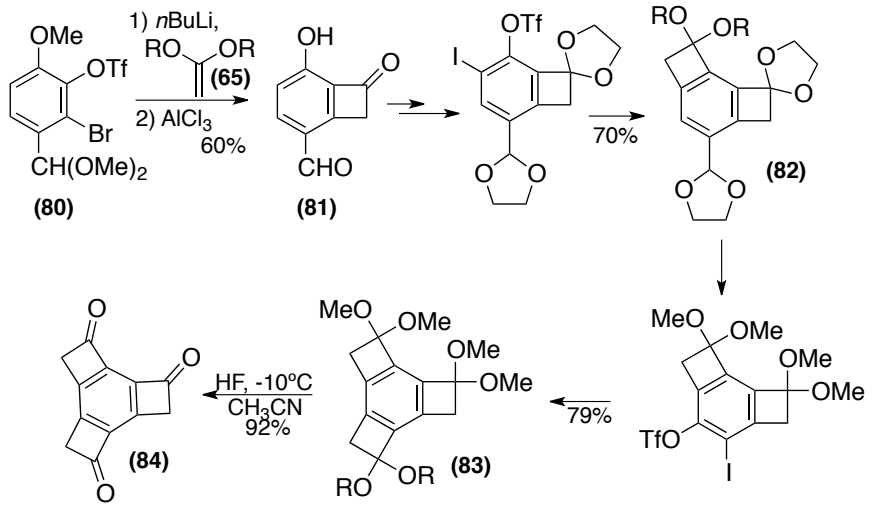


Figure 2.8

Taking into consideration the concerted nature of the [2+2]-cycloaddition,[72] the frontier molecular orbital theory predicts that the coupling reaction with olefins might also proceed in a stereospecific manner. As shown in Figure 2.9, this was indeed the case and the coupling of geometrically defined ketene silyl acetals **(85)** and **(86)** preceded with total stereoselectivity.[82]

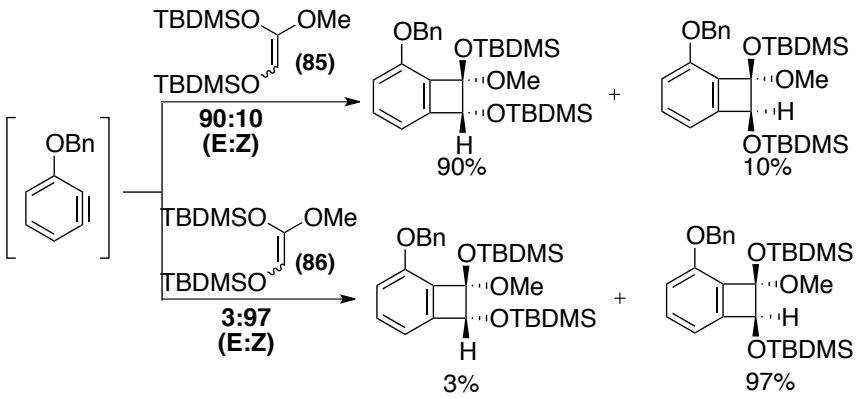


Figure 2.9

[82] Hosoya, T.; Hasegawa, T.; Kuriyama, Y.; Suzuki, K. *Tetrahedron Lett.* **1995**, *36*, 3377.

While benzyne routes are no doubt widely applicable and still in many instances are the route of choice for preparing benzocyclobutenones, the need for *ortho* substituents as well as the special electronic requirements for obtaining good regioselectivities still represents serious drawbacks to be overcome.[14] Additionally, these methodologies do not tolerate a wide range of functional groups, possibly due to the need for stoichiometric amounts of highly reactive organolithium derivatives. Furthermore, a synthetic effort is needed for preparing advanced intermediates in route to the benzyne motif, an issue that might potentially lower down the application profile of these methodologies. These features reinforced the notion that other pathways for preparing benzocyclobutenone motifs would be appreciated at the Community level.

2.3.2 Metal-mediated intramolecular reactions

While [2+2]-cycloaddition coupling reactions provide a rapid and modular entry to benzocyclobutenones, others have looked at alternative protocols for their synthesis. Among them, the method described by Ahuja and coworkers is particularly remarkable in which an *in situ* generated organolithium reagent attacks intramolecularly to a Weinreb amide motif **(88)** via the formation of a lithium chelate (Figure 2.10).[83] While moderate yields were generally obtained, it represents an excellent alternative to the [2+2]-cycloaddition reactions, particularly when electronic or steric effects do not come into play. Still, the need for stoichiometric amounts of highly reactive organolithium derivatives might have a negative impact when applying this methodology to molecules possessing particularly sensitive functional groups.

[83] Aidhen, I. S.; Ahuja, J. R. *Tetrahedron Lett.* **1992**, *33*, 5431.

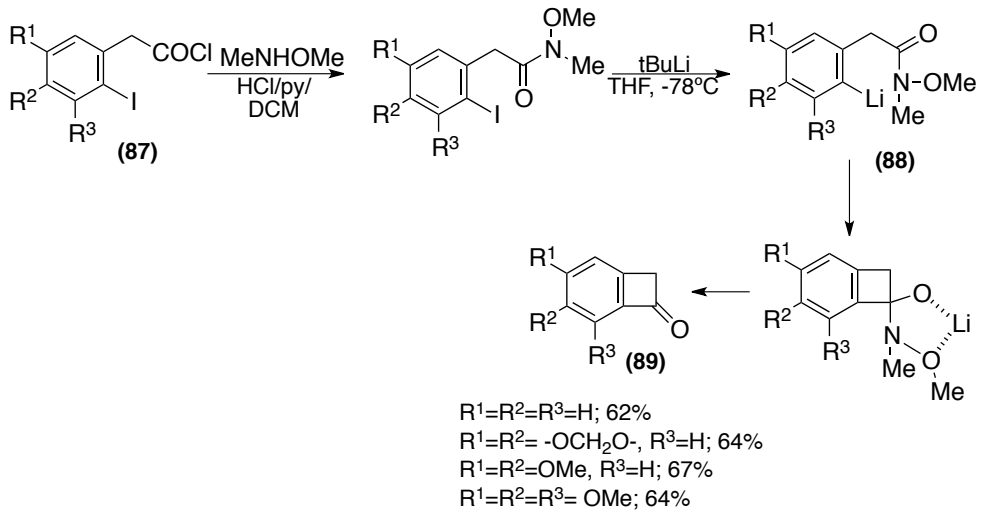


Figure 2.10

2.3.2.1 Metal-catalyzed cross-coupling reactions

The rapidly development and the ever-growing importance of palladium-catalyzed C-C bond-forming reactions have inspired chemists to initiate a quest for the discovery of new catalytic processes, thus opening up new perspectives in preparative organic chemistry. Within few years, these methodologies have become routine tools in modern organic synthesis, allowing their implementation in many areas of expertise ranging from polymers, agrochemicals and pharmaceuticals to natural products.[20]

2.3.2.2 Stille cross-coupling reactions

Prompted by the regioselectivity issues on the cycloaddition approaches employing benzyne derivatives, Liebeskind described in 1993 a Stille cross-coupling reaction of 4-chlorocyclobutenones **(90)** with 3-(tri-n-butylstannyl) cyclobutene **(91)** using $(PhCN)PdCl_2$ (0.4-1 mol%) and tris(2-furyl)phosphine

(TFP, 2 mol%) as ligand (Figure 2.11).[84] Interestingly, the Stille cross-coupling reaction set up the stage for a rather exclusive ring-expansion event that takes place in *one pot*, thus accessing tri-substituted benzocyclobutenone monoacetals in good yields.

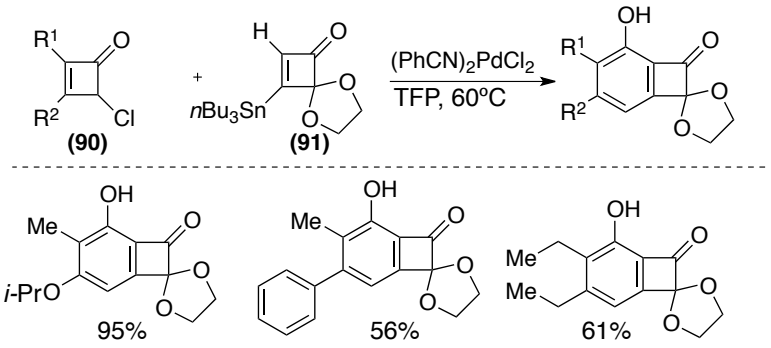


Figure 2.11

In 1991, Durst developed a synthesis of 2-benzylidenebenzocyclobutenones **(93)** *via* an intramolecular Pd-catalyzed Stille cross-coupling reaction. This methodology was based on an initial regioselective hydrostannylation event promoted by $SnBu_3H$ followed by an intramolecular cyclization (Figure 2.12).[85]

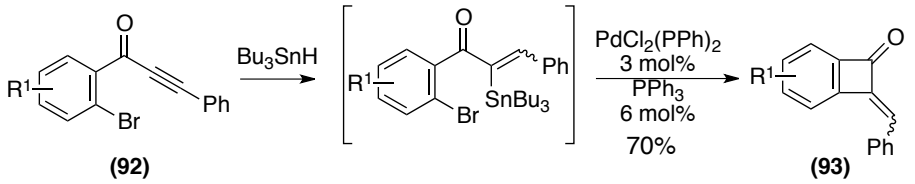


Figure 2.12

[84] Edwards, J. P.; Krysan, D. J.; Liebeskind, L. S. *J. Org. Chem.* **1993**, *58*, 3942.
[85] Bradley, J. C.; Durst, T. *J. Org. Chem.* **1991**, *56*, 5459

2.4

Synthetic application of benzocyclobutenones

2.4.1 Synthesis of polycyclic compounds via o-quinone methides

As for other cyclobutanones,[71] benzocyclobutenones undergo thermal conrotatory retro-4π cyclization, thus originating vinyl-ketene-type intermediates **(61)** that can participate in cycloaddition approaches (Figure 2.13, bottom pathway). Unfortunately, the high temperatures required for such transformation when utilizing benzocyclobutenones are oftentimes not practical when applying this concept to more functionalized and sensitive backbones. Interestingly, derivatives bearing electron-rich substituents on the cyclobutane ring such as oxy-anions **(94)** undergo the *retro* 4-π cyclization much easier, taking place at temperatures below 0ºC (Figure 2.13, top pathway).

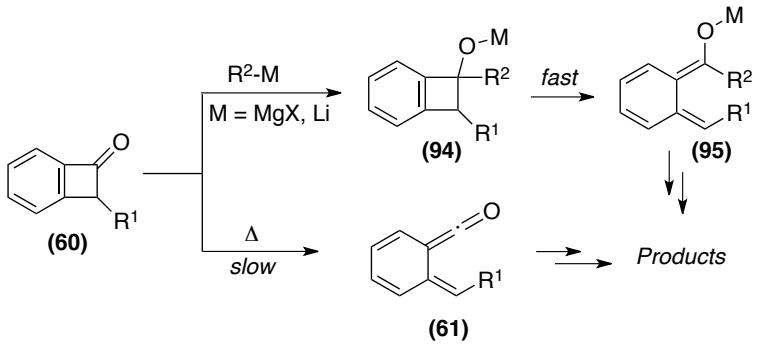


Figure 2.13

2.4.1.1 Synthesis of α-tetralones

Wandleworth described the thermal conversion of *in situ* generated alkenylbenzocyclobutanol **(96)** into α-tetralone derivatives **(99)** (Figure 2.14).[86] The key electrocyclic ring-opening reaction was accomplished *via* the intermediacy of a *o*-quinone methide **(97)** followed by a disrotatory 6π-electrocyclization event, giving rise to the enol derivative **(98)** that is in equilibrium with the corresponding substituted α-tetralone **(99)**.

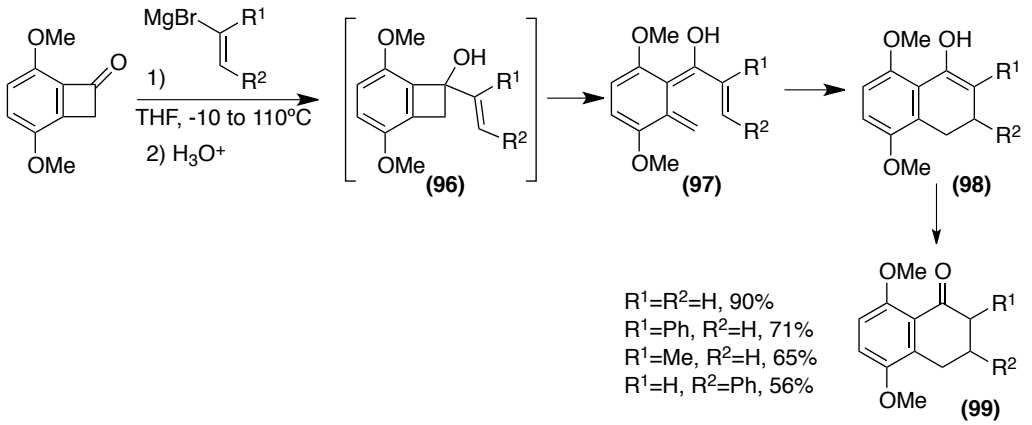


Figure 2.14

2.4.1.2 Synthesis of Benzo[n]annulenes

Benzo[n]annulenes are key structural constituents of many compounds with important biological properties such as *(-)-Presphaerene*,[87] *Dragmacidin E*,[88] *(-)-Colchicine*[89] or *Hamigeran C*,[90] among many others. Recently, Aguilar showed a methodology that directly converts benzocyclobutenones into benzo[7]annulenes

[86] Hickman, D. N.; Hodgetts, K. J.; Mackman, P. S.; Wallace, T. W.; Wardleworth, J. M. *Tetrahedron* **1996**, *52*, 2235
[87] Lee, J.; Hong, J. *J. Org. Chem.* **2004**, *69*, 6433
[88] Feldman, K. S.; Ngernmeesri, P. *Org. Lett*. **2011**, *13*, 5704.
[89] Graening, T.; Schmalz H. G. *Angew. Chem. Int. Ed*, **2004**, *43*, 3230.
[90] Choy, W.; Yang, H. *J. Org. Chem.*, **1988**, *53,* 5796.

via an unprecedented [4+3]-cycloaddition in which the initially generated *o*-quinone methides **(100)** act as a four-carbon synthon, Figure 2.15.[91] Interestingly, the solvent and the nature of the substituents dictated the selectivity pattern for preparing either benzocycloheptene ketals **(101)** or benzocycloheptenones **(102)**, respectively.

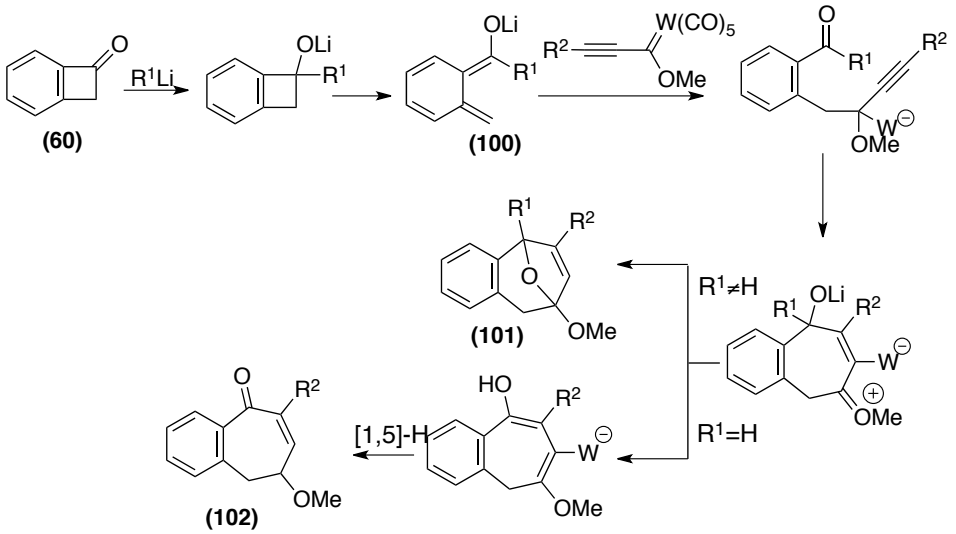


Figure 2.15

2.4.1.3 Synthesis of anthraquinones

Annulation approach can be employed for accessing angulary-fused anthraquinones **(104)** (Figure 2.16). In this particular case, the route commenced with the addition of an aryl lithium derivative to compound **(103)**, hydrolysis of the acetal, thermal retro-4π cyclization, 6π-electrocyclization and a final oxidation of the hydroquinone to afford the expected anthraquinone **(104)**.[92]

[91] Garcia-Garcia, P.; Novillo, C.; Fernandez-Rodriguez, M. A.; Aguilar, E. *Chem. Eur. J.* **2011**, *17*, 564.
[92] Tiedemann, R.; Heileman, M. J.; Moore, H. W.; *J. Org. Chem.* **1999**, *64*, 2170

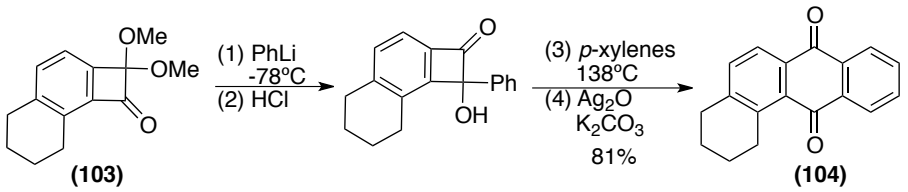


Figure 2.16

2.4.1.4 Synthesis of naphthalene derivatives

In analogy to the preparation of α-tetralones, the addition of an organometallic reagent facilitates the formation of a *o*-quinone methide **(105)** that subsequently triggers a disrotatory 6π-electrocyclization affording 1-naphthol derivatives **(**Figure 2.17). The utilization of allenyl or propargyl organometallic species, however, limits the scope of this reaction to 1,3-substituted naphthols.[93]

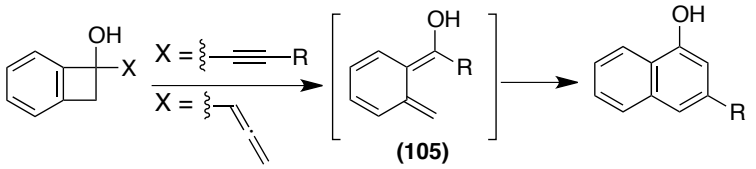


Figure 2.17

2.4.1.5 Synthesis of benzodiazepines

The reactivity of *in situ* generated *o*-quinone methides is certainly not limited to the construction of carbocycles.[71] Indeed, Nemoto demonstrated that these highly reactive intermediates can also participate in electrocyclization reactions for the synthesis of benzodiazepines **(110)** (Figure 2.18).[94] As for other related approaches, the addition of a diazomethylene anion **(107)** to the benzocyclobutenone **(106)** backbone precedes a fast retro-4π cyclization *via* an

[93] Bungard, C. J.; Morris, J. C., *J. Org. Chem,* **2002**, *67*, 2361.
[94] Matsuya, Y.; Ohsawa, N.; Nemoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 13072

oxy-anion intermediate **(108)** at low temperatures. Unlike the corresponding formation of 6-membered rings from *o*-quinone methides, the presence of a diazo derivative results in an 8π-electrocyclization, ultimately affording the benzodiazepine backbone in high yields and in one-pot procedure from the corresponding benzocyclobutenone **(106)**.

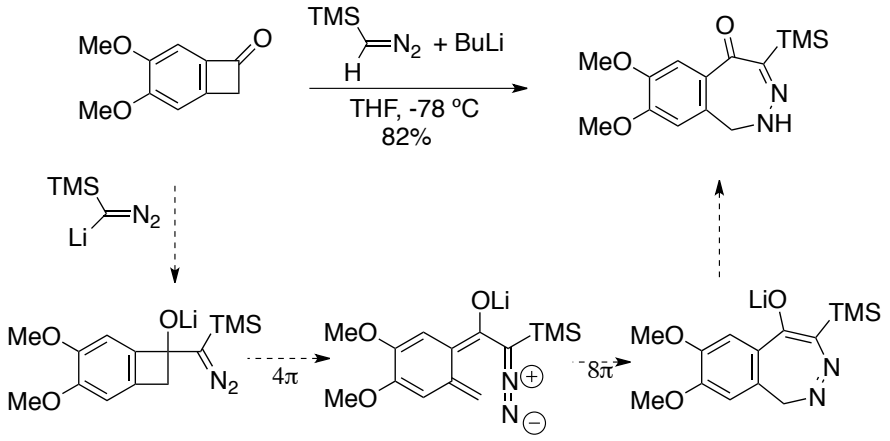


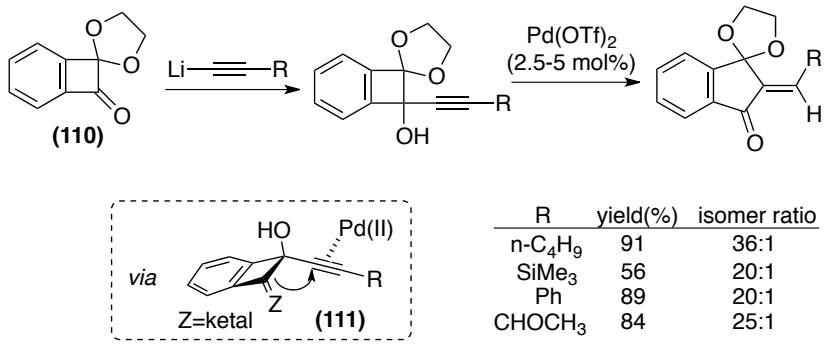
Figure 2.18

2.4.2 Synthesis of fused rings via non-electrocyclization techniques: Ring-expansions from four to five-membered rings.

2.4.2.1 Synthesis of Indanones

Benzocyclobutenones can also be employed as manifolds to promote ring-expansions from four to five-membered rings without the need of *o*-quinone methide intermediates. In 1987, Liebeskind described a synthesis of indanones *via* ring-expansion of ketal-protected benzocyclobutenone derivatives **(110)** with excellent yields and stereoselectivities in the presence of catalytic amounts of

$Pd(OTf)_2$ at room temperature (Figure 2.19).[95] The sequence is initiated by electrophilic activation of the alkyne derivative **(111)** with $Pd(OTf)_2$ followed by ring-expansion *via* C-C bond-cleavage.



R	yield(%)	isomer ratio
n-C_4H_9	91	36:1
$SiMe_3$	56	20:1
Ph	89	20:1
$CHOCH_3$	84	25:1

Figure 2.19

Suzuki reported an elegant ring-expansion of vinylsubstituted benzocyclobutanols **(112)** promoted by ICl, thus resulting in the preparation of indanones **(113)** with well-defined quaternary centers (Figure 2.20).[96] Where ICl was utilized to activate the π-system, thus inducing a ring expansion via C-C cleavage without the intermediacy of *o*-quinone methides. Other related systemas such as spiro-fused indanones were prepared via electrophilic activation of the heterocyclic core, setting up the stage for a ring-expansion event.[97]

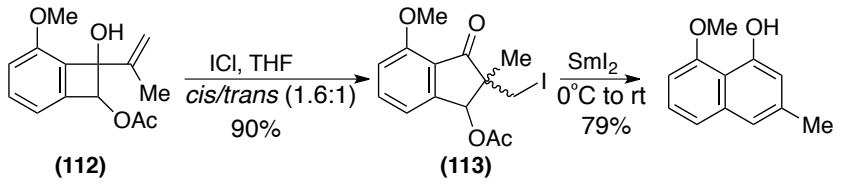


Figure 2.20

[95] Liebeskind, L. S.; Mitchell, D.; Foster, B. S. *J. Am. Chem. Soc.* **1987**, *109*, 7908
[96] Hamura, T.; Suzuki, T.; Matsumoto, T.; Suzuki, K. *Angew. Chem. Int. Ed.* **2006**, *45*, 6294.
[97] Hayashi, T.; Ohmori, K.; Suzuki, K. *Chem. Lett.* **2011**, *40*, 612.

2.4.2.2 Synthesis of phthalides

Suzuki reported an approach for the preparation of phtalides **(115)** without the use of a transition metal.[98] Formally, the sequence is based upon a regioselective Baeyer-Villiger oxidation of readily available *ortho*-substituted benzocyclobutenones **(114)** (Figure 2.21). Although other oxidants could be utilized, the employement of MMPP (magnesium monoperoxyphthalate hexahydrate) **(116)** provided the best results and a wide variety of compounds with a diverse set of substitution patterns could be utilized. Priority rules were established for controlling the regioselectivity with unsymmetrically substituted derivatives: tertiary>secondary>primary>methyl.

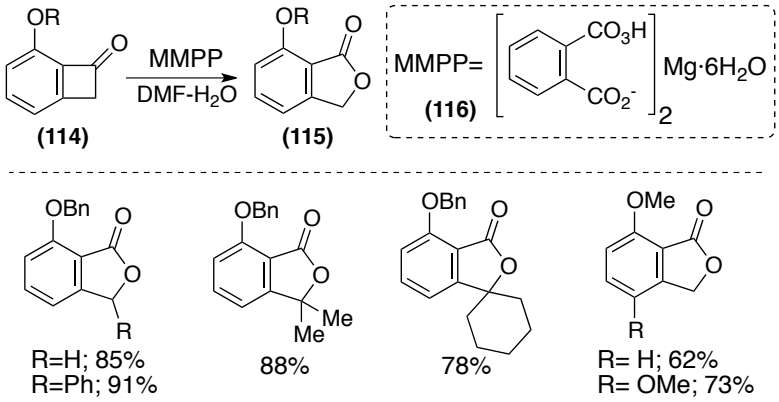


Figure 2.21

2.4.2.3 Synthesis of indolines and indoles

In 2010, Cho and Tokuyama described a reductive ring-expansion reaction of ketoximes **(117)** with DIBALH (Figure 2.22).[99] The reaction cleanly afforded a wide variety of bicyclic heterocycles containing the nitrogen neighboring the aromatic ring. The reaction mechanism could formally be understood as a

[98] Hosoya, T.; Kuriyama, Y.; Suzuki, K. *Synlett* **1995**, 635.
[99] Cho, H.; Iwama, Y.; Sugimoto, K.; Mori, S.; Tokuyama, H. *J. Org. Chem.* **2010**, *75*, 627

Beckmann-type rearrangement; however, in this case the reaction is initiated by reduction of the C-N double bond followed by rearrangement involving N-O bond-cleavage and after a final reduction the indoline derivative **(118)** is delivered.

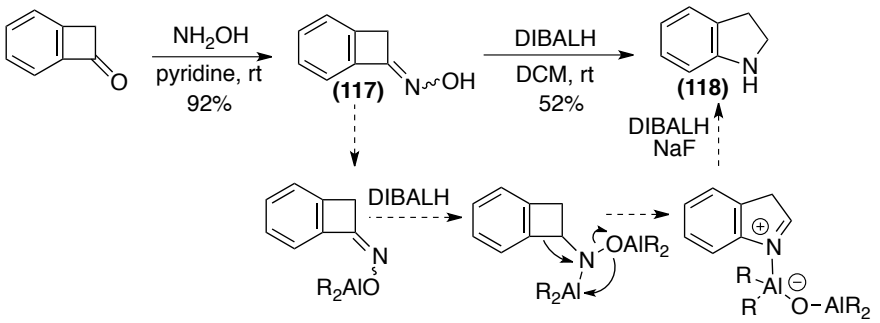


Figure 2.22

2.4.3 Synthesis of fused rings via non-electrocyclization techniques: Ring-expansions from four to six-membered rings

Murakami has demonstrated the feasibility for obtaining six-membered rings form benzocyclobutenones without generation of *o*-quinone dimethides intermediates (Figure 2.23). The reaction proceeded *via* alkoxyrhodium species **(121)** that undergo regioselective β-carbon elimination, alkyne insertion and intramolecular 1,2-addition across the C=O bond to give dehydronaphtalene derivatives **(122)**.[100]

[100] a) Ishida, N.; Sawano, S.; Masuda, Y.; Murakami, M.; *J. Am. Chem. Soc.* **2012**, *134*, 17502. (b) Aïssa, C. *Synthesis* **2011**, 3389; (c) Murakami, M.; Makino, M.; Ashida, S.; Matsuda, T. *Bull. Chem. Soc. Jpn.,* **2006**, *79***,** 1315

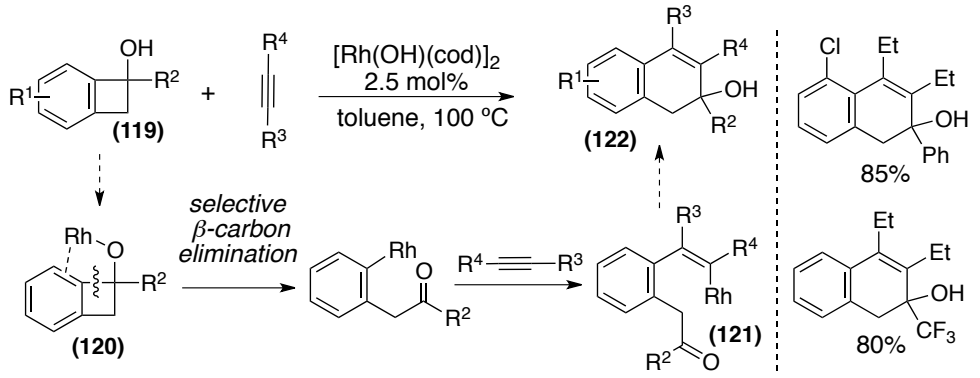


Figure 2.23

In a related procedure, Dong recently described an intramolecular Rh-catalyzed carboacylation of olefins in benzocyclobutenone backbones **(123)** in order to rapidly prepare polyfused ring systems of the type **(125)** (Figure 2.24).[101] As for Murakami´s approach, the later method involved a regioselective C-C bond-cleavage in order to generate a rather stable C(sp^2)-Rh intermediate **(124)** that coordinate with the pending alkene and triggers a migratory insertion and a final reductive elimination. Very recently, an enantioselective version of this reaction has been reported in the literature.[102]

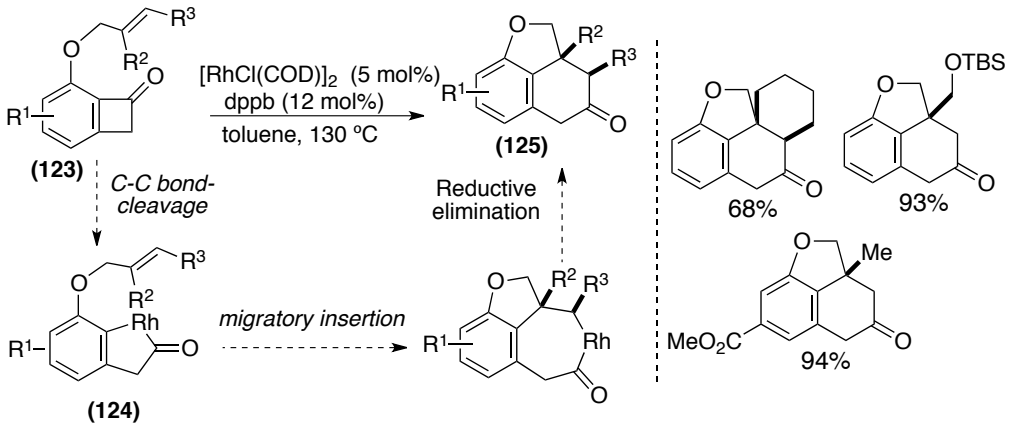


Figure 2.24

[101] Xu, T.; Dong, G.; *Angew Chem. Int. Ed.* **2012**, *51*, 7567.
[102] Xu, T.; Min Ko, H.; Savage, N. A.; Dong, G. *J. Am. Chem. Soc.* **2012**, *134*, 20005.

2.4.4 Base-induced C-C bond-cleavage

In principle, ring-opening of benzocyclobutenones with no *o*-quinone methide being generated can afford two different compounds that are regioisomeric to one another. Initial based-induced ring-opening studies revealed that the regioselectivity was indeed poor (1:1).[103] Further studies performed by Schiess showed that the critical C-C bond-cleavage was strongly influenced by the nature of the substituents present in the aromatic backbone.[104]

Interestingly, it was demonstrated that the proximal C-C bond cleavage to form 2-methylbenzoate derivatives was preferred when electron-withdrawing groups are located in R1 **(126)** (Figure 2.25). In sharp contrast, the distal C-C bond cleavage toward 2-phenylacetate compounds was only selective for an *ortho*-methyl substituent **(127)**. Still, such ring opening reaction had selectivity issues for heavily substituted benzocyclobutenone derivatives.[105]

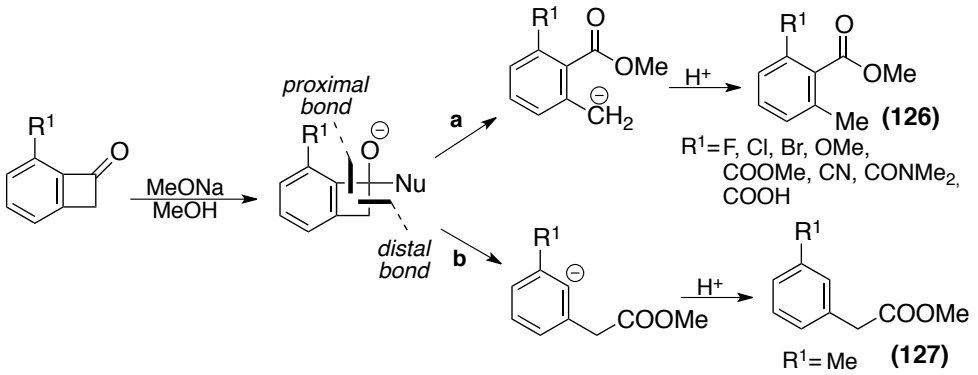


Figure 2.25

[103] Cava, M. P.; Muth, K. *J. Am. Chem. Soc.* **1960**, *82*, 652
[104] Gokhale, A.; Schiess, P. *Helv. Chim. Acta* **1998**, *81*, 251
[105] Bradley, J. C.; Durst, T. *Can. J. Chem.* **1995**, *73*, 1660

2.5

BCB's and their derivatives in natural product synthesis.

Once chemists realized the non-negligible potential of benzocyclobutenones as synthetic intermediates, their application to target-oriented and other areas of organic synthesis began to appear in the literature. In 2000, Suzuki reported the total synthesis of *Aquayamycin* **(131)**, an anthraquinone derivative with a *C*-glycoside structure that has shown to inhibit enzyme tyrosine hydroxylase (Figure 2.26) [106] The approach relied on the initial preparation of a benzocyclobutenone core **(129)** *via* [2+2]-cycloaddition of *in situ* generated benzyne derivative **(128)** with ketene silyl acetal in the presence of a sugar-type backbone. Subsequently, regioselective Baeyer-Villiger oxidation promoted by *m*CPBA delivered a 3-(phenylsulfonyl)phthalide **(130)** that engaged a Hauser-type reaction with an enone derivative, ultimately leading to *Aquayamycin* **(131)**.

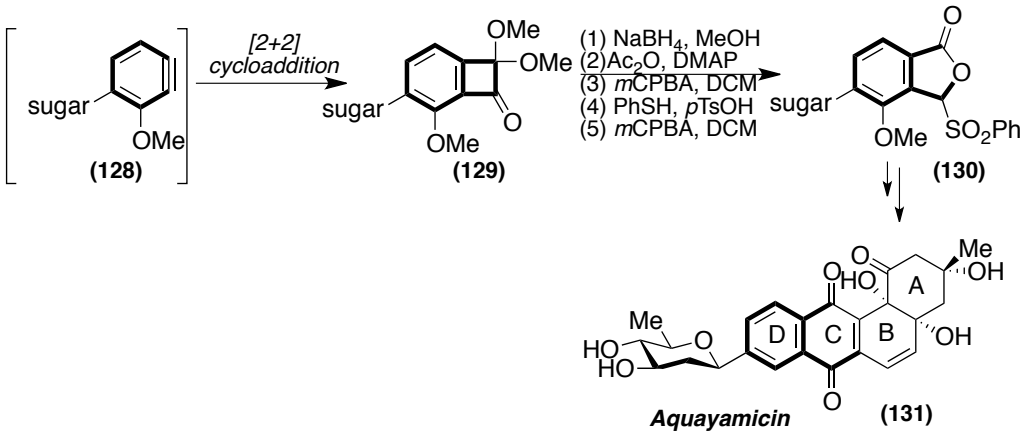


Figure 2.26

[106] Matsumoto, T.; Yamaguchi, H.; Hamura, T.; Tanabe, M.; Kuriyama, Y.; Suzuki, K. *Tetrahedron Lett.* **2000**, *41*, 8383.

Olofson and co-workers reported the total synthesis of *(±)-Peshawarine* **(134)** in an essentially two-step procedure (Figure 2.27).[107] The sequence is initiated by an oxy-anion accelerated ring-opening of a benzocyclobutenol **(132)** followed by cycloaddition with a heterodienophile **(133)**. It is quite remarkable that such hetero-Diels-Alder reaction occurred under mild reaction conditions and in the absence of a catalyst. A final oxidation in the presence of PCC cleanly affords the natural product in high overall yield.

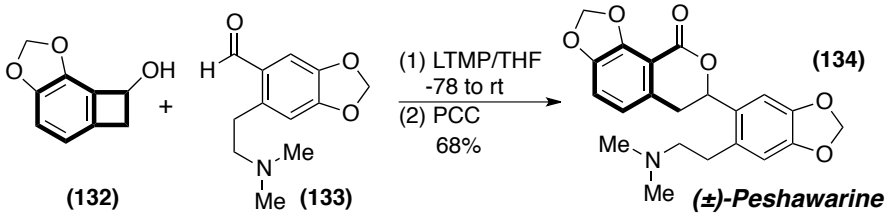


Figure 2.27

The application of benzozyclobutenones into the synthesis of advanced steroids **(137)** is illustrated in Figure 2.28.[108] The strategy was based upon an alkylation of an activated spirolactone **(136)** with an iodobenzocyclo-butenone core. Upon heating, this intermediate generated a *o*-xylene that rapidly underwent an intramolecular Diels-Alder-type cycloaddition, delivering the key polycyclic backbone in essentially one-step operation. Krapcho decarboxylation and a final Wacker oxidation finally afforded the steroid derivatives **(137)**.

[107] Fitzgerald, J. J.; Pagano, A. R.; Sakoda, V. M.; Olofson, R. A. *J. Org. Chem.* **1994**, *59*, 4117
[108] a) Maurin, P.; Ibrahim-Ouali, M,; Santelli, M. *Eur. J. Org. Chem.* **2002**, 151. (b) Michellys, P.; Maurin, P.; Toupet, L.; Pellissier, H.; Santelli, M. *J. Org. Chem.* **2001**, 66, 115. (c) Pellisier, H.; Santelli, M. *Tetrahedron,* **1996**, 52, 9093.

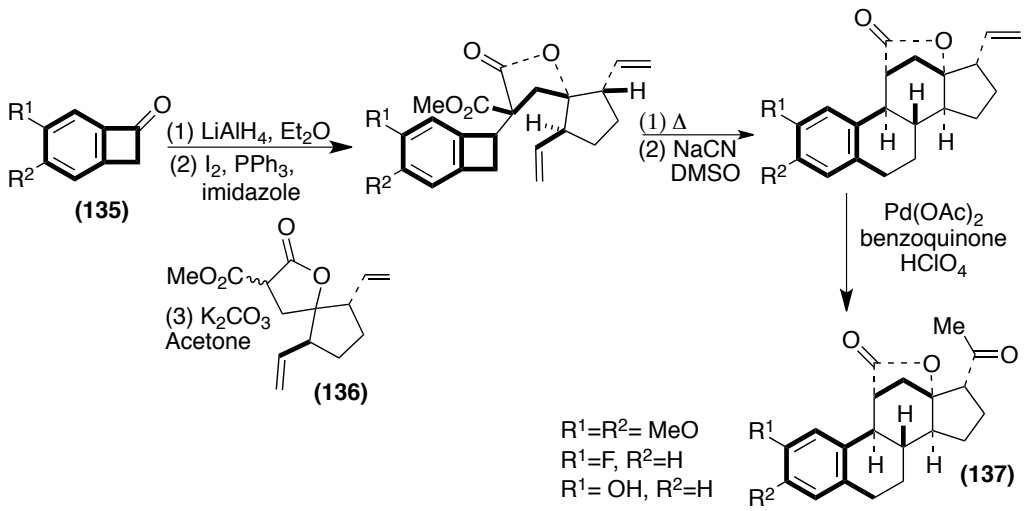


Figure 2.28

Sterically-congested biaryl compounds posessing atropoisomerism have shown to be highly ubiquitous in many compounds with important biological activities; however, their synthesis still constitute a great synthetic challenge.[109] Matsumoto and Suzuki reported an elegant synthesis of *(-)-Euxanmodin B* **(139)**,[110] an axially chiral natural product with an anthraquinone-xanthone composite structure (Figure 2.29). Notably, the anthraquinone backbone was efficiently secured by a thermal ring-expansion through initially-generated *o*-quinone methide derivatives.

[109] For a review in which atropoisomeric structures have been synthesized via Suzuki-Miyaura coupling reactions: Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461

[110] Takahashi, N.; Kanayama, T.; Okuyama, K.; Kataoka, H.; Fukaya, H.; Suzuki, K.; Matsumoto, T.; *Chem. Asian J.* **2011**, *6*, 1752.

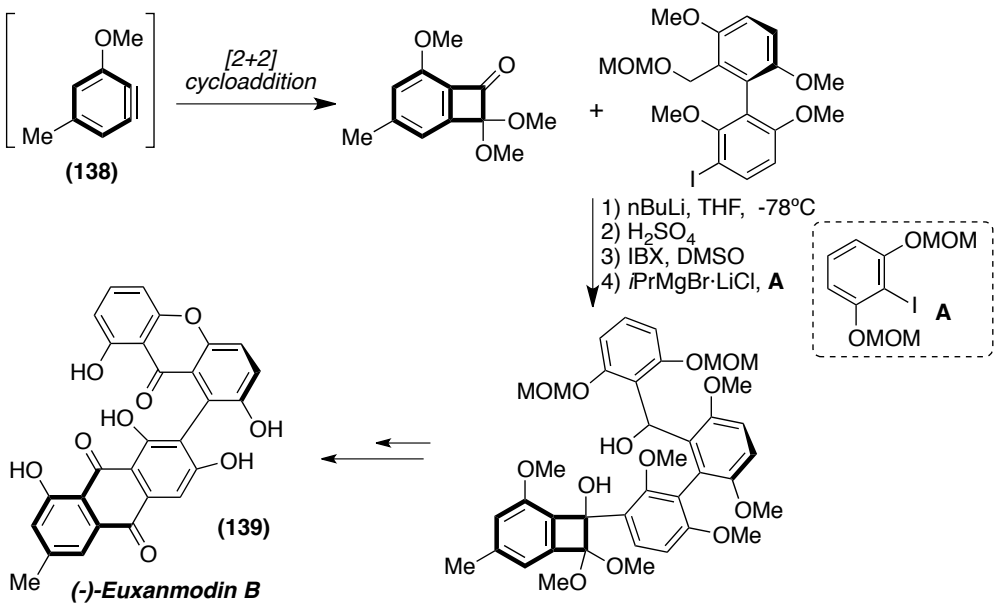


Figure 2.29

The total synthesis of *(-)-Nanaomycin D* **(142)** shown in Figure 2.30, a compound with potent inhibitory activity against fungi, represents another illustrative example of the synthetic utility of *in situ* generated *o*-quinone methides. [111] In this particular case, exposure of 3-methoxybenzocyclobutenedione **(140)** to a vinyllithium reagent in THF, trimethylsilyl quench and subsequent thermolysis followed by oxidation gave 9-*O*-methylnanaomycin *D* **(141)**. Demethylation in the presence of $AlCl_3$ finally delivered the natural product.

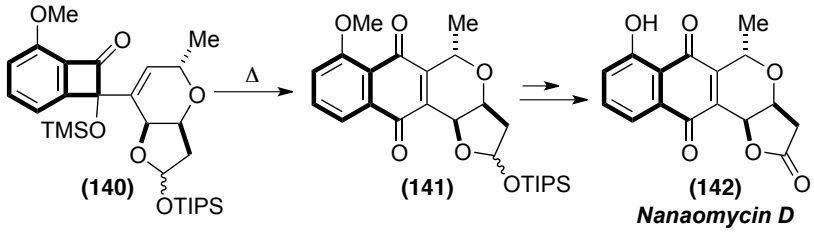


Figure. 2.30

[111] Winters, M. P.; Stranberg, M.; and Moore, H. W. *J. Org. Chem.* **1994**, *59*, 7572

The group of Suzuki reported the synthesis of Gilvocarcin-class antibiotics such as *Deacetylravidomycin M* **(145)** and *Defucogilvoracin M* **(146)** involving benzozyclobutenol intermediates, Figure 2.31.[112] Interestingly, the authors built up the key naphthalene backbone utilizing a rather efficient pericyclic reaction followed by aromatization via *in situ* elimination of methanol. A final cyclization event furnished the desired Gilvocarcin-type antibiotics.

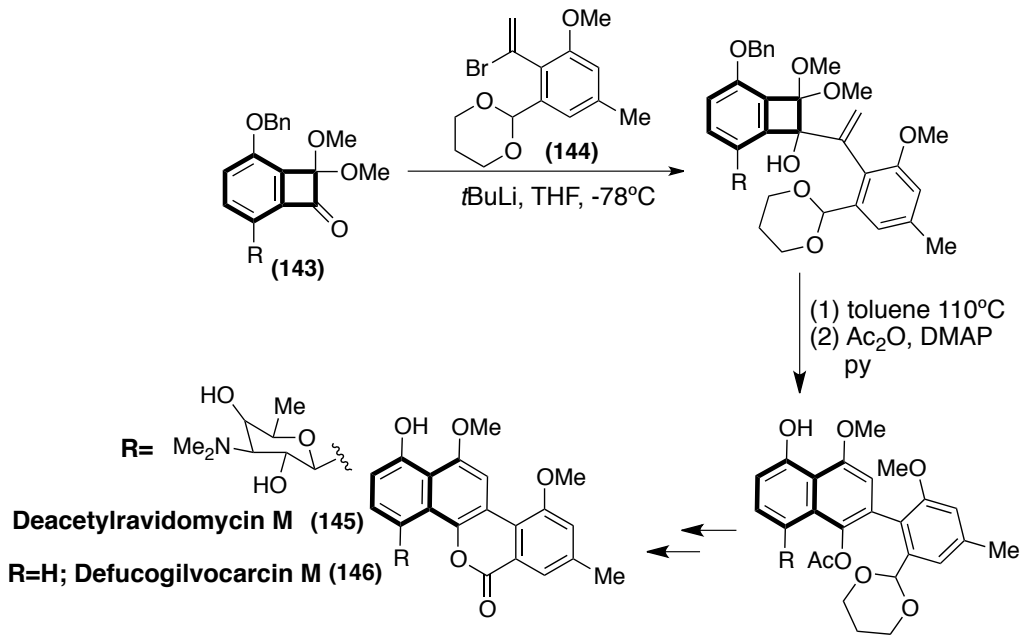


Figure 2.31

[112] a) Takemura, I.; Imura, K.; Matsumoto, T.; Suzuki, K. *Org. Lett.* **2004**, 6, 2503. b) Ben, A.; Hsu, D. S.; Matsumoto, T.; Suzuki, K. *Tetrahedron* **2011**, *67*, 6460.

2.6

Results and discussion

2.6.1 Synthesis of benzocyclobutenones

As mentioned in the previous sectio, the best synthetic routes to prepare benzocyclobutenones (BCBs) usually rely on an intramolecular cyclization of stochiometric amounts of organolithium or Grignard reagents to Weinreb amides (route a, Figure 2.32)[113] or [2+2] cycloadditions of silyl enol ethers with *in situ* formed benzyne derivatives (route b, Figure 2.32).[114] However, regioselectivity issues associated with the [2+2] cycloaddition approach using unsymmetrical benzynes as well as the need for stoichiometric amounts of highly reactive organometallic species greatly limited the scope of these reactions, particularly when dealing with densely functionalized backbones.

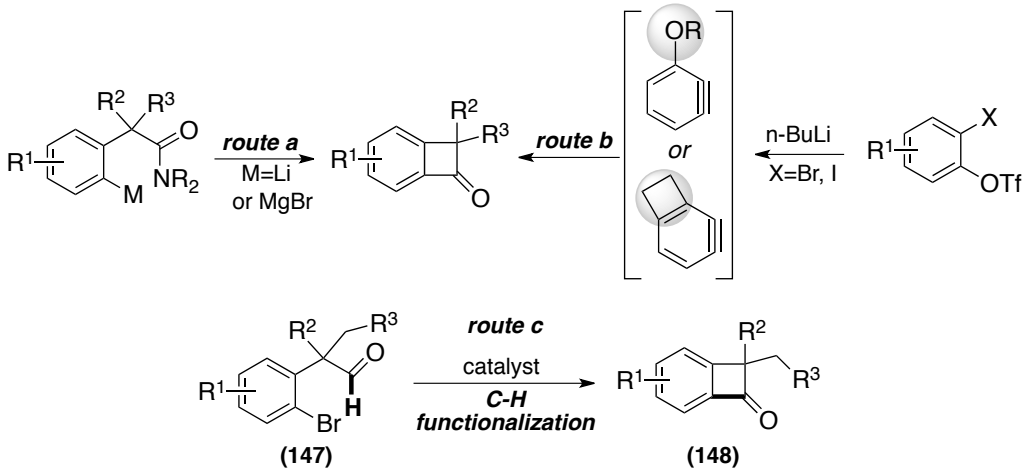


Figure 2.32

[113] See section 2.3.2
[114] See section 2.3.1

In view of the tremendous versatility of benzocyclobutenones as synthons in organic synthesis[115] there was a need for designing a new synthetic route that would face the challenges associated to the "classical" routes: (a) regioselectivity issues over the aryl backbone should be completely controlled; (b) the precursors should be easily accessible; (c) the method should tolerate the presence of functional groups and (d) the metal should be employed in catalytic amounts.

Prompted by these challenges, we wondered whether we could effect the synthesis of benzocyclobutenones **(148)** by a rather simple but challenging intramolecular acylation of aryl bromides **(147)** via metal-catalyzed C-H bond-functionalization (router c, Figure 2.32).[116] Taking a closer look into our proposed transformation, in principle the only byproduct generated would be the corresponding HBr; therefore, the presence of a catalyst and a base to neutralize the so-generated HBr would be enough to end up in the corresponding BCB. Moreover, such an intramolecular route would have the advantage of perfectly controlling the regioselectivity over the aryl backbone while dealing with easily accessible α-aryl aldehydes.[117]From a mechanistic point of view, we hypothesized that the reaction would be initiated by an oxidative addition of a low valent metal species to an aryl bromide **(147)** to yield complex **II**,[118] Figure 2.33. We anticipated that such complex would undergo C-H bond-functionalization with concomitant loss of HBr, thus forming a five-membered metallacycle **III.**[119] A final reductive elimination would then afford the desired benzocyclobutenone **(148)** while regenerating the catalytic metal species **I**. We expected that oxidative

[115] See section 2.4

[116] Álvarez-Bercedo, P.; Flores-Gaspar, A., Correa, A.; Martin, R., *J. Am. Chem. Soc.* **2010**, *132*, 466.

[117] (a) Martin, R.; Buchwald, S. L. *Org. Lett*. **2008**, *10*, 4561. (b) Vo, G. D.; Hartwig, J. F. *Angew. Chem., Int. Ed*. **2008**, *47*, 2127. (c) Martin, R.; Buchwald, S. L. *Angew. Chem., Int. Ed*. **2007**, *46*, 7236.

[118] a) Barrios-Landeros, F.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 6944. b) Stambuli, J. P.; Bühl, M.; Hartwig, J. F., *J. Am. Chem. Soc.* **2002**, *124*, 9346. c) Stambuli, J. P.; Incarvito, C. D.; Bühl, M.; Hartwig, J. F., *J. Am. Chem. Soc.* **2004**, *126*, 1184. d) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. e) Hartwig, J. F.; Paul, F.. *J. Am. Chem. Soc.* **1995**, *117*, 5373.

[119] a) Mahendar, L.; Krishna, J.; Reddy, A. G. K.; Ramulu, B. V.; Satyanarayana, G., *Org. Lett.,* **2012**, *14*, 628. b) Strieter, E. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 925.

addition to an aryl bromide was not going to be problematic due to the myriad of oxidative addition complexes described in the literature under relatively mild reaction conditions.[118a] However, we anticipated that both C-H bond-functionalization of an aldehyde motif and the final reductive elimination to deliver a rather strain ring would be particularly difficult.[71] In the latter, we speculated that a bidentate ligand backbone with a large bite angle would greatly facilitate reductive elimination. Still, as for many other coupling reactions, we also anticipated that the nature of the base and solvent will also play a critical role for success.[120]

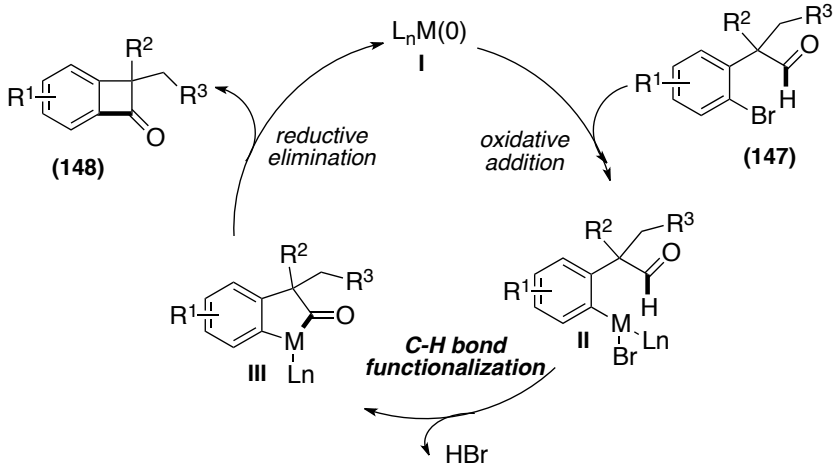


Figure 2.33

2.6.1.1 Screening of the reaction conditions for synthesis of BCB's.

Among all the metals that are known to actively participate in C-H bond-functionalization processes, palladium precatalysts undoubtedly play a dominant

[120] a) Proutiere, F.; Schoenebeck, F., *Angew. Chem. Int. Ed.* **2011**, *50*, 8192. b) Maiti, D.; Fors, B. P.; Henderson, J. L.; Nakamura, Y.; Buchwald, S. L. *Chem. Sci*. **2011**, *2*, 57. c) Meyers, C.; Maes, B. U. W.; Loones, K. T. J.; Bal, G.; Lemi_ere, G. L. F.; Dommisse, R. A. *J. Org. Chem.* **2004**, *69*, 6010.

role due to the functional group tolerance associated to these reactions and the ease for fine-tuning the properties of the catalytic species by the use of a proper ligand backbone.[121] While there are many Pd(0) compounds that have been employed as catalysts, namely $Pd(PPh_3)_4$ or $Pd_2(dba)_3$, among others, the presence of a strongly coordinating ligand such as PPh_3 or dba have shown to significantly retard the formation of the active species within the catalytic cycle. Not surprisingly, the most widely employed Pd precatalyst cross-coupling reaction methodologies is actually $Pd(OAc)_2$ that is reduced *in situ* to Pd(0) in the presence of either an excess of phosphine, reducing agent or by the aid of exogeneous amounts of water.[122]

We chose **(150)** as our model substrate, since it could be prepared in multigram scale in essentially two steps from commercially available 2-bromophenylacetonitrile (Figure 2.34). Thus, a simple deprotonation of 2-(2-bromophenyl)acetonitrile in the presence of NaHMDS in THF and further treatment with an excess of MeI provided **(149)** in essentially quantitative yield. With no need for purification, the crude reaction was treated with DIBAL-H in DCM at -78 ºC to afford aldehyde **(150)** in a 82% overall yield in essentially two-step procedure from 2-bromophenylacetonitrile.

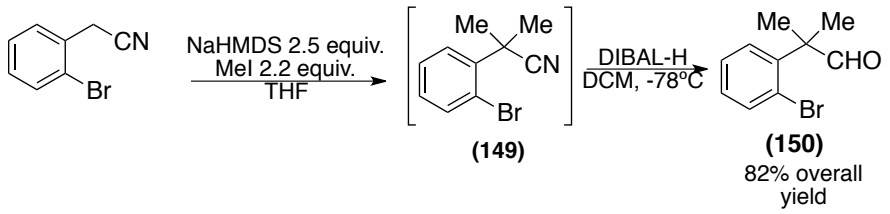
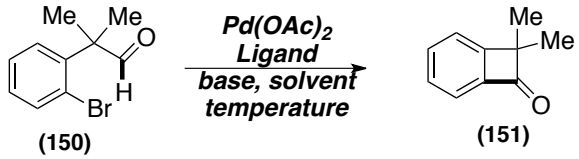


Figure 2.34

[121] Tsuji, J., "*Palladium reagents and catalysts: New Perspectives for the 21st Century"* Wiley-VCH, **2006.**

[122] a) Fors, B. P.; Krattiger, P.; Strieter, E.; Buchwald, S.L., *Org. Lett.,* 2008, 10, 3505. b) Amatore, C.; Jutand, A.; Thuilliez, A., *Organometallics,* **2001**, *20*, 3241. c) Wolfe, J. P.; Buchwald, S. L., *J. Org. Chem.* **2000**, *65*, 1144. d) C. Amatore, A. Jutand, Coord. *Chem. Rev*. **1998**, *511*, 178. e) Ozawa, F.; Kubo, A.; Hayashi, T. *Chem. Lett.* **1992**, 2177.

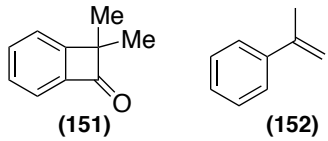
With substantial amounts of **(150)** in hand, a variety of experimental variables such as ligand, base and solvent were systematically examined using $Pd(OAc)_2$ as the pre-catalyst in order to find the best conditions in route to benzocyclobutenone **(151)** (Figure 2.35).



(150) (151)

Figure 2.35

Prompted by many other Pd-catalyzed cross-coupling reactions,[121] we hypothesized that the ligand backbone will exert the most critical influence on the reaction outcome. Thus, a series of reactions of **(150)** (0.25 mmol) in the presence of $Pd(OAc)_2$ (2 mol%), Ligand (3-6 mol%), Cs_2CO_3 (1.30 equiv.) and 1,4-dioxane (0.25 M) at 110 ºC was analyzed by GC after 12 h reaction time. Among the ligands examined, we decided to test monodentate as well as bidentate phosphine ligands with different electronic and steric environments. As judged by GC analysis of the crude reaction mixtures, **(150)** was converted into two main products in all cases: the expected benzocyclobutenone **(151)** and the α-methylstyrene product **(152)**.



(151) (152)

Figure 2.36

Formation of styrene derivatives in similar systems have been also observed by Larock an co-workers.[123] They observed that acyl C-H bonds can be activated

[123] Kasharwani, T.; Verma, K. A.; Emrich, D.; Ward, J. A.; Larock, R. C., *Org. Lett.,* **2009**, *11*, 2591.

"through space" migration of palladium[124] in *ortho*-iodo derivatives **(153)** to form carbamates **(155)** when starting from formamide derivatives and alcohols as nucleophiles, Figure 2.37-top. In the absence of a nucleophile and changing the amide functionality by a α,α-substituted carbon, the acylpalladium intermediate underwent decarbonylation, followed by β-hydride elimination, to give the corresponding styrene derivative **(152)**, Figure 2.37-bottom. This procedure permitted the formation of styrene derivatives although in low yields, in the absence of functional groups and very much restricted to aryl iodides as counterparts.

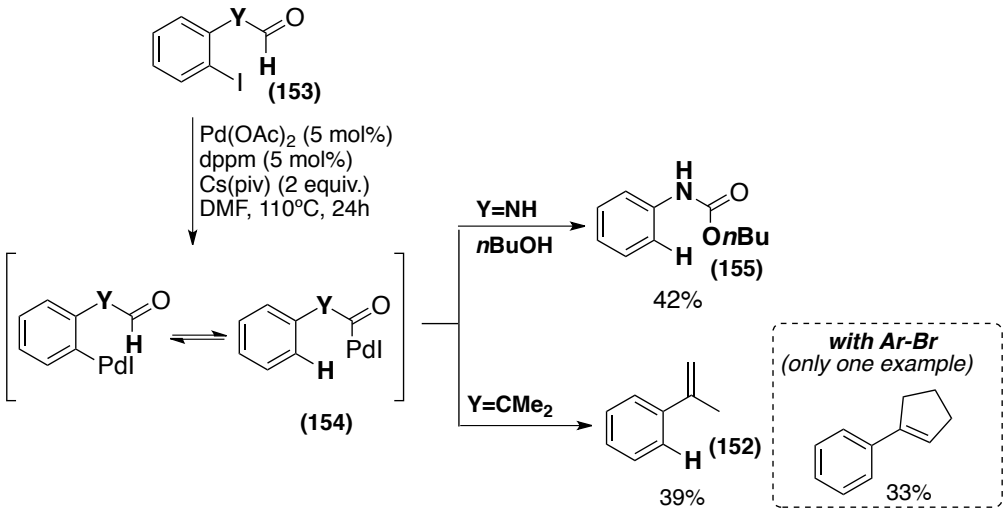


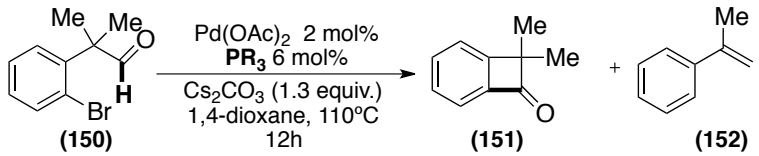
Figure 2.37

As judge by our initial screening shown in Table 1, low conversions of **(150)** as well as poor selectivity toward benzocyclobutenone (BCB) **(151)** product were observed systematically with the vast majority of monodentate ligands analyzed. Indeed, α-methyl styrene byproduct **(152)** was obtained with non-neglictable yields when utilizing monodentate ligand backbones. We believed that the so-formed acylpalladium intermediate **(154)** (Figure 2.37) underwent

[124] Larock, R. C., *J. Organomet. Chem.,* **1999**, *576*, 111.

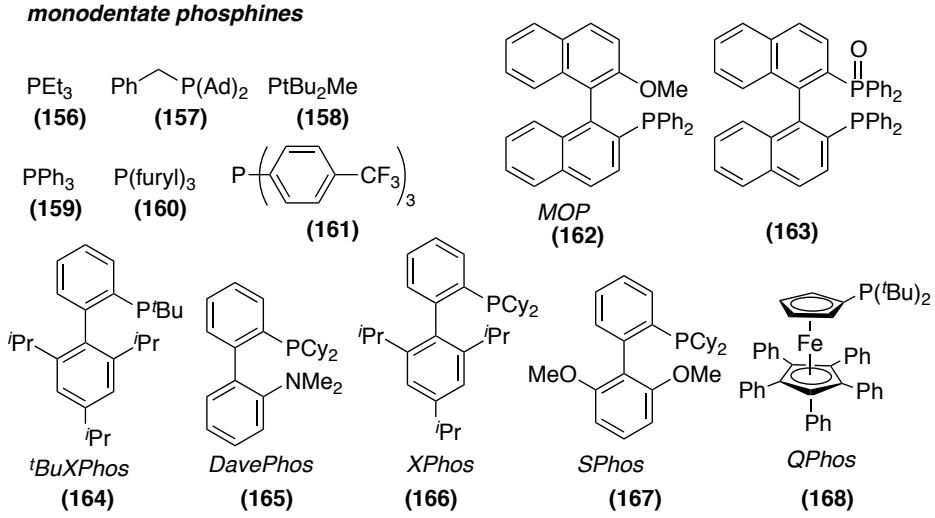
decarbonylation, followed by β-hydride elimination, to give the corresponding styrene derivative as was shown by Larock.[123]

Table 1. Screening of monodentated phosphines. [a]



Entry	PR_3	Conv. (%)[b]	**(151)** (%)[b]	**(152)** (%)[b]
1	**(156)**	41	3	25
2	**(157)**	61	0	48
3	**(158)**	56	11	34
4	**(159)**	30	3	15
5	**(160)**	12	8	3
6	**(161)**	44	6	11
7	**(162)**	15	8	5
8	**(163)**	67	19	16
9	**(164)**	24	10	4
10	**(165)**	15	10	3
11	**(166)**	53	33	14
12	**(167)**	67	51	13
13	**(168)**	75	2	42

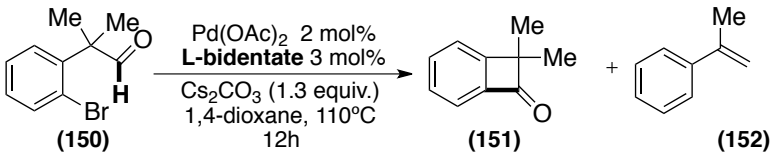
monodentate phosphines



[a] Aryl bromide (0.25 mmol), $Pd(OAc)_2$ (2 mol%), Ligand (6 mol%), Cs_2CO_3 (1.30 equiv.), dioxane (0.50 M) at 110 ºC. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.

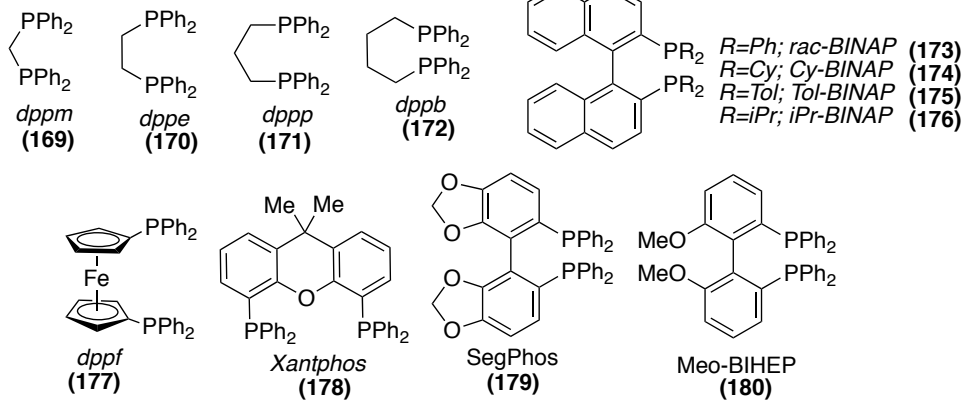
In sharp contrast, the utilization of bidentate phosphine ligands improved the conversion of **(150)** to benzocyclobutenone derivative **(151)** and lowering down the formation of the styrene **(152)**, Table 2.

Table 2. Screening of bidentate phosphines. [a]



Entry	**L-bidentate**	Conv. (%)[b]	**(151)** (%)[b]	**(152)** (%)[b]
1	**(169)**	27	19	0
2	**(170)**	70	23	38
3	**(171)**	77	22	41
4	**(172)**	51	4	29
5	**(173)**	100	84	0
6	**(174)**	100	85	0
7	**(175)**	100	83	0
8	**(176)**	100	86	0
9	**(177)**	60	10	23
10	**(178)**	45	25	8
11	**(179)**	54	33	0
12	**(180)**	57	34	0

bidentate phosphines



[a] Aryl bromide (0.25 mmol), $Pd(OAc)_2$ (2 mol%), Ligand (3 mol%), Cs_2CO_3 (1.30 equiv.), dioxane (0.50 M) at 110 ºC. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.

However, selectivities still were not ideal in many cases as significant amounts of α-methyl styrene **(152)** were generated (entries 1-4). Interestingly, we found that bidentate ligands based upon a binaphthyl backbone provided exquisite selectivity en route to **(151)** (entries 5-8). Unlike the aliphatic carbon spacer in **(169)-(172),** bidentate phosphines on a binaphthyl motif exert higher chemical stability without a serious increase of torsional strain. Quite surprisingly, the steric influence on the phosphine backbone did not have much effect on both reactivity and selectivity and **(173)-(176)** provided almost identical yields of **(151)**. Intriguingly, other bidentate phosphines without an aliphatic carbon spacer **(177)-(180)** neither gave better conversions nor selectivities toward **(151)**. While one might argue that the bite-angle of the bidentate phosphine might be the responsible for the selectivities observed,[125] a simple comparison of the bite angles indicate that this is indeed not the case. Thus, **(171)** (91º), **(173)** (92º) and **(177)** (95º) have similar bite angles but quite different reaction outcome.[125]

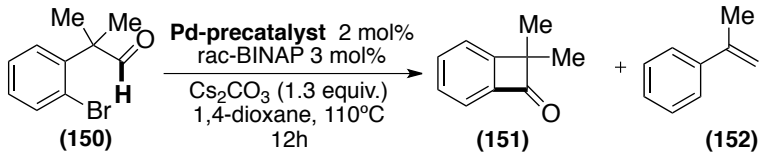
Although **(173)-(176)** gave comparable yields, we continued our optimization with *rac*-BINAP **(173)** due to the readily availability of this ligand as compared with **(174)-(176).** [126] We next decided to test whether other palladium precatalysts could be utilized as well with a catalytic system based upon **(173)**. We observed that Pd(0) sources such as Pd_2dba_3 and $Pddba_2$ (entry 2 and 3) gave selectively **(151)**, albeit in lower conversions. Such low activity might be explained to the presence of dba that competes for ligand binding at the metal center.[122]

Other palladium pre-catalysts such as $PdCl_2(PhCN)_2$, $[Pd(allyl)Cl]_2$ and $[Pd(cinnamyl)Cl]_2$ could be utilized as well (entries 3, 4 and 5). Although these Pd(II) precatalysts consistently gave better conversions than $Pddba_2$ (entry 3),

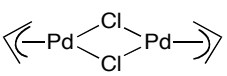
[125] Birkholz, M. –N.; Freixa, Z.; van Leeuwen, P. W. N. M., *Chem. Soc. Rev.,* **2009**, *38*, 1099.
[126] a) rac-BINAP: 5gr =113€ (www.sigmaaldrich.com). b) tol-BINAP: 500 mg =58.9€ (www.sigmaaldrich.com). c) For the synthesis of ^{i}Pr-BINAP and Cy-BINAP see: Gedelbach, T. Z.; Pregosin, P. S. *Organometallics,* **2003**, *22*, 1443.

the selectivity was much higher when utilizing $Pd(OAc)_2$ (entry 1). As for Pd_2dba_3 and $Pddba_2$, $[Pd(allyl)Cl]_2$ (entry 5) and [Pd(cinnamyl)Cl] (entry 6) generate, upon reduction to Pd(0), olefinic fragments that might compete for substrate binding.[122]

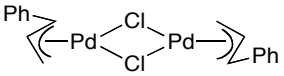
Table 3. Screening of Palladium precatalysts. [a]



Entry	**Pd-precatalyst**	Conv. (%)[b]	**(151)** (%)[b]	**(152)** (%)[b]
1	$Pd(OAc)_2$	100	84	0
2	$Pd_2(dba)_3$	17	16	0
3	$Pd(dba)_2$	26	22	0
4	$PdCl_2(PhCN)_2$	75	15	32
5	**Pd-1**	63	10	27
6	**Pd-2**	93	17	39



(181)



(182)

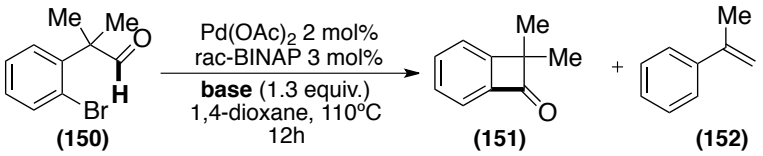
[a] Aryl bromide (0.25 mmol), $Pd(OAc)_2$ (2 mol%), rac-BINAP **(173)** (3 mol%), Cs_2CO_3 (1.30 equiv.), toluene (0.50 M) at 110 ºC. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.

The nature of the base also played a crucial role on the reaction outcome (Table 4). Thus, while Na_2CO_3 and K_2CO_3 (entries 2 and 3) gave low conversions to products, Cs_2CO_3 (entry 1) gave excellent yields of **(151)**. A possible explanation for such behavior can be attributed to its large cationic radius, low charge density and large polarizability, thus making the cesium ion the one with the lowest degree of solvation and ion-pairing as compared to the ions of analogous alkali metal salts, Figures 2.38 and 2.39.[127] Indeed, its solubility in

[127] Data table taken from: a) Lide, D. R., *Handbook of Chemistry and Physics*, 83. ed., CRC Press LLC **2002-2003**. b) Cella, J. R.; Bacon, S. W., *J. Org. Chem.*, **1984**, *49*, 1122.

aprotic solvents is higher than the other alkali metal salts, thus reinforcing the results obtained in 1,4-dioxane as the solvent of choice in our reaction conditions.

Table 4. Screening of bases. [a]



Entry	**Base**	Conv. (%)[b]	**(151)** (%)[b]	**(152)** (%)[b]
1	Cs_2CO_3	100	84	0
2	K_2CO_3	51	16	12
3	Na_2CO_3	0	0	0
4	K_3PO_4	53	8	23

[a] Aryl bromide (0.25 mmol), $Pd(OAc)_2$ (2 mol%), rac-BINAP **(173)** (3 mol%), Base (1.30 equiv.), dioxane (0.50 M) at 110 ºC. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.

Cation	Cationic radius r_i for cn=6 [Å]	Electronic polarizability α [10^{-24} cm^3]
Li^+	7.30	0.029
Na^+	32.55	0.179
K^+	36.64	0.83
Rb^+	38.25	1.40
Cs^+	47.24	2.42

Figure 2.38

Solvent	Cs_2CO_3	K2CO3
DMF	1.195	0.075
DMSO	3.625	0.470
DMAC	0.490	0.046
sulfolane	3.950	0.160
NMP	7.224	0.237

Figure 2.39

Although a "cesium effect" has been observed in other cross-coupling reactions,[122b, 128] the superiority of Cs_2CO_3 in our protocol is merely empirical and particularly difficult to clarify. Therefore, we hypothesized that the greater solubility of Cs_2CO_3 likely indicates a greater concentration of CO_3^{2-} in solution. We believed that such anion favors the key aldehydic C-H bond-functionalization event since carbonate base might also participate in a base-assisted deprotonation in a concerted manner (or concerted metalation-deprotonation pathway, CMD, see section 1.2).[27-30] Such hypothesis assumes that the carbonate base replaces the bromide in the coordination sphere on the metal center **IV**, leading to intermediate for the CMD that set up the stage for forming the five-membered palladacycle **III**, Figure 2.40.

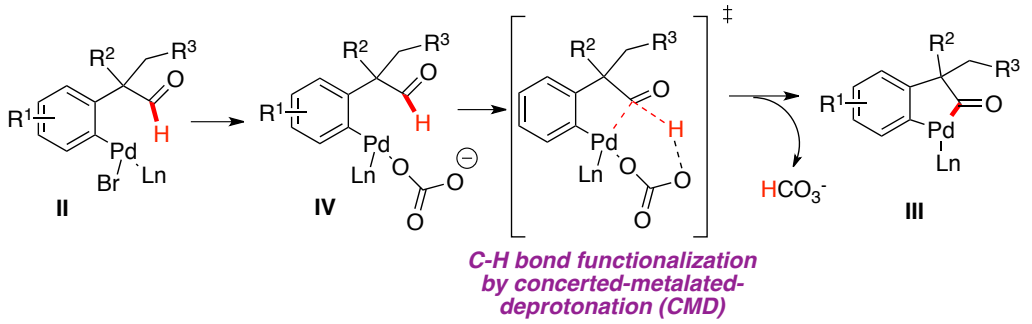
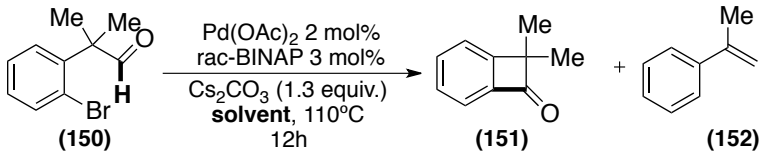


Figure 2.40

While in general other aprotic solvents such as toluene or DMF (Table 5, entries 2 and 3) consistently gave higher conversions to products, the low selectivities found for these solvents did not make these solvents appropriate for our reaction. At present, we don't have an explanation for such solvent effect. Not surprisingly, *n*Bu_2O showed a similar behavior as 1,4-dioxane and high yields and exclusive formation of **(150)** was observed (entry 4).

[128] a) Maes, B. U. W.; Loones, K. T. J.; Jonckers, T. H. M.; Lemière, G. L. F.; Dommisse, R. A.; Haemers, A., *Synlett* **2002**, *12*, 1995 b) Catellani, M.; Catucci, C.; Celentano, G.; Ferraccioli, R., Synlett **2001**, *6*, 803. c) Wright, S. W.; Hageman, D. L.; McClure, L. D., *J. Org. Chem.* **1994**, *59*, 6095. d) Maerten,E.; Hassouna, F.; Couve-Bonnaire, S.; Mortreux, A.; Carpentier, J. -F.; Castanet, Y., *Synlett* **2003**, *12*,1874.

Table 5. Screening of solvents. [a]

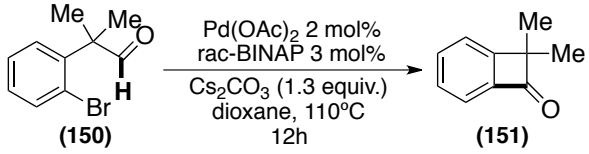


Entry	Solvent[a]	Conv. (%)[b]	**(151)** (%)[b]	**(152)** (%)[b]
1	dioxane	100	84	0
2	toluene	81	54	16
3	DMF	100	19	57
4	nBu_2O	96	78	0

[a] Aryl bromide (0.25 mmol), $Pd(OAc)_2$ (2 mol%), rac-BINAP **(173)** (3 mol%), Cs_2CO_3 (1.30 equiv.), solvent (0.50 M) at 110 ºC. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.

As shown in Table 6, blank experiments indicated that all variables utilized (Pd precatalys, ligand, base and solvent) were critical for obtaining the product **(151)** in good yields.

Table 6. Blank experiments. [a]



Entry	Conditions[a]			Conv.	**(151)**	**(152)**
	$Pd(OAc)_2$	**L18**	Cs_2CO_3	(%)[b]	(%)[b]	(%)[b]
1	✓	✓	✓	100	0	84
2	✓	✓	✗	0	0	0
3	✗	✓	✓	0	0	0
4	✓	✗	✓	0	0	0
5	✓	✗	✗	0	0	0
6	✗	✓	✗	0	0	0
7	✗	✗	✓	0	0	0
8	✗	✗	✗	0	0	0

[a] Aryl bromide (0.25mmol), $Pd(OAc)_2$ (2 mol%), rac-BINAP **(173)** (3mol%), Cs_2CO_3 (1.30 equiv.), dioxane (0.50 M) at 110ºC. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.

2.6.1.2 Synthesis of starting aryl bromide aldehydes.

Having established the optimized reaction conditions, we set out to explore the scope of this reaction by preparing a wide variety of a-aryl aldehydes possessing a bromide in *ortho*-position to the pending aldehyde motif.[129] As for the preparation of **(150)**, the general route to access these molecules involved an initial alkylation 2-(2-bromophenyl)acetonitrile using NaHMDS as the base and 2 equivalents of the alkylating agent yielding **(183)** (or 1 equivalent if forming a cyclic system or mono-alkylated compounds), followed by treatment with DIBALH to afford the corresponding aldehydes **(184)** (Figure 2.41). In this manner, a series of α-aryl aldehydes with different substitution in a position were prepared in good overall yields and in essentially two-step process at large scale. By utilizing such route, not only aliphatic but also cyclic motifs and mono substitution were introduced in α-position order to evaluate the influence of such groups in the intramolecular acylation event (Figure 2.41).

Alternatively, α-arylated aldehydes posessing differently substituted groups in α position could also be prepared in a relatively similar fashion. In this case, we conducted an initial alkylation of 2-(2-bromophenyl)acetonitrile with 1 equivalent of NaHMDS and 1 equivalent of 1-iodopropane, yielding compound **(196)** in a quantitative yield. Subsequently, another alkylation event in the presence of a second electrophile delivered the unsymmetrically α,α'-substituted phenylacetonitrile derivatives **(197)** that were treated with DIBALH, thus yielding the desired compounds. Figure 2.42 shows the compounds that we prepared following such synthetic route highlighting the yields of the overall sequence.

[129] In collaboration with Dr. Paula Avarez-Bercedo and Dr. Arkaitz Correa.

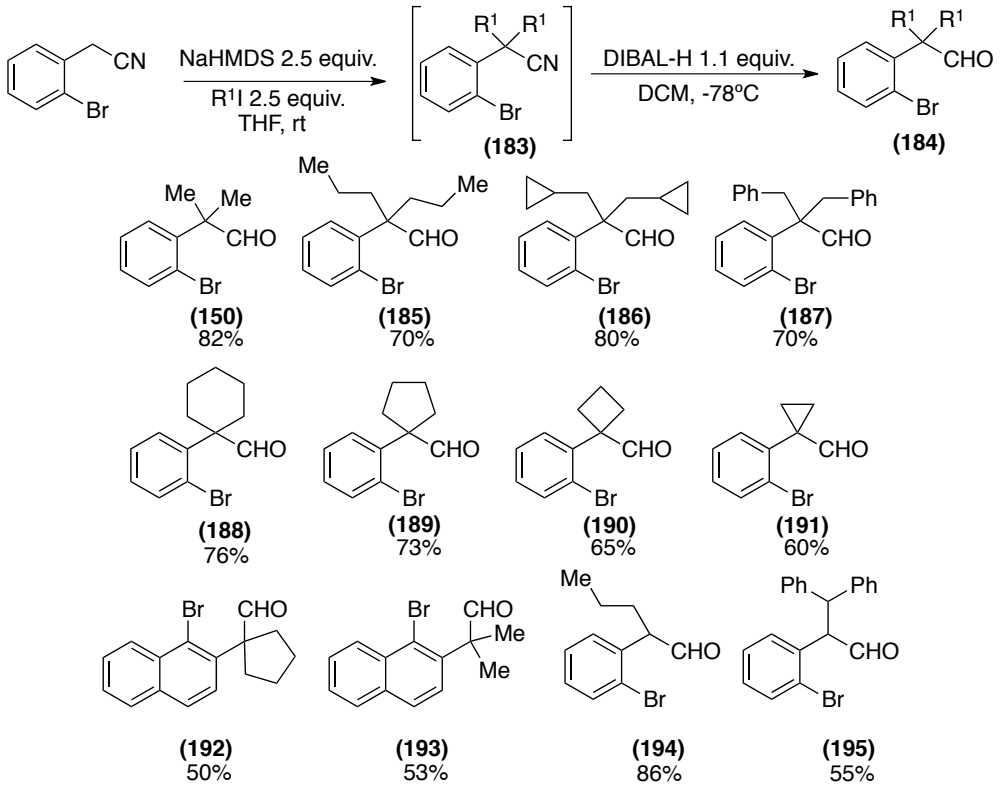


Figure 2.41

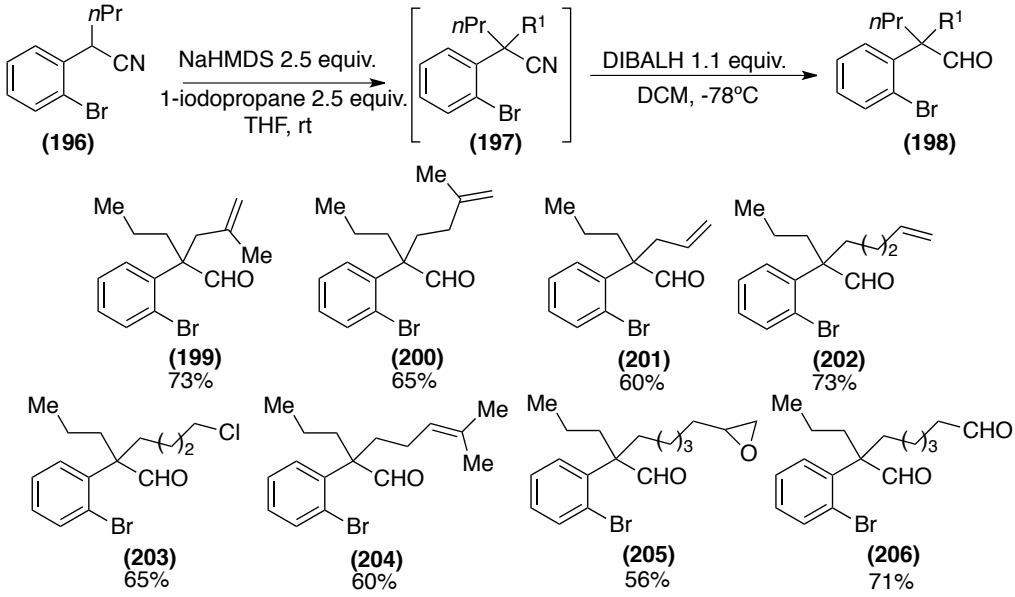


Figure 2.42

As shown, we decided to synthesize substrates with alkene residues in the side chain **(199)-(202)** in order to study whether Heck-type couplings would be competing or not with the productive formation of the desired benzocyclobutenone. Likewise, the introduction of an alkyl halide chain **(203)** would determine whether destructive β-elimination processes would be operating under our catalytic protocol. Similarly, we prepared substrates posessing highly sensitive epoxides **(205)** to evaluate the chemoselectivity of our protocol for preparing benzocyclobutenones.

A simple hydroboration of **(207)** in the presence of $BH_3{\cdot}SMe_2$ followed by oxidation with H_2O_2 delivered a primary alcohol. Subsequently, the hydroxyl group was protected as a *tert*-butyldimethylsilyl group by reaction with TBDMSCl and Imidazole in DMF as the solvent, thus yieldin **(208)** in 70% overall yield. A final reduction of the pending nitrile with DIBAL-H at low temperatures afforded an α-arylated aldehyde **(209)** with a silyl ether side chain in 83% yield (Figure 2.43).

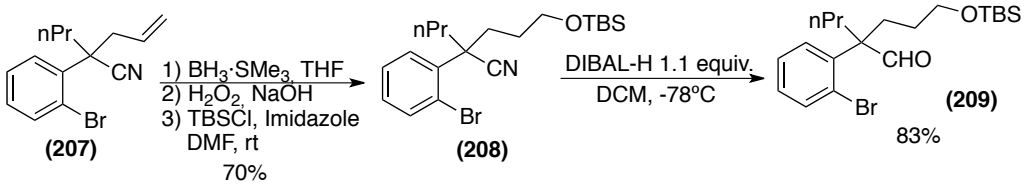


Figure 2.43

The preparation of an α-aryl aldehyde possessing a ketone in the side chain could be easily accomplished via cross-metathesis of **(202)** and 5-hexen-2-one in the presence of 2nd generation Grubb´s metathesis catalyst in DCM at 40 ºC (Figure 2.44). Although in low yields, **(210)** (*E/Z* = 9:1) would allow us to assess the functional group tolerance of our method in the presence of carbonyl groups possessing relatively acidic α-protons.

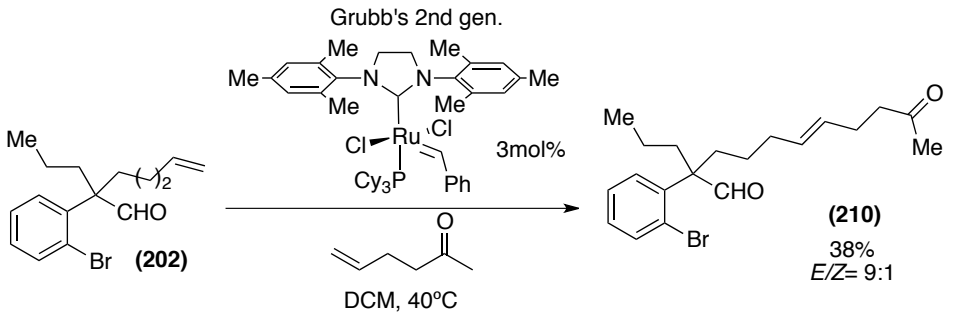


Figure 2.44

We decided to prepare α-arylated aldehydes posessing an heteroatom in α-position to see whether the C-H bond-functionalization event would be compromised. The sequence started by adding NaCN in DMSO to **(211)** followed by the protection of the free hydroxyl unit as a TBS group and reduction with DIBALH at -78 ºC, furnishing **(213)** in an overall 86% yield (Figure 2.45).

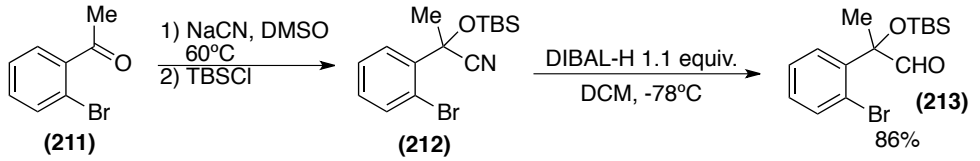


Figure 2.45

In order to study the site-selectivity of the aldehydic C-H bond-functionalization event, we prepared a substrate containing two different aldehydic residues, Figure 2.46. Simple alkylation of **(196)** (see Figure 2.40 for its preparation) with 1,5-dibromopentane afforded **(214)**; although rather unstable, such compound was rapidly treated with the lithium enolate of isobutyronitrile, yielding **(215)** in pure form. A final exhaustive reduction of both nitrile units with DIBALH in excess cleanly afforded **(216)** in 63% yield.

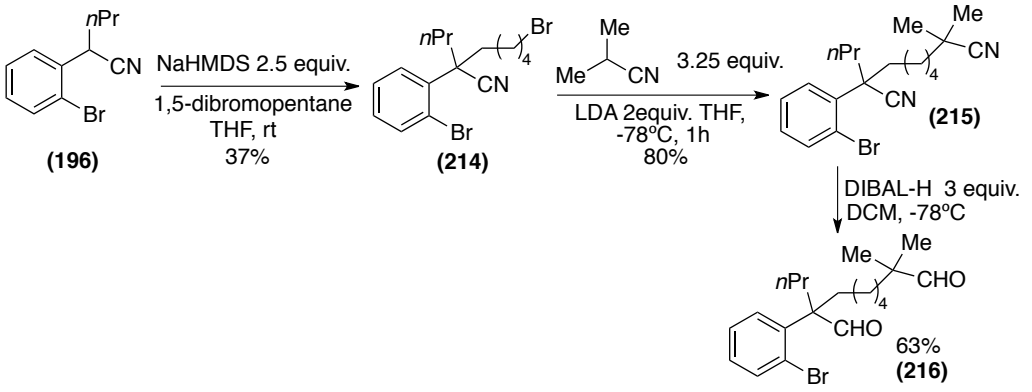


Figure 2.46

We also studied the influence of the substitution patterns and functional groups located on the aryl ring. The former is particularly important due to the fact that the classical [2+2]-cycloaddition approach toward benzocyclobutenones could not be employed for unsymmetrically-substituted and unbiased benzyne derivatives (see Figure 2.32). As for the previous synthetic approaches, the sequence commenced with the commertially available *ortho*-bromophenylacetonitrile derivatives followed by alkylation with NaHMDS with the proper electrophile and reduction of the nitrile motif **(217)** in the presence of DIBALH to achieved the corresponding aldehydes **(218)**, Figure 2.47

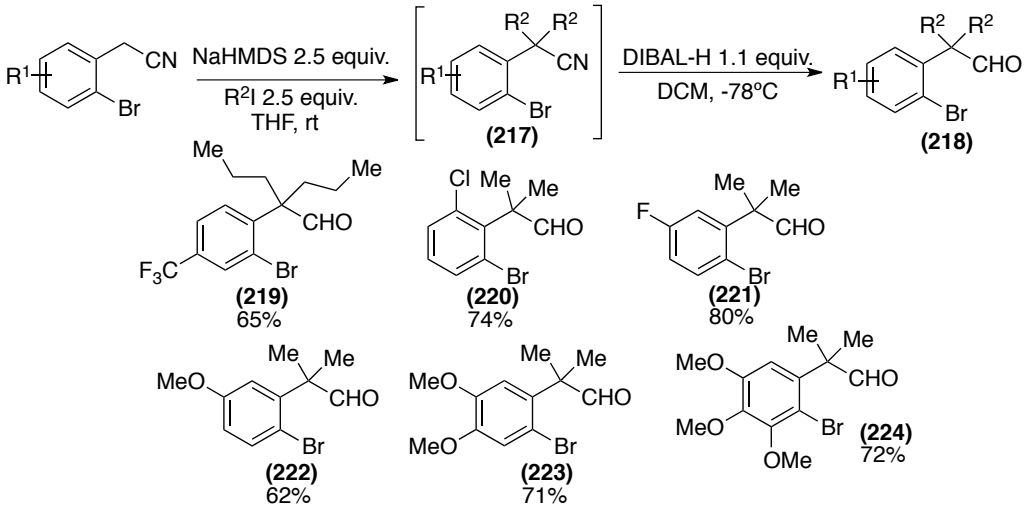


Figure 2.47

As for substrate **(227)** possessing a benzaldehyde motif, a different approach was followed, Figure 2.48. In this case, the commercially available 3-bromo-4-(bromomethyl) benzonitrile **(225)** derivative was treated with KCN in EtOH-H_2O, affording the corresponding *ortho*-bromophenylacetonitrile derivative. Subsequent exhaustive alkylation with 1-iodopropane in the presence of NaHMDS delivered **(226)** that was immediately reacted with an excess of DIBALH at -78 ºC, thus getting access **(227).**

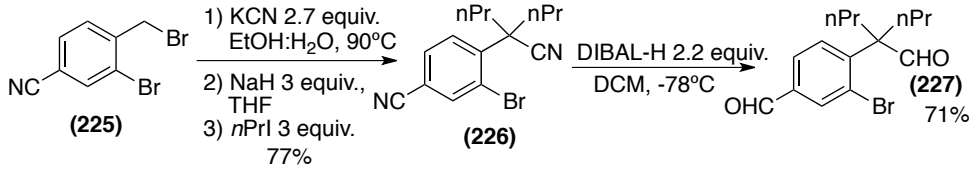


Figure 2.48

Although we prepared a substrate possessing an *ortho*-methoxy group, we also wished to evaluate the activity of less-electronically biased substrates having *ortho*-substitution as well, Figure 2.49. We started the synthetic sequence with the commertially available (2-bromo-3,5-dimethylphenyl)methanol **(228)**. Appel reaction with CBr_4 and PPh_3 afforded the corresponding benzyl bromide that was subsequently treated with NaCN in DMF. Subsequent alkylation in the presence of 1,5-dibromopentane yielded compound **(229)** in 67% overall yield. DIBALH reduction delivered the corresponding α-arylated aldehyde **(230)** in 88% yield.

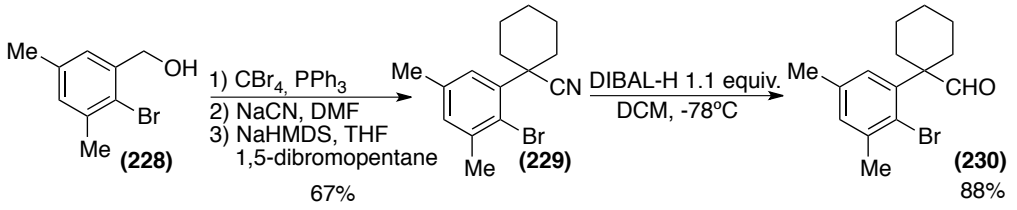


Figure 2.49

Next, we prepared substrates possessing an hydroxyl unit in *para* position to the bromide unit in order to evaluate the electronic effects on the cyclization event, Figure 2.50. To such end, we treated **(231)** in the presence of BBr_3, then reduction of the nitrile function with DIBALH at low temperatures yielded aldehyde **(232)** in 83% yield. Simple alkylation of **(232)** with either 4-(bromomethyl)-benzonitrile or benzyl bromoacetate cleanly afforded **(233)** and **(234)**, respectively. By accessing these compounds, we could not only study the electronic effects but also the tolerance towards esters and nitriles, a matter of particular importance due to the low functional group tolerance associated to the classical methods for preparing benzocyclobutenones.[75-82]

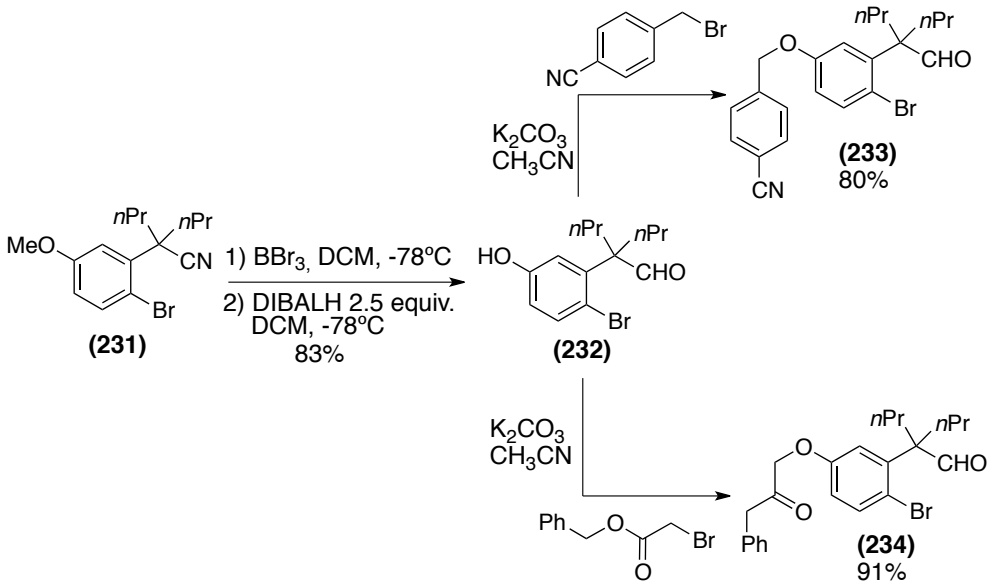


Figure 2.50

Unlike the previous substrates, the preparation of a substrate possessing an electron-withdrawing group in *para* position to the bromide function followed a different synthetic sequence. In this case, the reaction of the methyl 2-(2-bromophenyl)acetate **(235)** with 1,5-dibromopentane was followed by treatment with a mixture of nitric acid and sulfuric acid. As shown in Figure 2.51, the reaction proceeded with excellent regioselectivity, affording a single compound

(237). The indentity of such product was unequivocally assigned by NOESY experiments. Reduction of the ester fragment with excess DIBALH followed by oxidation of the primary alcohol with PCC/SiO_2 yielded the α-aryl aldehyde **(238)** with good overall yield.

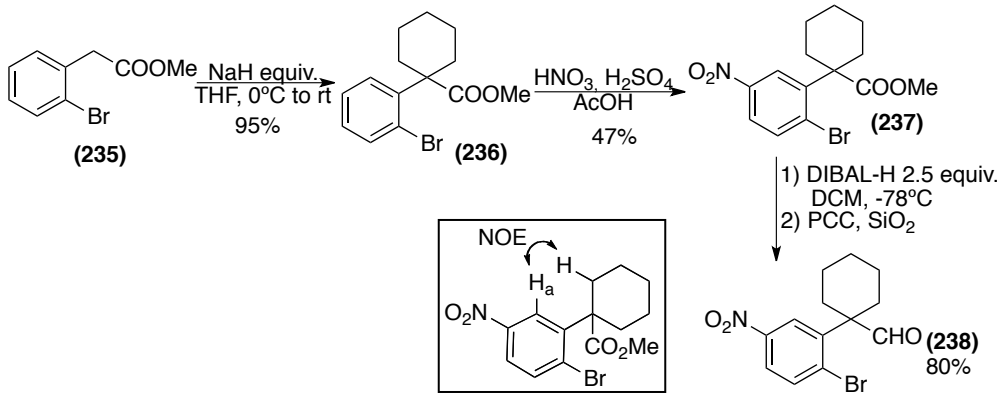


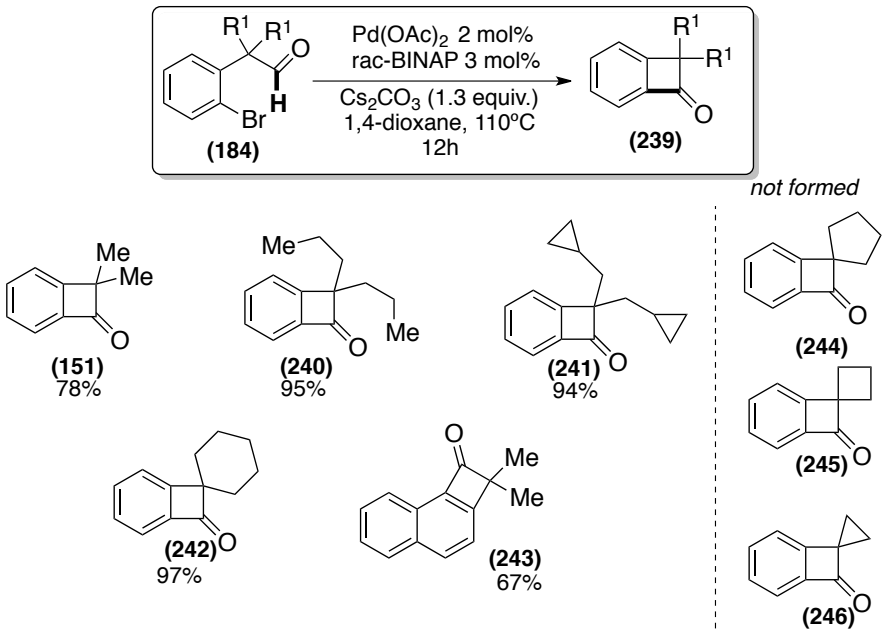
Figure 2.51

2.6.1.3 Scope of the reaction for the synthesis of benzocyclobutenones.

With substantial amounts in hand of differently substituted α-arylated aldehydes, we set out to explore the scope for the preparation of benzocyclobutenones (Table 7). As shown, the presence of both linear and cyclic chains in α-position did not have a significant effect on the reaction outcome, invariably affording benzocyclobutenones with high yields **(151)**, **(249)** and **(242)**. Likewise, strain motifs in a-position had a deleterious effect on reactivity and benzocyclobutenones could not be obtained in any case **(245)** and **(246)**. At present, we don't have explanation for the unsuccessful coupling of **(244)**. Although speculative, we believe that this is probably due to the inherent instability of both the aldehydes and the corresponding benzocyclobutenones under our reaction conditions. Notably, our protocol could be employed for

obtaining rather strain tricyclic compounds possessing a naphthyl backbone **(243)** in good yields.

Table 7 Synthesis of benzocyclobutenones.[a]

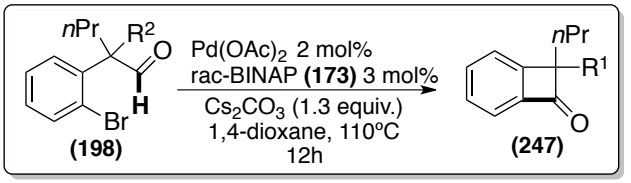


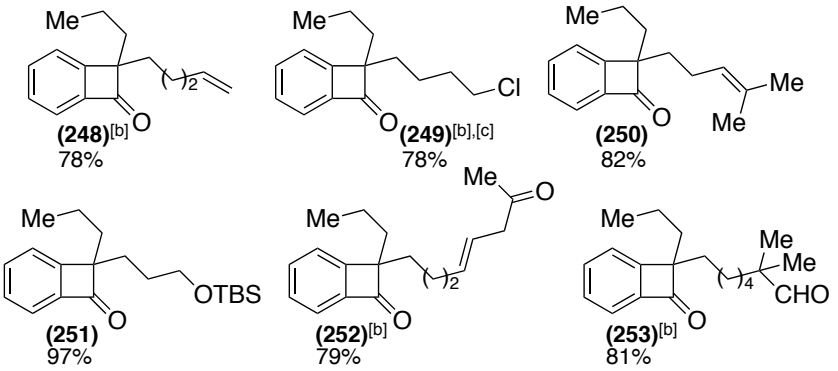
[a]Aryl bromide (0.50 mmol), $Pd(OAc)_2$ (2 mol%), *rac*-BINAP **(173)** (3 mol%), Cs_2CO_3 (1.30 equiv.), dioxane (2 mL) at 110 ºC. Isolated yields, average of two runs.

Under our reaction conditions, α-aryl aldehydes containing alkene motifs in the side chain could be coupled in good yields (Table 8, **(248)**, **(249)** and **(250)**). Not even traces of the corresponding Heck-type products were detected by NMR spectroscopy. Quite surprisingly, ketones posessing relatively α-acidic protons could equally be tolerated **(252)**. Under the limit of detection, we did not observe the formation of aldol-type products by NMR of the crude reaction mixtures. Likewise, the presence of silylated alcohols **(251)** as well as alkyl halides **(249)** could perfectly be accomodated; in the later, we did not observe even a trace of the corresponding terminal alkene via β-elimination processes. Much more interestingly, we could also demonstrate that our protocol could be amenable for site-selectivity among different aldehydic C-H bonds **(253)**. Thus, the reaction

with **(216)** cleanly afforded a single compound that was identified as the benzocyclobutenone **(253)** in high yield.

Table 8 Synthesis of benzocyclobutenones.[a]



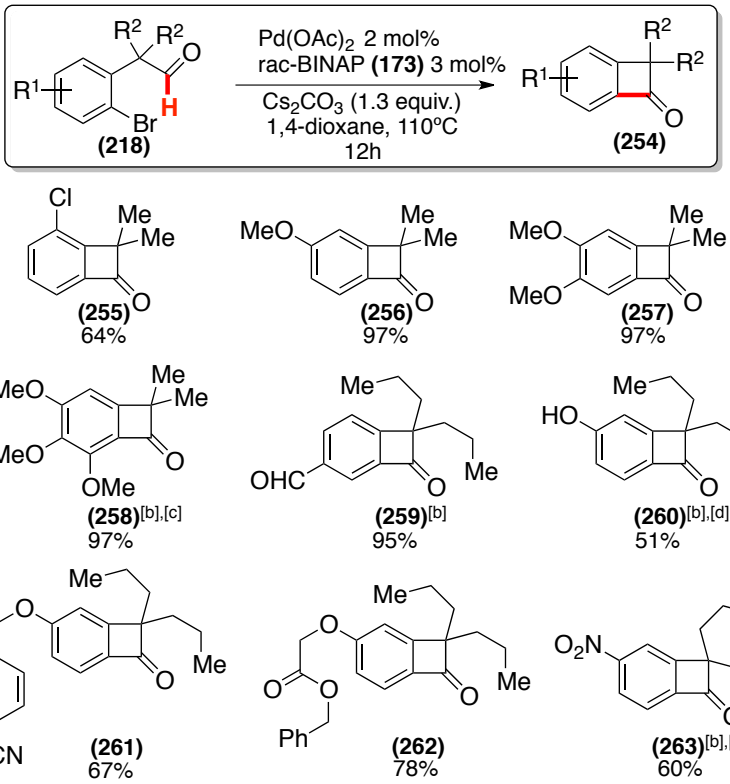


[a]Aryl bromide (0.50 mmol), $Pd(OAc)_2$ (2 mol%), *rac*-BINAP **(173)** (3 mol%), Cs_2CO_3 (1.30 equiv.), dioxane (2 mL) at 110 ºC. Isolated yields, average of two runs. [b]$Pd(OAc)_2$ (4 mol%), *rac*-BINAP **(173)** (6 mol%). [c] Using *rac*-*i*Pr-BINAP **(176)**

As shown in Table 9, the coupling of α-aryl aldehydes with different substitution patterns in either *ortho*-, *meta*- and *para* positions on the aryl backbone were perfectly accommodated. Particularly significant is the functional group tolerance profile obtained under this protocol, since aldehydes **(259)**, nitrile **(261)**, esters **(262)** and nitro groups **(263)** were perfectly accommodated, yielding the corresponding benzocyclobutenones from moderated to excellent yields. As shown for **(261)** and **(262)**, electronic effects do not play a prominent role on the formation of products. Likewise, the presence of an *ortho*-methoxy group to the aryl bromide motif does not hinder the reaction as well **(258)**. In this case, however, it was necessary the use of more bulky and electron-rich ligand **(176)** (under the same reaction conditions, *rac*-BINAP provided significantly lower yields). The better reactivity of **(176)** might be attributed to the fact that

oxidative addition to a less-activated aryl bromide and the C-H bond-functionalization is predicted to be faster with a more electron-rich ligand. Alternatively**, (176)** is bulkier than *rac*-BINAP **(173)** and as a result it can accelerate the final reductive elimination step. Notably, aryl chlorides were found to be inert **(255)**, thus providing a convenient functional handle for further functionalization.

Table 9 Synthesis of benzocyclobutenones.[a]



[a]Aryl bromide (0.50 mmol), $Pd(OAc)_2$ (2 mol%), rac-BINAP **(173)** (3 mol%), Cs_2CO_3 (1.30 equiv.), dioxane (2 mL) at 110 ºC. Isolated yields, average of two runs. [b]$Pd(OAc)_2$ (4 mol%), rac-BINAP (6 mol%). [c] Using rac-*i*Pr-BINAP **(176)**. [d] Cs_2CO_3 (1.30 equiv.)

As clearly seen by the formation of **(260)**, the developed protocol could be extended to the coupling of a remarkably electron-rich substrate possessing a free hydroxyl group in the presence of two equivalents of Cs_2CO_3. While in lower yields, it is certainly noteworthy that such coupling proceeds without the need for

protecting groups. Although the overall NMR data unambiguously identified the BCB core in **(260)**, we could independently confirm its structure by X-ray crystallographic analysis, Figure 2.52.

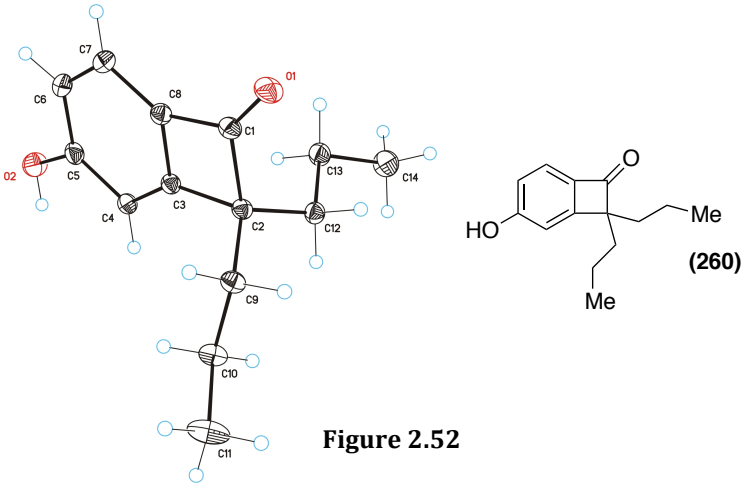


Figure 2.52

While the scope of the reaction was certainly very broad, we found that several substrates could not be coupled under our reaction conditions. For example, the presence of an epoxide in **(205)** (Figure 2.53) was not compatible with our protocol, leading to multiple products that could not be purified in pure form by column chromatography. We believe that the unsuccessful coupling is likely due to the lability of the corresponding epoxide under basic conditions. In line with the same notion, we could not prepare the benzocyclobutenones deriving from the coupling of mono-α-alkylated arylaldehydes (**(194)** and **(195)**) or bis-aldehyde **(206).** In these cases, the basic conditions utilized lead to aldol-type products. For **(194)** and **(195)**, formation of small amounts of the corresponding benzofuran derivatives via enolization followed by intramolecular C-O bond-formation were observed.

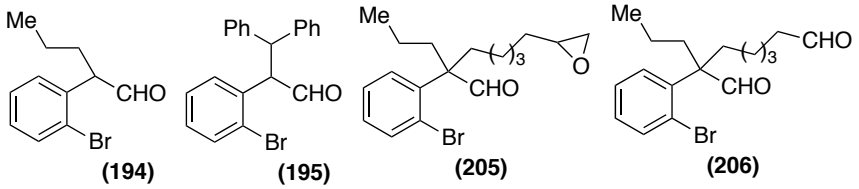


Figure 2.53

The presence of electron withdrawing groups either in *meta*-**(219)** or *para*-position **(221)** were not tolerated under our reaction conditions (Figure 2.54). Additionally, although *ortho*-substitution was tolerated in the formation of **(258)** (Table 9), the steric hindrance caused by methyl group in **(230)** was not compatible in our protocol (Figure 2.54).

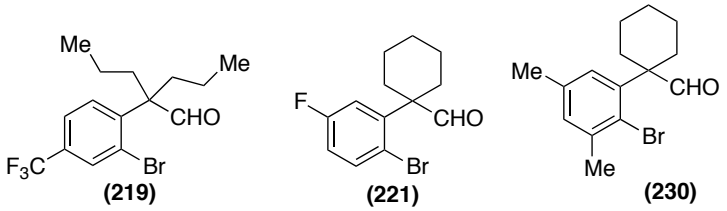


Figure 2.54

While we showed that **(248)** and **(249)** were obtained in pure form, it is worth noting that an otherwise analogous substrates **(199), (200)** and **(201)** could not be utilized. In the case of using **(199)** and **(201)** we detected a multiple amount of products, including the corresponding styrene derivatives that were observed in our initial screening study as well as still-not identified byproducts. Taking a closer look into **(199)** and **(201)** (Figure 2.55)**,** these substrates are designed for preventing the corresponding β-hydride elimination under a Heck-type protocol upon 5-*exo-trig* or 6-*exo-trig* cyclization, respectively.

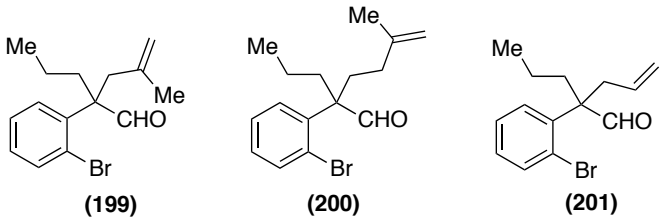


Figure 2.55

Thus, we decided to test the reactivity of an α-aryl aldehyde possessing a terminal alkene in its backbone **(199)** since such substrate could indeed trigger a Heck-type process. As shown in Figure 2.56, this was indeed the case and we did

not obtain the benzocyclobutenone **(265)** but rather the indane derivative with an exocyclic double bond **(264)**.

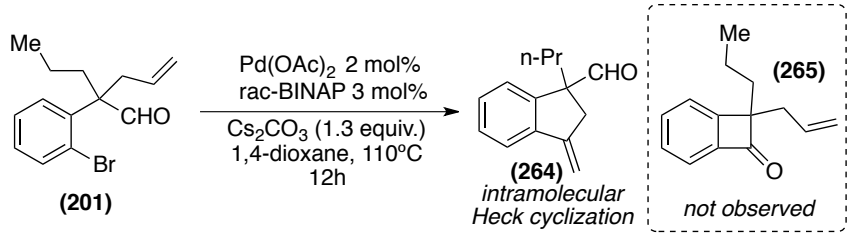


Figure 2.56

The mechanism by which this product is formed can be rationalize *via* a classical Heck-type coupling (Figure 2.57) that is initiated by an initial oxidative addition, 5-*exo-trig* cyclization and *β*-hydride elimination. The presence of the base then recovers back the active Pd(0) species.

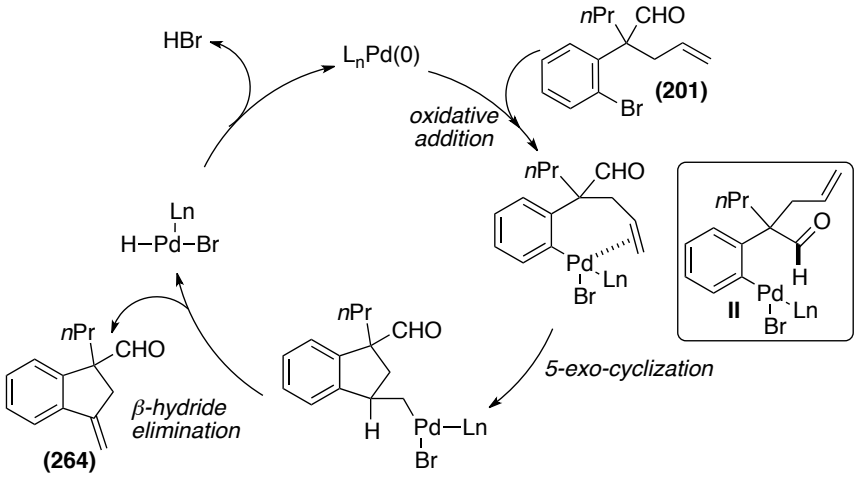


Figure 2.57

2.6.2 Large scale-synthesis of benzocyclobutenones.

In order to study the robustness of our methodology, we wondered whether the preparation of benzocyclobutenones could be accomplished in multi gram scale in an operationally-simple and user-friendly manner.[130] We chose **(185)** as the model substrate. As expected, technical problems arised when operating at large scale since temperatures needed to be perfectly controlled in order to minimize the formation of byproducts. Some chemical issues were observed in this large-scale reaction:

- For the reduction step, addition of DIBALH[131] in two batches (first 1.1 equivalents, then additional 0.50 equivalents) was shown to be critical. If not set up in this manner, the reduction of the nitrile motif was not as efficient and in some cases full conversion could not be achieved, giving an inseparable mixture of nitrile **(266)** and aldehyde **(185)**.
- The C-H bond-functionalization event required longer reaction times than our optimized protocol based upon 0.50 mmol scale (22 h vs 12 h). Such prolonged reaction times are the main responsible for observing traces amounts of methylstyrene, a side reaction that was not observed in small-scale reactions.

Despite the issues posed above, we finally found a way to minimize all these problems, resulting in a protocol that was amenable for preparing benzocyclobutenones in large scale, Figure 2.58. Importantly, other substrates could be coupled with similar results, indicating that such large-scale methodology can be applied for other benzocyclobutenones as well.

[130]; Martin R.; Flores-Gaspar, A., *Org. Synth*. **2012**, 89, 159.
[131] In order to know the real concentration of DIBALH solution we followed the procedure reported by Ryba for the titration of DIBAlH: Hoye, T. R.; Aspaas, A. W.; Eklov, B. M.; Ryba, T. D.; *Org. Lett.,* **2005**, 7, 2205.

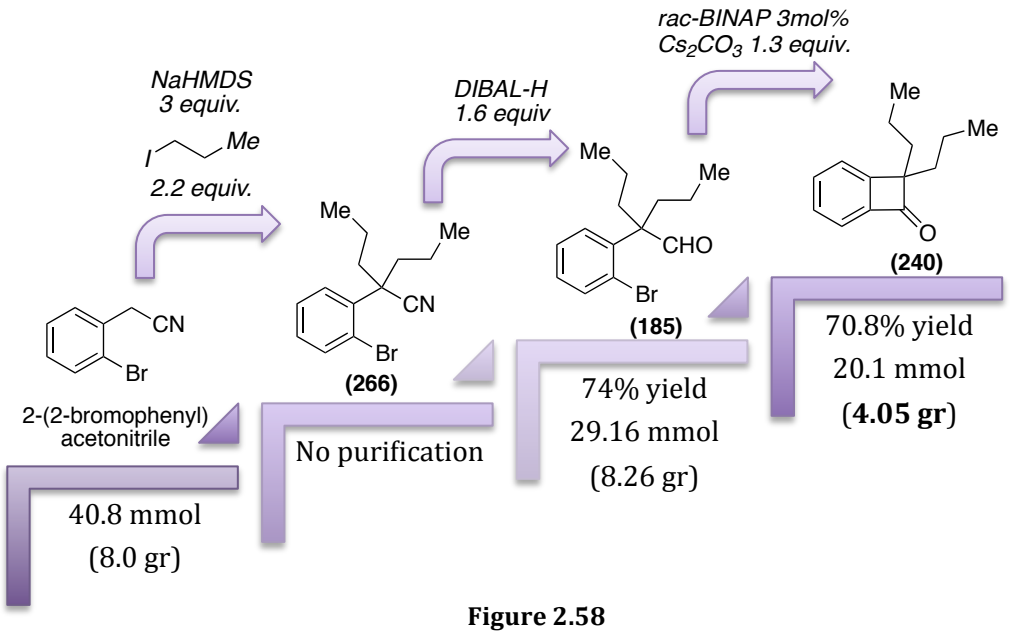

NaHMDS
3 equiv.
Me
I
2.2 equiv.
DIBAL-H
1.6 equiv
rac-BINAP 3mol%
Cs2CO3 1.3 equiv.
CN
Br
2-(2-bromophenyl)
acetonitrile
40.8 mmol
(8.0 gr)
Me
Me
CN
Br
(266)
No purification
Me
Me
CHO
Br
(185)
74% yield
29.16 mmol
(8.26 gr)
Me
Me
O
(240)
70.8% yield
20.1 mmol
(4.05 gr)

Figure 2.58

2.6.3 Synthetic application of benzocyclobutenone derivatives

We turned our attention to the synthetic applicability of the resulting BCB obtained by our method. The high reactivity of benzocyclobutenones is attributed to their relatively high ring-strain and the electrophilicity of the carbonyl group. Thus, we could effect a direct and straightforward transformation of BCB into the advanced intermediates shown in Figure 2.59.[132] Iodinated benzocyclobutanes represent an important building block in the synthesis of advanced steroids (see Figure 2.28, section 2.5).[108] Its synthesis can be achieved *via* two-step sequence by an initial reduction of the carbonyl group with $NaBH_4$ followed by reaction with PPh_3/I_2 in DCM. In this manner, **(267)** could be obtained in an overall 83% yield. Ring-expansion of the four-membered ring in the benzocyclobutenone core is an attractive transformation for preparing five-membered ring carbocycles (see section 2.4.2). When we treated **(240)** with the *in* situ formed alkenyl lithium reagent followed by ring-expansion with ICl we obtained a five-membered ring ketone **(268)** with two contiguous quaternary centres bearing an alkyl iodide moiety with a 78% overall yield (Figure 2.59).[97]

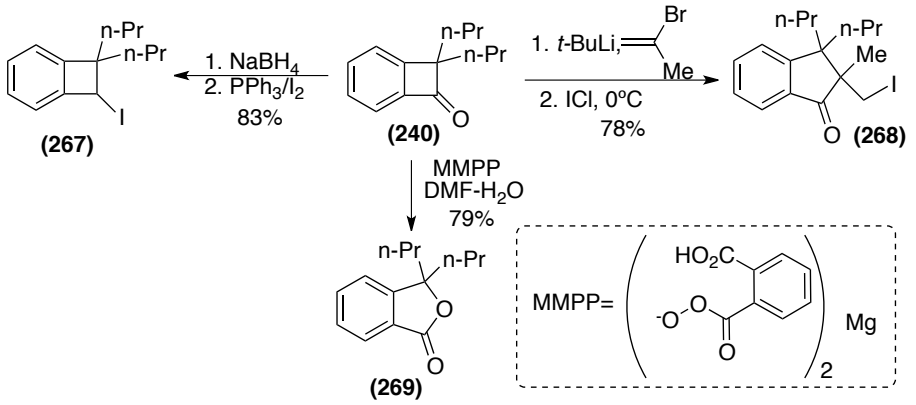


Figure 2.59

[132] In collaboration with Álvaro Gutierrez-Bonet. See: Master thesis "Synthesis and catalysis", Gutierrez-Bonet, A. Universitat Rovira i Virgili-ICIQ, June **2012**.

Likewise, phtalide **(269)** was also within reach by a methodology reported by Suzuki based upon the use of MMPP (magnesium monoperphthalate hexahydrate) as oxidant (see, figure 2.21, section 2.4.2).[98] Interestingly, while the use of mCPBA lead to two regioisomeric phthalides in 5:1 mixture, the use of MMPP cleanly produced a single regioisomer in which the oxygen is inserted into the most congested C-C bond (path a, Figure 2.60).

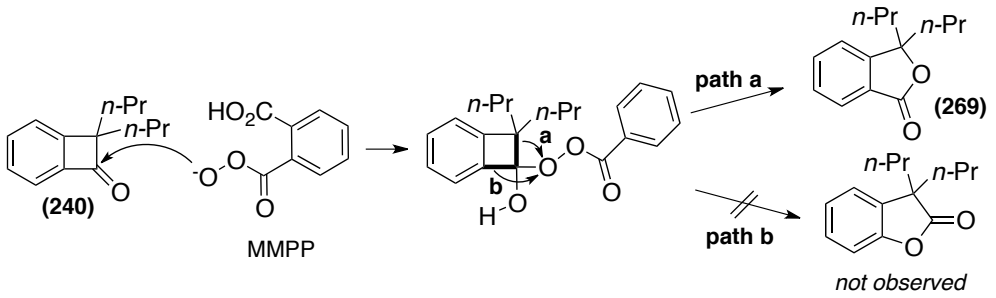


Figure 2.60

Similarly, we could also obtained benzodiazepine derivatives by a methodology reported by Nemoto.[102] Thus, the addition of a diazomethylene anion to the benzocyclobutenone **(242)** backbone set up the stage for a retro-4π-cyclization forming an oxyanion intermediate **(272)** at low temperatures (Figure 2.61). Then, an 8π-electrocyclization took place in the presence of the diazo moiety in **(273)** that upon hydrolytic workup afforded 43% yield of **(274)**. While in low yields, it is remarkable that such skeleton can be synthesized in a single step operation. It is worth noting that the reported methodology by Nemoto was limited to non-α-substituted benzocyclobutenones; as shown in Figure 2.61, we demonstrated that Nemoto's methodology could also be applied for α,α´-substituted benzocyclobutenones, although in slightly lower yields.

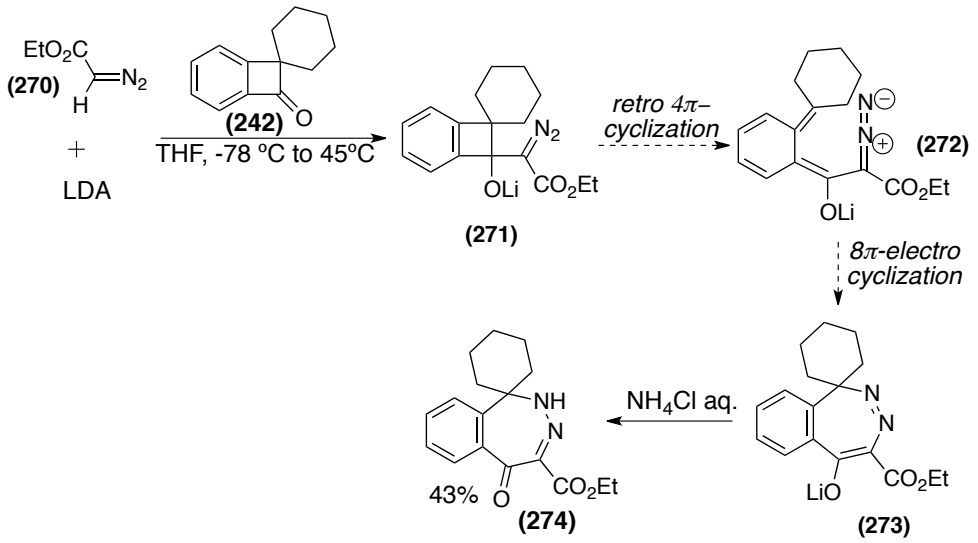


Figure 2.61

2.6.4 Mechanistic switch in Pd-catalyzed intramolecular acylation of aryl bromides.

The concept of selectivity is beautifully represented in nature by enzymes that can produce complex organic structures including proteins and nucleic acids from small-molecules through site-selective reactions. Following this concept, organic chemists have always had the hope to gain similar level of control over reaction outcomes by the catalyst design and reaction development to effect selective induction and help to make the strategy of selective reactions more useful. Indeed, in recent years a myriad of operationally simple and highly efficient transformations have been described in the literature where the use of ancillary ligands were capable to control the properties of the catalytic species, thus giving a subtle modulation of the active catalyst.[133] The field of selective catalysis (excluding enantioselectivity) is a vast and rapidly expanding area of research. In principle, selectivity can be achieved by two different means:

[133] For a review see: Mahatthananchai, J.; Dumas, A. M.; Bode, J. W., *Angew. Chem. Int. Ed.,* **2012**, *51*, 10954.

(1) ***Class A***. The initial interaction between the catalyst and the substrate leads to structurally distinct intermediates having divergent connectivity or structure. Thus, the formation of the products **D** or **E** is determined by the nature of the initial adduct (Figure 2.62).[134]

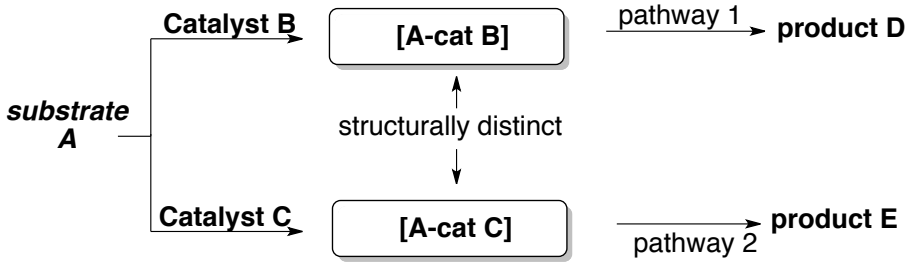


Figure 2.62

An example of the ***Class A*** of selectivity is the functionalization of heteroarenes. Itami *et al*. have shown that Pd-catalyzed arylation occurs at the more common α-position when the electron rich phospine PCy_3 is used as the ligand. However, the selectivity can be nearly completely reversed by the use of electron-poor phosphite ligand $P[OCH(CF_3)_2]_3$ (Figure 2.63). [135] Computational studies suggested that α-selectivity arised through concerted-metalation-deprotonation (CMD) intermediate **(275)**, while a Heck-type carbopalladation gives the β-product.[136] A similar argument was demonstrated by Gaunt and Sames when

[134] For selected examples see: a) Partridge, K. M.; Guzei, I. A.; Yoon, T. P., *Angew. Chem. Int. Ed.* **2010**, *49*, 930 b) Cho, J.-Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E.; Smith, M. R., *Science* **2002**, *295*, 305; Miyaura, N., *Bull. Chem. Soc. Jpn.* **2008**, *81*, 1535. c) Brice, J. L.; Harang, J. E.; Timokhin, V. I.; Anastasi, N. R.; Stahl, S. S., *J. Am. Chem. Soc.* **2005**, *127*, 2868; Timokhin, V. I.; Anastasi, N. R.; Stahl, S. S., *J. Am. Chem. Soc.* **2003**, *125*, 12996. d) Yang, G.; Zhang, W., *Org. Lett.* **2012**, *14*, 268. e) Goossen, L. J.; Paetzold, J.; Koley, D., *Chem. Commun.* **2003**, 706. f) Panne, P.; Fox, J. M., *J. Am. Chem. Soc.* **2007**, *129*, 22. g) Campeau, L.-C.; Schipper, D. J.; Fagnou, K., *J. Am. Chem. Soc.* **2008**, *130*, 3266. h) Seo, H.; Roberts, B. P.; Abboud, K. A.; Merz, K. M.; Hong, S., *Org. Lett.* **2010**, *12*, 4860. i) Baskar, B.; Bae, H. J.; An, S. E.; Cheong, J. Y.; Rhee, Y. H.; Duschek, A.; Kirsch, S. F., *Org. Lett.* **2008**, 10, 2605.
[135] Ueda, K.; Yanagisawa, S.; Yamaguchi, J.; Itami, K., *Angew. Chem. Int. Ed.* **2010**, *49*, 8946.
[136] Tang, S.-Y.; Guo, Q.-X.; Fu, Y., *Chem. Eur. J.* **2011**, *17*, 13866.

using Cu- or Pd-catalyzed C-H bond-functionalization reactions of indole derivatives to achieve either C2- or C3 selectivity.[137]

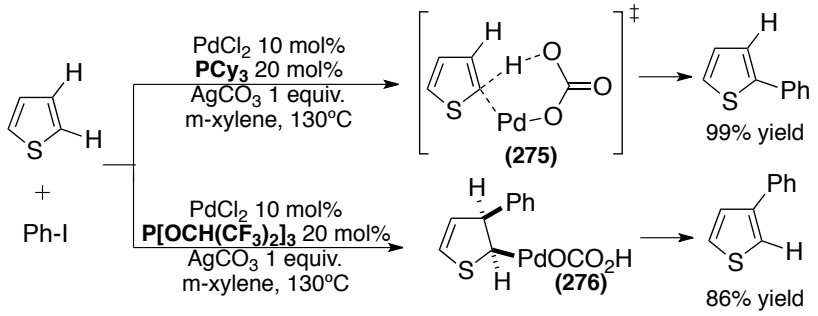


Figure 2.63

Buchwald et. al. nicely exemplified ligand-controlled selectivity toward the formation of different products starting from diarylamines substrates **(277)** .[138] Mechanistically aspects denoted different intermediates for each product. Formation of acridine derivatives **(278)** was achieved *via* an intramolecular Heck-type reaction when employing $P(^tBu)_3$ as ligand (figure 2.64-right). Notably, a switch in the reactivity was observed when using DavePhos, resulting in the formation of a 5*H*-dibenzazepine **(279)** via reductive elimination of an initially generated eight-membered palladacycle (Figure 2.64-left). The selective pathway toward carbazole compounds occured via intramolecular C-H functionalization to give a six-membered palladacycle, thus yielding 1-vinylcarbazoles **(280)** after reductive elimination, Figure 2.64-bottom).

[137] a) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S., *J. Am. Chem. Soc.* **2006**, *128*, 4972. b) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J., *J. Am. Chem. Soc.* **2008**, *130*, 8172.
[138] a) Tsvelikhovsky, D.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 14048. b) Tsvelikhovsky, D.; Buchwald, S. L. *J. Am. Chem. Soc.* **2011**, *133*, 14228.

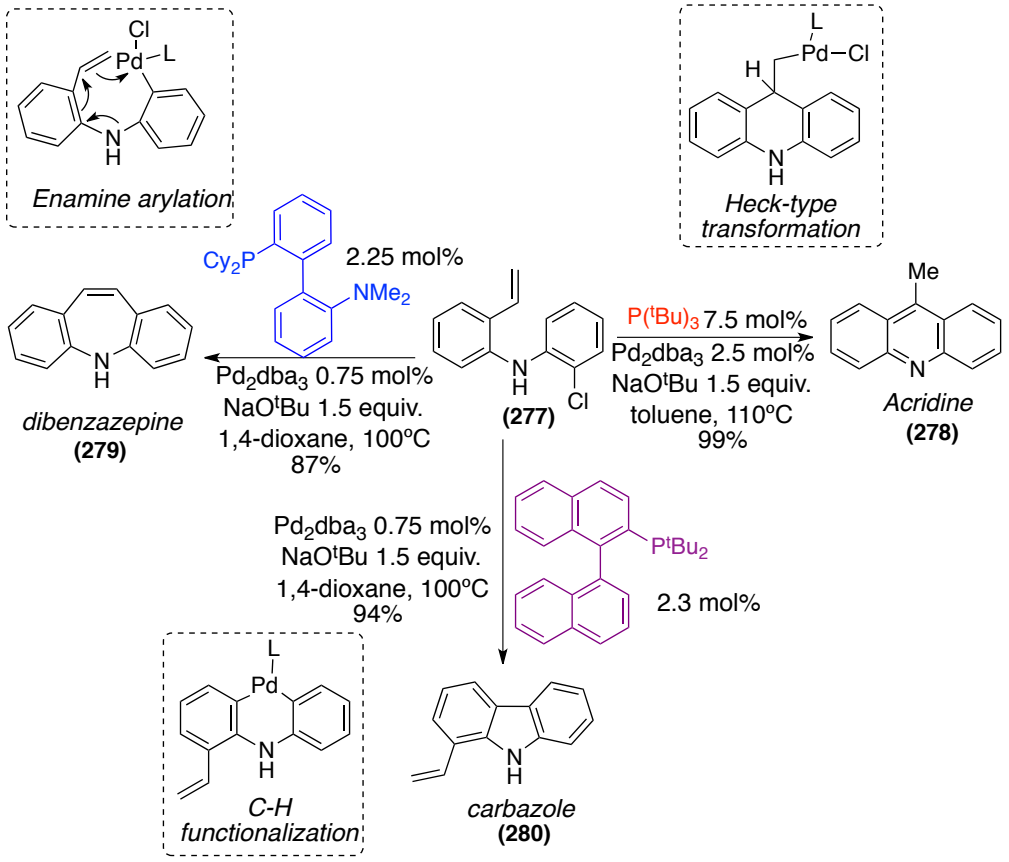


Figure 2.64

(2) ***Class B***. In this case, a substrate **A** undergoes reaction with either catalyst B or catalyst C to give a common intermediate **[A-cat]**, which undergoes successive reactivity by two different pathways. Depending on the properties of the ligand or the catalyst, selectively toward **D** or **E** can be achieved, Figure 2.65.[139]

[139] For selected examples see: a) Daugulis, O.; Zaitsev, V. G., *Angew. Chem. Int. Ed.* **2005**, *44*, 4046; Phipps, R. J.; Gaunt, M. J., *Science* **2009**, *323*, 1593. b) Chen, X.-Y.; Lin, R.-C.; Ye, S., *Chem. Commun.* **2012**, *48*, 1317. c) Xu, S.; Chen, R.; Qin, Z.; Wu, G.; He, Z.; *Org. Lett.* **2012**, *14*, 996. d) Doyle, M. P.; Yan, M.; Hu, W.; Gronenberg, L. S., *J. Am. Chem. Soc.* **2003**, *125*, 4692. e) Dai, J -J.; Liu, J.-H.; Luo, D.-F.; Liu, L., *Chem. Commun.* **2011**, *47*, 677. f) Daugulis, O.; Zaitsev, V. G., *Angew. Chem. Int. Ed.* **2005**, *44*, 4046; R. J. Phipps, M. J. Gaunt, *Science* **2009**, *323*, 1593.

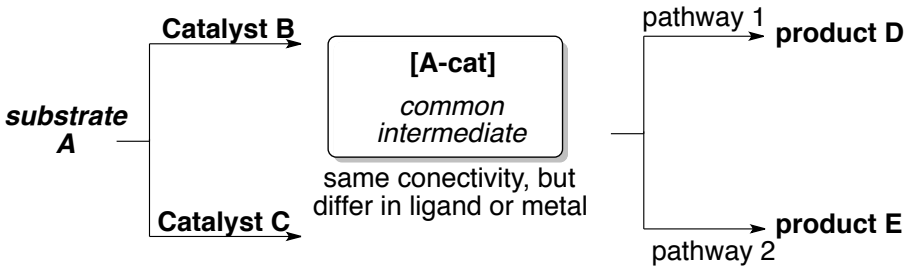


Figure 2.65

Hayashi observed ***Class B*** selectivity in Rh-catalyzed regioselective conjugate additions to 1-benzyl-1*H*-pyrrole-2,5-diones, where the phosphine ligand (in blue) gave predominantly attack on the more hindered site, while diene ligands (in red) added the nucleophile to the less hindered carbon, Figure 2.66. Both reactions proceeded through a common intermediate **(281)**, differing only on the ligand of the Rh complex.[140]

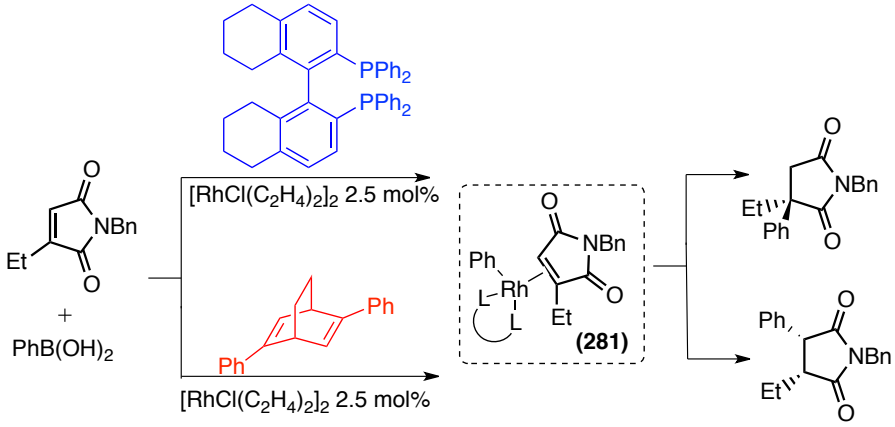


Figure 2.66

In 2006, Rovis reported an elegant Rh(I)-catalyzed formal [2+2+2] cycloaddition reaction between isocyanate compound and terminal alkynes. When TADDOL-derived phosphoramidite was used as ligand (in red, Figure 2.67), lactam **(282)** was obtained preferentially over the isomer **(283)** in 5:1 ratio and

[140] Shintani, R.; Duan, W.-L.; Hayashi, T., *J. Am. Chem. Soc*. **2006**, 128, 5628.

78% yield.[141] On the other hand, ligand-controlled decarbonylation-insertion was observed when using BINOL-derived phosphoramidite ligand (in blue, Figure 2.67), thus yielding vinylogous amide B in 75% yield with 1:6.2 ratio.[142] A similar case was observed by Montgomery in which the nature of the N-heterocyclic backbone dictates the selectivity in Ni-catalyzed reductive coupling reactions.[143]

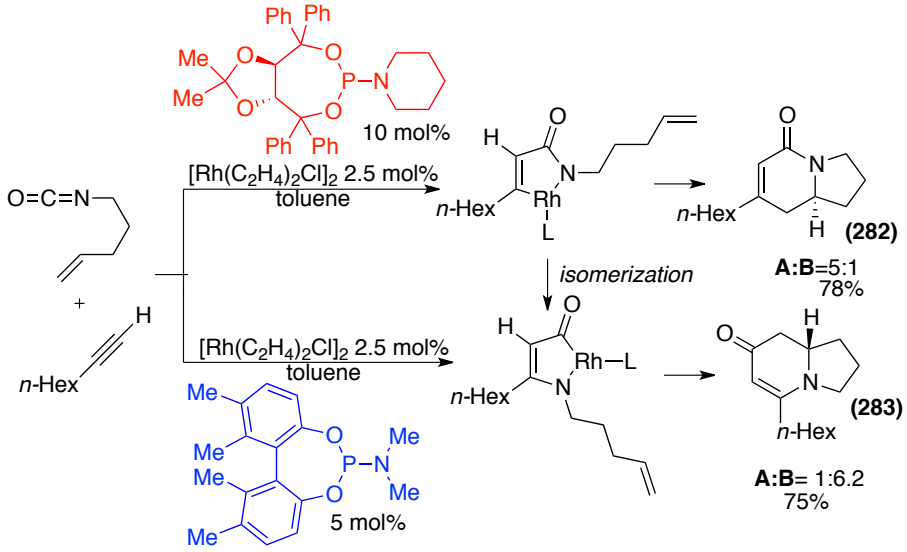


Figure 2.67

A similar, but equally impressive ligand-controlled selectivity has been disclosed by Breit et. al.[144] Intermolecular hydro-oxycarbonylation of terminal alkynes with carboxylic acids to furnish the corresponding *Z-anti*-Markovnikov enol esters **(285)** was achieved using diphenyl(2-pyridyl)phosphine (DPP) (Figure 2.68-top). On the other hand, formation of branched allylic esters **(286)** was accomplished employing by using DPEphos as ligand (Figure 2.68-bottom).

[141] Yu, R. T.; Rovis, T., *J. Am. Chem. Soc.* **2006**, *128*, 12370
[142] Yu, R. T.; Lee, E. E.; Malik, G.; Rovis, T. *Angew. Chem. Int. Ed.* 2009, *48*, 2379.
[143] a) Malik, H. A.; Sormunen, G. J.; Montgomery, J., *J. Am. Chem. Soc.* **2010**, *132*, 6304. b) Liu, P.; Montgomery, J.; Houk, K. N., *J. Am. Chem. Soc.* **2011**, *133*, 6956. c) Shareef, A.-R.; Sherman, D. H.; Montgomery, J., *Chem. Sci.* **2012**, *3*, 892.
[144] a) Lumbroso, A.;. Vautravers, N. R.; Breit, B., *Org. Lett*. **2010**, *12*, 5498. b) Lumbroso, A.; Koschker, P.; Vautravers, N. R.; Breit, B., *J. Am. Chem. Soc*. **2011**, *133*, 2386.

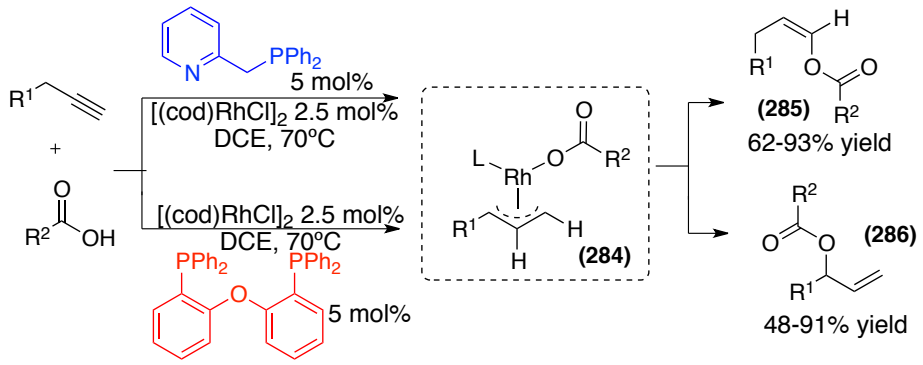


Figure 2.68

A conceptually related transformation is the arylation of ester compounds, where the formation of either α- or β-arylated product is controlled by the ligand. Hartwig and co-workers described the catalytic generation of palladium enolate complexes **(287)** from the ester derivatives, which undergoes reductive elimination to give the α-arylated product **(288)** using $P(^tBu)_3$ as ligand (Figure 2.69-top).[145] In a similar manifold, Baudoin reported the synthesis of the β-arylation product **(290)** using DavePhos as ligand (Figure 2.69, bottom).[146] Computational studies suggested that the rate-determining step was the Pd-enolate/homoenolate isomerization sequence, thus β-arylation was kinetically favored for DavePhos.[147]

[145] a) Lee, S.; Beare, N. A.; Hartwig, J. F., *J. Am. Chem. Soc*. **2001**, *123*, 8410. b) Jørgensen, M.; Lee, S.; Liu, X.; Wolkow-ski, J. P.; Hartwig, J. F., *J. Am. Chem. Soc*. **2002**, *124*, 12557.
[146] Renaudat, A.; Jean-Gerard, L.; Jazzar, R.; Kefalidis, C. E.; Clot, E., Baudoin, O. *Angew. Chem. Int. Ed.* **2010**, *49*, 7261.
[147] Larini, P.; Kefalidis, C. E.; Jazzar, R.; Renaudat, A.; Clot, E.; Baudoin, O., *Chem. Eur. J.* **2012**, *18*, 1932.

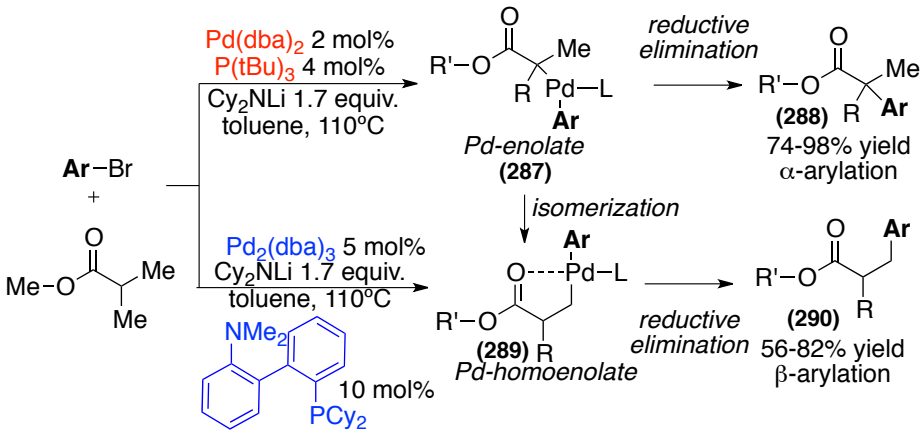


Figure 2.69

Particularly intriguing are both classes of selectivities for the generation of multiple compounds from common building blocks using ligand-modulated metal-catalyzed strategies for achieving high levels of reactivity, efficiency, practicality and reliability. In this regard, we were interested in the study of the ligand effect in our developed methodology for the synthesis of benzocyclobutenones. In this manner, we could improve our knowledge on catalyst design and we would gain a better understanding of the mechanism by which these reactions operate.

We previously demonstrated that bidentate ligands based upon a binaphthyl backbone provided exquisite selectivity en route to benzocyclobutenone derivatives. However, during the screening reaction we also observed that subtle changes on the ancillary ligand lead to a dramatic mechanistic switch in the reactivity allowing the formation of non-neglictable amounts of styrene **(152)** (Figure 2.70).

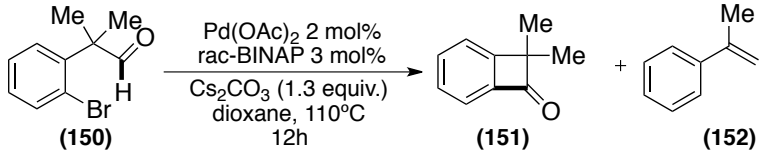


Figure 2.70

According to the above-mentioned classification of selective reactions, we hypothesized that the formation of the styrene **(291)** and benzocyclobutenone **(148)** is part of a ***Class B*** reactions in which a common intermediate should be present in both mechanistic scenarios (Figure 2.71). We tentatively propose that such common intermediate would be the Pd-five membered metalacycle **III** that is formed after C-H bond-functionalization *via* a concerted-metalation deprotonation pathway (**CMD**).

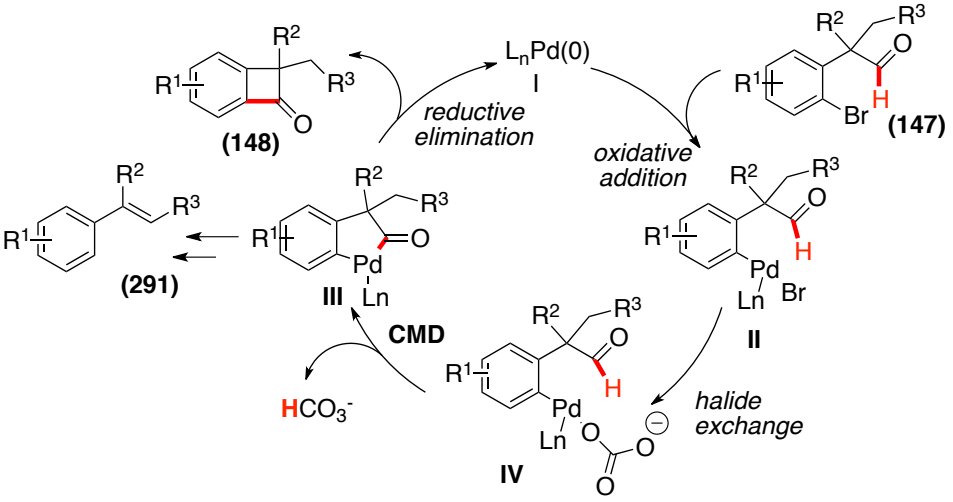


Figure 2.71

In order to go further in the study of the mechanistic switch by modulating the properties of the catalytic species, we decided to explore whether it might be possible to obtain in a selective way the formation of α,β-substituted styrene derivatives **(291)** from aldehydes **(147)** (Figure 2.72- left).[148]

[148] Flores-Gaspar, A.; R. Martin, *Adv. Synth. Catal.*, **2011**, *353*, 1223.

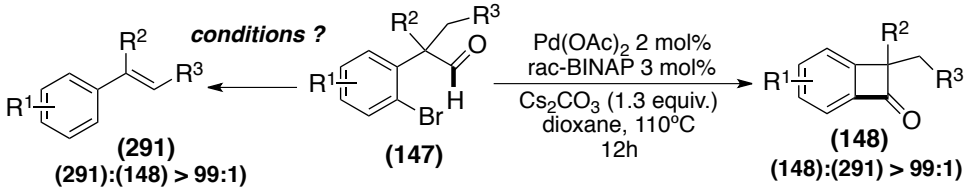


Figure 2.72

2.6.4.1 Screening of the reaction conditions for synthesis of α,β-substituted styrenes.

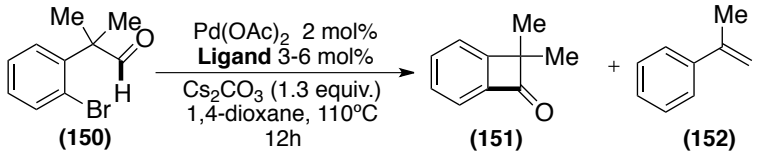
As shown in our initial screening (Table 2), we noticed that both electronic or steric effects on the phosphine binaphthyl backbone do not play a critical role for the selective formation of **(151)**. As a result, we hypothesized that the selectivity was primarily attributed to the binaphthyl motif. In order to evaluate such assumption, we decided to evaluate whether a more flexible bisphosphine would have a similar selectivity behaviour, Table 10.

Our first choice was to study the reactivity of dppb **(172)** and dcypb **(292)** as these ligands have the same carbon spacer between the phosphine units and the similar substituents as for *rac*-BINAP **(173)** and Cy-BINAP **(176)**. Strikingly, we observed a totally different chemical behavior for **(172)** and **(292)** as compared as *rac*-BINAP **(173)** and Cy-BINAP **(176)**. While *rac*-BINAP **(173)** cleanly afforded exclusive benzocyclobutenone **(151)**, **(172)** afforded mixtures of both **(151)** and **(152)**. Even more interesting is the comparison of Cy-BINAP **(176)** and **(292)**, the former giving access to styrene **(152)** exclusively and the later affording exclusively **(152)** with no **(151)** being detected by NMR spectroscopy of the crude reaction mixture. These suggested that subtle differences on the ligand backbone might lead to a dramatic switch on selectivity.[149] Additionally,

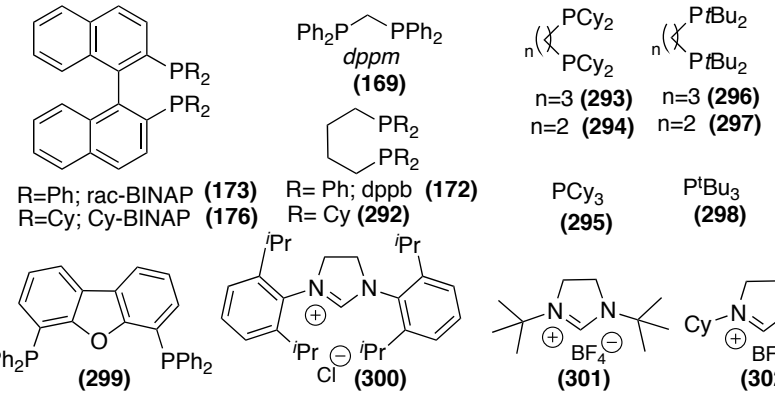
[149] For a recent mechanistic switch in a C-H bond activation protocol, see: Engle, K. M.; Wang, D. –H.; Yu, J. Q., *J. Am. Chem. Soc.* **2010**, *132*, 14137.

such results showed an unique opportunity to turn the flexibility exerted by these ligands into a strategic advantage.

Table 10. Screening of Ligands. [a]



Entry	**Ligand**[a]	Conv. (%)[b]	**(151)** (%)[b]	**(152)** (%)[b]
1	**(172)**	100	20	40
2	**(173)**	100	84	0
3	**(176)**	100	85	0
4	**(292)**	100	0	71
5	**(293)**	100	0	77
6	**(294)**	100	0	73
7	**(295)**	70	0	65
8	**(296)**	45	0	40
9	**(297)**	30	0	28
10	**(298)**	50	0	43
11	**(299)**	42	20	18
12	**(300)**	0	0	0
13	**(301)**	0	0	0
14	**(302)**	0	0	0
15	**(169)**[c]	20	0	19



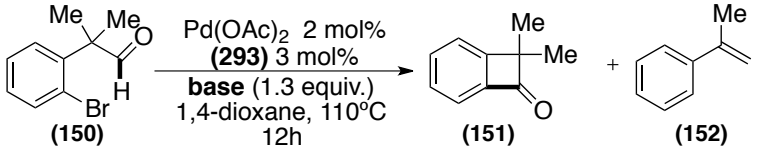
[a] Aryl bromide (0.25 mmol), $Pd(OAc)_2$ (2 mol%), Ligand (3-6 mol%), Cs_2CO_3 (1.30 equiv.), dioxane (0.50 M) at 110 ºC. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard. [c] Larock conditions: Aryl bromide (0.25 mmol), $Pd(OAc)_2$ (5 mol%), dppm **(169)** (5 mol%), Cs(piv) (2.0 equiv.), DMF, 110ºC, 24h.

A more systematic study demonstrated that a 3-carbon spacer provided the best results, with ligand **(293)** affording the highest yield of **(152)**. In light of these results, one might argue whether the selectivity toward either **(150)** or **(152)** could be attributed to the bite angle of ligand **(293)** as compared to *rac*-BINAP **(173)** or Cy-BINAP **(176)**. However, the calculated bite angle for ligand **(293)** is 95º, a value that is pretty much the same as for ligand **(173)** (94º), thus reinforcing the notion that another explanation must be needed for the observed selectivity.[125] Although in lower yields, the ability of PCy_3 **(295)** or P^tBu_3 **(298)** to selectively furnish **(152)** clearly supports the idea that **(295)** might act as a monodentate or hemilabile ligand in our reaction protocol. Remarkably, NHC's ligands **(300)-(302)** gave no conversion to either BCB **(151)** or styrene **(152).** In order to put these results into perspective, we performed a control experiment with the conditions previously described by Larock (entry 15);[123] only 19% yield was formed in this case, thus indicating the superior activity of the catalyst system based upon ligand **(293)**.

As for the synthesis of BCB, the better solubility of Cs_2CO_3 in aprotic solvents resulted in higher yields of **(152)** when comparing with other related inorganic bases (Table 11). Remarkably, K_3PO_4 (entry 2) gave similar conversion and selectivity toward **(152)**, thus indicating that polyatomic anions different to CO_3^{2-} are compatible in our system as well.

We also screened the ability of other solvents to promote the formation of styrene derivative **(152)**. As shown in in Table 12, we found that the selectivity was totally maintained when aprotic solvents were utilized. The employment of **(293)** in toluene provided the best results (entry 2), giving rise to **(152)** in a 89% yield.

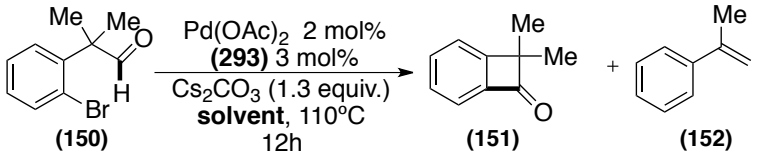
Table 11. Screening of bases. [a]



Entry	**Base**	Conv. (%)[b]	**(151)** (%)[b]	**(152)** (%)[b]
1	Cs_2CO_3	100	0	77
2	K_3PO_4	95	0	72
3	K_2CO_3	95	0	6
4	KF	54	0	8
5	$CaCO_3$	32	0	0

[a] Aryl bromide (0.25 mmol), $Pd(OAc)_2$ (2 mol%), **(293)** (3 mol%), Base (1.30 equiv.), dioxane (0.50 M) at 110 ºC. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.

Table 12. Screening of solvents. [a]

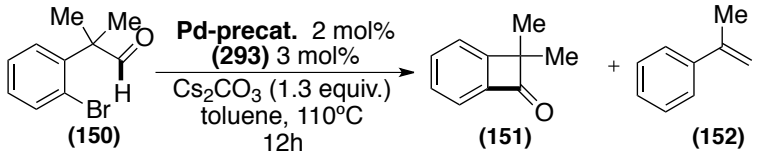


Entry	**Solvent**[a]	Conv. (%)[b]	**(151)** (%)[b]	**(152)** (%)[b]
1	dioxane	100	0	77
2	toluene	100	0	89
3	DMF	59	0	54
4	Cyclopentyl methyl ether	72	0	70
5	methyl cyclohexane	89	0	68
6	THF	61	0	56

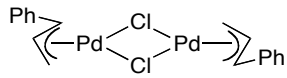
[a] Aryl bromide (0.25 mmol), $Pd(OAc)_2$ (2 mol%), **(293)** (3 mol%), Cs_2CO_3 (1.30 equiv.), solvent (0.50 M) at 110 ºC. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.

We evaluated other palladium precatalysts in our catalytic system (Table 13). Notably, all precatalysts gave total selectivity toward **(152)**, thus indicating that the ligand backbone was the only responsible factor for the observed switch in selectivity.

Table 13. Screening of Palladium pre-catalysts. [a]



Entry	**Pd-Precatalyst**[a]	t (h)	Conv. (%)[b]	**(151)** (%)[b]	**(152)** (%)[b]
1	$PdCl_2$	12 h	65	0	59
2	$PdCl_2(MeCN)_2$	12 h	41	0	32
3	**(182)**	12 h	38	0	30
4	$Pd(dba)_2$	12 h	82	0	76
5	$Pd_2(dba)_3$	12 h	32	0	30
6	$Pd(OAc)_2$	12h	100	0	89
7	$Pd(OAc)_2$	6 h	79	0	70
8	$Pd(OAc)_2$	4 h	68	0	60
9	$Pd(OAc)_2$	2 h	63	0	57
10	$Pd(OAc)_2$ (1 mol%)	24 h	80	0	72
11	$Pd(OAc)_2$ (0.5 mol%)	24 h	54	0	47
12	$Pd(OAc)_2$ 60ºC	12 h	18	0	12
13	$Pd(OAc)_2$ 80ºC	12 h	62	0	54



(182)

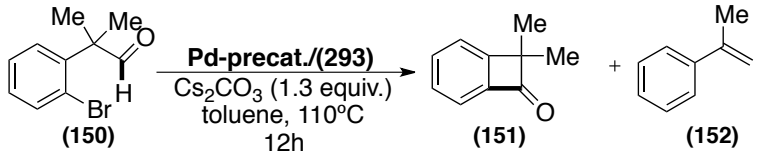
[a] Aryl bromide (0.25 mmol), Pd-precatalyst (2 mol%), **(293)** (3 mol%), Cs_2CO_3 (1.30 equiv.), toluene (0.50 M) at 110 ºC. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.

The highest selectivity was achieved when utilizing $Pd(OAc)_2$ (entry 1). As shown Table 13, the lowest yield was observed using Pd_2dba_3, an issue that is not truly surprising giving the strong chelating effect of dba that competes with ligand binding at the metal center. Indeed, conversions were significatively higher when using $Pd(dba)_2$ (entry 4) as compared to $Pd_2(dba)_3$ (entry 5). Other Pd(II) precatalysts such as $PdCl_2(MeCN)_2$ and $[Pd(cinnamyl)Cl]_2$ gave lower conversion and yield of **(152)** (entries 2 and 3). $PdCl_2$ could also be utilized, allowing the formation of **(152)** in moderated yield (entry 1). Gratifyingly, the formation of **(152)** could also be accomplished at only 0.5-1 mol% catalyst loading; however

longest reaction times were needed (entries 10 and 11). Lower temperatures affected considerably the catalyst activity and low or moderated yields of **(152)** were obtained when operating at either 60 ºC (entry 12) or 80ºC (entry 13).

In order to evaluate the ligand ratio dependency, we set up a series of experiments varying the Pd/L ratio (Table 14). While Pd/L= 1:1.5 gave the best results (entry 2), the use of a slightly higher Pd/L ratio (1:2) shutted down the reactivity. We hypothesized that using double amount of **(293),** we formed significant amounts of the 18 electron species PdL_2, thus slowing down the reactivity that is initiated via monoligated PdL species.[150]

Table 14. Screening of Pd/Ligand ratio. [a]



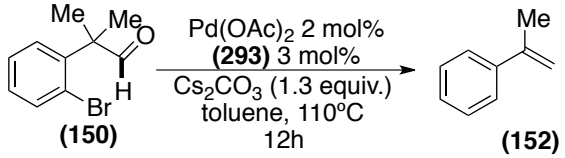
Entry	Ratio Pd:Ligand **(293)**[a]	Conv. (%)[b]	**(151)** (%)[b]	**(152)** (%)[b]
1	1:1	90	0	82
2	1:1.5	100	0	89
3	1:2	65	0	55

[a] Aryl bromide (0.25 mmol), $Pd(OAc)_2$ (2 mol%), **(293)** (2-4 mol%), Cs_2CO_3 (1.30 equiv.), toluene (0.50 M). [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.

As shown in Table 15, blank experiments indicated that all variables utilized (Pd precatalyst, ligand, base and solvent) were critical for obtaining the product (**152)** in good yields.

[150] Chirstmann, U.; Vilar, R., *Angew. Chem. Int. Ed.,* **2005**, *44*, 366.

Table 15. Blank experiments. [a]



Entry	Conditions[a]			Conv.	**(151)**	**(152)**
	$Pd(OAc)_2$	**(293)**	Cs_2CO_3	(%)[b]	(%)[b]	(%)[b]
1	✓	✓	✓	100	0	89
2	✓	✓	✗	0	0	0
3	✗	✓	✓	0	0	0
4	✓	✗	✓	0	0	0
5	✓	✗	✗	0	0	0
6	✗	✓	✗	0	0	0
7	✗	✗	✓	0	0	0
8	✗	✗	✗	0	0	0

[a] Aryl bromide (0.25 mmol), $Pd(OAc)_2$ (2 mol%), **L27** (3mol%), Cs_2CO_3 (1.30 equiv.), toluene (0.50 M). [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.

2.6.4.2 Synthesis of starting aryl bromide aldehydes.

In order to evaluate whether the formation of styrenes was general, we set out to explore the preparative scope of this reaction. Since the starting materials were the same as for the previous preparation of benzocyclobutenones, we took advantage of our synthetic route to a-aryl aldehydes to prepare other derivatives that could be coupled as well. Apart from the substrates shown in Figures 2.39-2.49, we also prepared the a-aryl aldehydes **(303)-(306)** (Figure 2.73) following an otherwise identical route as the one depicted in Figure 2.50.[151]

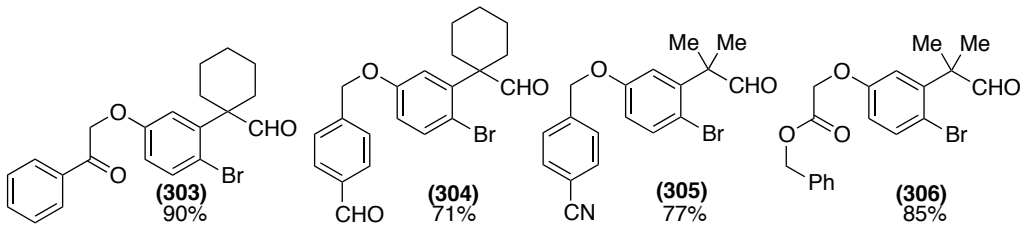


Figure 2.73

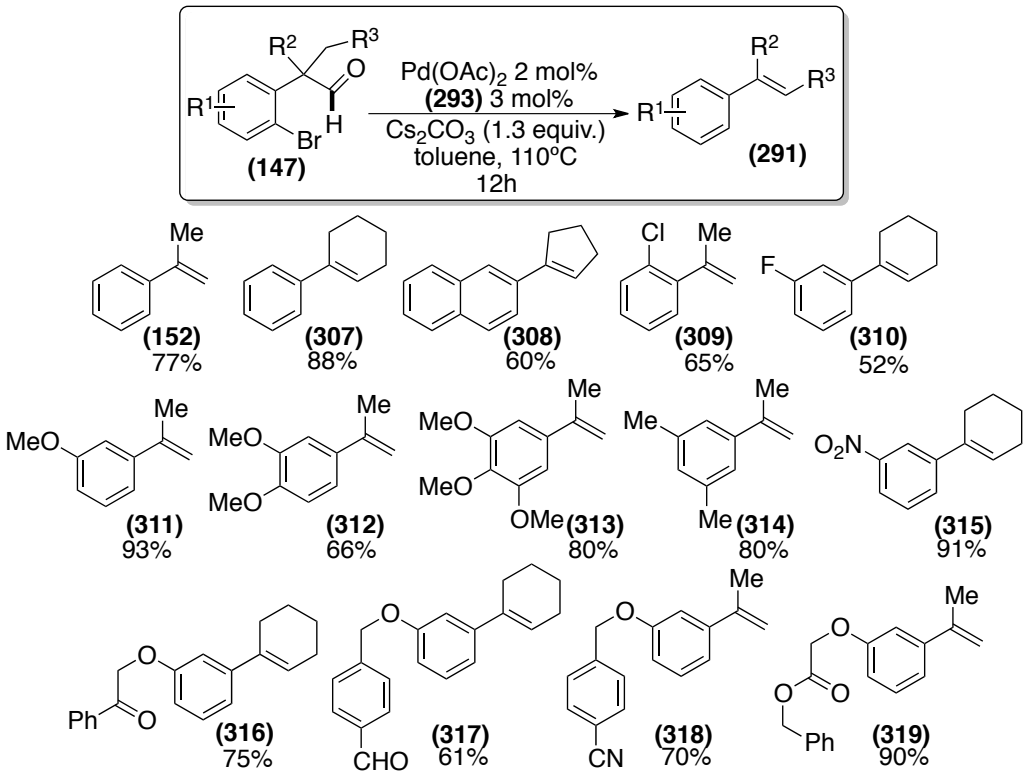
2.6.4.3 Scope of the reaction for synthesis of substituted styrenes.

As become apparent from the results compiled in Table 16, a host of aryl bromides with different substitution patterns reacted with good to excellent yields. The preparation of **(307)** and **(308)** in 88% and 60% yield indicated that cyclic and fused rings are compatible with this reaction. The productive formation of **(311)** and **(315)** in high yields (93% and 91%, respectively) indicates that the electronic factors do not play a prominent role in our reaction conditions. Furthermore, the presence of *ortho*-substituents did not hinder the reaction, as **(313)** and **(314)** could be efficiently prepared in 80% yield, respectively. Notably,

[151] The reported yields correspond for last two steps of the reaction (nitrile reduction followed by O-alkylation reaction).

the method showed a strong preference for the coupling of aryl bromides as aryl chlorides **(309)** and aryl fluorides **(310)** remained inert. Particularly noteworthy is the functional group tolerance profile of our method as substrates containing nitro groups **(315)**, ketones **(316)**, aldehydes **(317)**, nitriles **(318)**, and esters **(319)** were perfectly accommodated.

Table 16 Synthesis of α,β-substituted styrenes. [a]



[a] Aryl bromide (0.50 mmol), $Pd(OAc)_2$ (2 mol%), **(293)** (3mol%), Cs_2CO_3 (1.30 equiv.), toluene (2 mL) at 110ºC. Isolated yields, average of two runs

Interestingly, our protocol was also amenable for the synthesis of silyl enol ethers (Figure 2.74). Thus, we found that the coupling of α-aryl aldehyde **(320)** cleanly produced a silyl enol ether **(321)**. However, its high volatility heavily compromised the yield for such compound. Not surprisingly, the bulkier TBS-protected α-aryl aldehyde **(213)** gave also total conversion to products; in this case, however, we could isolate **(322)** in good yields.

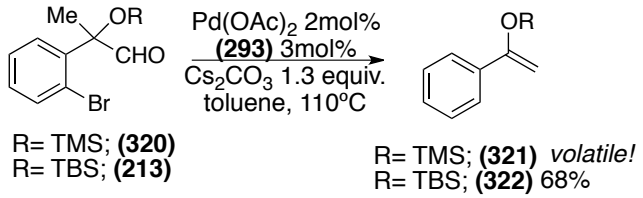
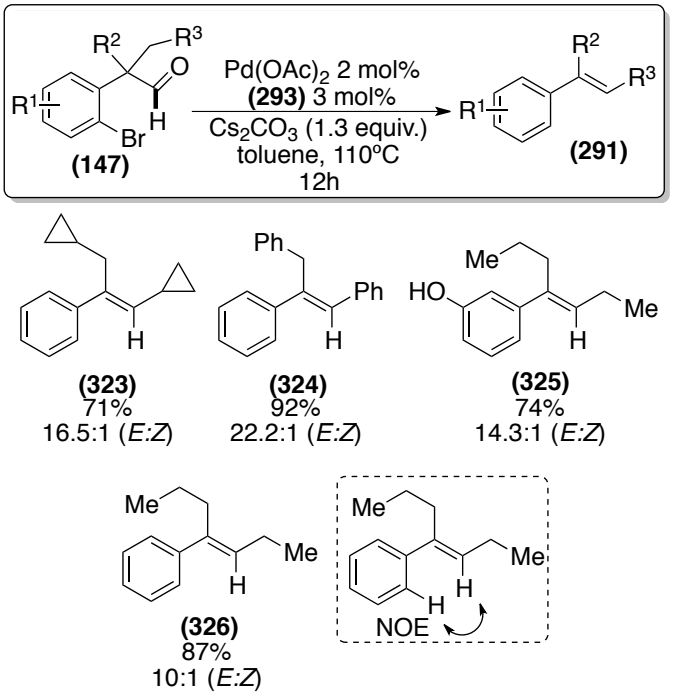


Figure 2.74

The preparation of configurationally-pure trisubstituted olefins in a regio- and diastereoselective manner, particularly with substituents possessing similar electronic or steric environments is still considered a great synthetic challenge.[152] Indeed, classical Wittig-type olefinations[153] or alkyne hydroarylation[154] are still ineffective in terms of regio- and diastereoselectivity. Similarly, the use of metal-catalyzed cross-coupling reactions is still problematic when preparing geometrically-defined alkenyl metal (halide) species having similar substituents over the alkene backbone.[152,155] As shown in Table 17, our catalytic reaction based upon ligand **(293)** allows for the preparation of trisubstituted olefins in high yields, even in the presence of free hydroxyl groups like in **(325)** that could potentially be problematic due to the nucleophilic attach of the alkoxide ion to the palladium(II) intermediates. NOE experiments revealed total regiocontrol and diastereoselectivities. For example, **(324)** was formed in 22.2:1 E:Z ratio and similar ratios were obtained for other substrates as well.

[152] Negishi, E. –I.; Huang, Z.; Wang, G.; Mohan, S.; Wang, C.; Hattori, H., *Acc. Chem. Res.* **2008**, *41*, 1474.
[153] a) *In Modern Carbonyl Olefination* (Eds.; T. Takeda), Wiley-VCH, Weinheim **2004**; b) B. E. Maryanoff, A. B. Reitz, *Chem. Rev.* **1989**, *89*, 863.
[154] a) Nevado, C.; Echavarren, A. M., *Synthesis* **2005**, 167; b) Ritleng, V.; Sirlin, C.; Pfeffer, M., *Chem. Rev.* **2002**, *102*, 1731.
[155] For alternative approaches using Heck-type processes: Beletskaya, I. P.; Cheprakov, A. V., *Chem. Rev.* **2000**, *100*, 3009.

Table 17 Synthesis of trisubstituted olefins. [a]



[a] Aryl bromide (0.50 mmol), $Pd(OAc)_2$ (2 mol%), **(293)** (3mol%), Cs_2CO_3 (1.30 equiv.), toluene (2 mL) at 110ºC. Isolated yields, average of two runs

2.7

Conclusions

❖ We have developed a new protocol for the intramolecular acylation of aryl bromides via C-H bond functionalization. The practicality of the method, as well as the vast array of functionalized substrates with a diverse substitution patterns that can be accessed renders this method a powerful alternative to other approaches for the synthesis of benzocyclobutenones (Figure 2.75).

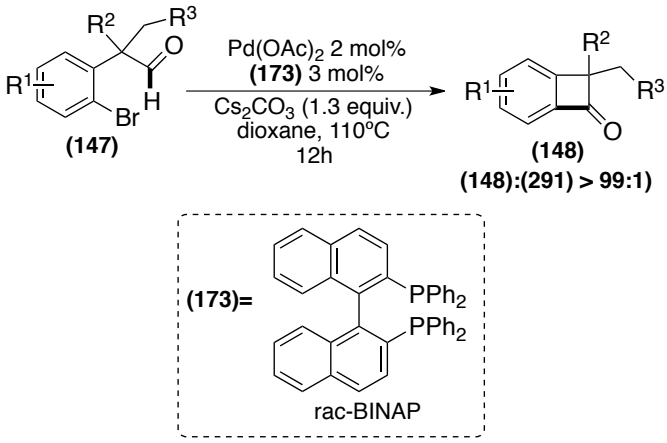


Figure 2.75

❖ We also developed a methodology for the large-scale synthesis of BCB and we demonstrated their applicability in the further transformation of advanced intermediates.

❖ We have found that a subtle modification on the phosphine ligand backbone leads to a new mechanistic manifold for the preparation of configurationally-pure α,β-substituted styrenes via C-H bond-functionalization. This procedure is distinguished by its excellent functional group tolerance and wide scope with total control of the regioselectivity and good diastereoselectivities as well (Figure 2.76).

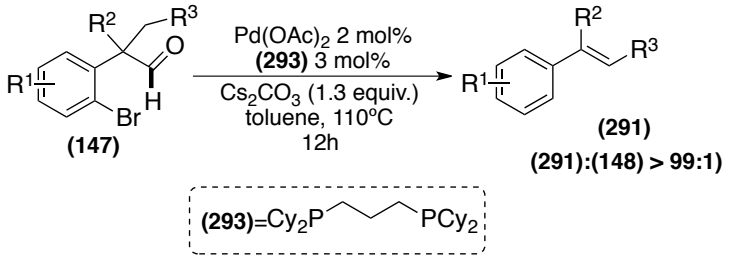


Figure 2.76

2.8

Experimental section

2.8.1 General Considerations

Reagents. All reactions were set up in the air (with no use of a glovebox) and carried out under an argon atmosphere in resealable screw-cap test tubes. $Pd(OAc)_2$ was a gift from Johnson Matthey. *rac*-BINAP **(173)** was purchased from Atomax Chemicals Co. LTD. *Rac*-^{i}*Pr*-BINAP **(176)** was prepared by a known literature procedure.[126] Powdered Cs_2CO_3 was purchased from Alfa Aesar. The bulk of Cs_2CO_3 was stored under nitrogen in a vacuum atmospheres glovebox. Small portions (~ 5 g) were removed from the glovebox in glass vials, stored in the air in a desiccator filled with anhydrous calcium sulfate, and weighed in the air. Anhydrous dioxane was purchased from Aldrich in Sure/Seal™ bottles. The a-aryl aldehydes used in this work were purified by column chromatography. All other reagents were purchased from commercial sources and used as received. Flash chromatography was performed with EM Science silica gel 60 (230-400 mesh).

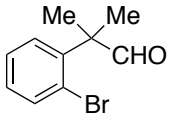
Analytical methods. ^{1}H NMR and ^{13}C NMR spectra and melting points (where applicable) are included for all compounds. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz at 20 ^{o}C. All ^{1}H NMR spectra are reported in parts per million (ppm) downfield of TMS and were measured relative to the signals for $CHCl_3$ (7.27 ppm). All ^{13}C NMR spectra were reported in ppm relative to residual $CHCl_3$ (77 ppm) and were obtained with ^{1}H decoupling. Coupling constants, *J*, are reported in hertz. Melting points were measured using open glass capillaries in a Büchi B540 apparatus. Infrared spectra were recorded on a Bruker Tensor 27. Elemental analyses were performed by the Unidade de Análise Elemental at the

Universidad de Santiago de Compostela (Spain). Kinetic experiments were performed using a React-IR 2000 instrument from Mettler-Toledo with a Diamond probe. Mass spectra were recorded on a Waters LCT Premier spectrometer. Gas chromatographic analyses were performed on Hewlett-Packard 6890 gas chromatography instrument with a FID detector using 25m x 0.20 mm capillary column with cross-linked methyl siloxane as the stationary phase.

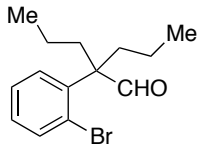
2.8.2 Synthesis of the starting materials

General procedure A for the preparation of α-aryl aldehydes from 2-bromophenylacetonitrile (Figure 2.41). A flask equipped with a magnetic stirring bar and a septum inlet was flushed with nitrogen. The flask was charged under nitrogen atmosphere with 2-bromophenylacetonitrile (1.0 equiv.) and dry THF (4 mL/1.0 mmol). Then, NaHMDS (2.2 equiv., 1M in THF) was added dropwise, and the solution was stirred for 20 min at rt. At this time, alkyl halide (2.20 equiv.) was introduced gradually by syringe. After stirring for 2 h at room temperature, 2 mL of aqueous saturated NH_4Cl solution were added and the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate, and finally concentrated under vacuum. The crude nitrile thus obtained was used directly in the next step without further purification.

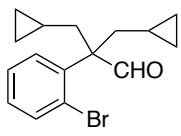
To a well-stirred solution of the above crude nitrile in dichloromethane (4 mL/1.0 mmol) under nitrogen atmosphere was added DIBALH (1.20 equiv., 1M in hexanes) and stirred for 2 h at -78 ºC. The reaction was then quenched after 2 hours of further stirring by slow addition of 2M HCl and ethyl acetate. The organic phase was washed twice with brine, dried over magnesium sulfate and concentrated. The crude was then purified by column chromatography on silica gel (hexanes/ethyl acetate) to give the corresponding α-aryl aldehyde.



2-(2-Bromophenyl)-2-methylpropanal (150). Following general procedure A, using 2-bromophenylacetonitrile (3.0 g, 15.40 mmol), NaHMDS (34.0 mL, 34.0 mmol, 1M in THF), methyl iodide (2.12 mL, 34.0 mmol) and DIBALH (18.50 mL, 18.50 mmol, 1M in hexanes). Column chromatography: silica gel, 18:1 hexanes/ethyl acetate. Colorless oil; yield: 2.85 g (82% overall yield). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 9.80 (s, 1H), 7.61 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.44-7.36 (m, 2H), 7.18 (ddd, *J* = 9.6, 7.2, 2.0 Hz, 1H), 1.52 (s, 3H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 203.1, 142.3, 134.4, 129.1, 128.6, 127.8, 123.4, 51.8, 23.2 ppm. IR (neat, cm^{-1}): 3059, 2974, 2933, 2872, 2802, 1721, 1656, 1465, 1424, 1389, 1360, 1157, 1043, 1020. Anal. Calcd for $C_{10}H_{11}BrO$: C, 52.89; H, 4.88. Found: C, 52.99; H, 4.82.

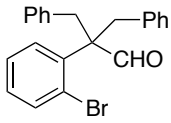


2-(2-Bromophenyl)-2-propylpropanal (185). Following general procedure A, using 2-bromophenylacetonitrile (1.95 g, 10.0 mmol), NaHMDS (24.0 mL, 24.0 mmol, 1M in THF), *n*-propyliodide (2.40 mL, 24.0 mmol) and DIBALH (12.0 mL, 12.0 mmol, 1M in hexanes). Column chromatography: silica gel, 18:1 hexanes/ethyl acetate. Colorless oil; yield: 1.97 g (70% overall yield). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 9.87 (s, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.37 (m, 2H), 7.18 (ddd, *J* = 8.4, 5.6, 2.8 Hz, 1H), 1.97 (m, 4H), 1.22 (m, 2H), 1.06 (m, 2H), 0.88 (t, *J* = 7.6 Hz, 3H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 204.3, 140.0, 134.8, 130.2, 128.9, 127.3, 123.7, 58.4, 35.0, 16.8, 14.6 ppm. IR (neat, cm^{-1}): 2957, 2871, 1719, 1561, 1465, 1431, 1377, 1322, 1268, 1199, 1152, 1113, 1024, 945. HRMS *calcd* for ($C_{14}H_{19}BrO$+Na): 305.0517, *found* 305.0511.

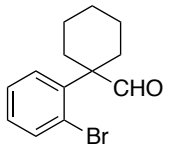


2-(2-Bromophenyl)-3-cyclopropyl-2-(cyclopropylmethyl) propanal (186). Following general procedure A, using 2-bromophenylacetonitrile (1.50 g, 7.70 mmol), NaHMDS (18.50 mL, 18.50 mmol, 1M in THF), (bromomethyl)cyclopropane (1.80 mL, 18.50 mmol) and DIBALH (9.50 mL, 9.50 mmol, 1M in hexanes). Column chromatography: silica gel, 20:1 hexanes/ethyl acetate. White solid; yield: 1.88 g (80% overall

yield). Mp = 60.3-61.5 ^{o}C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 10.1 (s, 1H), 7.61 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.53 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.39 (td, *J* = 8.0, 1.2 Hz, 1H), 7.19 (td, *J* = 8.0, 1.6 Hz, 1H), 2.32 (dd, *J* = 14.4, 5.6 Hz, 2H), 1.86 (dd, *J* = 14.4, 7.6 Hz, 2H), 0.56 (m, 2H), 0.44 (m, 2H), 0.29 (m, 2H), 0.04 (m, 2H), 0.11 (m, 2H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 205.4, 140.0, 134.6, 130.7, 128.9, 127.3, 123.8, 59.7, 39.1, 5.8, 5.5, 5.4 ppm. IR (neat, cm^{-1}): 3077, 3001, 2934, 2867, 1717, 1560, 1450, 1425, 1388, 1311, 1266, 1207, 1172, 1123, 1103, 981, 965, 894. HRMS *calcd* for ($C_{16}H_{19}BrO$+Na): 329.0517, *found* 329.0523.

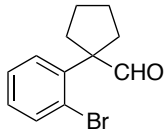


2-benzyl-2,3-diphenylpropanal (187). Following general procedure A using 2-bromophenylacetonitrile (3.0 g, 15.0 mmol) and dry THF (4 mL/1.0 mmol), NaHMDS (23.0 mL, 45.0 mmol, 2M in THF), (bromomethyl)benzene (3.90 mL, 33.0 mmol) and DIBALH (6.40 mL, 6.40 mmol, 1M in hexanes). Column chromatography: silica gel (95:5 hexanes/ethyl acetate). White solid; yield 3.5 g (70%). Mp = 94.5-95.7 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.03 (s, 1H), 7.67 (d, *J* = 9.3 Hz, 1H), 7.18 (ddd, *J* = 9.9, 5.7, 2.5 Hz, 8H), 7.12-7.09 (m, 1H), 6.95 (dd, *J* = 6.5, 2.9 Hz, 4H), 3.44 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.7, 135.8, 134.8, 131.8, 130.8, 129.3, 128.0, 127.0, 126.6, 59.6, 40.6. IR (neat, cm^{-1}): 3058, 3024, 2927, 2819, 2730, 1711, 1598, 1493, 1448, 1430, 1265, 1224, 1055, 1023, 758, 717, 696. HRMS *calcd* for [$C_{22}H_{19}BrO$+Na] 401.0517, *found* 401.0510.



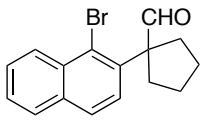
1-(2-Bromophenyl)-cyclohexanecarbaldehyde (188). Following general procedure A, using 2-bromophenylacetonitrile (3.0 g, 15.40 mmol), NaHMDS (34.0 mL, 34.0 mmol, 1M in THF), 1,5-dibromopentane (2.32 mL, 17.0 mmol) and DIBALH (18.50 mL, 18.50 mmol, 1M in hexanes). Column chromatography: silica gel, 18:1 hexanes/ethyl acetate. Colorless oil; yield: 3.11 g (76% overall yield). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 9.94 (s, 1H), 7.55 (dd, *J* = 7.2, 0.8 Hz, 1H), 7.49 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.35 (td, *J* = 7.2, 0.8 Hz, 1H), 7.15 (td, *J* = 8.0, 1.2 Hz, 1H), 2.31 (m, 2H), 1.98 (m, 2H), 1.66 (m, 5H),

1.43 (m, 1H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 204.2, 142.4, 134.8, 129.4, 128.8, 127.6, 123.3, 54.7, 31.6, 25.5, 22.4 ppm. IR (neat, cm^{-1}): 3059, 2929, 2855, 2040, 1703, 1585, 1465, 1450, 1352, 1273, 1194, 1162, 1095, 1008. HRMS *calcd* for ($C_{13}H_{15}BrO$+Na): 289.0204, *found* 289.0197.



1-(2-bromophenyl)cyclopentanecarbaldehyde (189).

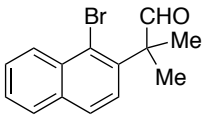
Following general procedure A, using 2-bromophenylacetonitrile (3.0 g, 15.40 mmol), NaHMDS (34.0 mL, 34.0 mmol, 1M in THF), 1,5-dibromobutane (17.0 mmol) and DIBALH (18.50 mL, 18.50 mmol, 1M in hexanes). Column chromatography: silica gel, 18:1 hexanes/ethyl acetate. Colorless oil; yield: 2.85 g (73% overall yield). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 9.72 (s, 1H), 7.52 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.31 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.19-7.16 (m, 2H), 2.21-1.97 (m, 4H), 1.56-1.46 (m, 4H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 201.8, 132.3, 149,6, 129,0,128.0, 127.3, 121.8, 58.0, 35.6, 25.1 ppm.



1-(1-bromo-2-naphthyl)cyclopentanecarbaldehyde (192).

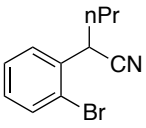
Following general procedure A, using 2-(1-bromonaphthalen-2-yl)acetonitrile [156] (5.50 g, 22.30 mmol) and dry THF (4 mL/1.0 mmol), NaHMDS (28.0 mL, 56.0 mmol, 2M in THF), 1,4-dibromobutane (2.90 mL, 24.50 mmol) and DIBALH (7.30 mL, 7.30 mmol, 1M in hexanes). Column chromatography: silica gel, 20:1 hexanes/ethyl acetate. Yellow oil; 3.4 g (50% overall yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.79 (s, 1H), 8.38 (d, *J* = 8.5 Hz, 1H), 7.86 (t, *J* = 8.0 Hz, 2H), 7.65-7.57 (m, 1H), 7.57-7.52 (m, 2H), 2.53 (dt, *J* = 13.8, 7.0 Hz, 2H), 2.29-2.18 (m, 2H), 1.93-1.72 (m, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 201.9, 14.0, 133.7, 133.1, 127.9, 127.9, 127.7, 127.6, 126.8, 125.5, 125.1, 64.7, 34.8, 25.2. IR (neat, cm^{-1}): 2949, 2868, 2799, 1717, 1586, 954, 863, 809, 772, 744, 655, 528. HRMS *calcd* for [$C_{16}H_{15}OBr$+Na] 325.0204, *found* 325.0219.

[156] Barfield, M.; Collins, M. J.; Gready, J. E.; Sever, S.; Tansey, C. W. *J. Am. Chem. Soc.* **1989**, *111*, 4285.



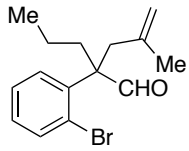
2-(1-Bromo-2-naphthyl)-2-methylpropanal (193). Following general procedure A, using (1-bromo-2-naphthyl) acetonitrile[156] (2.18 g, 8.90 mmol), NaHMDS (21.40 mL, 21.40 mmol, 1M in THF), methyl iodide (1.34 mL, 21.40 mmol) and DIBALH (10.70 mL, 10.70 mmol, 1M in hexanes). Column chromatography: silica gel, 8:1 hexanes/ethyl acetate. Colorless oil; yield: 1.30 g (53% overall yield).^{1}H-NMR ($CDCl_3$, 400 MHz) δ 9.81 (s, 1H), 8.26 (d, *J* = 8.8 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.51 (td, *J* = 6.8, 1.2 Hz, 1H), 7.24 (m, 2H), 1.54 (s, 6H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 203.0, 140.4, 133.7, 132.8, 128.4, 127.9, 127.8, 127.5, 126.9, 125.2, 123.9, 52.7, 23.7 ppm. IR (neat, cm^{-1}): 2975, 2916, 2877, 1719, 1550, 1500, 1466, 1359, 1320, 1261, 1233, 1145, 1103, 1026, 993, 955. HRMS *calcd* for ($C_{14}H_{13}BrO$+Na): 299.0047, *found* 299.0051.

General procedure B for the preparation of α-aryl aldehydes possessing differently substituted gropus in α position from 2-(2-Bromophenyl)pentanenitrile (Figure 2.42). General procedure A was followed, using 2-(2-Bromophenyl)pentanenitrile **(196)** followed by another alkylation event in the presence of a second electrophile to deliver the unsymmetrically α,α'-substituted phenylacetonitrile derivatives that were treated with DIBALH, thus yielding the desired compounds.

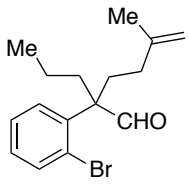


2-(2-Bromophenyl)pentanenitrile (196). A flask equipped with a magnetic stirring bar and a septum inlet was flushed with nitrogen. The flask was charged under nitrogen atmosphere with 2-bromophenylacetonitrile (6.0 mL, 46.20 mmol) and 100 mL of dry THF. Then, NaHMDS (46.20 mL, 46.20 mmol, 1M in THF) was added dropwise, and the solution was stirred for 20 min at rt. At this time, *n*-propyliodide (4.52 mL, 46.20 mmol) was introduced gradually by syringe. After stirring for 2 h at room temperature, 40 mL of aqueous saturated NH_4Cl solution were added and the mixture was extracted with ethyl acetate (2 x 40 mL). The combined organic layers were washed with water brine (40 mL), dried over magnesium sulfate, and

finally concentrated under vacuum. The crude was then purified by column chromatography on silica gel (20:1 hexanes/ethyl acetate) to give the title compound as a colorless oil (10.06 g, 92% yield). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.60 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.39 (td, *J* = 7.6, 0.8 Hz, 1H), 7.20 (td, *J* = 7.6, 1.6 Hz, 1H), 4.31 (dd, *J* = 8.2, 6.0 Hz, 1H), 1.86 (m, 2H), 1.60 (m, 2H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 135.6, 133.2, 129.6, 128.9, 128.2, 122.8, 120.3, 36.9, 36.4, 20.3, 13.3 ppm. IR (neat, cm^{-1}): 2978, 2899, 2236, 1673, 1556, 1463, 1435, 1389, 1240, 1114, 1021, 846. Anal. Calcd for $C_{11}H_{12}BrN$: C, 55.48; H, 5.08. Found: C, 55.17; H, 5.25.

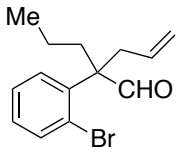


2-(2-bromophenyl)-4-methyl-2-propylpent-4-enal (199). Following general procedure B, using 2-(2-bromophenyl)pentanenitrile (1.5 g, 6.33 mmol), NaHMDS (7.60 mL, 7.60 mmol, 1M in THF), 4-bromo-2-methylbut-1-ene (7.60 mmol) and DIBALH (7.50 mL, 7.50 mmol, 1M in hexanes). Column chromatography: silica gel, 16:1 hexanes/ethyl acetate. Colorless oil; yield: 1.36 g (73% overall yield).^{1}H-NMR ($CDCl_3$, 400 MHz) δ 9.72 (s, 1H), 7.52 (dd *J* = 8.4, 1.2 Hz, 1H), 7.31 (ddd, *J* = 7.5, 6.4, 1.5, 1H), 7.16 (m, 2H), 5.11 (dd, *J* = 2.1, 1H), 4.92 (dd, *J* = 2.1, 1H), 2.67 (m, 2H), 1.87 (m, 5H), 1.33 (m, 2H), 0.98 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 201.8, 145.8, 142.7, 132.5, 130.3, 128.1, 127.5, 123.1, 110.6, 51.6, 42.4, 33.4, 22.8, 17.5, 14.4 ppm.

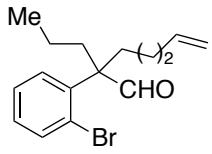


2-(2-bromophenyl)-5-methyl-2-propylhex-5-enal (200). Following general procedure B, using 2-(2-bromophenyl)pentanenitrile (1.5 g, 6.33 mmol), NaHMDS (7.60 mL, 7.60 mmol, 1M in THF), 5-bromo-2-methylpent-1-ene (7.60 mmol) and DIBALH (7.50 mL, 7.50 mmol, 1M in hexanes). Column chromatography: silica gel, 16:1 hexanes/ethyl acetate. Colorless oil; yield: 1.66 g (85% overall yield).^{1}H-NMR ($CDCl_3$, 400 MHz) δ 9.72 (s, 1H), 7.52 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.31-7.16 (m, 3H), 5.11 (dd, *J* = 2.1, 1H), 4.92 (dd, *J* = 2.1, 1H), 1.96-1.82 (m, 9H), 1.33 (m, 2H), 0.90 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ

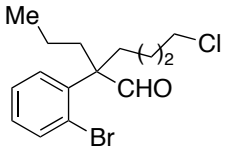
201.8, 145.8, 142.7, 132.5, 130.3, 128.1, 127.5, 123.1, 110.6, 54.8, 34.2, 33.1, 29.5, 22.5, 17.4, 14.4 ppm.



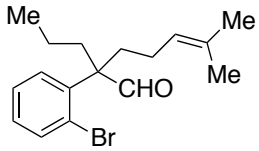
2-(2-bromophenyl)-2-propylpent-4-enal (201). Following general procedure B, using 2-(2-bromophenyl)pentanenitrile (1.5 g, 6.33 mmol), NaHMDS (7.60 mL, 7.60 mmol, 1M in THF), 3-bromoprop-1-ene (7.60 mmol) and DIBALH (7.50 mL, 7.50 mmol, 1M in hexanes). Column chromatography: silica gel, 16:1 hexanes/ethyl acetate. Colorless oil; yield: 1.10 g (60% overall yield).^{1}H-NMR ($CDCl_3$, 400 MHz) δ 9.86 (s, 1H), 7.75–7.54 (m, 1H), 7.39–7.32 (m, 2H), 7.21–7.13 (m, 1H), 5.57–5.42 (m, 1H), 5.05 (d, *J* = 5.3 Hz, 1H), 2.84 (qd, *J* = 14.4, 7.3 Hz, 2H), 2.14–1.87 (m, 2H), 1.36–1.02 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H)ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 203.8, 139.3, 134.8, 132.5, 130.3, 129.1, 127.4, 123.7, 118.8, 57.9, 367.0, 35.2, 16.7, 14.7 ppm.



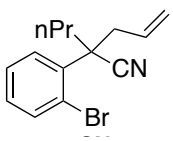
2-(2-Bromophenyl)-2-propyl-6-heptenal (202). Following general procedure B, using 2-(2-bromophenyl)pentanenitrile (1.5 g, 6.33 mmol), NaHMDS (7.60 mL, 7.60 mmol, 1M in THF), 1-bromo-4-pentene (0.90 mL, 7.60 mmol) and DIBALH (7.50 mL, 7.50 mmol, 1M in hexanes). Column chromatography: silica gel, 16:1 hexanes/ethyl acetate. Colorless oil; yield: 1.63 g (85% overall yield).^{1}H-NMR ($CDCl_3$, 400 MHz) δ 9.89 (s, 1H), 7.63 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.38 (m, 2H), 7.21 (ddd, *J* = 8.4, 6.4, 2.8 Hz, 1H), 5.76 (m, 1H), 4.99 (m, 2H), 2.04 (m, 6H), 1.33 (m, 2H), 1.12 (m, 2H), 0.93 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 204.1, 139.8, 138.0, 134.8, 130.2, 128.9, 127.3, 123.7, 115.0, 58.2, 35.0, 34.0, 31.9, 22.7, 16.8, 14.6 ppm. IR (neat, cm^{-1}): 3072, 2956, 2870, 1719, 1639, 1587, 1561, 1465, 1432, 1381, 1264, 1166, 1110, 1026, 990, 911. HRMS *calcd* for ($C_{16}H_{21}BrO$+Na): 331.0673, *found* 331.0679.



2-(2-Bromophenyl)-6-chloro-2-propylhexanal (203). Following general procedure highlighted in Scheme 2, using 2-(2-bromophenyl)-6-chloro-2-propylhexanenitrile (1.70 g, 5.20 mmol) and DIBALH (6.24 mL, 6.24 mmol, 1M in hexanes). Column chromatography: silica gel, 12:1 hexanes/ethyl acetate. Colorless oil; yield: 1.43 g (84% overall yield).^{1}H-NMR ($CDCl_3$, 400 MHz) δ 9.89 (s, 1H), 7.63 (dd, *J* = 6.4, 1.2 Hz, 1H), 7.41-7.35 (m, 2H), 7.21 (ddd, *J* = 6.4, 5.6, 1.6 Hz, 1H), 3.50 (m, 2H), 2.05 (m, 4H), 1.75 (m, 2H), 1.39 (m, 1H), 1.25 (m, 1H), 1.12 (m, 1H), 0.92 (t, *J* = 6.0 Hz, 3H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 203.9, 139.5, 134.9, 130.2, 129.1, 127.4, 123.6, 58.1, 44.5, 35.1, 32.8, 31.5, 20.8, 16.7, 14.6 ppm. IR (neat, cm^{-1}): 2987, 2954, 2879, 1718, 1465, 1428, 1380, 1309, 1178, 1022, 854. Anal. Calcd for $C_{15}H_{20}BrClO$: C, 54.32; H, 6.08. Found: C, 54.07; H, 6.26.

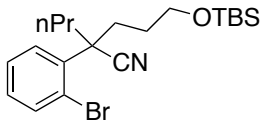


2-(2-Bromophenyl)-6-methyl-2-propyl-5-heptenal (204). Following general procedure highlighted in Scheme 2, using 2-(2-bromophenyl)-6-methyl-2-propyl-5-heptenenitrile (2.36 g, 7.40 mmol) and DIBALH (8.45 mL, 8.45 mmol, 1M in hexanes). Column chromatography: silica gel, 18:1 hexanes/ethyl acetate. Colorless oil; yield: 1.86 g (78% overall yield).^{1}H-NMR ($CDCl_3$, 400 MHz) δ 9.91 (s, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 4.0 Hz, 2H), 7.21 (m, 1H), 5.07 (tt, *J* = 6.8, 1.6 Hz, 1H), 2.11 (m, 4H), 1.89 (m, 1H), 1.75 (m, 1H), 1.69 (s, 3H), 1.54 (s, 3H), 1.27 (m, 1H), 1.10 (m, 1H), 0.93 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 196.7, 160.1, 146.0, 134.8, 131.9, 129.0, 123.9, 123.0, 120.7, 73.8, 37.2, 34.6, 25.6, 24.3, 18.8, 17.5, 14.5 ppm. IR (neat, cm^{-1}): 2959, 2871, 2814, 1719, 1678, 1562, 1466, 1376, 1244, 1109, 1020, 856. HRMS *calcd* for ($C_{17}H_{23}BrO$+Na): 345.0830, *found* 345.0821.



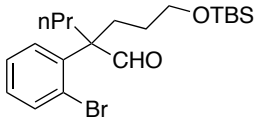
2-(2-Bromophenyl)-2-propyl-4-pentenenitrile (207). Following general procedure B, using 2-(2-bromophenyl)pentanenitrile (2.0 g, 8.44 mmol), NaHMDS (10.1 mL, 10.1 mmol, 1M in THF) and allyl bromide (0.88 mL, 10.1 mmol). Column

chromatography: silica gel, 16:1 hexanes/ethyl acetate. Colorless oil; yield: 2.17 g (93% overall yield). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.68 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.63 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.33 (td, *J* = 7.6, 1.2 Hz, 1H), 7.18 (td, *J* = 7.6, 1.2 Hz, 1H), 5.61 (m, 1H), 5.12 (m, 2H), 3.32 (dd, *J* = 14.4, 7.2 Hz, 1H), 2.81 (dd, *J* = 14.4, 7.6 Hz, 1H), 2.62 (m, 1H), 2.01 (m, 1H), 1.47 (m, 1H), 1.18 (m, 1H), 0.94 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 135.9, 134.8, 131.4, 129.4, 127.6, 122.2, 120.5, 119.7, 50.3, 41.2, 38.5, 18.8, 13.9 ppm. IR (neat, cm^{-1}): 3073, 2960, 2931, 2870, 2233, 1639, 1589, 1563, 1468, 1425, 1379, 1327, 1269, 1210, 1114, 1020, 991, 910. Anal. Calcd for $C_{14}H_{16}BrN$: C, 60.44; H, 5.80. Found: C, 60.69; H, 5.52**.**

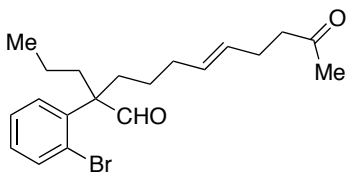


2-(2-Bromophenyl)-5-*tert*-butyl(dimethylsilyl)oxy-2-propylpentanenitrile (208). To a solution of 2-(2-bromophenyl)-2-propyl-4-pentenenitrile (2.0 g, 7.30 mmol) in THF (40 mL) under nitrogen atmosphere was added $BH_3{\cdot}SMe_2$ (4.80 mL, 9.60 mmol, 2M in THF) at 0 °C. The mixture was stirred for 2 h at 0 °C and then MeOH (0.10 mL) was added dropwise followed by addition of H_2O_2 (7.0 mL, 30% aqueous solution) and NaOH 3M (7.0 mL, 21.0 mmol). The mixture was then stirred for an additional 2 h at room temperature and then H_2O (20 mL) and Et_2O (40 mL) were added. The combined organic phases were extracted with aqueous saturated NH_4Cl solution (20 mL), dried over magnesium sulfate and concentrated. The crude was used directly to the next step without further purification.To a slurry of the above crude and imidazole (0.98 g, 14.60 mmol) in dry DMF (15 mL) was added dropwise a solution of TBDMSCl (1.96 g, 14.60 mmol) in DMF (5 mL) at room temperature. The reaction mixture was stirred for 8 h at that temperature, at which time TLC showed complete conversion. Finally, the mixture was worked up by addition of water (15 mL) and ethyl acetate (20 mL). The organic phases were back extracted with water (2 x 10 mL), dried over magnesium sulfate, and finally concentrated under vacuum and purified by column chromatography (silica gel, 20:1 hexanes/ethyl acetate) to give 1.99 g of the title compound (70% overall yield) as a colorless oil. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.72 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.62 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.34 (td, *J* = 7.6,

1.2 Hz, 1H), 7.18 (td, *J* = 7.6, 1.6 Hz, 1H), 3.61 (t, *J* = 5.6 Hz, 2H), 2.69 (m, 1H), 2.06 (m, 1H), 1.63 (m, 1H), 1.45 (m, 1H), 1.35 (m, 1H), 1.18 (m, 1H), 0.93 (t, *J* = 7.2 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 136.0, 135.1, 131.5, 129.3, 127.6, 122.8, 120.4, 62.4, 50.4, 39.3, 33.8, 28.9, 26.0, 18.9, 18.3, 13.9, -5.4 ppm. IR (neat, cm^{-1}): 2954, 2928, 2856, 2235, 1564, 1469, 1425, 1385, 1360, 1253, 1097, 1021, 972, 938, 831. Anal. Calcd for $C_{20}H_{32}BrNOSi$: C, 58.52; H, 7.86. Found: C, 58.26; H, 7.99.

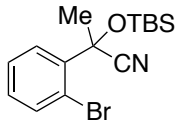


2-(2-bromophenyl)-5-*tert*-butyl(dimethylsilyl)oxy-2-propylpentanal (209). To a well-stirred solution of 2-(2-bromophenyl)-5-*tert*-butyl(dimethylsilyl)oxy-2-propyl-pentanenitrile (0.96 g, 2.34 mmol) in dichloromethane (20 mL) under nitrogen atmosphere was added DIBALH (2.80 mL, 2.80 mmol, 1M in hexanes) and stirred for 2 h at -78 ºC. The reaction was then quenched after 2 hours of further stirring by slow addition of 2M HCl (20 mL) and ethyl acetate (20 mL). The organic phase was washed twice with brine (20 mL), dried over magnesium sulfate and concentrated. The crude was then purified by column chromatography on silica gel (16:1 hexanes/ethyl acetate) to give the title compound as a colorless oil (0.77 g, 83% yield). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 9.88 (s, 1H), 7.61 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.38 (m, 2H), 7.18 (td, *J* = 8.0, 2.0 Hz, 1H), 3.57 (t, *J* = 6.0 Hz, 2H), 2.15-1.94 (m, 4H), 1.44 (m, 1H), 1.27 (m, 2H), 1.04 (m, 1H), 0.91 (t, *J* = 6.3 Hz, 3H), 0.89 (s, 9H), -0.04 (s, 6H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 204.1, 139.8, 134.8, 130.3, 128.9, 127.3, 123.7, 63.0, 58.0, 34.9, 28.9, 26.8, 25.9, 18.2, 16.7, 14.6, -5.4 ppm. IR (neat, cm^{-1}): 2955, 2928, 2865, 1721, 1468, 1384, 1360, 1252, 1094, 1025, 937, 832. HRMS *calcd* for ($C_{20}H_{33}BrO_2Si$+Na): 435.1331, *found* 435.1340.

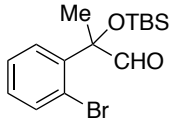


2-(2-Bromophenyl)-2-propyl-10-oxo-6-undecenal (210). A solution of 2-(2-bromophenyl)-2-propyl-6-heptenal (**202**) (137 mg, 0.45 mmol) in dichloromethane (1 mL) was added to a stirred solution of Grubbs' catalyst (second generation, 11.3 mg, 3 mol%) in

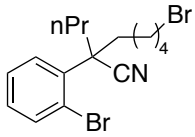
dichloromethane (2 mL) was added. Then, 5-hexen-2-one (0.15 mL, 1.33 mmol) was added and the resulting mixture was heated to 40 ºC overnight. Then, the solution was filtrate through a pad of silica gel and washed with dichloromethane (3x5 mL). The solvent was removed under reduced pressure and the obtained residue was purified by column chromatography (hexanes/EtOAc, 8/2) to deliver aldehyde **(210)** (63.2 mg, 38% yield, *E*/*Z*=9:1) as a colorless oil. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 9.84 (s, 1H), 7.59 (d, *J* = 7.5 Hz, 1H), 7.38-7.31 (m, 2H), 7.19-7.15 (m, 1H), 5.36-5.33 (m, 2H), 2.48-2.44 (m, 2H), 2.28-2.20 (m, 2H), 2.12 (s, 3H), 2.09-1.90 (m, 7H), 1.30-1.17 (m, 2H), 1.10-0.99 (m, 2H), 0.89 (t, *J* = 7.20 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 208.4, 204.1, 139.7, 134.8, 130.4, 130.2, 129.0, 128.9, 127.3, 123.6, 58.1, 43.3, 34.9, 32.7, 31.8, 29.6, 23.1, 16.7, 14.6. IR (neat, cm^{-1}): 2957, 1707, 1464. HRMS *calc. for* ($C_{20}H_{27}O_2Br$+Na): 401.1092, *found* 401.1103.



2-(2-bromophenyl)-2-((*tert*-butyldimethylsilyl)oxy)propanenitrile (212). A Schlenk containing a stirring bar was charged with NaCN (1.1 g, 22.4 mmol). The Schlenk was evacuated and back-filled with dry argon and then dry DMSO (10 mL) and 1-(2-bromophenyl)ethanone (1.5 mL, 11.2 mmol) were added by syringe. The mixture was then placed in a pre-heated oil bath (60 ºC) and stirred for 15 min. Afther 15 min of stirring at 60ºC a solution of TBSCl (2.03 g, 13.4 mmol) in dry DMSO (3 mL) was added dropwise. The mixture was stirred for one more hour and then allowed to warm to room temperature, diluted with hexane (3 x 10 mL) The organic phases were concentrated and purified by column chromatography on silica gel (hexanes) to give the title compound as a colorless oil (3.29 g, 86% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.38 (t, *J* = 7.7 Hz, 1H), 7.22 (t, *J* = 7.6 Hz, 1H), 2.04 (s, 3H), 1.01 (s, 9H), 0.34 (s, 3H), 0.29 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 139.6, 135.1, 130.0, 127.6, 127.1, 120.3, 120.1, 71.1, 29.6, 25.7, 18.4, -3.0, -3.8. IR (neat, cm^{-1}): 2954, 2931, 2857, 1701, 1464, 1429 1256, 1215, 1157, 1127, 1105, 1084, 1024, 987, 832, 779, 721. HRMS *calcd* for [$C_{15}H_{22}BrNOSi$+Na] 362.0552, *found* 362.0566.

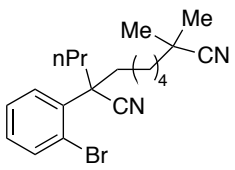


2-(2-bromophenyl)-2-*tert*-butyl(dimethylsilyl)oxy-propanal (213). Following general procedure highlighted in Scheme 1, 2-(2-bromophenyl)-2-*tert*-butyl(dimethylsilyl)oxy-propanenitrile (3.3 gr, 9.7 mmol), dichloromethane (4 mL/1.0 mmol) and DIBALH (14.0 mL, 14.0 mmol, 1M in hexanes) were used. Column chromatography: silica gel, hexanes. Colorless oil; yield 2.31 g (70%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.83 (s, 1H), 7.68 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.57 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.38 (td, *J* = 7.8, 1.2 Hz, 1H), 7.21 (td, *J* = 7.7, 1.6 Hz, 1H), 1.73 (s, 3H), 0.95 (s, 9H), 0.09 (s, 3H), -0.04 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.6, 142.1, 134.0, 129.8, 128.6, 127.3, 121.4, 80.9, 25.8, 22.9, -2.4, -2.9. IR (neat, cm^{-1}): 3413, 2953, 2930, 2889, 2856, 1699, 1465, 1428, 1254, 1161, 993, 833, 754. HRMS *calcd* for [$C_{15}H_{23}O_2Si$+Na] 365.0548, *found* 365.0562.

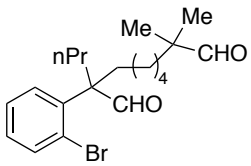


7-Bromo-2-(2-bromophenyl)-2-propylheptanenitrile (214). A flask equipped with a magnetic stirring bar and a septum inlet was flushed with nitrogen. The flask was charged under nitrogen atmosphere with 2-(2-bromophenyl)pentanenitrile **11-CN** (4.03 g, 17.0 mmol) and 60 mL of dry THF. Then, NaHMDS (30.0 mL, 30.0 mmol, 1M in THF) was added dropwise, and the solution was stirred for 30 min at rt. At this time, 1,5-dibromopentane (2.6 mL, 18.4 mmol) was added dropwise. After stirring for 1 h at room temperature, 30 mL of aqueous saturated NH_4Cl solution were added and the mixture was extracted with ethyl acetate (2 x 15 mL). The combined organic layers were dried over magnesium sulfate, and concentrated under vacuum. The crude was then purified by column chromatography on silica gel 20:1 hexanes/ethyl acetate to afford the *rather unstable* title compound as a colorless oil (2.40 g, 37% yield). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.71 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.62 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.33 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.18 (dd, *J* = 7.7, 1.5 Hz, 1H), 3.36 (t, *J* = 6.8 Hz, 2H), 2.64 (m, 2H), 1.99 (m, 2H), 1.83 (q, *J* = 7.1 Hz, 2H), 1.46 (m, 4H), 1.12 (m, 2H), 0.92 (t, *J* = 7.3 Hz , 3H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 136.0, 135.0, 131.6, 129.4, 127.7, 122.9, 120.1, 50.9, 39.3, 37.0, 33.5, 32.3,

27.9, 24.7, 19.0 13.9 ppm. IR (neat, cm^{-1}): 2962, 2933, 2872, 1702, 1467, 1427, 1262, 1209, 1023, 757. MS (ES, *m/*z): 408.0 ((M-2)+Na, 44%), 410.0 (M+Na, 100%), 412 ((M+2)+Na, 41%).

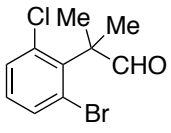


2-(2-Bromophenyl)-8,8-dimethyl-2-propylnonane dinitrile (215). Isobutyronitrile (0.77 mL, 8.20 mmol) was added to a solution of LDA (2.50 mL, 5.0 mmol, 2M in THF) in dry THF (10 mL) at -78 ºC under nitrogen atmosphere. After 20 min of stirring, 7-bromo-2-(2-bromophenyl)-2-propylheptanenitrile (0.98 g, 2.50 mmol) was added dropwise. After 1 h, the mixture was allowed to reach room temperature and at that time was quenched with a saturated solution of NH_4Cl (5 mL) and Et_2O (2 x 10 mL), dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by silica gel chromatography 20:1 hexanes:ethyl acetate to afford the title compound as a colorless oil (0.74 g, 80% yield).^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.71 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.61 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.33 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.18 (dd, *J* = 7.7, 1.1 Hz, 1H), 2.64 (m, 2H), 1.97 (m, 2H), 1.52-1.21 (m, 14H), 1.12 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 136.0 135.0, 131.6, 129.33, 127.6, 125.0, 122.9, 120.1, 50.8, 40.8, 39.2, 36.9, 32.3, 29.2, 26.6, 26.5, 25.2, 24.8, 18.9, 13.4 ppm. IR (neat, cm^{-1}): 2971, 2935, 2864, 2233, 1738, 1470, 1427, 1022, 761. Anal. Calcd for $C_{20}H_{27}BrN_2$: C, 64.00; H, 7.25. Found: C, 64.34; H, 7.06.

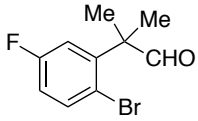


2-(2-Bromophenyl)-8,8-dimethyl-2-propylnonanedial (216). To a well-stirred solution of 2-(2-bromophenyl)-8,8-dimethyl-2-propylnonanedinitrile (0.74 g, 1.9 mmol) in CH_2Cl_2 (15 mL) under nitrogen atmosphere was added DIBALH (5.80 mL, 5.80 mmol, 1M in hexanes) and stirred for 4 h at -78 ºC. The reaction was then quenched by slow addition of 2M HCl (5 mL) and ethyl acetate (10 mL). The organic phase was dried over $MgSO_4$ and concentrated. The crude was then purified by column chromatography on silica gel 10:1 hexanes/ethyl acetate to give **1j** as a colorless oil (0.47 g, 63% yield). ^{1}H-NMR ($CDCl_3$, 400 MHz)

δ 9.85 (s, 1H), 8.41 (s, 1H), 7.60 (dd, *J* = 8.5, 0.96 Hz, 1H), 7.34 (m, 2H), 7.17 (m, 1H), 2.06-1.92 (m, 5H), 1.40-1.36 (m, 2H), 1.27-1.13 (m, 7H), 1.01 (m, 6H), 0.89 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 206.3, 204.2, 139.8, 134.9, 130.2, 128.9, 127.3, 123.7, 60.4, 58.2, 45.8, 37.1, 35.0, 32.4, 30.7, 24.0, 21.3, 21.3, 16.8, 14.7 ppm. IR (neat, cm^{-1}): 2957, 2932, 2869, 1723, 1379, 1025, 758, 638. Anal. Calcd for $C_{20}H_{29}BrO_2$: C, 62.99; H, 7.67. Found: C, 62.63; H, 7.99.



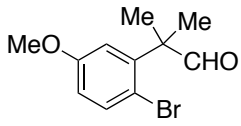
2-(2-Bromo-6-chlorophenyl)-2-methylpropanal (220). Following general procedure A, using (2-bromo-6-chlorophenyl) acetonitrile[157] (2.28 g, 9.91 mmol), NaHMDS (23.80 mL, 23.80 mmol, 1M in THF), methyl iodide (1.48 mL, 23.80 mmol) and DIBALH (11.90 mL, 11.90 mmol, 1M in hexanes). Column chromatography: silica gel, 15:1 hexanes/ethyl acetate. Colorless oil; yield: 4.58 g (74% overall yield). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 9.83 (s, 1H), 7.60 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.41 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.09 (t, *J* = 8.0 Hz, 1H), 1.73 (s, 6H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 200.1, 139.5, 135.4, 134.5, 131.3, 128.9, 124.1, 54.0, 23.0 ppm. IR (neat, cm^{-1}): 2975, 2933, 2802, 1719, 1573, 1551, 1465, 1415, 1390, 1363, 1227, 1209, 1187, 1117, 1072, 1043, 988. HRMS *calcd* for ($C_{10}H_{10}BrClO$+Na): 282.9501, *found* 282.9509.



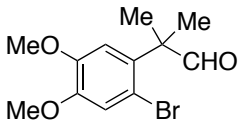
1-(2-bromo-5-fluorophenyl)cyclohexanecarbaldehyde (221). Following general procedure highlighted in Scheme 1, using 2-(2-bromo-5-fluorophenyl)[158] (1.0 g, 4.7 mmol), dry THF (4 mL/1.0 mmol), NaHMDS (5.90 mL, 11.80 mmol, 2M in THF), 1,4-dibromobutane (0.70 mL, 5.10 mmol) and DIBALH (5.60 mL, 5.60 mmol, 1M in hexanes). Column chromatography: silica gel (95:5 hexanes/ethyl acetate). White solid; yield: 1.07 g (80% overall yield). Mp= 54.2-54.9 ^{o}C ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.95 (s, 1H), 7.54 (dd, *J* = 8.7, 5.7 Hz, 1H), 7.22 (dd, *J* = 10.8, 3.0 Hz, 1H), 6.89 (ddd, *J* = 8.7, 7.3, 3.0 Hz, 1H), 2.39-2.28 (m, 2H), 1.98-1.86 (m, 2H), 1.80-1.60

[157] Hitce, J.; Baudoin, O. *Adv. Synth. Catal.* **2007**, *11-12*, 2054.
[158] Mohammadi, K., Maleki, B., Azrifar, D. *Heterocycles*, **2007**, *74*, 683.

(m, 5H), 1.51-1.39 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 203.7, 135.9 (d, *J* = 8.1 Hz), 117.2, 117.0, 115.9, 115.7, 54.6, 31.6, 25.4, 22.3. IR (neat, cm^{-1}): 2960, 2933, 2873 1726, 1466, 1250, 1142, 1100, 966. HRMS *calcd* for ($C_{13}H_{14}OBrF$+Na): 307.0110, *found* 307.0169.



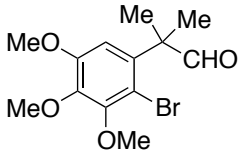
2-(2-Bromo-5-methoxyphenyl)-2-methylpropanal (222). Following general procedure A, using (2-bromo-5-methoxyphenyl)acetonitrile[159] (4.95 g, 22.0 mmol), NaHMDS (52.8 mL, 52.8 mmol, 1M in THF), methyl iodide (3.29 mL, 52.8 mmol) and DIBALH (26.50 mL, 26.50 mmol, 1M in hexanes). Column chromatography: silica gel, 10:1 hexanes/ethyl acetate. White solid; yield: 3.49 g (62% overall yield). Mp = 57.7-58.9 ^{o}C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 9.80 (s, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.01 (d, *J* = 3.2 Hz, 1H), 6.76 (dd, *J* = 8.8, 3.2 Hz, 1H), 3.85 (s, 3H), 1.53 (s, 6H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 202.9, 159.2, 143.4, 134.9, 115.7, 113.6, 113.4, 55.4, 51.7, 23.1 ppm. IR (neat, cm^{-1}): 3080, 2989, 2944, 1723, 1599, 1570, 1465, 1442, 1379, 1357, 1288, 1252, 1198, 1187, 1143, 1110, 1040, 1014 . HRMS *calcd* for ($C_{11}H_{13}BrO_2$+Na): 278.9997, *found* 278.9990.



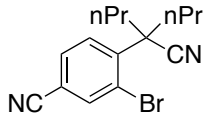
2-(2-Bromo-4,5-dimethoxyphenyl)-2-methylpropanal (223). Following general procedure highlighted in Scheme 1, using (2-bromo-4,5-dimethoxyphenyl)acetonitrile [160] (5.10 g, 20.0 mmol), NaHMDS (48.0 mL, 48.0 mmol, 1M in THF), methyl iodide (2.99 mL, 48.0 mmol) and DIBALH (24.0 mL, 24.0 mmol, 1M in hexanes). Column chromatography: silica gel, 6:1 hexanes/ethyl acetate. Colorless oil; yield: 4.06 g (71% overall yield). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 9.77 (s, 1H), 7.07 (s, 1H), 6.91 (s, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 1.51 (s, 6H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 203.3, 148.8, 148.4, 134.3, 117.2, 111.7, 56.2, 51.4, 23.3 ppm. IR (neat, cm^{-1}): 2934, 288, 1717, 1599, 1568, 1498, 1461, 1438, 1363, 1320, 1294, 1254, 1208,

[159] Muratake, H.; Natsume, M. *Tetrahedron* **2007**, *62*, 7056.
[160] Molander, G. A.; Pack, S. K. *Tetrahedron* **2003**, *59*, 10581

1172, 1122, 1026, 986, 929. Anal. Calcd for $C_{12}H_{15}BrO_3$: C, 50.19; H, 5.27. Found: C, 50.48; H, 5.07.



2-(2-Bromo-3,4,5-dimethoxyphenyl)-2-methylpropanal (224). Following general procedure A, using (2-bromo-3,4,5-trimethoxyphenyl)acetonitrile[161] (3.90 g, 13.68 mmol), NaHMDS (32.90 mL, 32.90 mmol, 1M in THF), methyl iodide (2.06 mL, 32.90 mmol) and DIBALH (16.5 mL, 16.5 mmol, 1M in hexanes). Column chromatography: silica gel, 5:1 hexanes/ethyl acetate. White solid; yield: 3.11 g (72% overall yield). Mp = 70.4-71.7 ºC. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 9.77 (s, 1H), 6.76 (s, 1H), 3.90 (s, 6H), 3.88 (s, 3H), 1.50 (s, 6H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 203.0, 152.7, 151.4, 142.5, 138.1, 110.3, 107.8, 61.0, 60.9, 56.2, 51.9, 23.5 ppm. IR (neat, cm^{-1}): 2998, 2967, 2935, 2837, 1718, 1566, 1484, 1458, 1441, 1383, 1325, 1248, 1212, 1191, 1155, 1102, 1024, 1007, 987. Anal. Calcd for $C_{13}H_{17}BrO_4$: C, 49.23; H, 5.40. Found: C, 49.01; H, 5.59.

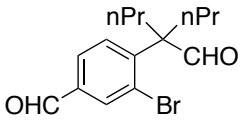


3-Bromo-4-(4-cyanoheptan-4-yl)benzonitrile (226). To a slurry of KCN (0.48 g, 7.31 mmol) in EtOH (20 mL) and water (9 ml) at 90 ºC, was added dropwise 3-bromo-4-(bromomethyl)benzonitrile[162] (0.74 g, 2.70 mmol) in EtOH (5 mL). The mixture was stirred at 90 ºC for 45 minutes and then was allowed to reach room temperature overnight. The solvent was concentrated under reduced pressure and the residue was extracted with brine (15 mL) and ethyl acetate (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was used without further purification in the next step.

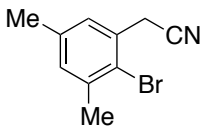
To a slurry of NaH (0.20 g, 8.1 mmol) in anhydrous THF (10 mL) under argon at 0 ºC was added dropwise the above nitrile crude in THF (10 mL). After stirring the mixture for 30 minutes at room temperature, *n*-propyliodide (0.79 mL, 8.1

[161] Kumar, S.; Peruncheralathan, S.; Ila, H.; Junjappa, H. *Org. Lett.* **2008**, *10*, 965.
[162] Kim, K. T.; Cornelissen J. J. L. M.; Nolte, R. J. M.; van Hest, J. C. M. *J. Am. Chem. Soc.,* **2009**, *131*, 13908.

mmol) was added by syringe and the mixture was stirred for 3 additional hours at this temperature. The resulting mixture was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The crude was then purified by column chromatography on silica gel (4:1 hexanes/ethyl acetate) to give the title compound as a white solid (0.63 g, 77% overall yield). Mp = 74.4-75.5 ºC. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.89 (d, *J* = 1.7 Hz, 1H), 7.83 (d, *J* = 8.2 Hz, 1H), 7.65 (dd, *J* = 8.2, 1.7 Hz, 1H), 2.56 (ddd, *J* = 14.0, 12.3, 4.5 Hz, 2H), 1.98 (ddd, *J* = 14.0, 12.2, 4.5 Hz, 2H), 1.48-1.37 (m, 2H), 1.13-1.00 (m, 2H), 0.90 (t, *J* = 7.2 Hz, 6H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 140.9, 138.7, 132.0, 130.9, 121.8, 120.7, 116.4, 113.4, 51.1, 38.7, 18.8, 13.7 ppm. IR (neat, cm^{-1}): 2961, 2932, 2874, 2233, 1479, 1464, 1453, 1375, 1039, 877, 810, 660. Anal. Calcd for $C_{15}H_{17}BrN_2$: C, 59.03; H, 5.61. Found: C, 58.79; H, 5.99.

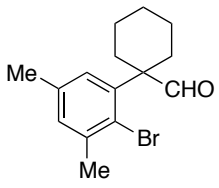


3-Bromo-4-(4-formylheptan-4-yl)benzaldehyde (227). A solution of 3-bromo-4-(4-cyanoheptan-4-yl)benzonitrile (0.63 g, 2.1 mmol) in dry CH_2Cl_2 (10 mL) was cooled to –78ºC under argon and DIBALH (5.0 mL, 5.0 mmol, 1M in hexanes) was added dropwise by syringe. The reaction was then quenched after 1 hour of further stirring by slow addition of 2M HCl (7 mL) and ethyl acetate (10 mL). The organic phase was washed twice with brine (10 mL), dried over magnesium sulfate and concentrated. The crude was then purified by column chromatography on silica gel (12:1, hexanes/ethyl acetate) to give the title compound as a colorless oil (0.46 g, 71% yield). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 10.9 (s, 1H), 9.9 (s, 1H), 8.08 (d, *J* = 1.7 Hz, 1H), 7.84 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.52 (d, *J* = 8.1 Hz, 1H), 2.11-1.96 (m, 4H), 1.26-1.17 (m, 2H), 1.07-0.96 (m, 2H), 0.88 (t, *J* = 7.2 Hz, 6H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 203.0, 190.1, 146.8, 136.5, 135.7, 130.9, 127.9, 124.2, 58.8, 34.9, 16.7, 14.5 ppm. IR (neat, cm^{-1}): 2959, 2930, 2870, 1761, 1699, 1597, 1460, 1195, 1077, 940, 835. HRMS *calcd* for ($C_{15}H_{19}BrO_2$+Na): 333.0466, *found* 333.0457.



(2-bromo-3,5-dimethylphenyl)acetonitrile.

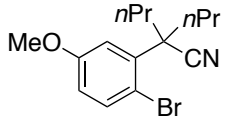
2-bromo-3,5-dimethylbenzyl alcohol[163] (2.38 g, 11.07 mmol) was dissolved in THF (70 mL) and CBr_4 (5.61 g, 16.60 mmol) and PPh_3 (4.35 g, 16.60 mmol) were subsequently added at 0 ºC. The resulting mixture was stirred at 0 ºC for 2 hours and the solvent was evaporated. A mixture of hexane/ether (1/1) was added to precipitate the triphenylphosphine oxide out. The resulting crude was purified by column chromatography (hexane/EtOAc, 9/1). White solid; 3.05 g (99% yield). Mp 46-48 ºC. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.13 (m, 1H), 7.03 (m, 1H), 4.63 (s, 2H), 2.42 (s, 3H), 2.3 (s, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 138.9, 137.0, 136.8, 131.8, 129.3, 123.6, 34.7, 23.5, 20.6. IR (neat, cm^{-1}): 2951, 1459, 1091, 945, 855, 786, 720, 660, 600. HRMS *calc.* 2-Bromo-1-(bromomethyl)-3,5-dimethyl benzene (10.87 mmol, 3.0 g) was dissolved in DMF (16 mL) and NaCN (43.48 mmol, 2.17 g) was added at room temperature. The resulting mixture was stirred at room temperature for 2 hours and then water was added. The aqueous phase was extracted with EtOAc (3 x 15 mL) and the combined organic phases were dried over $MgSO_4$. The resulting crude was purified by column chromatography (8:2, hexanes:EtOAc). White solid; 1.62 g (67% yield). Mp 87-89 ºC. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.15 (m, 1H), 7.0(m, 1H), 3.76 (s, 2H), 2.37 (s, 3H), 2.29 (s, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 138.6, 137.2, 131.2, 129.6, 127.5, 122.4, 117.0, 25.2, 23.3, 20.5. IR (neat, cm^{-1}): 2952, 2249, 1457, 1178, 1029, 958, 891, 849, 697. HRMS *calc.* for [$C_{10}H_{10}Br$+Na] 245.9894, *found* 245.9900.for [$C_9H_{10}Br_2$]



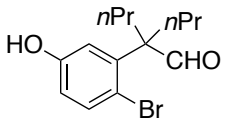
1-(2-bromo-3,5-dimethylphenyl)cyclohexanecarbaldehyde (230). Following general procedure A, 2-Bromo-3,5-dimethylbenzylcyanide (1.60 g, 7.20 mmol) and dry THF (4 mL/1.0 mmol), NaHMDS (10.80 mL, 21.50 mmol, 2M in THF), 1,4-dibromopentane (0.98 mL, 24.50 mmol) and DIBALH (8.60 mL, 8.60 mmol, 1M in hexanes). Column chromatography: silica gel (9:1 hexanes/ethyl acetate).

[163] Moorthy, J. M.; Samanta, S. *J. Org. Chem.* **2007**, *72*, 9786.

White solid; yield: 1.9 g (88% overall yield). Mp 71-73 ºC. ^{1}H-RMN ($CDCl_3$, 400 MHz) δ 10.0 (brs, 1H), 7.13 (s, 1H), 7.02 (s, 1H), 2.37-2.30 (m, 8H), 1.94 (dd, *J* = 16.7, 6.1 Hz, 1H). 1.75-1.67 (m, 5H), 1.54-1.36 (m, 1H). ^{13}C-RMN ($CDCl_3$, 100 MHz) δ 204.8, 142.9, 139.4, 136.7, 130.8, 127.7, 122.4, 122.6, 54.7, 32.1, 25.6, 24.5, 22.4, 21.0. IR (neat, cm^{-1}): 2696, 1718, 1593, 1291, 1079, 982, 926, 785, 744. HRMS *calc.* for [$C_{15}H_{19}OBr$+Na] 317.0517, f*ound* 317.0518.

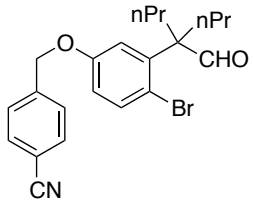


2-(2-Bromo-5-methoxyphenyl)-2-propylpentanenitrile (231). Following general procedure A, using (2-bromo-5-methoxyphenyl)acetonitrile (3.50 g, 15.70 mmol), NaHMDS (37.80 mL, 37.80 mmol, 1M in THF), *n*-propyl iodide (3.70 mL, 37.80 mmol). Column chromatography: silica gel, 8:1 hexanes/ethyl acetate. Colorless oil; yield: 4.56 g (94% overall yield). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.52 (d, *J* = 8.8 Hz, 1H), 7.31 (d, *J* = 2.8 Hz, 1H), 6.74 (dd, *J* = 8.8, 2.2 Hz, 1H), 3.85 (s, 3H), 2.64 (ddd, *J* = 16.8, 12.4, 4.4 Hz, 2H), 1.97 (ddd, *J* = 16.4, 12.4, 4.8 Hz, 2H), 1.51 (m, 2H), 1.19 (m, 2H), 0.95 (t, *J* = 7.6 Hz, 6H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 158.7, 136.5, 136.3, 122.9, 117.9, 114.2, 110.3, 55.4, 50.9, 39.1, 18.9, 13.9 ppm. IR (neat, cm^{-1}): 2960, 2933, 2872, 2234, 1736, 1593, 1570, 1464, 1399, 1288, 1237, 1177, 1110, 1045, 1017, 909. Anal. Calcd for $C_{15}H_{20}BrNO$: C, 58.07; H, 6.50. Found: C, 58.43; H, 6.31.



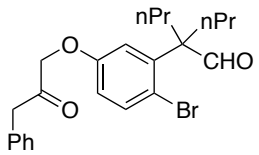
2-(2-Bromo-5-hydroxyphenyl)-2-propylpentanal (232). A flask equipped with a magnetic stirring bar and a septum inlet was flushed with nitrogen. The flask was charged under nitrogen atmosphere with 2-(2-bromo-5-methoxyphenyl)-2-propylpentanenitrile **33-CN** (4.0 g, 12.94 mmol) and 50 ml of dry CH_2Cl_2. Then, pure BBr_3 (2.50 mL, 26.0 mmol, 1M in THF) was added dropwise at -78 ºC, and the solution was allowed to reach room temperature overnight. After stirring for 14 h at room temperature, 40 mL of H_2O were added and the mixture was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layers were washed with water brine (30 mL), dried over magnesium sulfate, and finally concentrated under vacuum.

The crude was used in the next step withour further purification. To a well-stirred solution of 2-(2-bromo-5-hydroxyphenyl)-2-propylpentane-nitrile (3.20 g, 10.94 mmol) in dichloromethane (50 mL) under nitrogen atmosphere was added DIBALH (32.80 mL, 32.80 mmol, 1M in hexanes) and stirred for 2 h at -78 ºC. The reaction was then quenched after 2 hours of further stirring by slow addition of 2M HCl (20 mL) and ethyl acetate (50 mL). The organic phase was washed twice with brine (20 mL), dried over magnesium sulfate and concentrated. The crude was then purified by column chromatography on silica gel (5:1 hexanes/ethyl acetate) to give the title compound as a white solid (2.71 g, 83% yield). Mp = 127.4-128.8 ^{o}C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 9.9 (s, 1H), 7.43 (d, *J* = 8.4 Hz, 1H), 6.93 (d, *J* = 2.8 Hz, 1H), 6.72 (dd, *J* = 8.4, 2.8 Hz, 1H), 1.97 (m, 4H), 1.24 (m, 2H), 1.12 (m, 2H), 0.92 (t, *J* = 7.2 Hz, 6H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 205.5, 155.2, 141.2, 135.4, 117.7, 116.2, 113.6, 58.3, 34.7, 16.7, 14.6 ppm. IR (neat, cm^{-1}): 3383, 2954, 2867, 1891, 1705, 1608, 1571, 1460, 1448, 1391, 1376, 1299, 1249, 1226, 1183, 1108, 1014, 987, 881. HRMS *calcd* for ($C_{14}H_{19}BrO_2$+Na): 321.0466, *found* 321.0461.

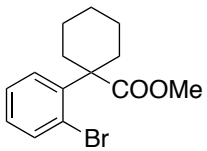


4-[4-Bromo-3-(1-formyl-1-propylbutyl)phenoxy] methylbenzonitrile (233). An oven-dried screw-cap test tube containing a stirring bar was charged with 2-(2-bromo-5-hydroxyphenyl)-2-propylpentanal (0.59 g, 2.0 mmol), K_2CO_3 (0.17 g, 2.40 mmol), sodium iodide (60 mg, 0.40 mmol) and 4-(bromomethyl)benzonitrile (0.39 g, 2.0 mmol). The test tube was evacuated and back-filled with dry argon and then dry acetonitrile (4 mL) was added by syringe. The mixture was then placed in a pre-heated oil bath (70 ^{o}C) and stirred for 8 h. The mixture was then allowed to warm to room temperature, diluted with ethyl acetate (5 mL) and filtered through a Celite® plug, eluting with additional ethyl acetate (10 mL). The filtrate was concentrated and purified by column chromatography on silica gel (4:1 hexanes/ethyl acetate) to give the title compound as a white solid (0.67 g, 80% yield). Mp = 68.7-69.8 ^{o}C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 9.84 (s, 1H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.50 (d, *J* =

8.8 Hz, 1H), 6.95 (d, *J* = 2.8 Hz, 1H), 6.76 (dd, *J* = 8.8, 2.8 Hz, 1H), 5.14 (s, 2H), 1.94 (m, 4H),1.21 (m, 2H), 1.04 (m, 2H), 0.89 (t, *J* = 7.2 Hz, 6H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 203.8, 157.3, 141.8, 141.6, 135.4, 132.4, 127.6, 118.5, 118.1, 114.8, 114.3, 111.9, 69.2, 58.3, 34.7, 16.7, 14.6 ppm. IR (neat, cm^{-1}): 2955, 2869, 2224, 1712, 1610, 1587, 1568, 1456, 1377, 1295, 1282, 1230, 1184, 1108, 1029, 1015, 986. Anal. Calcd for $C_{22}H_{24}BrNO_2$: C, 63.77; H, 5.84. Found: C, 64.05; H, 5.71.



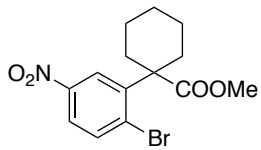
Benzyl [4-bromo-3-(1-formyl-1-propylbutyl) phenoxy] acetate (234). The procedure for the synthesis of 4-[4-bromo-3-(1-formyl-1-propylbutyl)phenoxy] methyl benzonitrile was followed, using 2-(2-bromo-5-hydroxyphenyl)-2-propylpentanal (0.59 g, 2.0 mmol), K_2CO_3 (0.17 g, 2.40 mmol), sodium iodide (60 mg, 0.40 mmol) and benzyl bromoacetate (0.32 mL, 2.0 mmol). Column chromatography: silica gel, 4:1 hexanes/ethyl acetate. Colorless oil; yield: 0.80 g (91% yield). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 9.85 (s, 1H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.40 (m, 5H), 7.01 (d, *J* = 3.2 Hz, 1H), 6.70 (dd, *J* = 8.4, 3.2 Hz, 1H), 5.29 (s, 2H), 4.71 (s, 2H), 1.96 (m, 4H), 1.22 (m, 2H), 1-07 (m, 2H), 0.91 (t, *J* = 7.2 Hz, 6H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 203.8, 168.3, 157.0, 141.6, 135.3, 134.9, 128.6, 128.5, 118.3, 115.2, 113.8, 67.2, 65.5, 58.3, 34.6, 16.7, 14.6 ppm. IR (neat, cm^{-1}): 2957, 2871, 1757, 1718, 1593, 1568, 1497, 1456, 1409, 1298, 1175, 1084, 1027, 959. HRMS *calcd* for ($C_{23}H_{27}BrO_4$+Na): 469.0990, *found* 469.0983.



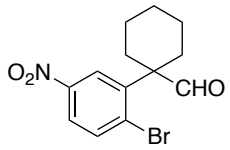
Methyl 1-(2-bromophenyl)cyclohexanecarboxylate (236). To a suspension of NaH (2.53 g, 105 mmol) in dry THF (100 mL) under argon at 0 ºC was added dropwise methyl 2-(2-bromophenyl)acetate[164] (8.0 g, 35 mmol) in dry THF (100 mL). After stirring the mixture for 30 minutes at room temperature, 2,5-dibromopentane (5.24 mL, 38.5 mmol) was added and the mixture was stirred for 2 days at room temperature. The resulting mixture was quenched with NH_4Cl aq. sat. and extracted with EtOAc

[164] Beckwith, A. L. J.; Gerba, S. *Aust. J. Chem.* **1992**, *45*, 289.

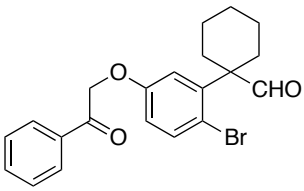
(3 x 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The crude was then purified by column chromatography on silica gel (9:1 hexanes/ethyl acetate) to give the title compound as a white solid (8.95 g, 95% yield). Mp = 71.8-72.8 ºC. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.56 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.51 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.33 (td, *J* = 15.3, 1.4 Hz, 1H), 7.10 (td, *J* = 15.2, 1.6 Hz, 1H), 3.65 (s, 3H), 2.42-2.39 (m, 2H), 1.99-1.93 (m, 2H), 1.86-1.77 (m, 2H), 1.68-1.60 (m, 3H), 1.45-1.36 (m, 1H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 176.2, 143.3, 134.8, 128.2, 128.0, 127.3, 123.6, 52.1, 51.6, 33.9, 25.7, 22.4 ppm. IR (neat, cm^{-1}): 3067, 2940, 2859, 1731, 1448, 1430, 1214, 1181, 1133, 1008, 986, 745, 680. HRMS *calcd* for ($C_{14}H_{17}BrO_2$+Na): 319.0310, *found* 319.0296.



Methyl 1-(2-bromo-5-nitrophenyl)cyclohexanecarboxylate (237). HNO_3 (3.70 mL, 37.4 mmol) was added to a solution of methyl 1-(2-bromophenyl)cyclohexanecarboxylate (2.20 g, 7.50 mmol) in H_2SO_4 (27 mL) and CH_3CO_2H (48 mL) in a flask equipped with a magnetic bar. The reaction mixture was stirred overnight under reflux and then it was allowed to reach room temperature. Then, H_2O (40 mL) and EtOAc (20 mL) were added to the crude mixture. The aqueous phase was back-extracted with EtOAc (2 x 10 mL) and the combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel 10:1 hexanes/ethyl acetate to afford the title compound as a single diastereoisomer, as a white solid (1.20 g, 47% yield). Mp = 122.5-123.6 ºC. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.38 (d, *J* = 2.6 Hz, 1H), 7.95 (dd, *J* = 8.7, 2.6 Hz, 1H), 7.73 (d, *J* = 8.7 Hz, 1H), 3.64 (s, 3H), 2.45 (m, 2H), 1.96 (m, 2H), 1.83 (m, 2H) 1.62 (m, 3H), 1.42 (m, 1H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 174.9, 147.1, 145.6, 135.6, 130.9, 123.5, 122.6, 52.3, 51.8, 33.7, 25.4, 22.2 ppm. IR (neat, cm^{-1}): 2935, 1734, 1512, 1490, 1340, 1207, 1048, 883, 737, 645. Anal. Calcd for $C_{14}H_{16}BrNO_4$: C, 49.14; H, 4.71. Found: C, 48.89; H, 4.88. According to the observed NOE of H_a with the hydrogens of the cyclohexyl ring, the compound corresponded to the title compound:

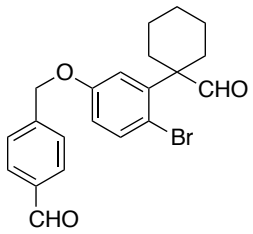


(1-(2-Bromo-5-nitrophenyl)cyclohexanecarbaldehyde (238). To a well-stirred solution of methyl 1-(2-bromo-5-nitrophenyl)cyclohexanecarboxylate (0.98 g, 2.57 mmol) in CH_2Cl_2 (20 mL) under nitrogen atmosphere was added dropwise DIBALH (7.0 mL, 7.0 mmol, 1M in hexanes) at -78 ºC. After 4 h of stirring, the reaction mixture was quenched with 2M HCl (10 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic phases were dried over $MgSO_4$ and evaporated under reduced pressure. The crude alcohol thus obtained was used directly in the next step without further purification. A flask equipped with a magnetic stirring bar was charged with 1-(2-bromo-5-nitrophenyl)cyclohexenylmethanol (0.75 g, 2.40 mmol) and CH_2Cl_2 (10 mL). Then, SiO_2 (1.30 g) and PCC (1.03 g, 4.8 mmol) were added under argon atmosphere. The reaction mixture was stirred overnight at room temperature and then the crude was filtered over silica gel, eluting with CH_2Cl_2. The residue was purified by flash chromatography 8:2 hexanes/ethyl acetate to afford **1l** as a yellow pale solid (0.60 g, 80% overall yield). Mp= 98.8-99.6 ºC. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 10.0 (s, 1H), 8.38 (d, *J* = 2.6 Hz, 1H), 8.0 (dd, *J* = 8.7, 2.7 Hz, 1H), 7.78 (d, *J* = 8.7 Hz, 1H), 2.39 (m, 2H), 2.02 (m, 2H), 1.76 (m, 5H) 1.51 (m, 1H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 202.3, 147.3, 144.9, 135.8, 130.5, 124.7, 123.3, 54.8, 31.7, 25.3, 22.2 ppm. IR (neat, cm^{-1}): 2935, 2846, 1734, 1512, 1340, 1207, 1129, 883, 867, 753, 737, 645. Anal. Calcd for $C_{13}H_{14}BrNO_3$: C, 50.02; H, 4.52. Found: C, 50.39; H, 4.22.

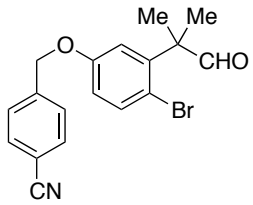


1-(2-bromo-5-(2-oxo-2-phenylethoxy)phenyl) cyclohexanecarbaldehyde (303). Following general procedure A, 1-(2-bromo-5-hydroxyphenyl) cyclohexane carbaldehyde (1.4 g, 4.9 mmol), K_2CO_3 (0.44 g, 5.9 mmol), sodium iodide (0.15 g, 0.98 mmol), 2-bromoacetophenone (1.1 g, 5.4 mmol) and acetonitrile (2mL/1.0 mmol) were used. Column chromatography: silica gel (5:1 hexanes/ethyl acetate). Yellow pale solid; yield: 1.77 g (90% yield). Mp=81.5-82.6 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.91 (s, 1H), 8.00 (d, *J* = 7.5 Hz, 2H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.53 (t, *J* = 7.7 Hz, 2H), 7.46 (d, *J* =

8.7 Hz, 1H), 7.16 (d, *J* = 3.0 Hz, 1H), 6.68 (dd, *J* = 8.7, 3.0 Hz, 1H), 5.28 (s, 2H), 2.40–2.23 (m, 2H), 2.02–1.83 (m, 2H), 1.80–1.55 (m, 5H), 1.42 (tt, *J* = 14.9, 7.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.0, 194.0, 157.5, 144.0, 135.4, 134.4, 134.1, 128.9, 128.1, 118.0, 114.6, 113.9, 70.9, 54.7, 31.5, 25.5, 22.3. IR (neat, cm^{-1}): 2926, 2862, 1712, 1692, 1586, 1446, 1306, 1216, 1178, 963, 814, 751, 682, 618. HRMS *calcd* for [$C_{21}H_{21}BrO_3$+Na] 423.0572, *found* 423.0552.

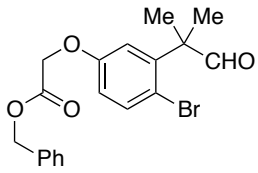


4-((4-bromo-3-(1-formylcyclohexyl)phenoxy)methyl) benzaldehyde (304). Following general procedure A, 4-((4-bromo-3-(1-cyanocyclohexyl) phenoxy)methyl) benzonitrile (1.5 gr, 3.9 mmol) and dichloromethane (4 mL/1.0 mmol), DIBALH (14.1 mL, 14.1 mmol, 1M in hexanes). Column chromatography: silica gel (2:1 hexanes/ethyl acetate). Yellow oil; yield 1.12 g (71%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.04 (s, 1H), 9.94 (s, 1H), 7.93 (d, *J* = 8.1 Hz, 2H), 7.61 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 8.7 Hz, 1H), 7.13 (d, *J* = 3.0 Hz, 1H), 6.75 (dd, *J* = 8.7, 2.9 Hz, 1H), 5.15 (s, 2H), 2.37 -2.26 (m, 2H), 1.99-1.88 (m, 2H), 1.79-1.56 (m, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 203.9, 191.6, 157.6, 143.7, 143.2, 135.9, 135.3, 135.1, 129.9, 129.8, 127.4, 127.3, 113.9, 69.3, 54.4, 31.4, 22.2. IR (neat, cm^{-1}): 3390, 2930, 2857, 1692, 1607, 1591, 1567, 1454, 1387, 1280, 1232, 1207, 1173, 1012, 810, 730. HRMS *calcd* for [$C_{21}H_{21}BrO_3$+Na] 423.0572, *found* 423.0590.



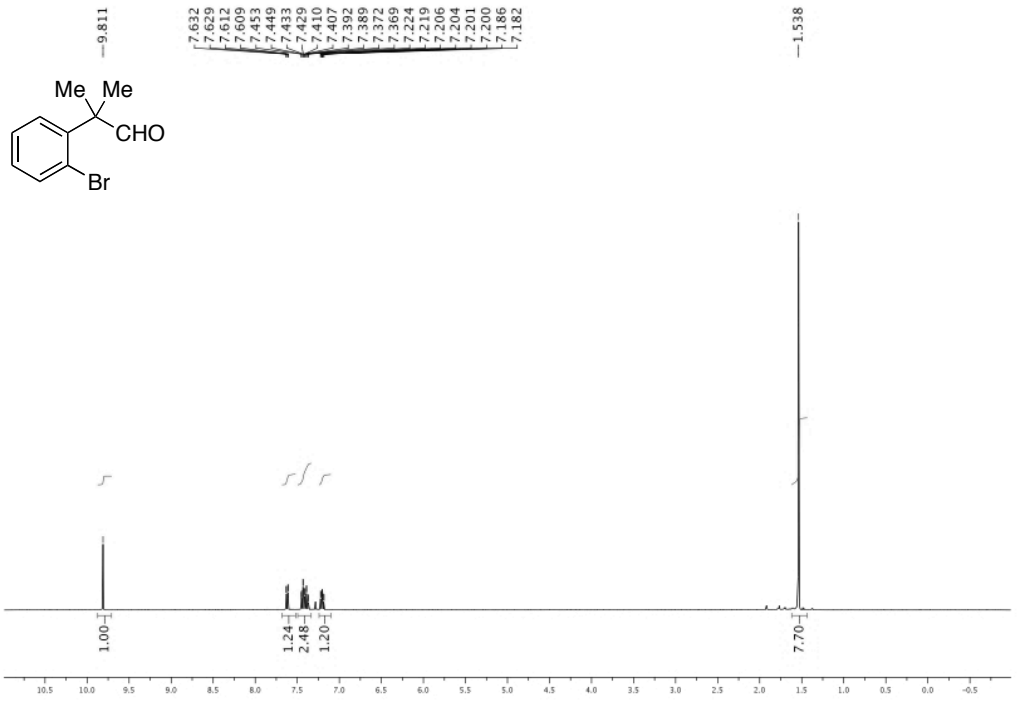
4-((4-bromo-3-(1,1-dimethyl-2-oxoethyl)phenoxy) methyl))benzonitrile (305). Following general procedure A, 2-(2-bromo-5-hydroxyphenyl)-2-methylpropanal (1.90 g, 7.80 mmol), K_2CO_3 (0.70 g, 9.40 mmol), sodium iodide (0.23 g, 1.60 mmol), 4-(bromomethyl)benzonitrile (1.50 g, 7.80 mmol) and acetonitrile (2 mL/1.0 mmol) were used. Column chromatography: silica gel (6:1 hexanes/ethyl acetate). White solid; yield 2.14 g (77%). Mp = 95.1-98.4 ^{o}C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.79 (s, 1H), 7.75-7.67 (m,

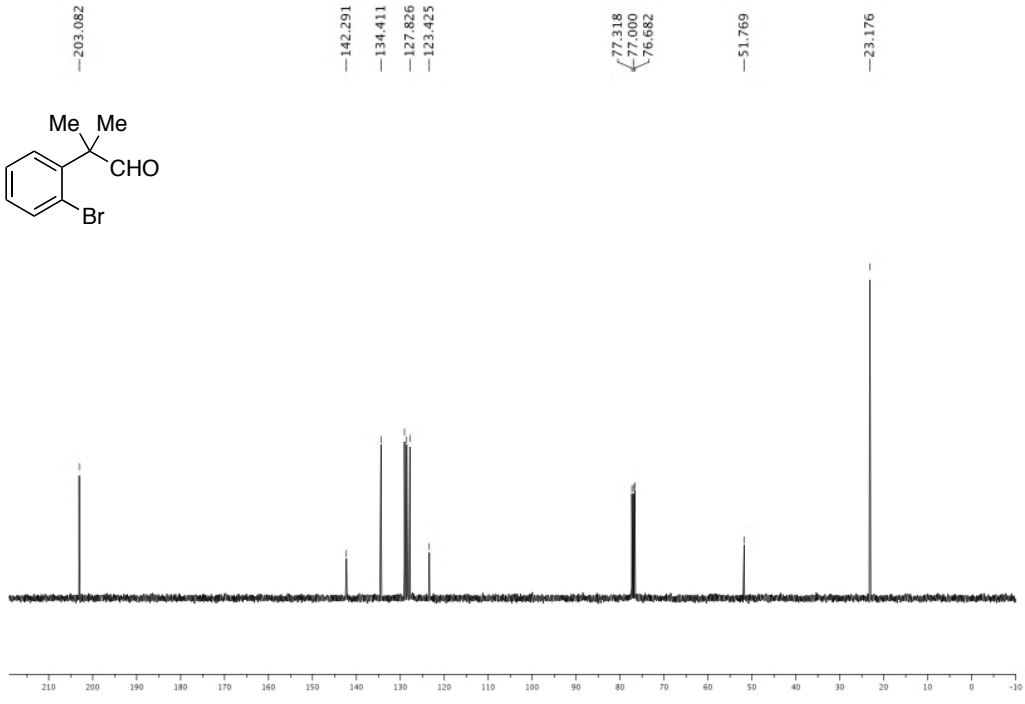
2H), 7.56 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.7 Hz, 1H), 7.05 (d, *J* = 3.0 Hz, 1H), 6.76 (dd, *J* = 8.7, 3.0 Hz, 1H), 5.13 (s, 2H), 1.51 (s, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 202.8, 157.8, 143.9, 141.8, 135.1, 132.5, 127.6, 118.5, 116.7, 114.5, 114.2, 112.0, 69.2, 51.7, 23.2. IR (neat, cm^{-1}): 3458, 3415, 2968, 2926, 2870, 2225, 1716, 1597, 1566, 1459, 1374, 1289, 1209, 1036, 1017, 899, 804. HRMS *calcd* for [$C_{18}H_{16}BrNO_2$+Na] 380.0262, *found* 380.0276.

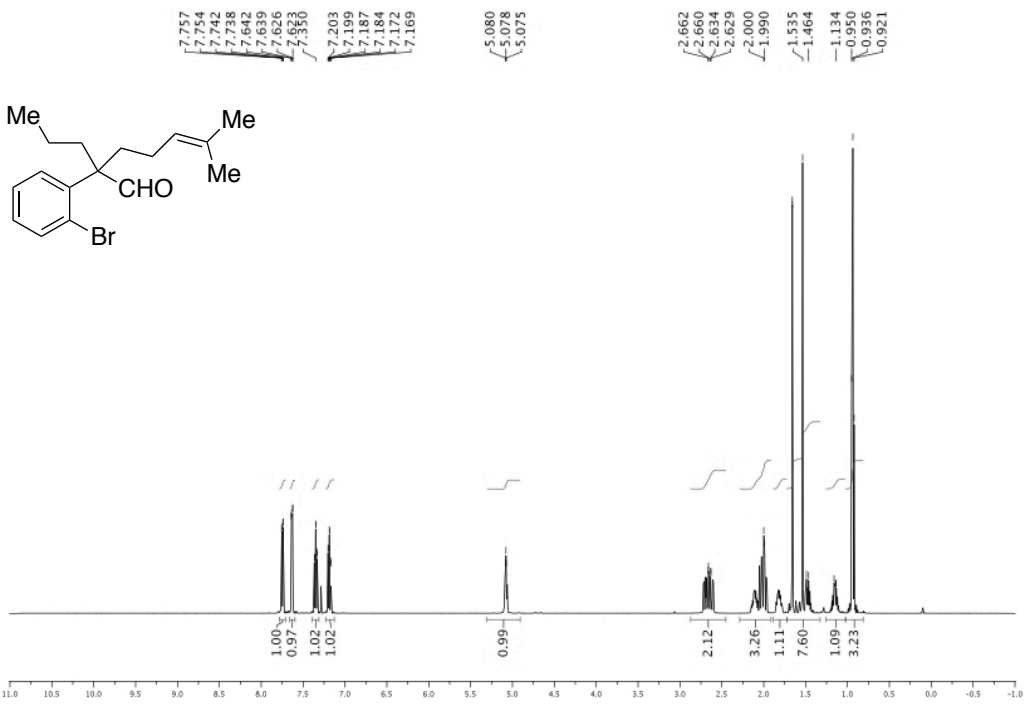


Benzyl 2-(4-bromo-3-(1,1-dimethyl-2-oxoethyl) phenoxy)acetate (306). Following general procedure A, 2-(2-bromo-5-hydroxyphenyl)-2-propylpentanal (2.0 g, 8.4 mmol), K_2CO_3 (0.75 g, 10.0 mmol), sodium iodide (0.23 g, 1.6 mmol), benzyl bromoacetate (1.34 mL, 8.4 mmol) and acetonitrile (2mL/1.0 mmol) were used. Column chromatography: silica gel (5:1 hexanes/ethyl acetate). Colorless oil; yield: 2.7 g (85% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.75 (s, 1H), 7.47 (d, *J* = 8.7 Hz, 1H), 7.40-7.33 (m, 5H), 7.02 (d, *J* = 3.0 Hz, 1H), 6.67 (dd, *J* = 8.7, 3.0 Hz, 1H), 5.26 (s, 2H), 4.67 (s, 2H), 1.46 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.7, 168.3, 157.4, 143.8, 135.0, 128.6, 116.7, 114.9, 114.0, 65.5, 51.7, 23.1. IR (neat, cm^{-1}): 3034, 2975, 2806, 2705, 1756, 1724, 1594, 1569, 1460, 1296, 1181, 1081, 1020, 958, 733, 699. HRMS *calcd* for [$C_{19}H_{19}BrO_4$+Na] 413.0364, *found* 413.0369.

2.8.3 Selected examples of NMR spectra



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7.639
7.626
7.623
7.350
7.203
7.199
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7.184
7.172
7.169
5.080
5.078
5.075
2.662
2.660
2.634
2.629
2.000
1.990
1.535
1.464
1.134
0.950
0.936
0.921
Me
Me
Me
CHO
Br
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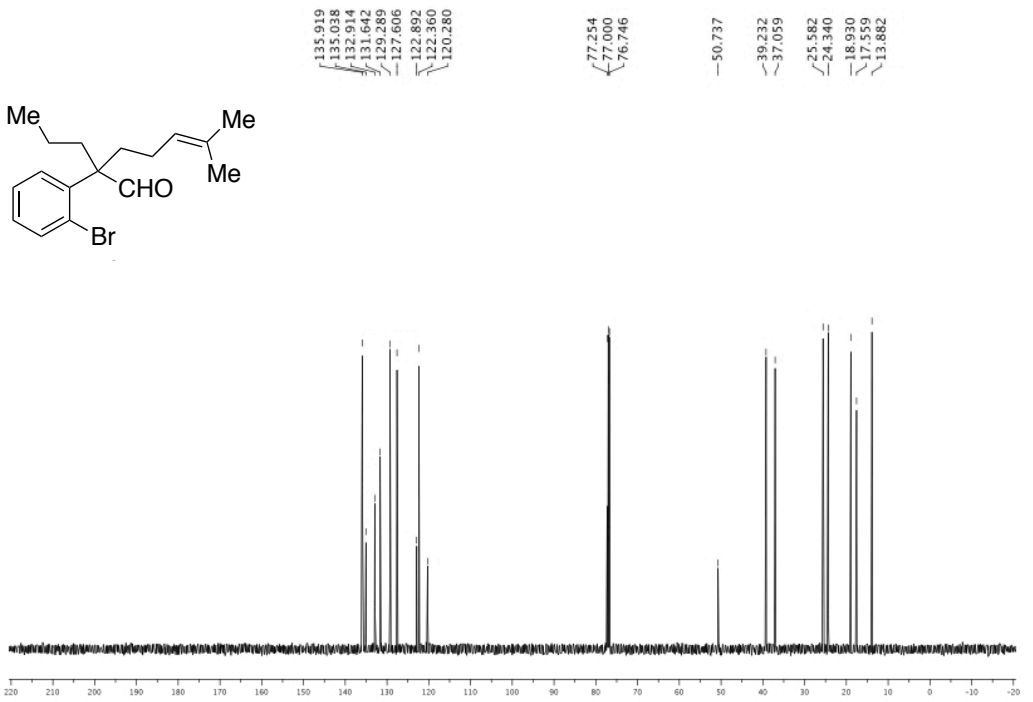
1.02
1.02
0.99
2.12
3.26
1.11
7.60
1.09
3.23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77.000
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50.737
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37.059
25.582
24.340
18.930
17.559
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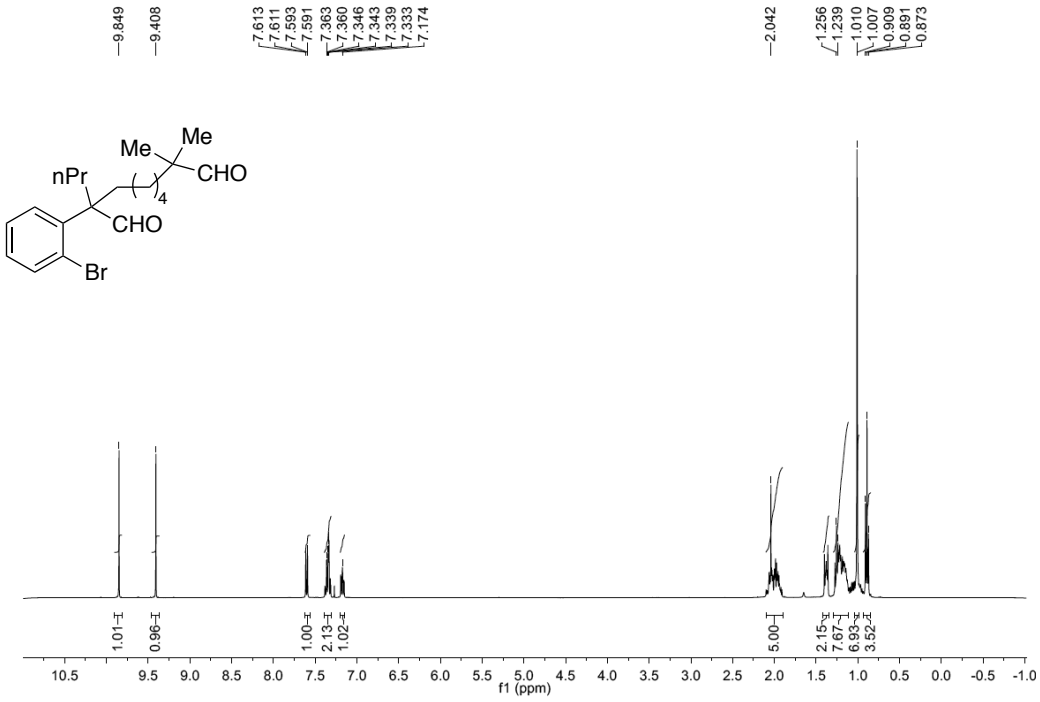
Me
Me
CHO
Br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7.591
7.363
7.360
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7.343
7.339
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7.174
2.042
1.256
1.239
1.010
1.007
0.909
0.891
0.873
Me
Me
nPr
CHO
4
CHO
Br
1.01
0.96
1.00
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1.02
5.00
2.15
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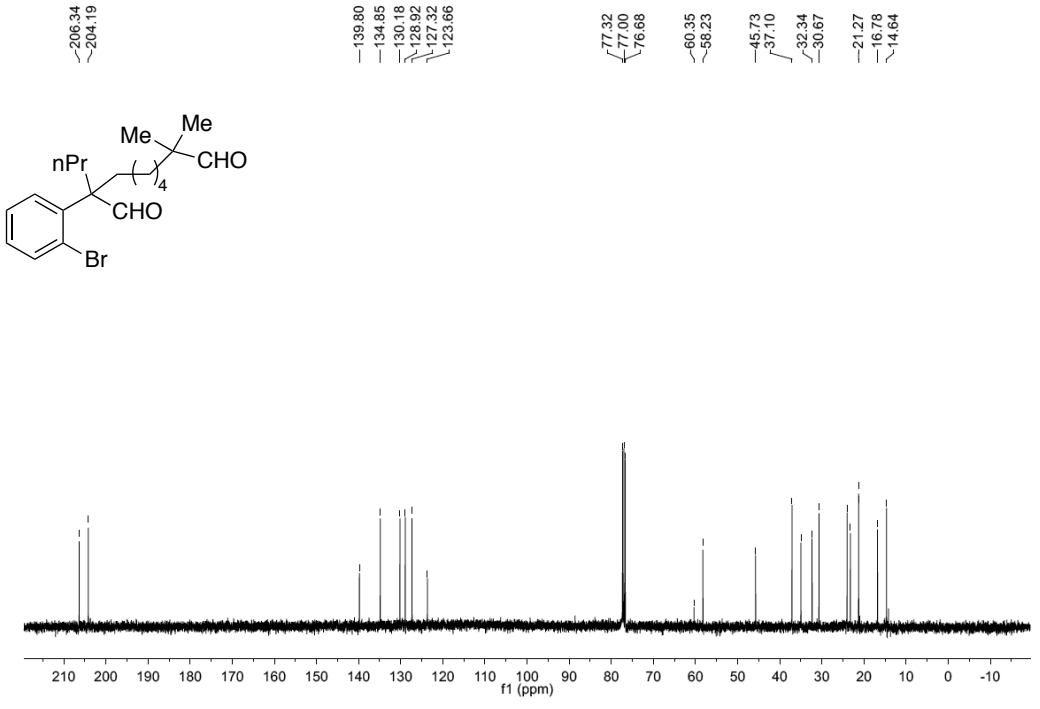
6.93
3.52
f1 (ppm)


206.34
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130.18
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123.66
77.32
77.00
76.68
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58.23
45.73
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21.27
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Me
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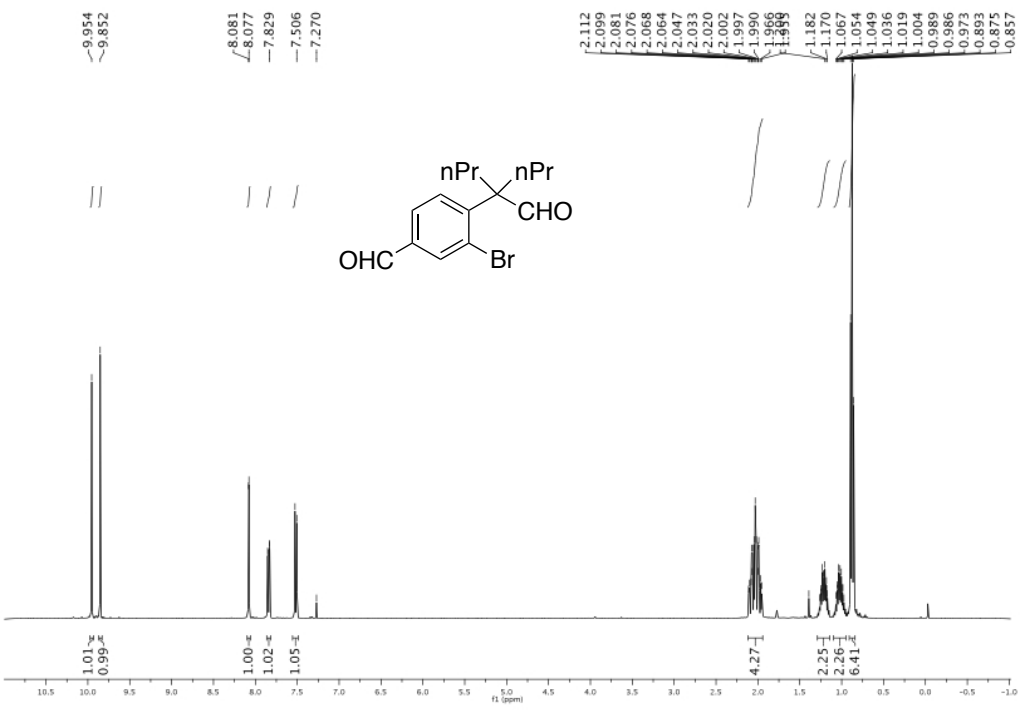
f1 (ppm)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CHO
OHC
Br
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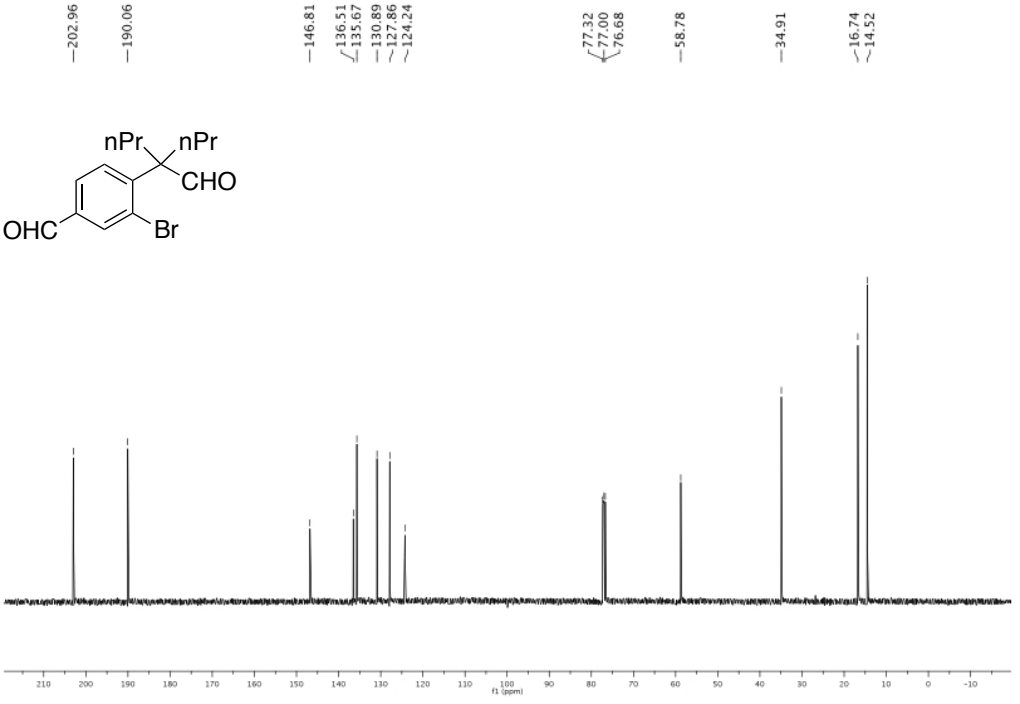
0.99
1.00
1.02
1.05
4.27
2.25
2.26
6.41
f1 (ppm)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190.06
146.81
136.51
135.67
130.89
127.86
124.24
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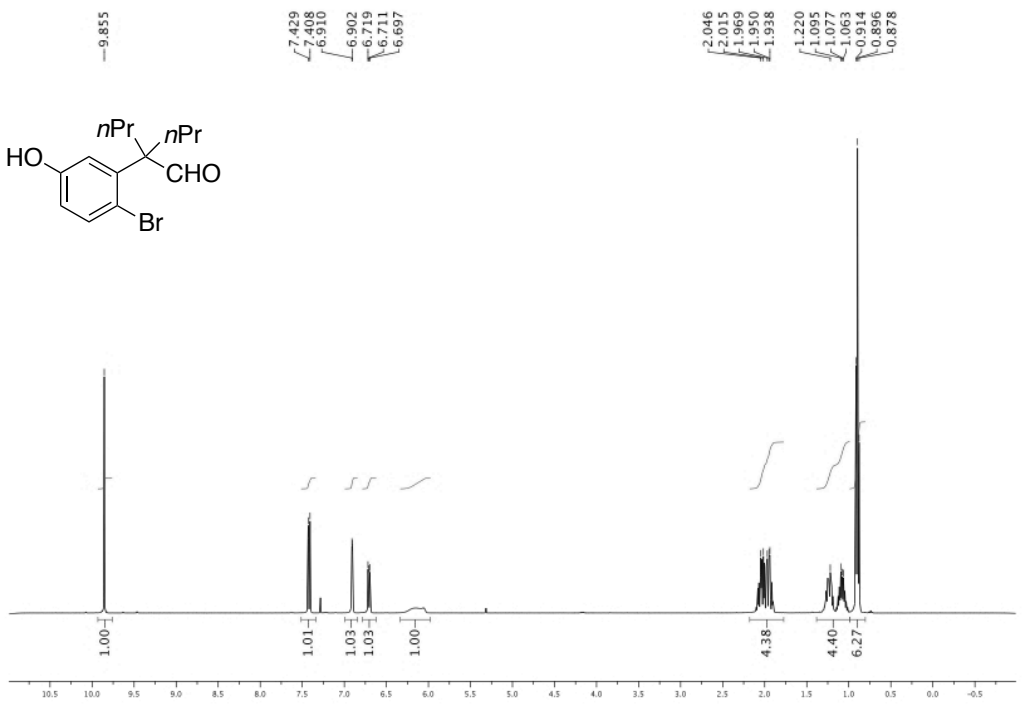
77.00
76.68
58.78
34.91
16.74
14.52
nPr
nPr
CHO
OHC
Br
f1 (ppm)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7.429
7.408
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6.719
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6.697
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1.938
1.220
1.095
1.077
1.063
0.914
0.896
0.878
nPr
nPr
HO
CHO
Br
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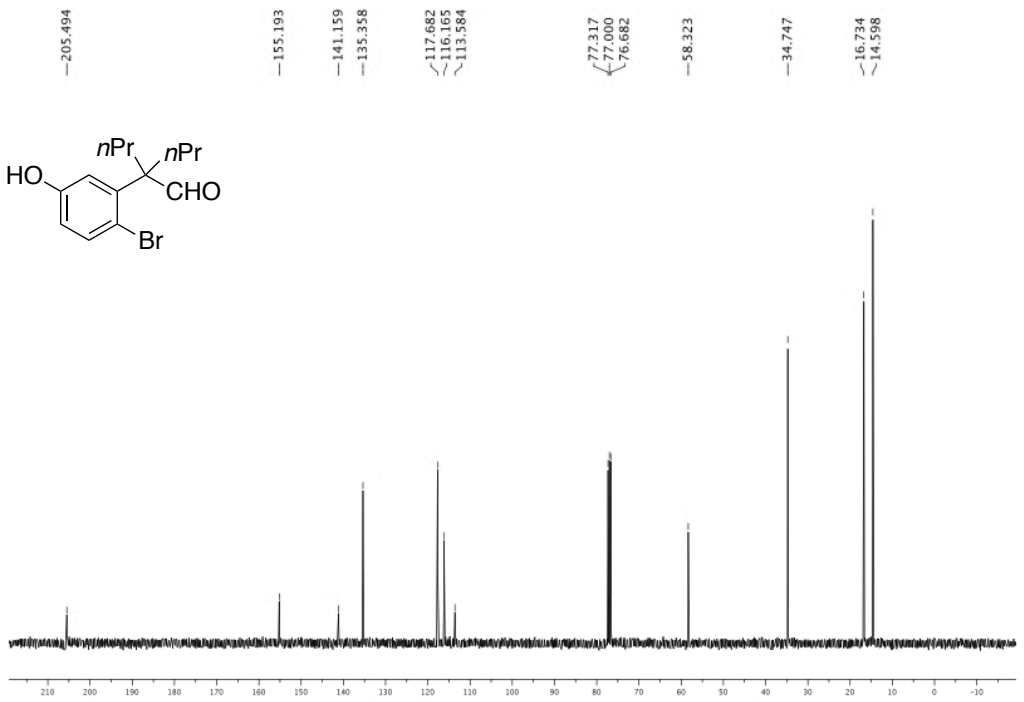
1.01
1.03
1.03
1.00
4.38
4.40
6.27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155.193
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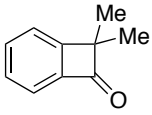
117.682
116.165
113.584
77.317
77.000
76.682
58.323
34.747
16.734
14.598
nPr
nPr
HO
CHO
Br

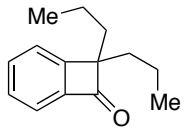
2.8.4 Synthesis of Benzocyclobutenones

General procedure C for the synthesis of benzocyclobutenones via Pd-catalyzed intramolecular acylation of aryl bromides (Tables 7-9) An oven-dried screw-cap test tube containing a stirring bar was charged with $Pd(OAc)_2$ (2.3 mg, 2.0 mol%), *rac*-BINAP **(173)** (9.5 mg, 3.0 mol%), Cs_2CO_3 (0.23 g, 0.60 mmol) and the aryl bromide (0.50 mmol), if a solid. The test tube was evacuated and back-filled with dry argon (this sequence was repeated three times). The aryl bromide (if liquid) and dioxane (2 mL) were then added by syringe. The mixture was then placed in ultrasounds apparatus for 1 min and the mixture was then stirred in a pre-heated oil bath (110 ^{o}C) for 14 h. The mixture was then allowed to warm to room temperature, diluted with EtOAc (5 mL) and filtered through a Celite® plug, eluting with additional EtOAc (10 mL). The filtrate was concentrated and purified by column chromatography on silica gel (eluting with hexanes/ethyl acetate mixtures).

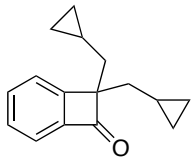
General procedure D for the synthesis of benzocyclobutenones via Pd-catalyzed intramolecular acylation of aryl bromides (Tables 7-9). General procedure A was followed, but $Pd(OAc)_2$ (4.6 mg, 4.0 mol%) and *rac*-^{i}Pr-BINAP **(176)** (14.6 mg, 6.0 mol%) were used.



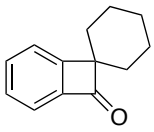
8,8-Dimethylbicyclo[4.2.0]octa-1,3,5-trien-7-one (151). Following general procedure C, 2-(2-bromophenyl)-2-methylpropanal (113 mg, 0.50 mmol) was used. Column chromatography: silica gel, 16:1 hexanes/ethyl acetate. Colorless oil; yield: 58 mg (80% yield). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.53-7.46 (m, 2H), 7.44-7.37 (m, 2H), 1.47 (s, 3H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 196.7, 162.8, 144.4, 135.2, 129.1, 121.5, 121.4, 65.3, 22.7 ppm. IR (neat, cm^{-1}): 2958, 2924, 2857, 1743, 1581, 1458, 1363, 1336, 1285, 1233, 1165, 1132, 1088, 1041, 1018, 962. Anal. Calcd for $C_{10}H_{10}O$: C, 82.16; H, 6.89. Found: C, 81.83; H, 6.98.



8,8-Dipropylbicyclo[4.2.0]octa-1,3,5-trien-7-one (240). Following general procedure C, 2-(2-bromophenyl)-2-propylpropanal (141 mg, 0.50 mmol) was used. Column chromatography: silica gel, 15:1 hexanes/ethyl acetate. Colorless oil; yield: 95 mg (94% yield).^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.49 (td, *J* = 6.0, 0.8 Hz, 1H), 7.44 (dt, *J* = 6.0, 0.8 Hz, 1H), 7.41 (td, *J* = 6.0, 0.8 Hz, 1H), 7.36 (dt, *J* = 6.0, 0.8 Hz, 1H), 1.77 (m, 4H), 1.24 (m, 4H), 0.87 (t, *J* = 6.0 Hz, 6H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 197.0, 160.4, 145.9, 134.9, 129.0, 122.9, 120.7, 74.0, 37.1, 18.9, 14.5 ppm. IR (neat, cm^{-1}): 3087, 2976, 2856, 1745, 1634, 1566, 1478, 1415, 1285, 1234, 1180, 1144, 1032, 1019, 966. Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 82.77; H, 9.14.

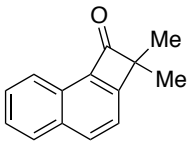


8,8-Bis(cyclopropylmethyl)bicyclo[4.2.0]octa-1,3,5-trien-7-one (241). Following general procedure C, 2-(2-bromophenyl)-3-cyclopropyl-2-(cyclopropylmethyl) propanal (153 mg, 0.50 mmol) was used. Column chromatography: silica gel, 18:1 hexanes/ethyl acetate. Colorless oil; yield: 108 mg (96% yield). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.57-7.40 (m, 4H), 1.93 (dd, *J* = 14.4, 6.4 Hz, 2H), 1.68 (dd, *J* =14.4, 7.6 Hz, 2H), 056 (m, 2H), 0.33 (m, 4H), 0.05 (m, 4H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 196.9, 160.3, 146.1, 134.6, 128.8, 123.5, 120.5, 74.8, 39.8, 7.6, 4.9, 4.5 ppm. IR (neat, cm^{-1}): 3075, 3001, 2899, 1747, 1581, 1459, 1438, 1335, 1301, 1265, 1168, 1141, 1100, 1046, 1017, 944. HRMS *calcd* for ($C_{16}H_{18}O$ +Na): 249.1255, *found* 249.1248**.**

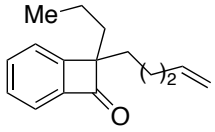


8,8-Cyclohexylbicyclo[4.2.0]octa-1,3,5-trien-7-one (242). Following general procedure C, 1-(2-bromophenyl)-cyclohexanecarbaldehyde (133 mg, 0.50 mmol) was used. Column chromatography: silica gel, 15:1 hexanes/ethyl acetate. Colorless oil; yield: 91 mg (98% yield). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.55 (d, *J* = 7.2 Hz, 1H), 7.50 (t, *J* = 7.2 Hz, 1H), 7.42 (d, *J* = 7.6 Hz, 1H), 7.39 (t, *J* = 6.0 Hz, 1H), 1.94-1.79 (m, 6H), 1.65-1.49 (m, 4H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 196.7, 162.4, 144.8, 134.8, 129.0,

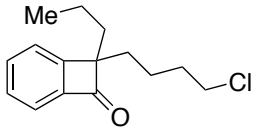
122.6, 11.3, 70.8, 32.6, 25.7, 23.6 ppm. IR (neat, cm^{-1}): 3064, 2925, 2850, 1749, 1579, 1458, 1364, 1333, 1271, 1165, 1105, 1044, 968. Anal. Calcd for $C_{13}H_{14}O$: C, 83.83; H, 7.58. Found: C, 84.07; H, 7.31.



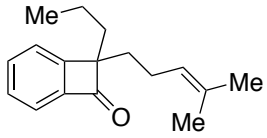
2,2-Dimethylcyclobuta[a]naphthalen-1(2H)one (243). Following general procedure C, 2-(1-bromo-2-naphthyl)-2-methylpropanal (138 mg, 0.50 mmol), $Pd(OAc)_2$ (4.6 mg, 4.0 mol%), **L18** (19.0 mg, 6.0 mol%) were used. Column chromatography: silica gel, 9:1 hexanes/ethyl acetate. Colorless oil; yield: 63 mg (64% yield). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.14 (d, *J* = 8.0 Hz, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.66 (td, *J* = 7.2, 1.2 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.54 (td, *J* = 7.2, 1.2 Hz, 1H), 1.56 (s, 6H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 194.8, 164.9, 139.4, 137.0, 133.9, 129.2, 129.0, 126.6, 126.5, 124.4, 118.9, 64.6, 22.8 ppm. IR (neat, cm^{-1}): 2958, 2891, 1752, 1677, 1631, 1562, 1458, 1439, 1376, 1258, 1206, 1141, 1046, 1015, 981. Anal. Calcd for $C_{14}H_{12}O$: C, 85.68; H, 6.16. Found: C, 85.96; H, 6.02.



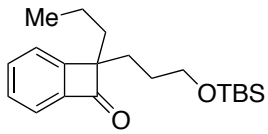
8-(4-Pentenyl)-8-propylbicyclo[4.2.0]octa-1,3,5-trien-7-one (248). Following general procedure C, 2-(2-bromophenyl)-2-propyl-6-heptenal (154 mg, 0.50 mmol), $Pd(OAc)_2$ (4.6 mg, 4.0 mol%) and **(173)** (19.0 mg, 6.0 mol%) were used. Column chromatography: silica gel, 5:1 hexanes/ethyl acetate. Colorless oil; yield: 89 mg (78% yield, *E*/*Z*=9:1).^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.55-7.36 (m, 4H), 5.74 (m, 1H), 4.95 (m, 2H), 2.03 (dd, *J* = 14.0, 7.2 Hz, 2H), 1.82 (m, 4H), 1.39-1.23 (m, 4H), 0.89 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 196.8, 160.2, 145.8, 138.2, 134.9, 129.0, 122.9, 120.7, 114.7, 73.7, 37.1, 34.4, 34.0, 24.8, 18.8, 14.4 ppm. IR (neat, cm^{-1}): 3011, 2956, 2930, 2871, 1749, 1638, 1581, 1459, 1439, 1338, 1272, 1166, 1142, 1094, 990, 911. Anal. Calcd for $C_{16}H_{20}O$: C, 84.16; H, 8.83. Found: C, 83.87; H, 8.96.



8-(4-Chlorobutyl)-8-propylbicyclo[4.2.0]octa-1,3,5-trien-7-one (249). Following general procedure C, 2-(2-bromophenyl)-6-chloro-2-propylhexanal (165 mg, 0.50 mmol), $Pd(OAc)_2$ (4.6 mg, 4.0 mol%) and rac-^{i}Pr-BINAP **L21** (6.0 mol%) were used was used. Column chromatography: silica gel, 9:1 hexanes/ethyl acetate. Colorless oil; yield: 96 mg (77% yield). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.54-7.37 (m, 4H), 3.47 (t, *J* = 6.8 Hz, 2H), 1.85 (m, 6H), 1.71 (m, 2H), 1.27 (m, 2H), 0.86 (t, *J* = 7.6 Hz, 3H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 196.5, 160.0, 145.8, 135.0, 129.2, 122.9, 120.8, 73.6, 44.5, 37.0, 34.0, 32.8, 22.8, 18.9, 14.4 ppm. IR (neat, cm^{-1}): 3063, 2955, 2931, 2879, 1747, 1581, 1459, 1376, 1309, 1275, 1167, 1142, 1102, 1081, 1019, 884. HRMS *calc. for* ($C_{15}H_{19}ClO$+Na): 273.1022, *found* 273.1011**.**

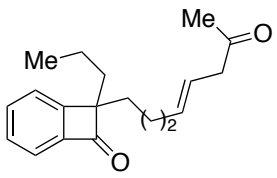


8-(4-Methyl-3-pentenyl)-8-propylbicyclo[4.2.0]octa-1,3,5-trien-7-one (250). Following general procedure C, 2-(2-bromophenyl)-6-methyl-2-propyl-5-heptenal (161 mg, 0.50 mmol) was used. Column chromatography: silica gel, 18:1 hexanes/ethyl acetate. Colorless oil; yield: 98 mg (81% yield). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.56-7.37 (m, 4H), 5.03 (tt, *J* = 7.2, 1.2 Hz, 1H), 1.96-1.79 (m, 6H), 1.65 (s, 3H), 1.48 (s, 3H), 1.29 (m, 2H), 0.90 (t, *J* = 7.6 Hz, 3H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 196.7, 160.2, 146.0, 134.8, 131.9, 129.0, 123.9, 123.0, 120.7, 73.8, 37.2, 34.6, 25.5, 24.3, 18.8, 17.4, 14.5 ppm. IR (neat, cm^{-1}): 2958, 2929, 2872, 1748, 181, 1459, 1377, 1229, 1143, 976, 911. HRMS *calcd* for ($C_{17}H_{22}O$+Na): 265.1568, *found* 265.1577.

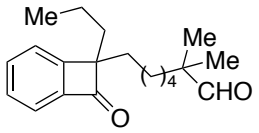


8-(3-(*tert*-Butyl(dimethylsilyl)oxy)propyl-8-propyl-bicyclo[4.2.0]octa-1,3,5-trien-7-one (251). Following general procedure C, 2-(2-bromophenyl)-5-*tert*-butyl(dime-thylsilyl)oxy-2-propylpentanal (206 mg, 0.50 mmol) was used. Column chromatography: silica gel, 18:1 hexanes/ethyl acetate. Colorless oil; yield: 161 mg (97% yield). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.57-7.39 (m, 4H), 3.59 (t, *J* = 6.4 Hz, 2H), 1.86 (m, 4H), 1.49 (m, 2H), 1.29 (m, 2H), 0.91 (t, *J* = 6.4 Hz, 3H), 0.90 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 196.8, 160.3, 145.9, 135.0, 129.1, 123.0, 120.8, 73.5, 63.2, 37.1, 31.1, 28.8, 25.9, 18.9, 18.3, 14.5,

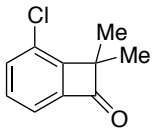
-5.3 ppm. IR (neat, cm^{-1}): 3065, 2954, 2928, 1752, 1582, 1460, 1386, 1360, 1302, 1252, 1166, 1142, 1096, 1005, 966. Anal. Calcd for $C_{20}H_{32}O_2Si$: C, 72.23; H, 9.70. Found: C, 72.49; H, 9.53.



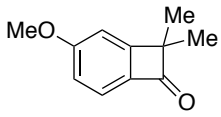
8-[(4*E*)-8-Oxo-4-nonenyl]-8-propylbicyclo[4.2.0]octa-1,3,5-trien-7-one (252). Following general procedure D, 2-(2-Bromophenyl)-2-propyl-10-oxo-6-undecenal (63.2 mg, 0.17 mmol), $Pd(OAc)_2$ (4.6 mg, 4.0 mol%) and **L18** (19.0 mg, 6.0 mol%) were used. Column chromatography: silica gel, 9:1 hexanes/ethyl acetate. Colorless oil; yield: 36 mg (79% yield, *E*/Z=9:1). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.50-7.46 (m, 1H), 7.42-7.37 (m, 2H), 7.34-7.32 (m, 1H), 5.32-5.26 (m, 2H), 2.44-2.41 (m, 2H), 2.24-2.17 (m, 2H), 2.09 (s, 3H), 1.94-1.87 (m, 2H), 1.76-1.72 (m, 4H), 1.30-1.11 (m, 4H), 0.84 (t, *J* = 7.2 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 208.4, 196.9, 160.3, 145.8, 134.9, 130.7, 129.0, 128.7, 122.9, 120.8, 73.7, 43.4, 37.0, 34.3, 32.7, 29.9, 26.7, 25.3, 18.8, 14.4. IR (neat, cm^{-1}): 1750, 1713, 1459. HRMS *calc. for* ($C_{20}H_{26}O_2$+Na): 321.1831, *found* 321.1826.



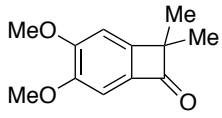
8-(6,6-Dimethylheptanal)-8-propylbicyclo[4.2.0]octa-1,3,5-trien-7-one (253). Following general procedure C, 2-(2-bromophenyl)-8,8-dimethyl-2-propylnonanedial (190 mg, 0.50 mmol), $Pd(OAc)_2$ (4.6 mg, 4.0 mol%) and **(173)** (19.0 mg, 6.0 mol%) were used. Column chromatography: silica gel, 10:1 hexanes/ethyl acetate. Colorless oil; yield: 121 mg (81% yield). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 9.4 (s, 1H), 7.45 (dd, *J* = 7.3, 0.95 Hz, 1H), 7.42 (m, 2H), 7.35 (d, *J* = 7.6 Hz, 1H), 1.76 (m, 4H), 1.40-1.36 (m, 2H), 1.26-1.18 (m, 8H), 0.99 (s, 6H), 0.86 (t, *J* = 7.3 Hz, 3H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 206.4, 196.9, 160.3, 145.9, 135.0, 129.0, 122.9, 120.8, 73.8, 45.8, 37.2, 37.1, 34.8, 30.6, 25.4, 24.1, 21.3, 21.3, 18.9, 14.5 ppm. IR (neat, cm^{-1}): 2957, 2930, 2858, 1753, 1726, 1582, 1460, 1143, 879, 761. Anal. Calcd for $C_{20}H_{28}O_2$: C, 79.96; H, 9.39. Found: C, 79.59; H, 9.56.



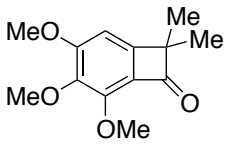
2-Chloro-8,8-dimethylbicyclo[4.2.0]octa-1,3,5-trien-7-one (255). Following general procedure C, 2-(2-bromo-6-chlorophenyl)-2-methylpropanal (130 mg, 0.50 mmol) was used. Column chromatography: silica gel, 15:1 hexanes/ethyl acetate. Colorless oil; yield: 57 mg (63% yield). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.49 (d, *J* = 8.0 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 1.61 (s, 6H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 195.1, 158.8, 146.2, 135.2, 130.7, 128.9, 119.8, 66.4, 21.5 ppm. IR (neat, cm^{-1}): 2953, 2921, 2855, 1737, 1647, 1582, 1490, 1463, 1422, 1264, 1209, 1188, 1099, 1033, 967. HRMS *calcd* for ($C_{10}H_9ClO$+Na): 203.0240, *found* 203.0233.



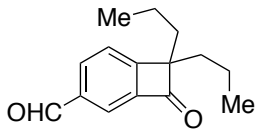
3-Methoxy-8,8-dimethylbicyclo[4.2.0]octa-1,3,5-trien-7-one (256). Following general procedure C, 2-(2-bromo-5-methoxyphenyl)-2-methylpropanal (128 mg, 0.50 mmol) was used. Column chromatography: silica gel, 8:1 hexanes/ethyl acetate. Colorless oil; yield: 85 mg (96% yield). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.29 (d, *J* = 8.8 Hz, 1H), 6.93 (m, 2H), 3.89 (s, 3H), 1.44 (s, 3H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 194.3, 165.5, 165.2, 135.9, 123.6, 117.9, 104.9, 63.7, 55.6, 22.5 ppm. IR (neat, cm^{-1}): 2958, 2866, 1737, 1576, 1474, 1458, 1436, 1361, 1332, 1285, 1217, 1176, 1104, 1049, 1015, 964. Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.70; H, 6.99.



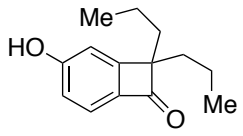
3,4-Dimethoxy-8,8-dimethylbicyclo[4.2.0]octa-1,3,5-trien-7-one (257). Following general procedure C, 2-(2-bromo-4,5-dimethoxyphenyl)-2-methylpropanal (143 mg, 0.50 mmol) was used. Column chromatography: silica gel, 5:1 hexanes/ethyl acetate. White solid; yield: 76 mg (74% yield). Mp = 53.5-54.4 ^{o}C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 6.93 (s, 1H), 6.82 (s, 1H), 3.97 (s, 3H), 3.84 (s, 3H), 1.41 (s, 6H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 194.0, 157.8, 155.9, 151.6, 134.8, 103.1, 103.0, 64.0, 56.3, 56.1, 22.8 ppm. IR (neat, cm^{-1}): 3088, 2954, 2922, 2880, 1736, 1575, 1469, 1436, 1415, 1377, 1361, 1343, 1294, 1236, 1204, 1178, 1117, 1051, 1019, 993, 868. Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 70.14; H, 6.68.



3,4,5-Trimethoxy-8,8-dimethylbicyclo[4.2.0]octa-1,3,5-trien-7-one (258). Following general procedure D, 2-(2-bromo-3,4,5-dimethoxyphenyl)-2-methylpropanal (157 mg, 0.50 mmol) was used. Column chromatography: silica gel, 4:1 hexanes/ethyl acetate. White solid; yield: 99 mg (85% yield). Mp = 82.0-82.9 ^{o}C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 6.60 (s, 1H), 4.17 (s, 3H), 3.94 (s, 3H), 3.78 (s, 3H), 1.42 (s, 6H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 190.2, 160.5, 157.6, 148.8, 137.7, 122.1, 97.0, 62.8, 60.7, 56.4, 22.6 ppm. IR (neat, cm^{-1}): 3097, 2929, 2858, 1739, 1594, 1563, 1478, 1464, 1406, 1345, 1305, 1236, 1202, 1186, 1173, 1132, 1045, 1032, 988. Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.47; H, 6.71.

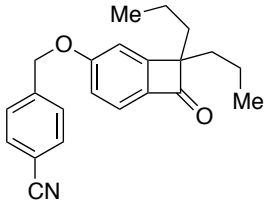


8-oxo-7,7-Dipropylbicyclo[4.2.0]octa-1,3,5-triene-3-carbaldehyde (259). Following general procedure C, 3-bromo-4-(4-formylheptan-4-yl)benzaldehyde (155 mg, 0.50 mmol), $Pd(OAc)_2$ (4.6 mg, 4.0 mol%) and **(173)** (19.0 mg, 6.0 mol%) were used. Column chromatography: silica gel, 14:1 hexanes/ethyl acetate. Colorless oil; yield: 82 mg (73% yield). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 10.05 (s, 1H), 8.08 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.83 (s, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 1.80 (ddd, *J* = 9.1, 6.5, 2.2 Hz, 4H), 1.30-1.16 (m, 4H), 0.86 (t, *J* = 7.3 Hz, 6H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 195.7, 191.1, 166.5, 146.9, 137.5, 135.7, 123.7, 122.4, 74.7, 36.8, 18.9, 14.4 ppm. IR (neat, cm^{-1}): 2958, 2930, 2872, 1761, 1699, 1598, 1079, 939, 835. HRMS *calcd* for ($C_{15}H_{18}O_2$+H): 231.1385, *found* 231.1379.

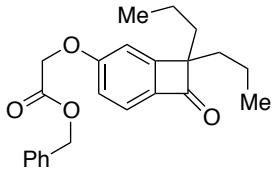


3-Hydroxy-8,8-dipropylbicyclo[4.2.0]octa-1,3,5-trien-7-one (260). Following general procedure C, 2-(2-bromo-5-hydroxyphenyl)-2-propylpentanal (148 mg, 0.50 mmol), $Pd(OAc)_2$ (4.6 mg, 4.0 mol%), **(173)** (19.0 mg, 6.0 mol%) and Cs_2CO_3 (0.46 g, 1.20 mmol) were used. Column chromatography: silica gel, 4:1 hexanes/ethyl acetate. White solid; yield: 57 mg (52% yield). Mp = 95.4-96.6 ^{o}C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.30 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.07 (brs, 1H), 6.97-6.94 (m, 2H), 1.77 (m, 4H), 1.28 (m, 4H), 0.90 (t, *J* = 7.2 Hz, 6H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 195.7,

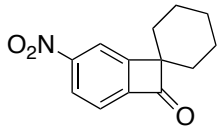
163.0, 162.5, 137.1, 123.4, 118.2, 109.3, 73.0, 37.0, 18.9, 14.5 ppm. IR (neat, cm^{-1}): 3227, 2959, 2929, 2871, 1713, 1600, 1571, 1461, 1375, 1316, 1291, 1268, 1251, 1225, 1192, 1138, 1111, 1041, 1003, 937, 894. Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.80; H, 8.49**.**



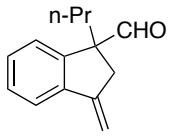
4-((7-Oxo-8,8-dipropylbicyclo[4.2.0]octa-1,3,5-trien-3-yl)oxy)methyl benzonitrile (261). Following general procedure C, 4-[4-bromo-3-(1-formyl-1-propylbutyl)phenolxy]methylbenzonitrile (206 mg, 0.50 mmol) was used. Column chromatography: silica gel, 4:1 hexanes/ethyl acetate. Colorless oil; yield: 117 mg (70% yield). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.76 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.06 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.01 (brs, 1H), 5.24 (s, 2H), 1.77 (m, 4H), 1.27 (m, 4H), 0.88 (t, *J* = 7.2 Hz, 6H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 194.4, 163.6, 163.0, 141.3, 138.5, 132.6, 127.6, 123.0, 118.5, 117.8, 112.1, 107.7, 72.6, 69.2, 37.0, 18.9, 14.5 ppm. IR (neat, cm^{-1}): 2956, 2929, 2870, 2228, 1742, 1580, 1508, 1455, 1416, 1378, 1333, 1273, 1235, 1187, 1088, 1017, 916. Anal. Calcd for $C_{22}H_{23}NO_2$: C, 79.25; H, 6.95. Found: C, 79.47; H, 6.74**.**



Benzyl-((7-oxo-8,8-dipropylbicyclo[4.2.0]octa-1,3,5-trien-3-yl)oxy)acetate (262). Following general procedure C, Benzyl [4-bromo-3-(1-formyl-1-propylbutyl)phenoxy] acetate (223 mg, 0.50 mmol) was used. Column chromatography: silica gel, 5:1 hexanes/ethyl acetate. Colorless oil; yield: 137 mg (75% yield). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.40 (m, 5H), 7.32 (d, *J* = 8.4 Hz, 1H), 6.97 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.91 (d, *J* = 2.0 Hz, 1H), 5.30 (s, 2H), 4.78 (s, 2H), 1.78 (m, 4H), 1.23 (m, 4H), 0.89 (t, *J* = 7.2 Hz, 6H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 194.4, 167.9, 163.2, 162.5, 138.7, 134.9, 128.7, 128.4, 122.9, 117.5, 107.8, 67.2, 65.4, 36.9, 18.8, 14.5 ppm. IR (neat, cm^{-1}): 2956, 2929, 2871, 1743, 1579, 1498, 1463, 1363, 1334, 1279, 1173, 1074, 960, 915. HRMS *calcd* for ($C_{23}H_{26}O_4$+Na): 389.1729, *found* 389.1721.

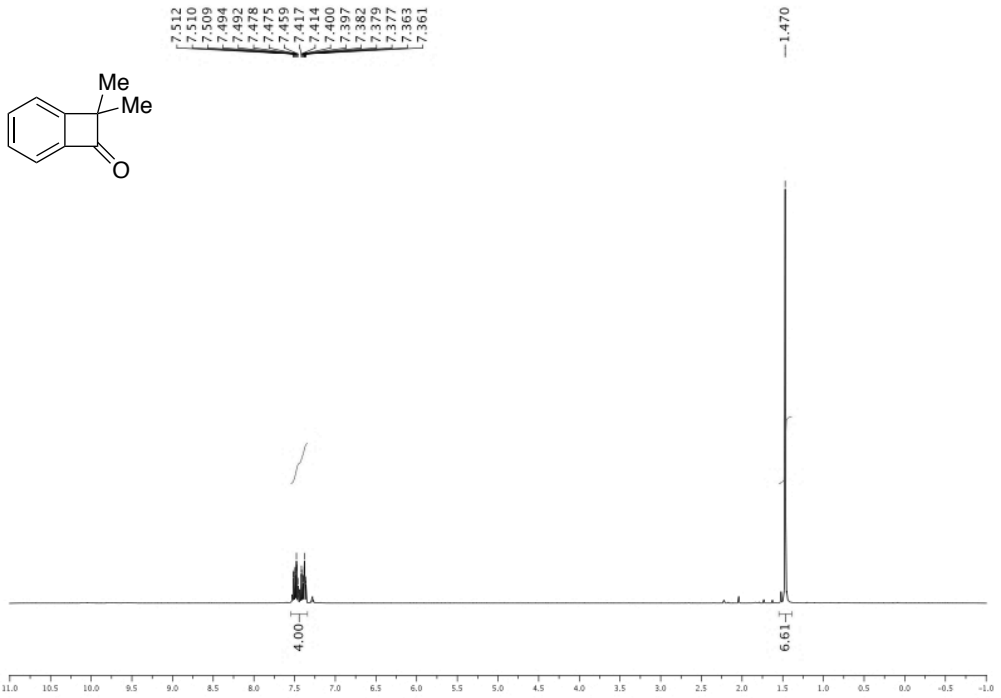


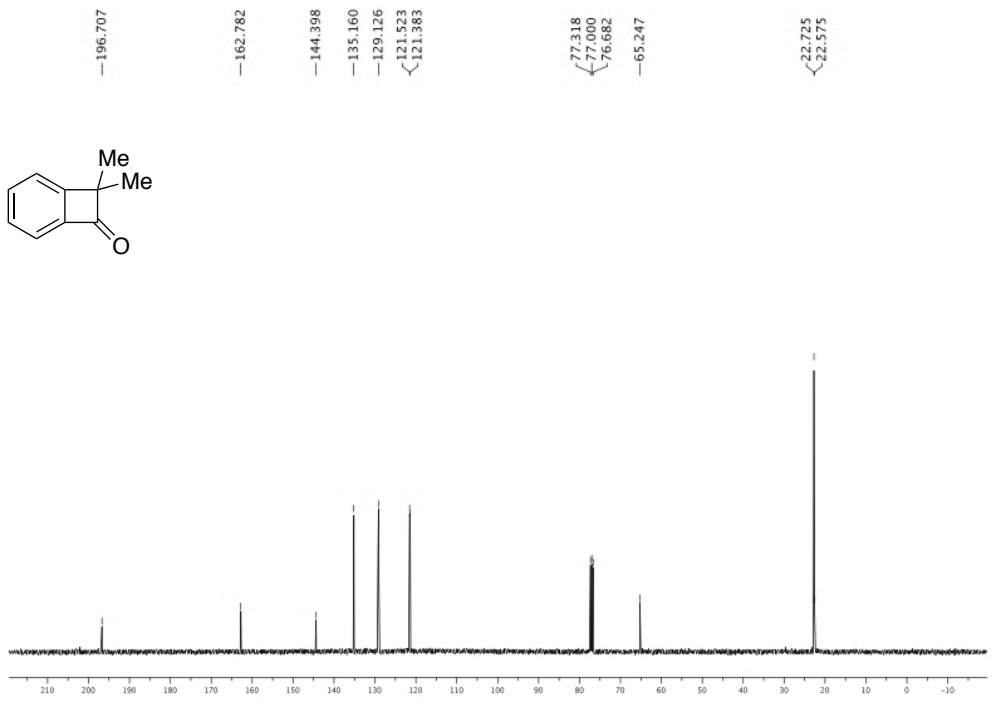
3-Nitro-8,8-cyclohexylbicyclo[4.2.0]octa-1,3,5-trien-7-one (263). Following general procedure D, (1-(2-bromo-5-nitrophenyl)cyclohexanecarbaldehyde (156 mg, 0.50 mmol) was used. Column chromatography: silica gel, 10:1 hexanes/ethyl acetate. Yellow pale solid; yield: 64 mg (60% yield). Mp= 82.5-83.1 ºC. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.34 (m, 1H), 8.33 (d, *J* = 1.8 Hz, 1H), 7.56 (d, *J* = 0.68 Hz, 1H), 1.97 (m, 2H), 1.85 (m, 4H), 1.74-1.56 (m, 4H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 194.3, 162.9, 151.6, 150.1, 125.1, 122.5, 118.1, 71.2, 32.2, 25.4, 23.4 ppm. IR (neat, cm^{-1}): 3085, 2929, 2849, 1763, 1522, 1448, 1332, 1107, 960, 902, 732, 655. Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67. Found: C, 67.35; H, 6.03.

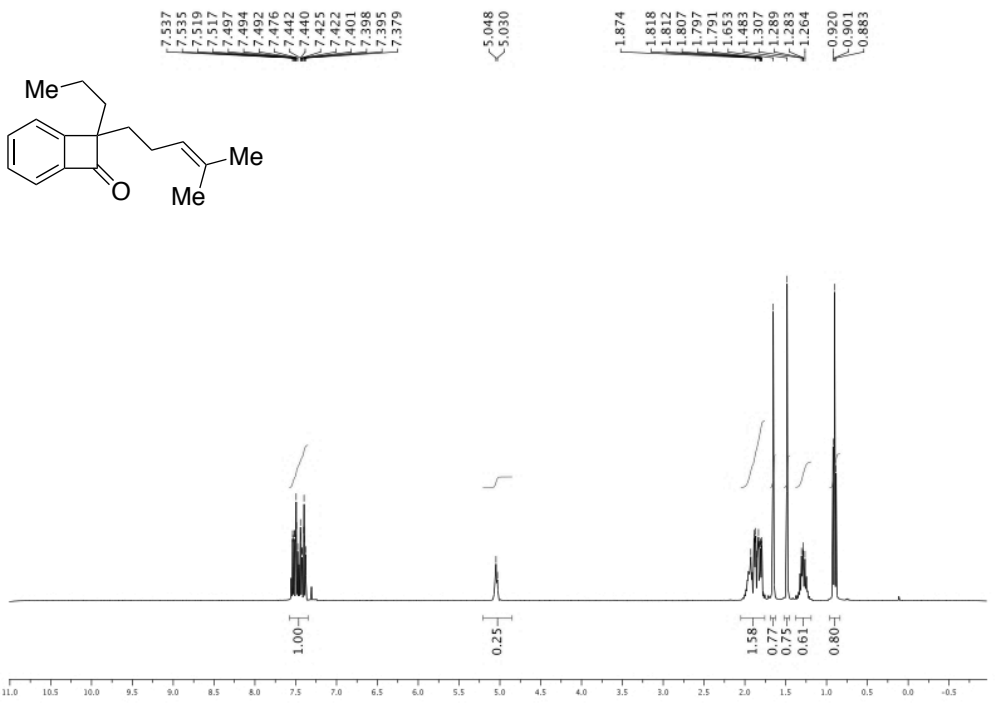


3-methylene-1-propyl-2,3-dihydro-1*H*-indene-1-carbaldehyde (264). Following general procedure D, 2-(2-bromophenyl)-2-propylpent-4-enal, (100.1 mg, 0.50 mmol) was used. Column chromatography: silica gel, 14:1 hexanes/ethyl acetate. Yellow pale solid; yield: 64 mg (60% yield). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 9.57 (s, 1H), 7.61–7.49 (m, 1H), 7.42–7.19 (m, 3H), 5.55 (t, *J* = 2.4 Hz, 1H), 5.16 (t, *J* = 2.0 Hz, 1H), 3.32 (dt, *J* = 16.9, 2.1 Hz, 1H), 2.75 (dt, *J* = 16.9, 2.3 Hz, 1H), 2.05–1.93 (m, 1H), 1.86–1.71 (m, 1H), 1.39 – 1.06 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.2, 146.8, 144.2, 141.3, 128.7, 128.1, 124.4, 120.9, 104.1, 61.2, 36.9, 36.8, 17.5, 14.3.

2.8.5 Selected examples of NMR spectra



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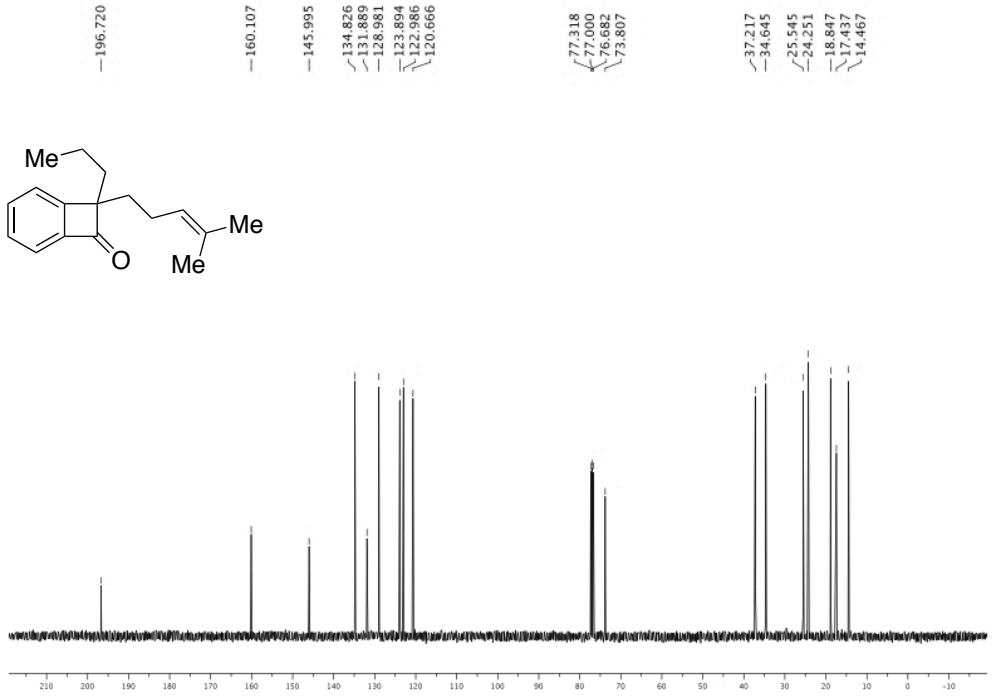
7.535
7.519
7.517
7.497
7.494
7.492
7.476
7.442
7.440
7.425
7.422
7.401
7.398
7.395
7.379
5.048
5.030
1.874
1.818
1.812
1.807
1.797
1.791
1.653
1.483
1.307
1.289
1.283
1.264
0.920
0.901
0.883
Me
Me
Me
O
1.00
0.25
1.58
0.77
0.75
0.61
0.80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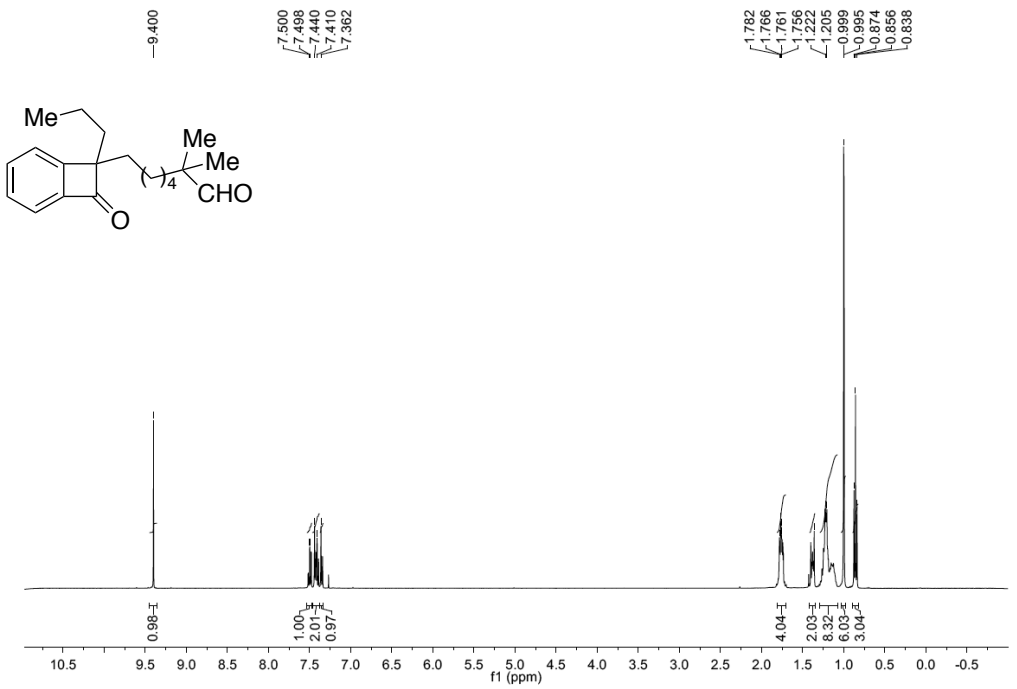
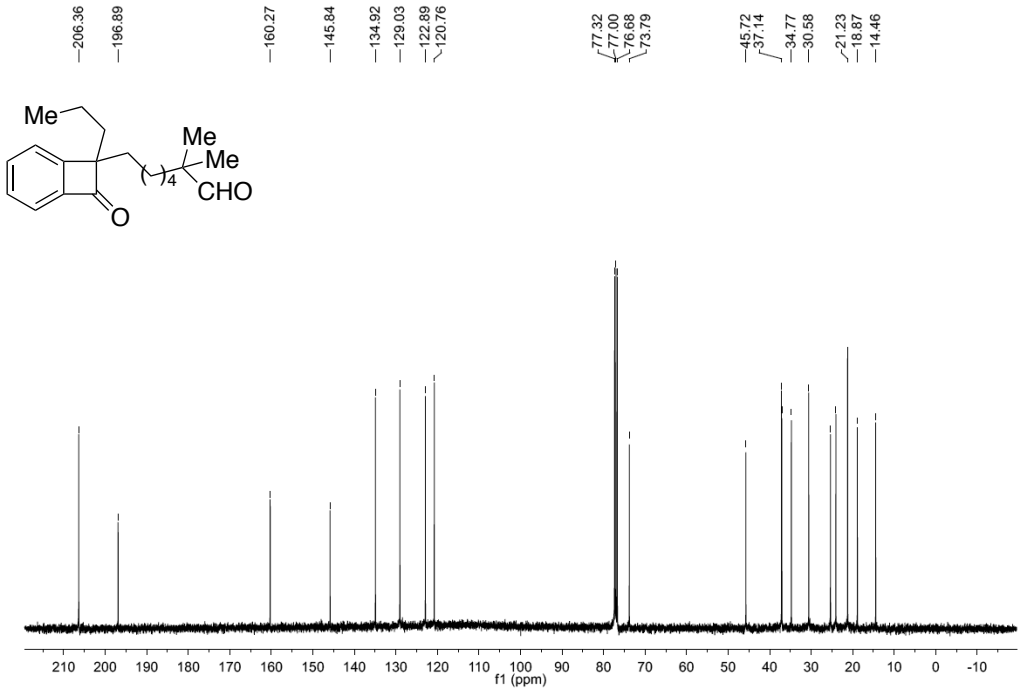
145.995
134.826
131.889
128.981
123.894
122.986
120.666
77.318
77.000
76.682
73.807
37.217
34.645
25.545
24.251
18.847
17.437
14.467
Me
Me
Me
O


9.400
7.500
7.498
7.440
7.410
7.362
1.782
1.766
1.761
1.756
1.222
1.205
0.999
0.995
0.874
0.856
0.838
Me
Me
Me
4
CHO
O
0.98
1.00
2.01
0.97
4.04
2.03
8.32
6.03
3.04
f1 (ppm)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196.89
160.27
145.84
134.92
129.03
122.89
120.76
77.32
77.00
76.68
73.79
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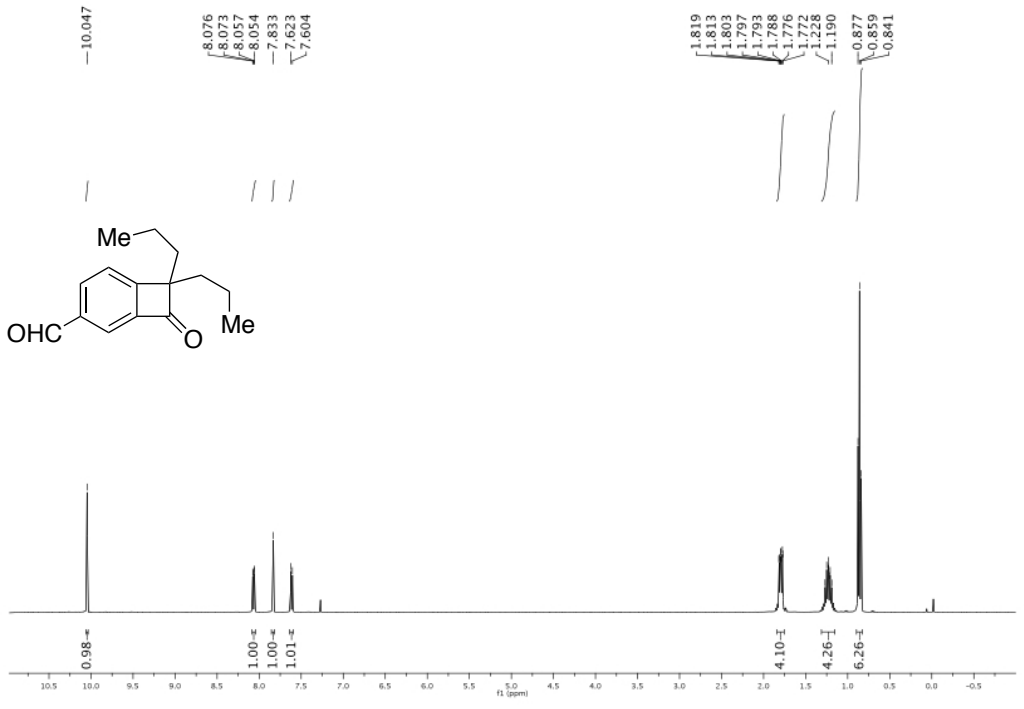
14.46
Me
Me
Me
4
CHO
O
f1 (ppm)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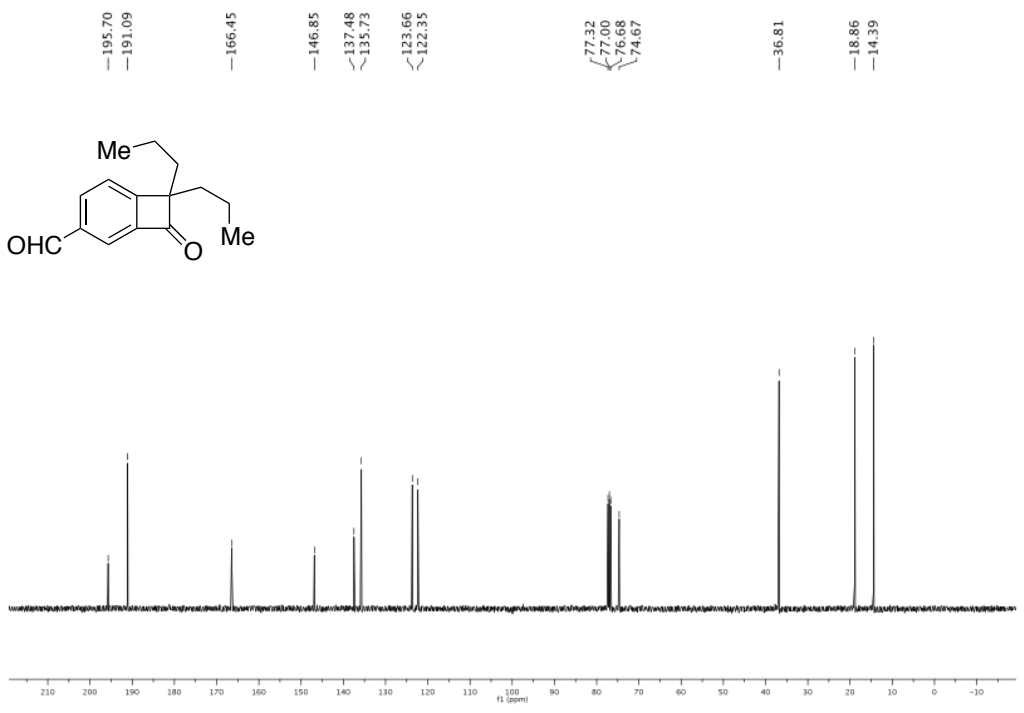
8.076
8.073
8.057
8.054
7.833
7.623
7.604
1.819
1.813
1.803
1.797
1.793
1.788
1.776
1.772
1.228
1.190
0.877
0.859
0.841
Me
OHC
O
Me
0.98
1.00
1.00
1.01
4.10
4.26
6.26
f1 (ppm)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137.48
135.73
123.66
122.35
77.32
77.00
76.68
74.67
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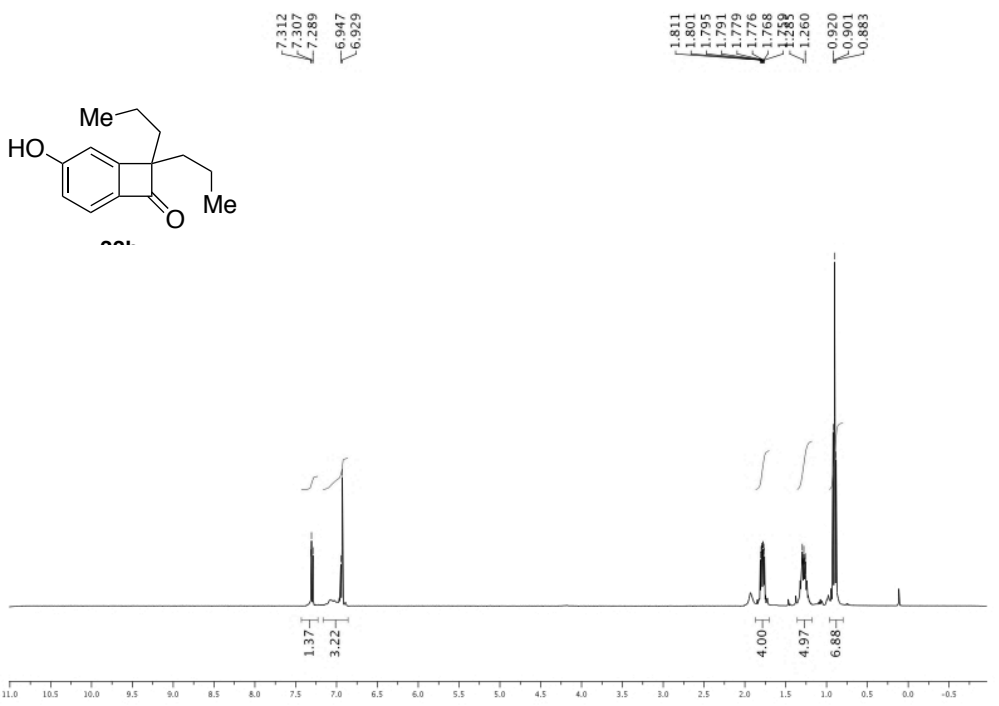
18.86
14.39
Me
OHC
O
Me
f1 (ppm)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1.795
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1.779
1.776
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0.901
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Me
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Me
O
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3.22
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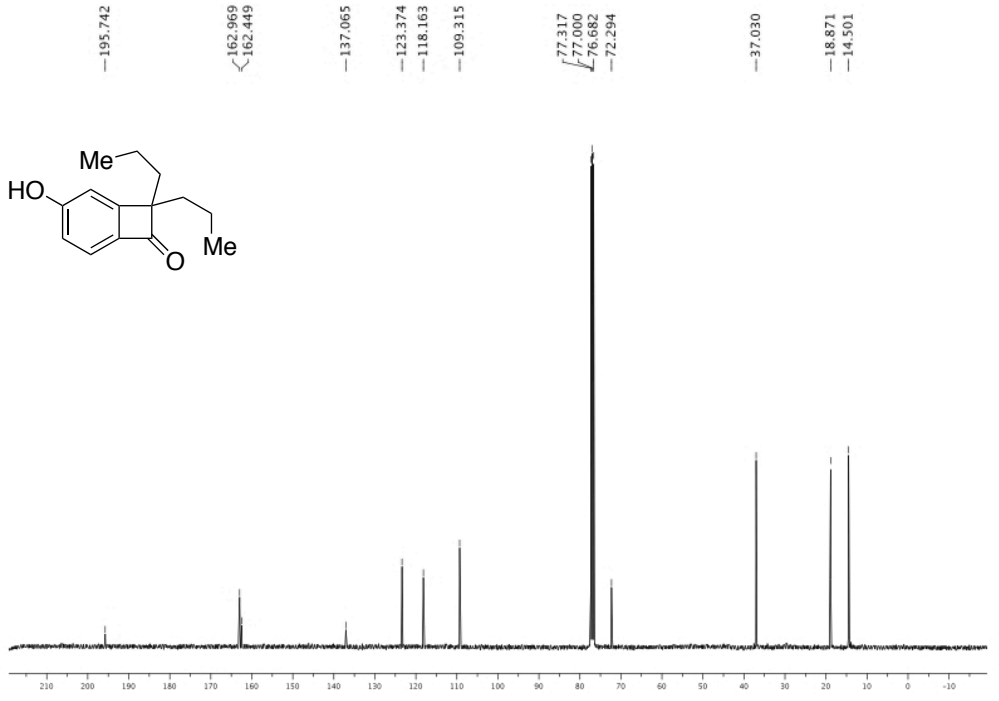
4.97
6.88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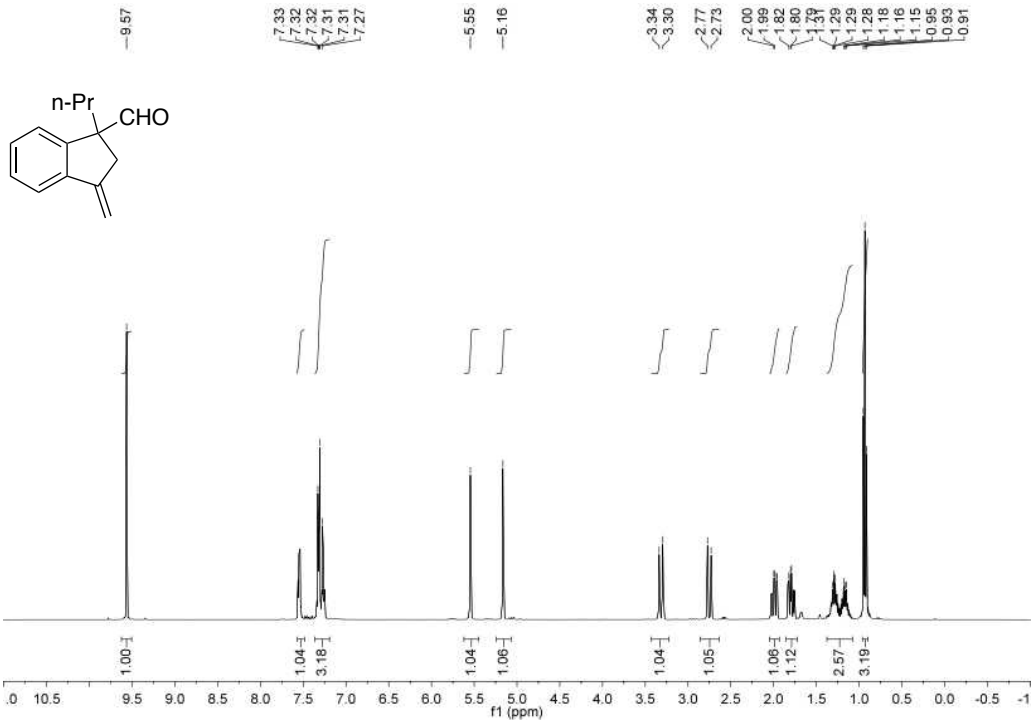
Me
HO
Me
O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7.31
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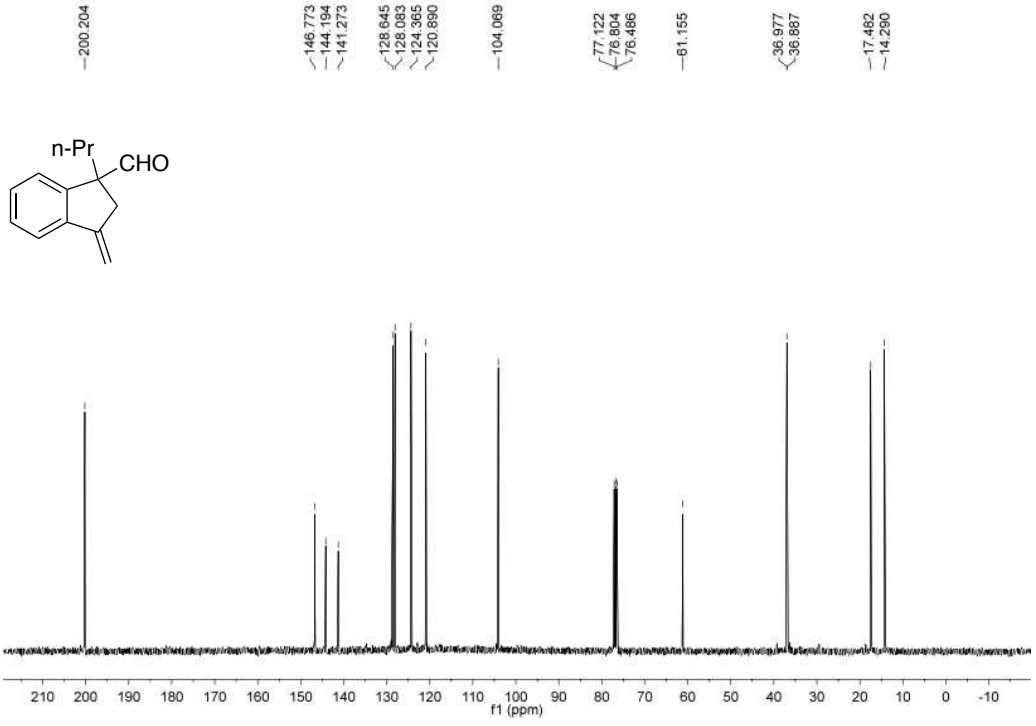
3.30
2.77
2.73
2.00
1.99
1.82
1.80
1.31
1.29
1.29
1.28
1.18
1.16
1.15
0.95
0.93
0.91
n-Pr
CHO
1.00
1.04
3.18
1.04
1.06
1.04
1.05
1.06
1.12
2.57
3.19
f1 (ppm)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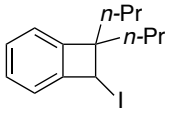
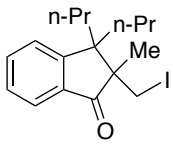
146.773
144.194
141.273
128.645
128.083
124.365
120.890
104.069
77.122
76.804
76.486
61.155
36.977
36.887
17.482
14.290
n-Pr
CHO
f1 (ppm)

2.8.6 Synthetic applications



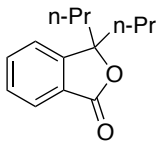
8-iodo-7,7-dipropylbicyclo[4.2.0]octa-1,3,5-triene (267). To a solution of 8,8-dipropylbicyclo[4.2.0]octa-1,3,5-trien-7-one (0.40 g, 2 mmol) in MeOH (15 mL) was added sodium borohydride (94.5 mg, 2.5 mmol) at 0 ºC. After 30 min at 0 ºC, the reaction was quenched by addition of water. The crude was then extracted with EtOAc (3 x 10 mL), washed with brine (2 x 10 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude alcohol was used directly into the next step without further purification.To a slurry containing the alcohol crude, PPh_3 (0.70 g, 2.66 mmol) and imidazole (0.18 g, 2.66 mmol) in dichloromethane (10 mL) at 0 ºC was added iodine (0.68 g, 2.66 mmol) in one portion. The solution was then heated up at reflux and stirred for 40 h, at which time almost full conversion was observed as judged by TLC analysis. The solution was then quenched by addition of saturated aqueous $NaHCO_3$ (2 x 5 mL), aqueous $Na_2S_2O_3$ (2 x 5 mL). The organic phases were then washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The product was purified by silica gel flash column chromatography (hexanes, 100%) to give the title compound as a colorless oil (0.52 g, 83% overall yield in two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 2H), 7.18 (d, *J* = 19.2 Hz, 1H), 7.06 (d, *J* = 19.2 Hz, 1H), 5.49 (s, 1H), 1.84-1.35 (m, 8H), 1.01 (t, *J* = 7.2 Hz, 3H), 0.95 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.3, 143.4, 128.9, 128.4, 123.2, 121.1, 57.0, 39.9, 38.2, 33.2, 19.0, 18.1, 14.6, 14.5 ppm. IR (neat, cm^{-1}): 2957, 2866, 1531, 1365, 1212, 977, 910, 834, 770. Anal Calcd for $C_{14}H_{19}I$: C, 53.52; H, 6.10. Found: C, 53.77; H, 6.01.



2-(iodomethyl)-2-methyl-3,3-dipropyl-2,3-dihydro-1*H*-inden-1-one (268). To a solution of 2-bromopropene (0.27 mL, 3.07 mmol) in Et_2O (5 mL) was added *t*-BuLi (3.64 mL, 5.71 mmol, 1.57 M in pentane) at -78 ºC and the reaction was further stirred for 1 h. At this time, a solution of dipropylbicyclo[4.2.0]octa-1,3,5-trien-7-one (0.40 g, 2

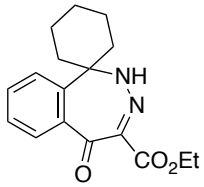
mmol) in Et_2O (5 mL) was added dropwise. After 2 h stirring at -78 ºC, the reaction was quenched with saturated aqueous NH_4Cl (5 mL). The crude reaction mixture was extracted with Et_2O and brine (2 x 5 mL) and the combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The crude alcohol was used into the next step without further purification.

To a solution of the ICl (0.49 g, 3 mmol) in THF (30 mL) was added dropwise a solution of the crude alcohol in THF (15 mL) at 0 ºC. After stirring at 0 ºC for 30 min, the reaction mixture was allowed to reach room temperature and stirred for an additional 30 min, at which time aqueous $Na_2S_2O_3$ (10 mL) was added. The reaction mixture was then extracted with Et_2O (2 x 10 mL) and brine (2 x 10 mL) and the organic phases were concentrated in vacuo. The product was purified by silica gel flash column chromatography (hexanes/ethyl acetates, 15:1) to give the title compound **2e** as a colorless oil (0.57 g, 78% overall yield in two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.5 Hz, 1H), 7.57 (td, *J* = 6.0, 1.8 Hz, 1H), 7.40 (m, 2H), 3.45 (d, *J* = 9.9 Hz, 1H), 3.22 (d, *J* = 9.9 Hz, 1H), 1.96 (m, 1H), 1.79 (m, 2H), 1.38 (m, 3H), 1.35 (s, 3H), 1.11 (m, 2H), 0.97 (t, *J* = 7.2 Hz, 3H), 0.77 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.2, 158.2, 134.0, 133.9, 127.7, 124.7, 124.2, 56.3, 52.3, 41.0, 35.9, 19.6, 18.1, 17.9, 14.9, 14.5, 14.3 ppm. IR (neat, cm^{-1}): 3017, 2977, 2841, 1741, 1598, 1466, 1365, 1209, 981, 789. Anal Calcd for $C_{17}H_{23}IO$: C, 55.14; H, 6.26. Found: C, 55.31; H, 6.15.



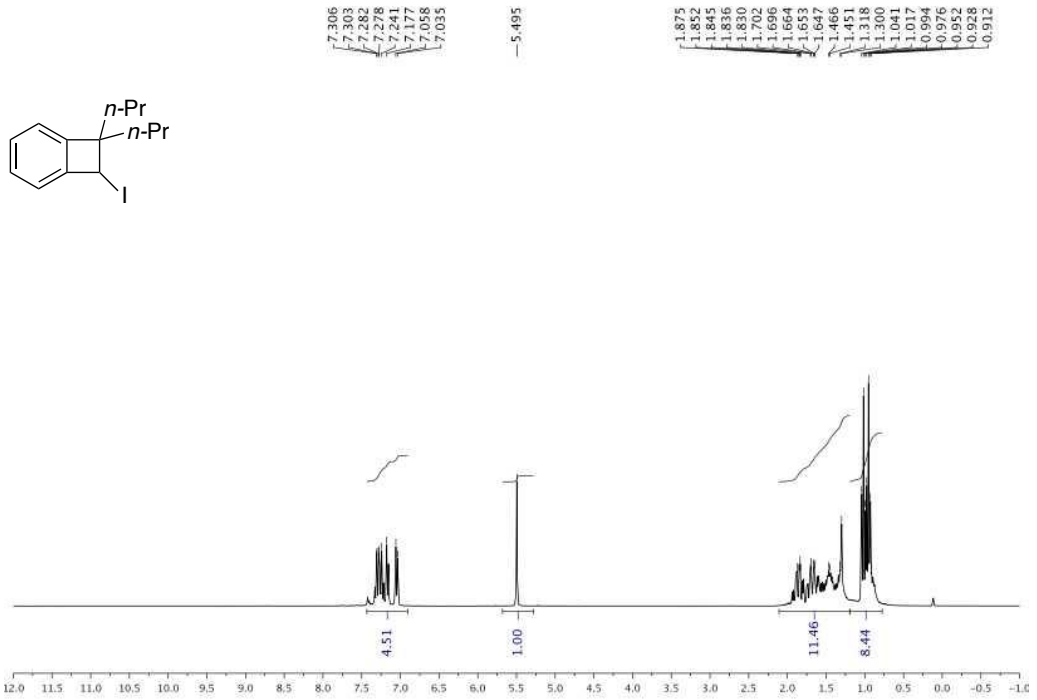
3,3-dipropylisobenzofuran-1(3*H*)-one (269). To a solution of dipropylbicyclo[4.2.0]octa-1,3,5-trien-7-one (0.15 g, 0.60 mmol) in DMF (3 mL) and water (1 ml), magnesium monoperphthalate hexahydrate (0.82 g, 1.20 mmol) was added and the mixture was heated at 40 ºC for 14 hours. The solution was cooled to room temperature, and then a saturated aqueous $Na_2S_2O_3$ (2 mL) and a saturated aqueous $NaHCO_3$ (2 mL) were sequentially added. The product was extracted with Et_2O and the combined organic extracts were washed with brine, dried over magnesium sulfate and concentrated. The crude was then purified by column chromatography on silica

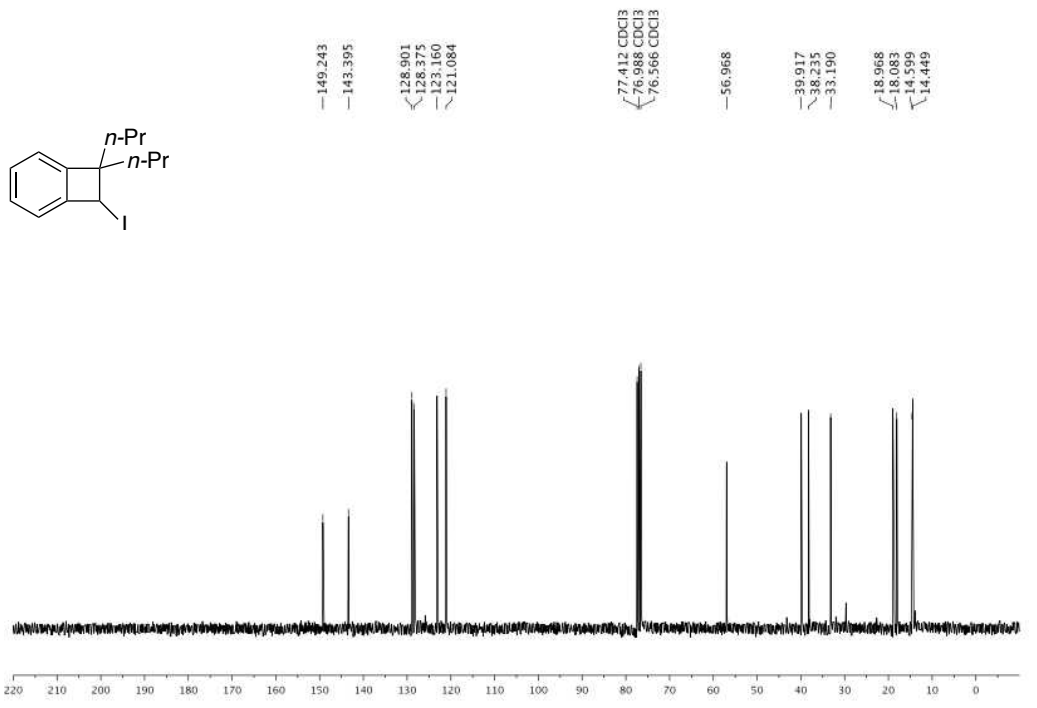
gel (8:1, hexanes/ethyl acetate) to give the title compound as a colorless oil (0.10 g, 79% yield). ^{1}H-RMN ($CDCl_3$, 400 MHz) δ 7.83 (d, *J* = 7.8 Hz, 1H), 7.64 (td, *J* = 7.5, 1.2 Hz, 1H), 7.45 (td, *J* = 7.8, 1.2 Hz, 1H), 7.32 (d, *J* = 7.5 Hz, 1H), 2.0 (m, 2H), 1.83 (m, 2H), 1.24 (m, 2H), 0.91 (m, 2H), 0.81 (t, *J* = 6.9 Hz, 6H) ppm. ^{13}C-RMN ($CDCl_3$, 100 MHz) δ 170.3, 152.5, 133.8, 128.7, 126.7, 125.4, 121.1, 90.2, 40.8, 16.4, 13.9 ppm. IR (neat, cm^{-1}): 3023, 2981, 2878, 1707, 1634, 1514, 1410, 1346, 1218, 1190, 978, 814. Anal Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.34; H, 8.23.

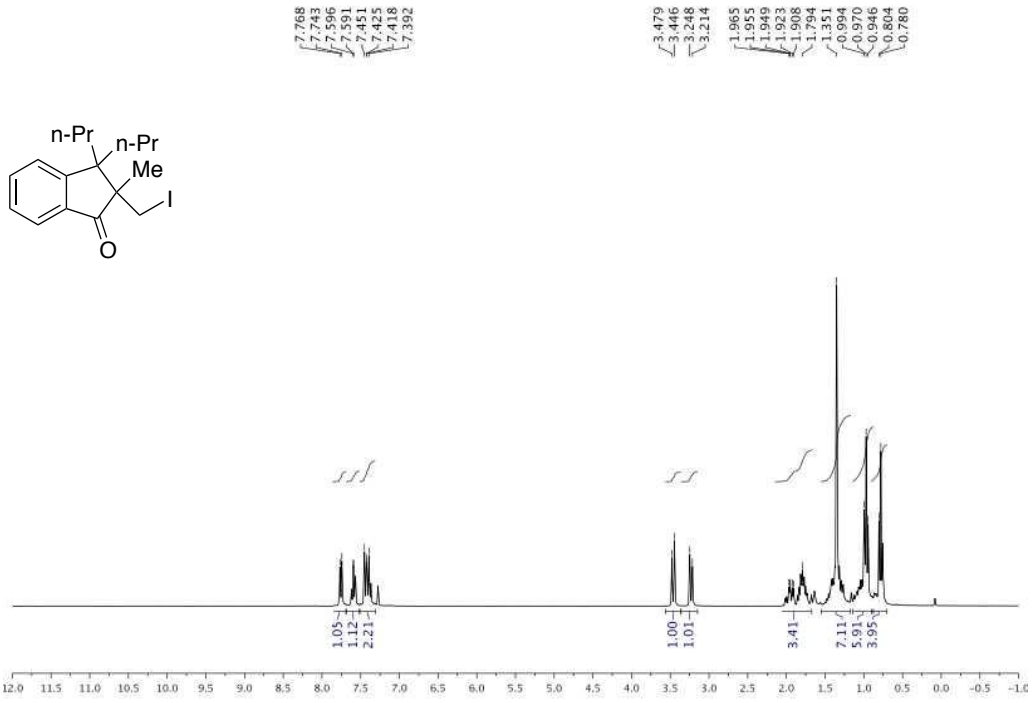


1,1-Cyclohexyl-4-ethoxycarbonyl-1,2-dihydro-2,3-benzodiazepin-5-one (274). To a solution of LDA (2.0 M in THF, 1.71 mmol) was added ethyl diazoacetate (0.154 mL, 1.45 mmol), and the mixture was stirred at -78 ºC for 30 min. A solution of the benzocyclobutenone **2d** (91 mg, 0.49 mmol) in THF (2.5 mL) was added, and after stirring for 15 min at the same temperature the reaction was warm up to 45 ºC overnight. Then, the reaction mixture was diluted with a sat. aq. NH_4Cl solution, and extracted with dichloromethane and dried over $MgSO_4$. The solvent was evaporated in vacuum and the resulting residue was purified by column chromatography (hexane/EtOAc, 1/1) to deliver diazepine **5** (63 mg, 43% yield) as an orange solid. Mp 148-150 ºC. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.05 (brs, 1H), 7.67 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.55 (dt, *J* = 7.9, 1.5 Hz, 1H), 7.39-7.35 (m, 1H), 7.28-7.26 (m, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 2.40-2.37 (m, 2H), 1.92-1.66 (m, 6H), 1.56-1.47 (m, 2H), 1.34 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 188.8, 164.1, 140.5, 140.4, 133.2, 129.3, 128.7, 128.1, 122.5, 62.7, 61.2, 31.6, 24.9, 21.5, 14.2 ppm. IR (neat, cm^{-1}): 3281, 3239, 1697, 1621. Anal. Calcd for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71. Found: C, 67.56; H, 6.89.

2.8.7 NMR spectra of synthetic applications



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7.591
7.451
7.425
7.418
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3.479
3.446
3.248
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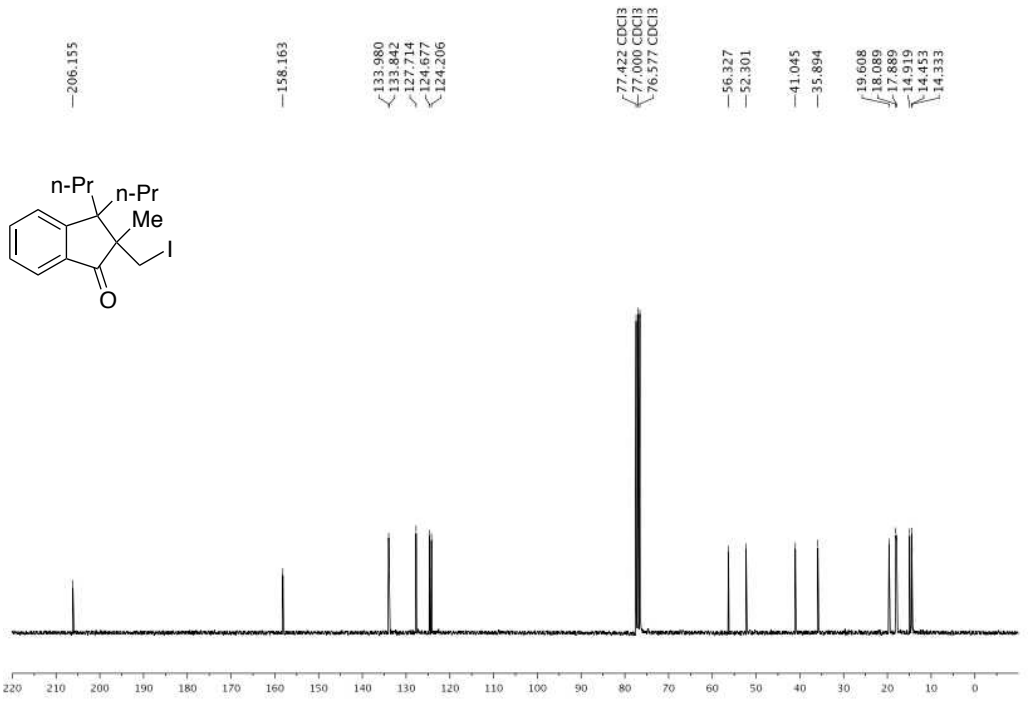
1.965
1.955
1.949
1.923
1.908
1.794
1.351
0.994
0.970
0.946
0.804
0.780
n-Pr
n-Pr
Me
I
O
1.05
1.12
2.21
1.00
1.01
3.41
7.11
5.91
3.95
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0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158.163
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133.842
127.714
124.677
124.206
77.422 CDCl3
77.000 CDCl3
76.577 CDCl3
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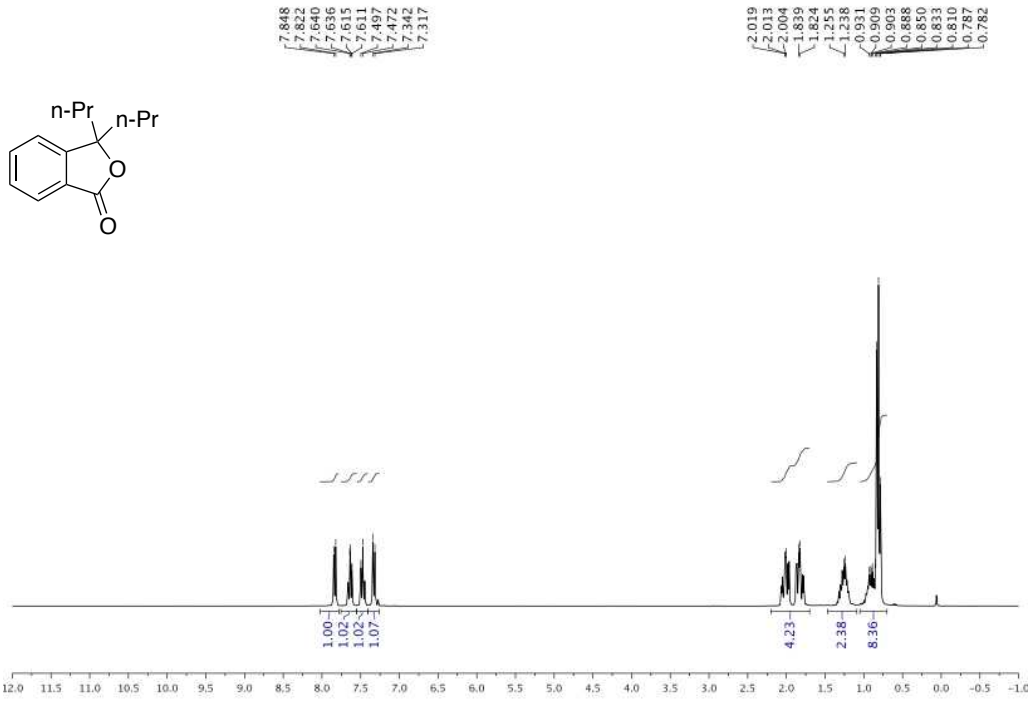
52.301
41.045
35.894
19.608
18.089
17.889
14.919
14.453
14.333
n-Pr
n-Pr
Me
I
O
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0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7.822
7.640
7.636
7.615
7.611
7.497
7.472
7.342
7.317
2.019
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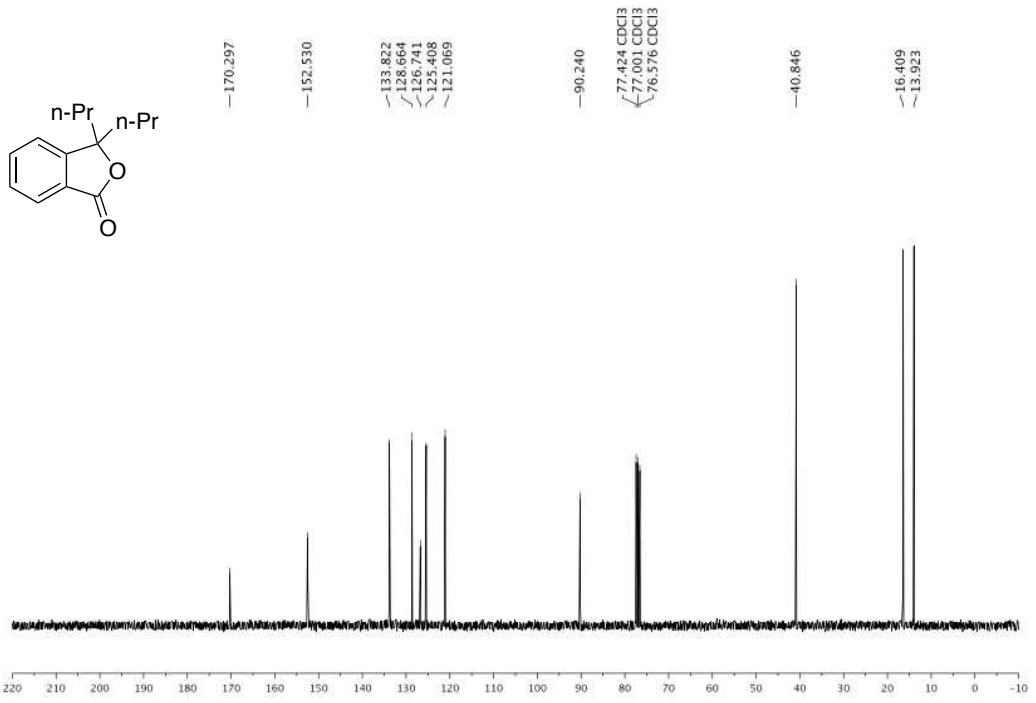
2.004
1.839
1.824
1.255
1.238
0.931
0.909
0.903
0.888
0.850
0.833
0.810
0.787
0.782
n-Pr
n-Pr
O
O
1.00
1.02
1.02
1.07
4.23
2.38
8.36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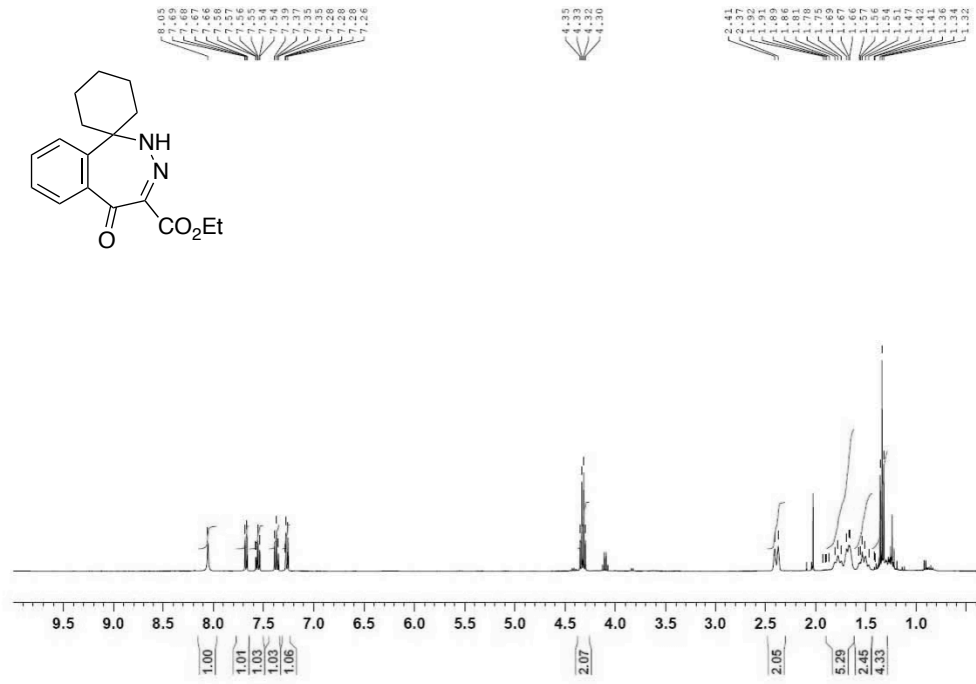
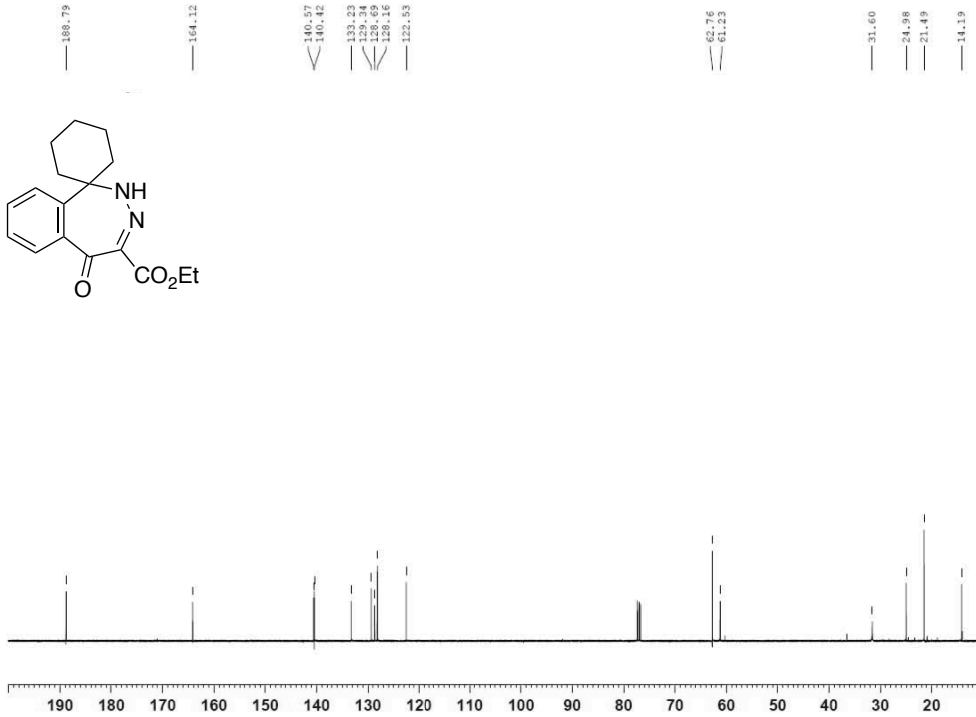
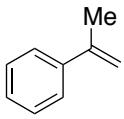
133.822
128.664
126.741
125.408
121.069
90.240
77.424 CDCl3
77.001 CDCl3
76.576 CDCl3
40.846
16.409
13.923
n-Pr
n-Pr
O
O


NH
N
O
CO2Et
ppm

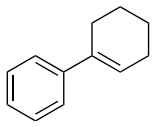

NH
N
O
CO2Et
ppm

2.8.8 Synthesis of α-aryl styrenes

General procedure E for the synthesis of α-aryl styrenes. An oven-dried screw-cap test tube containing a stirring bar was charged with $Pd(OAc)_2$ (2.3 mg, 2.0 mol%), 1,3-dicyclohexylphosphinepropane·$2HBF_4$ (**293**) (9.2 mg, 3.0 mol%), Cs_2CO_3 (0.21 g, 0.65 mmol) and the aryl bromide (0.50 mmol), if a solid. The test tube was evacuated and back-filled with dry argon (this sequence was repeated three times). The aryl bromide (if liquid) and toluene (2 mL) were then added by syringe. The mixture was then placed in ultrasounds apparatus for 1 min and the mixture was then stirred in a pre-heated oil bath (110 °C) for 14 h. The mixture was then allowed to warm to room temperature, diluted with EtOAc (5 mL) and filtered through a Celite® plug, eluting with additional EtOAc (10 mL). The filtrate was concentrated and purified by column chromatography on silica gel (eluting with hexanes/ethyl acetate mixtures).



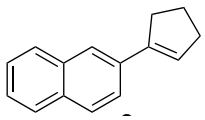
Prop-1-en-2-ylbenzene (152). Following general procedure C, 2-(2-bromophenyl)-2-methylpropanal (113.6 mg, 0.5 mmol) was used. Column chromatography: silica gel, hexanes. Colorless oil; yield: 44.9 mg (76% yield). The spectroscopic data was in full accordance with those described in the literature.[165] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59–7.53 (m, 2H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.35 (dd, *J* = 8.2, 6.3 Hz, 1H), 5.46 (s, 1H), 5.18 (d, *J* = 1.4 Hz, 1H), 2.25 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.3, 141.2, 128.2, 127.4, 125.5, 112.4, 21.8.



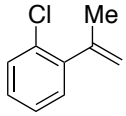
Cyclohex-1-en-1-ylbenzene (307). Following general procedure C, 1-(2-bromophenyl)-cyclohexanecarbaldehyde (134 mg, 0.50 mmol) was used. Column chromatography: silica gel (20:1

[165] Geckle, J. M., Fraenkel, G. *J. Am. Chem. Soc.,* **1982**, 2869.

hexanes/Ethyl acetate). Yellow oil; 73.3 mg (86% yield). The spectroscopic data was in full accordance with those described in the literature.[166] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 8.2, 1.1 Hz, 2H), 7.35-7.29 (m, 2H), 7.23 (ddd, *J* = 7.3, 3.8, 1.2 Hz, 1H), 6.17-6.11 (m, 1H), 2.47-2.40 (m, 2H), 2.28-2.18 (m, 2H), 1.87-1.76 (m, 2H), 1.73-1.64 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 142.7, 136.6, 128.2, 126.5, 124.9, 124.8, 27.4, 25.9, 23.1, 22.2.

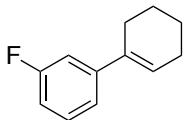


2-cyclopent-1-en-1-ylnaphthalene (308). Following general procedure C, 1-(1-bromo-2-naphthyl)cyclopentanecarbaldehyde (152 mg, 0.50 mmol) was used. Column chromatography: silica gel, hexanes. White solid; yield: 85.1 mg (61% yield). The spectroscopic data was in full accordance with those described in the literature.[167] Mp= 76.5-78.9 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91-7.74 (m, 5H), 7.56-7.46 (m, 2H), 6.40 (s, 1H), 2.91 (t, *J* = 7.5 Hz, 2H), 2.70-2.62 (m, 2H), 2.20-2.09 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 142.4, 134.1, 133.6, 132.5, 128.0, 127.6, 127.5, 126.9, 126.00, 125.5, 124.2, 124.0, 33.5, 33.2, 23.3. HRMS *calcd* for [$C_{15}H_{14}$] 194.1096, *found* 194.1080.

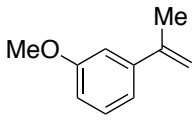


1-chloro-2-isopropenylbenzene (309). Following general procedure C, 2-(2-bromo-6-chlorophenyl)-2-methylpropanal (131 mg, 0.50 mmol) was used. Column chromatography: silica gel, hexanes. Colorless oil; yield: 49.4 mg (72% yield). The spectroscopic data was in full accordance with those described in the literature.[168] ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.37 (dt, *J* = 6.5, 1.5 Hz, 1H), 7.24-7.18 (m, 3H), 5.26-5.23 (m, 1H), 4.98 (dd, *J* = 1.8, 0.9 Hz, 1H), 2.12 (dd, *J* = 1.4, 1.0 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 144.4, 142.8, 131.8, 129.8, 129.6, 128.1, 126.6, 116.1, 23.3. HRMS *calcd* for [C_9H_9Cl] 152.0393, *found* 152.0386.

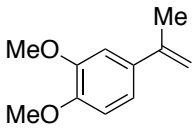
[166] Scheiper, B., Bonnekessel, M., Krause, H., Fürstner, A. *J. Org. Chem.* **2004**, *69*, 3943.
[167] Clifford M. U., Mahatam S., Roland E. L. *J. Org. Chem.,* **1987**, *52*, 5574.
[168] Hatano, B., Sato, H., Ito, T., Ogata, T. *Synlett*, **2007,** *13*, 2130.



1-cyclohex-1-en-1-yl-3-fluorobenzene (310). Following general procedure C, 1-(2-bromo-5-fluorophenyl)cyclohexane-carbaldehyde (143 mg, 0.50 mmol) was used. Column chromatography: silica gel, hexanes. Colorless oil; yield: 47.8 mg (54% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.34-7.28 (m, 1H), 7.20 (d, *J* = 7.9 Hz, 1H), 7.12 (dd, *J* = 13.0, 2.1 Hz, 1H), 6.95 (ddd, *J* = 8.2, 2.5, 1.2 Hz, 1H), 6.23-6.19 (m, 1H), 2.43 (ddd, *J* = 8.2, 4.0, 2.0 Hz, 2H), 2.31-2.23 (m, 2H), 1.88-1.79 (m, 2H), 1.72 (dt, *J* = 5.6, 4.6 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 164.2, 161.8, 145.0 (d, *J* = 7.4 Hz), 135.6 (d, *J* = 2.2 Hz), 129.4 (d, *J* = 8.5 Hz), 125.9, 120.4 (d, *J* = 2.6 Hz), 113.1 (d, *J* = 21.3 Hz), 111.8 (d, *J* = 21.7 Hz), 27.3, 25.8, 22.9, 22.0. IR (neat, cm^{-1}): 2927, 2858, 2835, 1609, 1580, 1488, 1437, 1261, 1158, 872, 840, 775, 686. HRMS *calcd* for [$C_{12}H_{13}F$+H] 177.1080, *found* 177.1081.



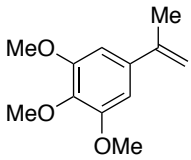
1-isopropenyl-3-methoxybenzene (311). Following general procedure C, 2-(2-bromo-5-methoxyphenyl)-2-methylpropanal (129 mg, 0.50 mmol) was used. Column chromatography: silica gel, hexanes/ethyl acetate 5:1. Colorless oil; yield: 66.8 mg (90% yield). The spectroscopic data was in full accordance with those described in the literature.[169] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.28 (t, *J* = 8.0 Hz, 1H), 7.10 (dd, *J* = 7.7, 2.5 Hz, 1H), 7.05-7.03 (m, 1H), 6.86 (dd, *J* = 8.2, 3.3 Hz, 1H), 5.40 (d, *J* = 0.7 Hz, 1H), 5.13-5.11 (m, 1H), 3.85 (s, 3H), 2.18 (dd, *J* = 1.3, 0.7 Hz, 3H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ159.5, 143.2, 142.8, 129.1, 118.1, 112.6, 111.5, 55.2, 21.8. IR (neat, cm^{-1}): 2954, 2923, 2854, 1602, 1578, 1489, 1375, 1232, 1051, 891, 783, 725.



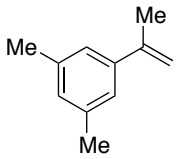
4-isopropeynl-1,2-dimethoxybenzene (312). Following general procedure C, 2-(2-bromo-4,5-dimethoxyphenyl)-2-methylpropanal (144 mg, 0.50 mmol) was used. Column chromatography: silica gel, hexanes/ethyl acetate 5:1. Colorless oil; yield: 61.8 mg (69% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07-6.99 (m, 2H), 6.83 (d, *J* = 8.9 Hz,

[169] Lebel, H., Davi, M., Díez-González, S., Nolan, S. P., *J. Org. Chem.*, **2007**, *72*, 144.

1H), 5.30 (d, *J* = 0.6 Hz, 1H), 5.05-4.98 (m, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 2.15 (d, *J* = 0.4 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 148.6, 148.5, 142.7, 134.1, 117.9, 110.9, 110.7, 108.8, 55.8, 55.7, 21.8. IR (neat, cm^{-1}): 2925, 2853, 1580, 1513, 1459, 1298, 1251, 1145, 1026, 881, 854, 808, 766. HRMS *calcd* for [$C_{11}H_{14}O_2$+Na] 201.0891, *found* 201.0884.

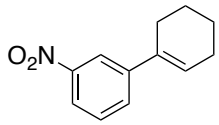


4-isopropenyl-1,2,3-trimethoxybenzene (313). Following general procedure D, using 2-(2-bromo-3,4,5-trimethoxy phenyl)-2-methylpropanal (154 mg, 0.50 mmol), 3-dicyclohexyl phosphinepropane·2HBF$_4$ (**293**) (18.4 mg, 6.0 mol%), $Pd(OAc)_2$ (4.5 mg, 4.0 mol%), Cs_2CO_3 (0.42 g, 1.3 mmol) and 2mL of toluene. Column chromatography: silica gel, hexanes/eter 2:1. White solid; yield: 82.4 mg (79% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (s, 2H), 5.30 (d, *J* = 0.5 Hz, 1H), 5.06 (s, 1H), 3.88 (s, 6H), 3.86 (s, 3H), 2.14 (d, *J* = 0.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.8, 143.2, 137.7, 137.1, 112.1, 102.9, 60.8, 56.0, 21.9. IR (neat, cm^{-1}): 2938, 2835, 1578, 1505, 1450, 1410, 1337, 1231, 1124, 1006, 883, 733. HRMS *calcd* for [$C_{12}H_{16}O_3$+Na] 231.0997, *found* 231.0984.

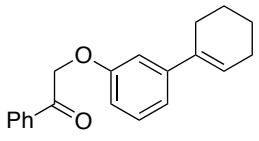


1-cyclohex-1-en-1-yl-3,5-dimethylbenzene (314). Following general procedure D, 1-(2-bromo-3,5-dimethylphenyl) cyclohexanecarbaldehyde (147 mg, 0.50 mmol) was used. Column chromatography: silica gel, hexanes. Colorless oil; yield: 85.1 mg (83% yield). The spectroscopic data was in full accordance with those described in the literature.[170] ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.04 (s, 2H), 6.91 (s, 1H), 6.10-6.13 (m, 1H), 2.41-2.45 (m, 2H), 2.35 (s, 6H), 2.21-2.25 (m, 2H), 1.78-1.84 (m, 2H), 1.66-1.72 (m, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 142.8, 137.4, 136.7, 128.1, 124.3, 122.9, 27.5, 25.8, 23.1, 22.2, 21.3.

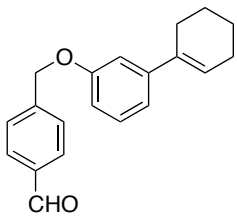
[170] Hirose, K.; Aksharanandana, P.; Suzuki, M.; Wada, K.; Naemura, K.; Tobe, Y. *Heterocycles* **2005**, *66*, 405.



1-cyclohex-1-en-1-yl-3-nitrobenzene (315). Following general procedure C, (1-(2-bromo-5-nitrophenyl)cyclohexanecarbaldehyde (156 mg, 0.50 mmol) was used. Column chromatography: silica gel, hexanes. Yellow oil; yield: 89.5 mg (89% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.20 (t, *J* = 1.9 Hz, 1H), 8.04 (ddd, *J* = 8.2, 2.1, 0.9 Hz, 1H), 7.71-7.65 (m, 1H), 7.44 (t, *J* = 8.0 Hz, 1H), 6.26 (ddd, *J* = 5.6, 3.9, 1.6 Hz, 1H), 2.45-2.38 (m, 2H), 2.28-2.21 (m, 2H), 1.85-1.76 (m, 2H), 1.72-1.63 (m, 2H). ^{13}C-NMR δ (100 MHz, $CDCl_3$) 148.3, 144.1, 134.7, 130.7, 128.9, 127.5, 121.1, 119.6, 27.1, 25.8, 22.7, 21.8. IR (neat, cm^{-1}): 2927, 2858, 2833, 1522, 1343, 1280, 797, 733, 693, 676. HRMS *calcd* for [$C_{12}H_{13}NO_2$+H] 204.1025, *found* 204.1025.

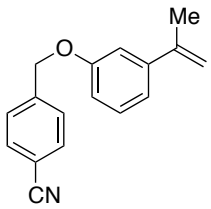


2-(3-cyclohexenylphenoxy)-1-phenylethanone (316). Following general procedure C, using 1-(2-bromo-5-(2-oxo-2-phenylethoxy)phenyl)cyclohexane carbaldehyde (201 mg, 0.50 mmol). Column chromatography: silica gel, 9:1 hexanes/ethyl acetate. Colorless oil; yield: 112.9 mg (77% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13–7.91 (m, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.7 Hz, 2H), 7.23 (t, *J* = 7.9 Hz, 1H), 7.13–6.95 (m, 2H), 6.80 (dd, *J* = 8.1, 2.3 Hz, 1H), 6.13 (dt, *J* = 5.4, 1.8 Hz, 1H), 5.27 (s, 2H), 2.49–2.30 (m, 2H), 2.28–2.15 (m, 2H), 1.94–1.73 (m, 2H), 1.73–1.60 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.6, 158.0, 144.4, 136.2, 134.6, 133.7, 129.1, 128.8, 128.1, 125.3, 118.5, 112.4, 111.9, 70.9, 27.3, 25.8, 23.0, 22.1. IR (neat, cm^{-1}): 2928, 2856, 2831, 1704, 1603, 1573, 1481, 1447, 1287, 1180, 1094, 978, 750, 683. HRMS *calcd* for [$C_{20}H_{20}O_2$+Na] 315.1361, *found* 315.1373.

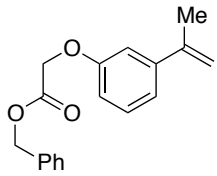


4-((3-cyclohexenylphenoxy)methyl)benzaldehyde (317). Following general procedure C, using 2-(2-bromo-5-hydroxyphenyl)-2-methylpropanal (201 mg, 0.50 mmol), 1,3-dicyclohexylphosphinepropane·2HBF$_4$ (**293**) (18.4 mg, 6.0 mol%) and $Pd(OAc)_2$ (4.5 mg, 4.0 mol%). Column chromatography: silica gel, 9:1 hexanes/ethyl acetate. Colorless oil; yield: 92.9 mg

(63% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.02 (s, 1H), 7.91 (d, *J* = 8.1 Hz, 2H), 7.62 (d, *J* = 8.2 Hz, 2H), 7.25 (t, *J* = 8.2 Hz, 1H), 7.08-7.01 (m, 2H), 6.84 (dd, *J* = 7.4, 2.0 Hz, 1H), 6.18-6.12 (m, 1H), 5.16 (s, 2H), 2.45-2.37 (m, 2H), 2.28-2.18 (m, 2H), 1.86-1.76 (m, 2H), 1.73-1.63 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 191.8, 158.3, 144.3, 144.1, 136.2, 135.8, 129.9, 129.1, 127.4, 125.2, 118.1, 112.5, 111.7, 69.0, 27.3, 25.8, 22.9, 22.0. IR (neat, cm^{-1}): 2925, 2857, 1695, 1601, 1574, 1484, 1430, 1283, 1256, 1184, 1166, 1045, 1011, 775. HRMS *calcd* for ($C_{20}H_{20}O_2$+H): 293.1542, *found* 293.1556.

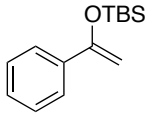


4-[(3-isopropenylphenoxy)methyl]benzonitrile (318).
Following general procedure C, 4-((4-bromo-3-(1,1-dimethyl-2-oxoethyl)phenoxy)methyl)) benzonitrile (179 mg, 0.50 mmol) was used. Column chromatography: silica gel, hexanes/eter 4:1. Colorless oil; yield: 87.2 mg (71% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.28 (t, *J* = 8.0 Hz, 1H), 7.16-7.11 (m, 1H), 7.10-7.07 (m, 1H), 6.87 (dd, *J* = 8.2, 2.5 Hz, 1H), 5.38 (s, 1H), 5.15 (s, 2H), 5.13-5.11 (m, 1H), 2.17-2.15 (m, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 158.1, 143.0, 142.8, 142.5, 132.3, 129.3, 127.5, 118.8, 118.6, 113.3, 112.9, 112.4, 111.6, 68.8, 21.8. IR (neat, cm^{-1}): 3082, 2922, 2862, 2228, 1748, 1574, 1488, 1436, 1317, 1216, 1044, 889, 783, 547. HRMS *calcd* for [$C_{17}H_{15}NO$+H] 250.1232, *found* 250.1232.

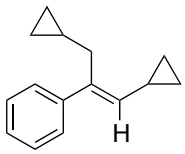


1-(3-isopropenylphenoxy)-3-phenylacetone (319).
Following general procedure C, benzyl 2-(4-bromo-3-(1,1-dimethyl-2-oxoethyl)phenoxy)acetate (189 mg, 0.50 mmol) was used. Column chromatography: silica gel, hexanes/ethyl acetate 4:1. Colorless oil; yield: 153.9 mg (91% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.35 (m, 5H), 7.26 (t, *J* = 8.0 Hz, 1H), 7.17-7.10 (m, 1H), 7.07-7.03 (m, 1H), 6.82 (dd, *J* = 8.1, 2.5 Hz, 1H), 5.37 (s, 1H), 5.27 (s, 2H), 5.13-5.09 (m, 1H), 4.70 (s, 2H), 2.14 (d, *J* = 0.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 157.7, 142.9, 142.8, 135.1, 129.2, 128.6, 128.5, 128.4, 119.1, 113.1, 112.9, 112.4, 66.9, 65.4,

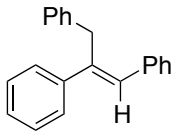
21.7. IR (neat, cm^{-1}): 3033, 2970, 1759, 1736, 1603, 1576, 1493, 1272, 1115, 1082, 891, 728, 696. HRMS *calcd* for [$C_{18}H_{18}O_3$+Na] 305.1154, *found* 305.1161.



***tert*-butyldimethyl(1-phenylvinyloxy)silane (322).** Following general procedure C, 2-(2-bromo-5-hydroxyphenyl)-2-methylpropanal (172 mg, 0.50 mmol) was used. Column chromatography: silica gel, hexanes. Colorless oil; yield: 165.3 mg (51% yield, by GC: 68% yield using 3-dicyclohexyl phosphinepropane·$2HBF_4$ (**L27**) (18.4 mg, 6.0 mol%) and $Pd(OAc)_2$ (4.5 mg, 4.0 mol%)). The spectroscopic data was in full accordance with those described in the literature.[171] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.3 Hz, 2H), 7.41-7.30 (m, 3H), 4.92 (s, 1H), 4.46 (s, 1H), 1.04 (s, 9H), 0.25 (s, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 156.0, 137.8, 128.1, 128.0, 125.3, 90.9, 25.9, -4.6.



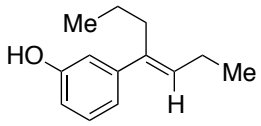
[(*E*)-2-cyclopropyl-1-(cyclopropylmethyl)vinyl]benzene (323). Following general procedure C, 2-(2-bromophenyl)3-cyclopropyl-2-(cyclopropyl)propanal (154 mg, 0.50 mmol) was used. Column chromatography: silica gel, hexanes. Colorless oil; yield: 71.9 mg (73% yield, 16.5:1 (*E*:*Z*)). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.44-7.36 (m, 2H), 7.36-7.30 (m, 2H), 7.23 (t, *J* = 7.2 Hz, 1H), 5.11 (d, *J* = 9.6 Hz, 1H), 2.64 (d, *J* = 6.5 Hz, 2H), 1.75-1.62 (m, 1H), 0.95-0.79 (m, 3H), 0.53-0.37 (m, 4H), 0.23-0.13 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 143.4, 138.2, 133.3, 128.1, 126.2, 126.1, 34.2, 11.2, 10.6, 7.5, 4.6. (*NMR shifts correspond to the major E isomer*). IR (neat, cm^{-1}): 3078, 3002, 2925, 2858, 1638, 1599, 1458, 1444, 1075, 1044, 950, 760, 744, 695. HRMS *calcd* for [$C_{15}H_{18}$+H] 199.1487, *found* 199.1492.



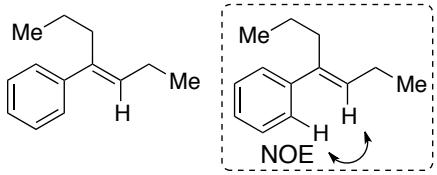
[(*E*)-1-benzyl-2-phenylvinyl]benzene (324). Following general procedure D, 2-benzyl-2,3-diphenylpropanal (189 mg, 0.50 mmol) was used. Column chromatography: silica gel, 95:5

[171] Orban, J., Turner, J. V., Twitchin, B., *Tetrahedron Lett.* **1984**, *25*, 5099.

hexanes/ethyl acetate. White solid; yield: 87.0 mg (91% yield, 22.2:1 (*E:Z*)). Mp= 54.9-57.9 ºC. The spectroscopic data was in full accordance with those described in the literature.[172] ^{1}H-NMR δ (400 MHz, $CDCl_3$) 7.67-7.62 (m, 2H), 7.53-7.24 (m, 14H), 4.28 (s, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 142.4, 139.6, 139.0, 137.7, 130.3, 128.6, 128.5, 128.3, 128.3, 127.2, 126.9, 126.5, 125.9, 36.1. (*NMR shifts correspond to the major E isomer*).



(*E*)-3-(hept-3-en-4-yl)phenol (325). Following general procedure C, using 2-(2-bromo-5-hydroxyphenyl)-2-methylpropanal (150 mg, 0.50 mmol), 3-dicyclohexyl phosphinepropane·2HBF$_4$ (**L27**) (18.4 mg, 6 mol%), $Pd(OAc)_2$ (4.5 mg, 4.0 mol%), Cs_2CO_3 (0.42 g, 1.3 mmol) and 4mL of toluene. Column chromatography: silica gel, 9:1. Colorless oil; yield: 58.9 mg (62% yield, 14.3:1 (*E:Z)*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (t, *J* = 7.9 Hz, 1H), 6.93 (d, *J* = 7.7 Hz, 1H), 6.87–6.78 (m, 1H), 6.70 (dd, *J* = 8.0, 2.5 Hz, 1H), 5.67 (t, *J* = 7.2 Hz, 1H), 4.62 (s, 1H), 2.49–2.38 (m, 2H), 2.21 (p, *J* = 7.4 Hz, 2H), 1.38 (dq, *J* = 14.7, 7.3 Hz, 2H), 1.06 (t, *J* = 7.5 Hz, 3H), 0.89 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.5, 145.3, 139.0, 131.0, 129.2, 118.8, 113.4, 113.3, 45.4, 31.6, 21.8, 21.8, 14.4, 13.9. (*NMR shifts correspond to the major E isomer*). IR (neat, cm^{-1}): 3415, 2986, 2939, 1604, 1577, 1456, 1393, 1278, 1236, 1023, 866, 809, 610. HRMS *calcd* for ($C_{13}H_{18}O$-H): 189.1279, *found* 189.1276.

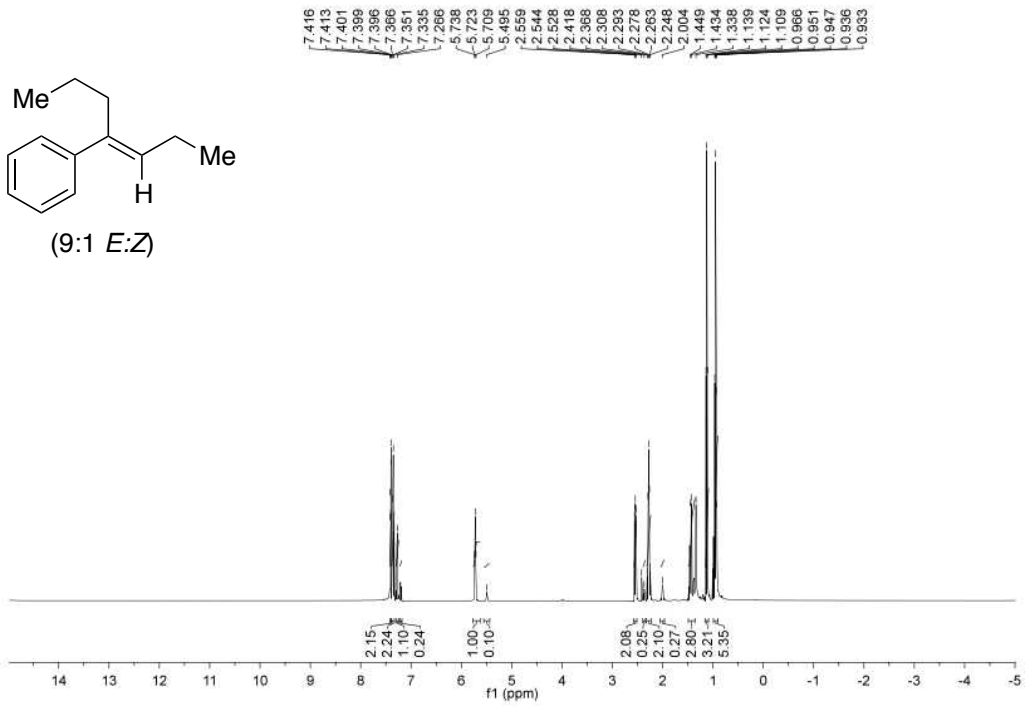


[(1*E*)-1-propylbut-1-enyl]benzene (326). Following general procedure C, 2-(2-bromophenyl)-2-propylpropanal (142 mg, 0.50 mmol) was used. Column chromatography: Silica gel, hexanes. Colorless oil; yield: 77.7 mg (87% yield, 9:1 (*E:Z*)). The spectroscopic data was in full accordance with those described in the

[172] Banert, K., Hagedorn, M., Liedtke, C., Melzer, A., Schöffler, C., *Eur. J. Org. Chem.*, **2000**, 257.

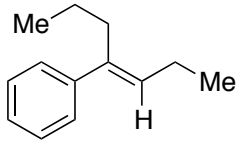
literature[173]; the major isomer was confirmed by NOE experiments. ^{1}H-NMR δ (400 MHz, $CDCl_3$) 7.42-7.39 (m, 2H), 7.38-7.32 (m, 2H), 7.29-7.24 (m, 1H), 5.72 (t, *J* = 7.2 Hz, 1H), 2.54 (t, *J* = 15.3 Hz, 2H), 2.28 (q, *J* = 7.4 Hz, 2H), 1.49-1.40 (m, 2H), 1.12 (t, *J* = 7.5 Hz, 3H), 0.98-0.92 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 139.4, 130.9, 128.1, 126.4, 126.3, 41.3, 31.6, 21.9, 21.8, 14.4, 13.9. (*NMR shifts correspond to the major E isomer*).

2.8.9 Selected examples of NMR spectra

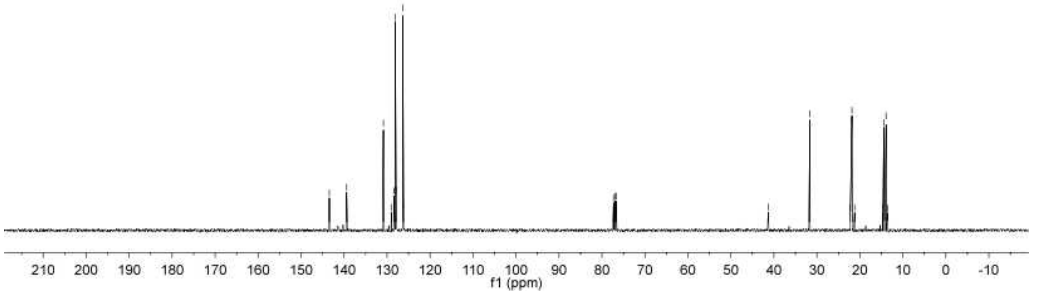


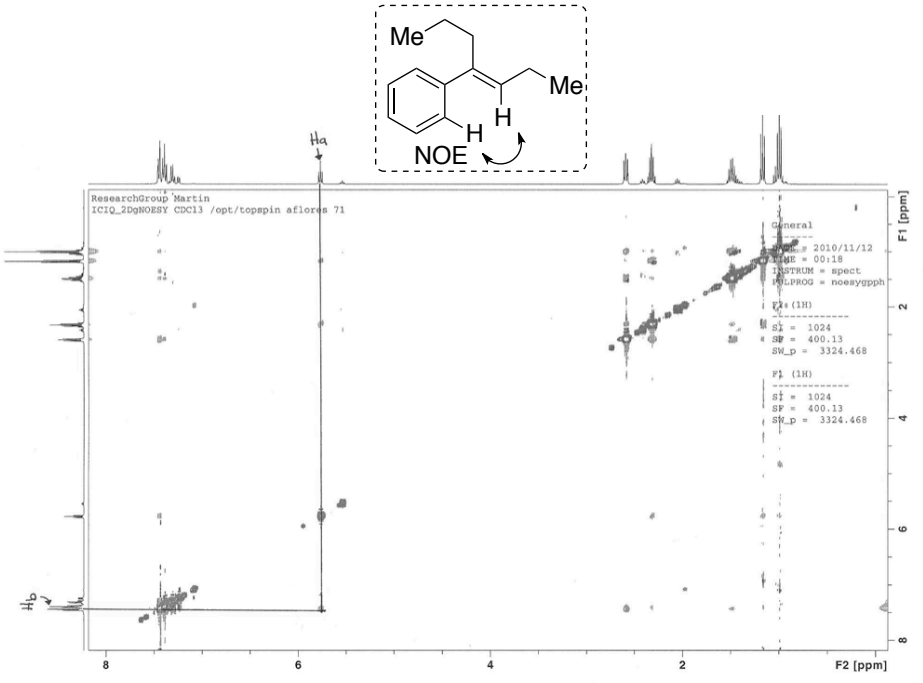
[173] Kesharwani, T., Verma A. K., Emrich, D., Ward, J. A., Larock, R. C., *Org. Lett.* **2009**, *11*, 2591.

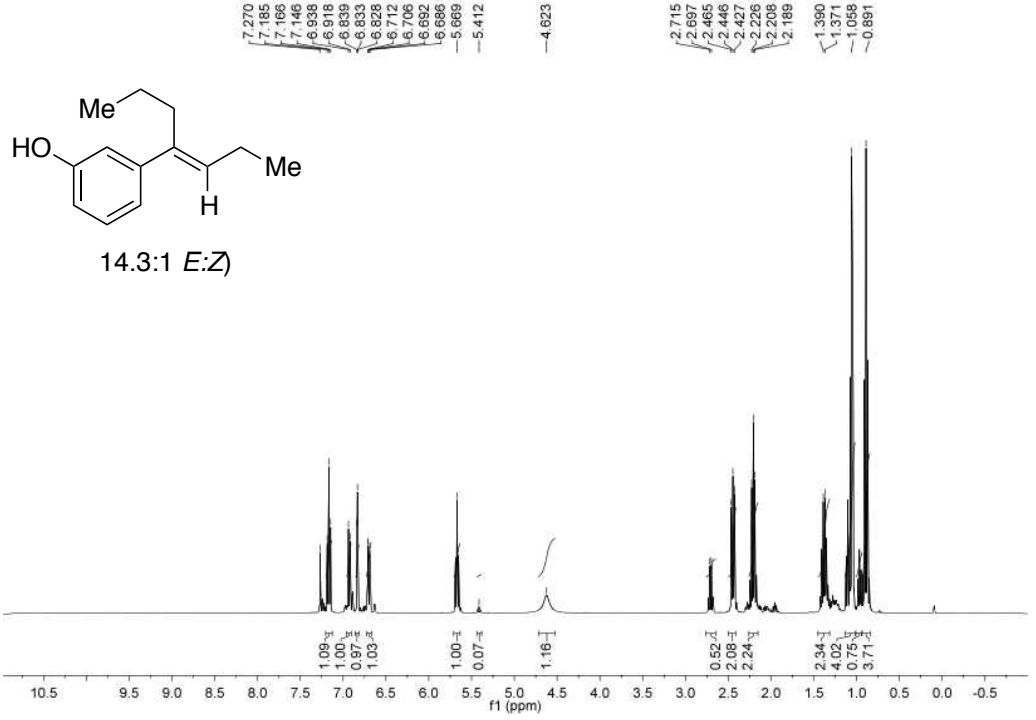

143.43
139.40
130.85
129.04
128.38
128.08
127.89
126.35
126.32
126.23
77.32
77.00
76.68
41.32
31.64
22.22
21.88
21.84
21.22
14.73
14.43
13.91
13.58


Me
Me
H

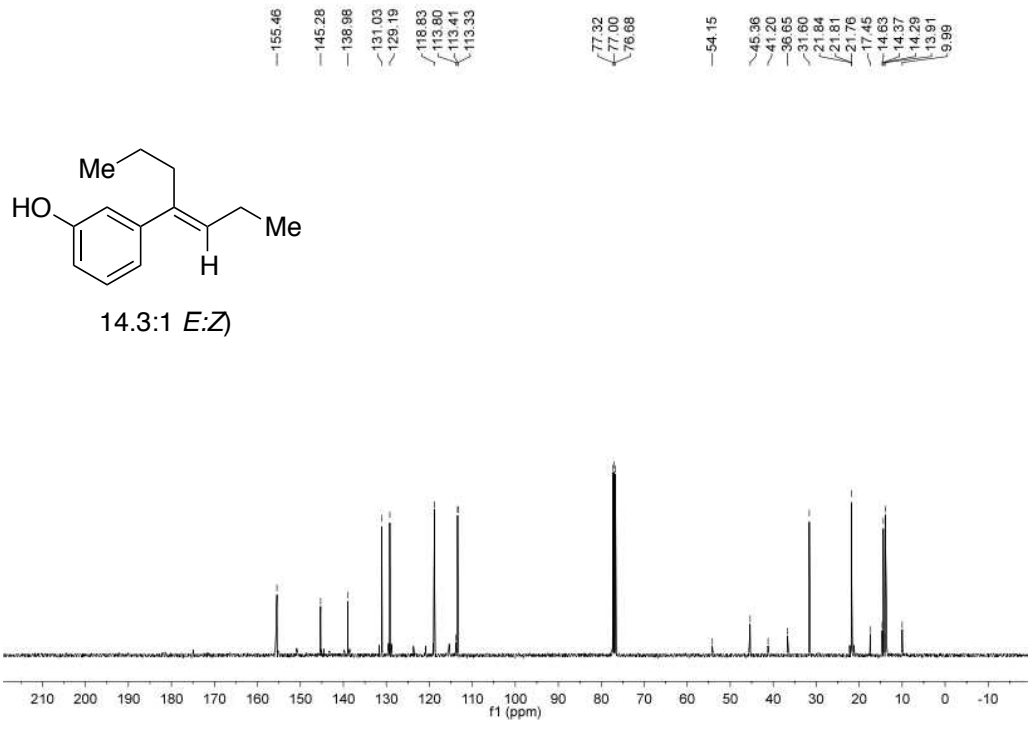
(9:1 *E:Z*)


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

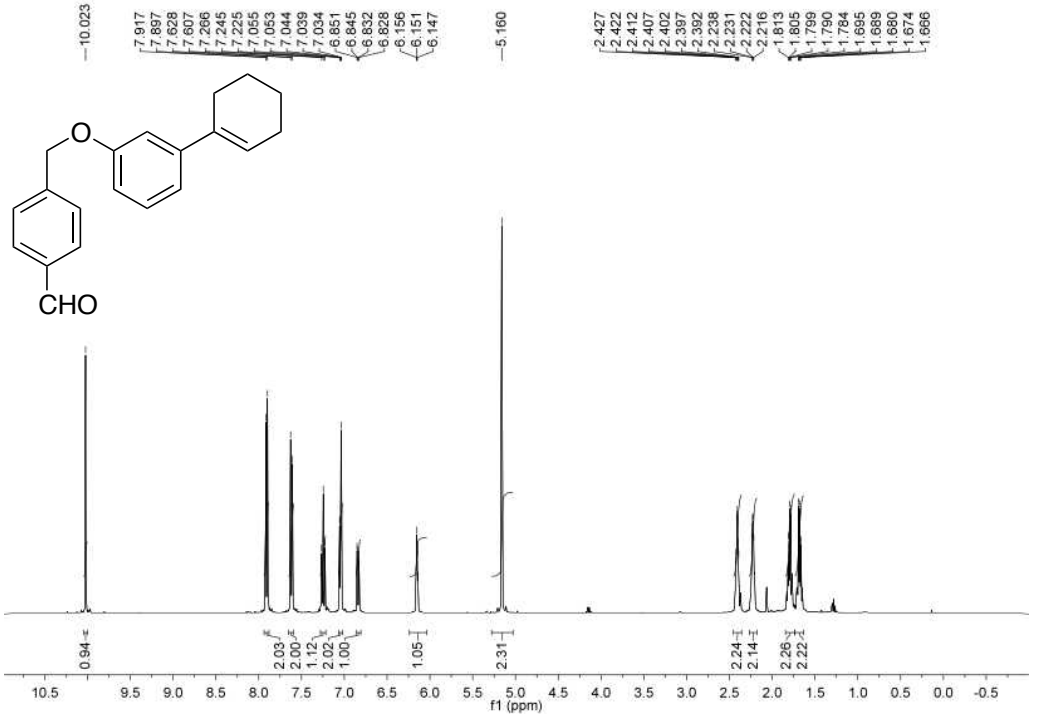

Me
Me
H
H
NOE
Ha
Hb
ResearchGroup Martin
ICIQ_2DgNOESY CDCl3 /opt/topspin aflores 71
General
DATE = 2010/11/12
TIME = 00:18
INSTRUM = spect
PULPROG = noesygpph
F2 (1H)
SI = 1024
SF = 400.13
SW_p = 3324.468
F1 (1H)
SI = 1024
SF = 400.13
SW_p = 3324.468
F1 [ppm]
F2 [ppm]
8
6
4
2

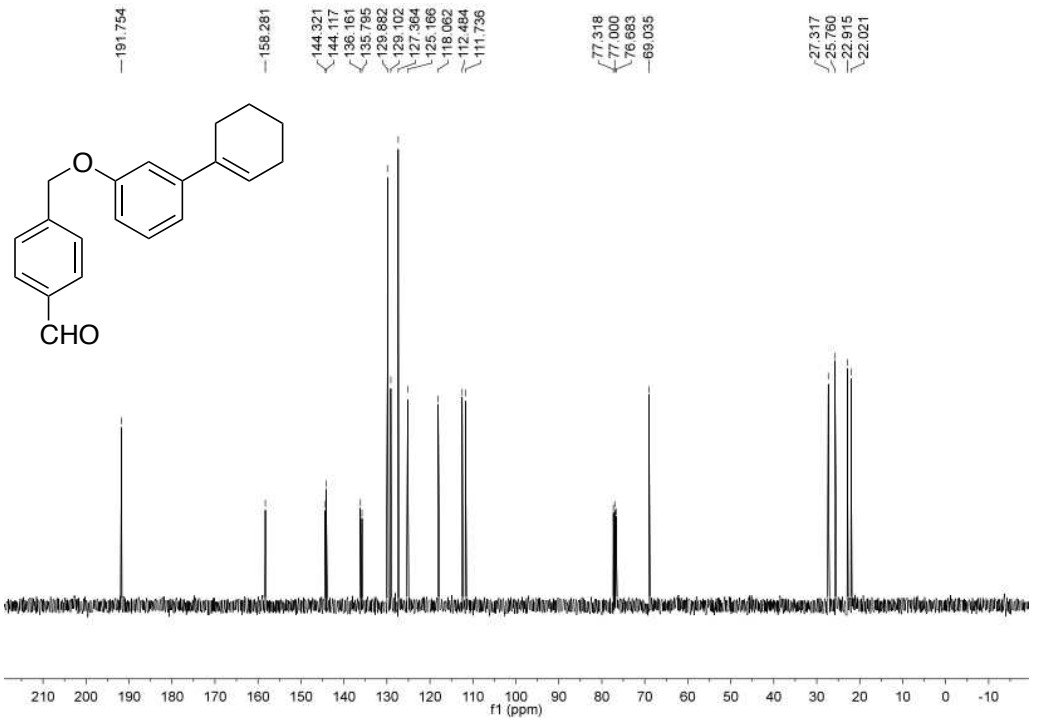


14.3:1 *E*:*Z*)



14.3:1 *E*:*Z*)


10.023
7.917
7.897
7.628
7.607
7.266
7.245
7.225
7.055
7.053
7.044
7.039
7.034
6.851
6.845
6.832
6.828
6.156
6.151
6.147
5.160
2.427
2.422
2.412
2.407
2.402
2.397
2.392
2.238
2.231
2.222
2.216
1.813
1.805
1.799
1.790
1.784
1.695
1.689
1.680
1.674
1.666
O
CHO
0.94
2.03
2.00
1.12
2.02
1.00
1.05
2.31
2.24
2.14
2.26
2.22
f1 (ppm)


191.754
158.281
144.321
144.117
136.161
135.795
129.882
129.102
127.364
125.166
118.062
112.484
111.736
77.318
77.000
76.683
69.035
27.317
25.760
22.915
22.021
O
CHO
f1 (ppm)

Chapter 3

Toward the understanding of the C-H bond functionalization of aldehydic bonds with aryl bromides as substrates

3.1

Objectives

The objectives of this chapter is the following:

- To provide experimental and computational evidence toward a better understanding of the mechanism for forming either benzocyclobutenones or styrene derivatives from common α-aryl aldehydes depending on the ligand of choice.

3.2

Introduction

All but the simplest chemical reactions proceed by a series of steps, which are in general bimolecular reactions. The rate of the total reaction is determined or limited by the slowest step. The use of a catalyst to accelerate, or more exactly by circumventing, this slowest step is determined by the change of the rate of the chemical reaction under the action of this catalyst that follows an alternative route with a lower activation energy. It is very probable when using a catalyst unit that the components of the reaction formed intermediates that reacted to give the expected product and restore the unchanged catalyst molecule. In this manner if we study the route that the catalyst and the substrate follow along the catalytic cycle to yield a product, we could be able to get a better understanding of the reaction.[174]

Calculations have thus contributed to the discovery of new pathways for chemical reactions.[175] Computing the energy profile for the entire catalytic cycle is a daunting task but it leads to a better understanding of the relative activation barriers for the individual steps.[175] It also allows us to tackle the essential aspect of selectivity by comparing catalytic cycles leading to different products. Computation of the full energy profile also gives access to the rate-determining step for the transformation of interest and enables us, in principle, to propose alterations of the catalyst and experimental conditions to improve activity and selectivity. One key piece of information for the studies of reaction mechanisms, which is not available by any other method, is the characterization of the

[174] Balcells, D.; Clot.; Eisenstein, O., *Chem. Re*v. **2010**, *110*, 749.
[175] For reviews related with computational studies of C- H bond functionalizations see: a) Niu, S.; Hall, M. B. *Chem. Re*v. **2000**, *100*, 353. b) Torrent, M.; Solà, M.; Frenking, G. *Chem. Re*v. **2000**, *100*, 439. c) Dedieu, A. *Chem. Re*v. **2000**, *100*, 543.

transition state (TS) on the potential energy surface (PES). The energy of the transition state allows the evaluation of an energy barrier (ΔEq or ΔHq) or an activation barrier (ΔGq), which can be compared with experimental values from kinetic studies, when available.

The electronic structure of the TS allows characterization in more detail of the mechanism of the reaction in terms of bonds that are broken and made. The reactants and products connected by a given TS are also easy to obtain from calculations giving access to the thermodynamics of the reaction. Calculations are also useful to locate intermediates, which may be too unstable to be observed, and to suggest modifications to the experimental systems to favor or disfavor these proposed intermediates. In this regard, computational studies of the structure and reactivity of organometallic complexes have now proven to be an essential tool for accessing to difficult information, if not impossible, to obtain directly from experiments. Many of the mechanistic questions raised in these studies may be probed effectively *via* combined experimental and theoretical studies.[174]

In this chapter we were interested in provide mechanistic insights in the intramolecular C-H bond functionalization of aryl bromide aldehydes toward benzocyclobutenone derivatives as well as highlight how subtle changes in the ligand play a crucial role in the selectivity of the reaction.

3.3

Results and discussion

3.3.1 Mechanistic studies in route to BCB derivatives.

We have observed that the metal-catalyzed intramolecular acylation of aryl bromides *via* aldehydic C-H bond-functionalization using binaphthyl-type ligands provided exclusive selectivity toward benzocyclobutenone motifs.[116,148] While the scope of the reaction was thoroughly investigated in the Chapter 2, the rationale behind the mechanism of such transformation will be studied along this chapter in a combined experimental and theoretical study that not only demonstrates the origin of such selectivity toward BCB products but also the observed switch of selectivity to achieve styrene derivatives. Theoretical calculations were performed in collaboration with Dr. Alex Hamilton at Prof. Carles Bo´s group at ICIQ.[176]

In Chapter 2 we proposed a mechanistic pathway for the formation of benzocyclobutenone products **(148)** (mechanism A, Figure 3.1). The reaction was initiated by oxidative addition followed by halide exchange with the carbonate base, thus affording **IV**. Subsequently, **IV** would undergo a C-H bond-functionalization *via* a concerted-metalation-deprotonation (CMD) pathway[25] yielding a palladium five-membered metalacycle **III** and a final reductive elimination event allowed the formation of benzocyclobutenone derivative **(148)**. Such proposal, though, was merely speculative and we did not have empirical evidence for such possibility. Alternatively, there might be another possibility (mechanism B, Figure 3.1) that invokes an addition of the Pd-C bond across the

[176] ICIQ - Institut Català d'Investigació Química. Avgda. Països Catalans 16, 43007 Tarragona (Spain).

aldehydic C-O bond, giving rise to **V**.[177] Subsequently, a final β-hydride elimination would then lead to the desired benzocyclobutenone core **(148)** while recovering back the active species **I**.

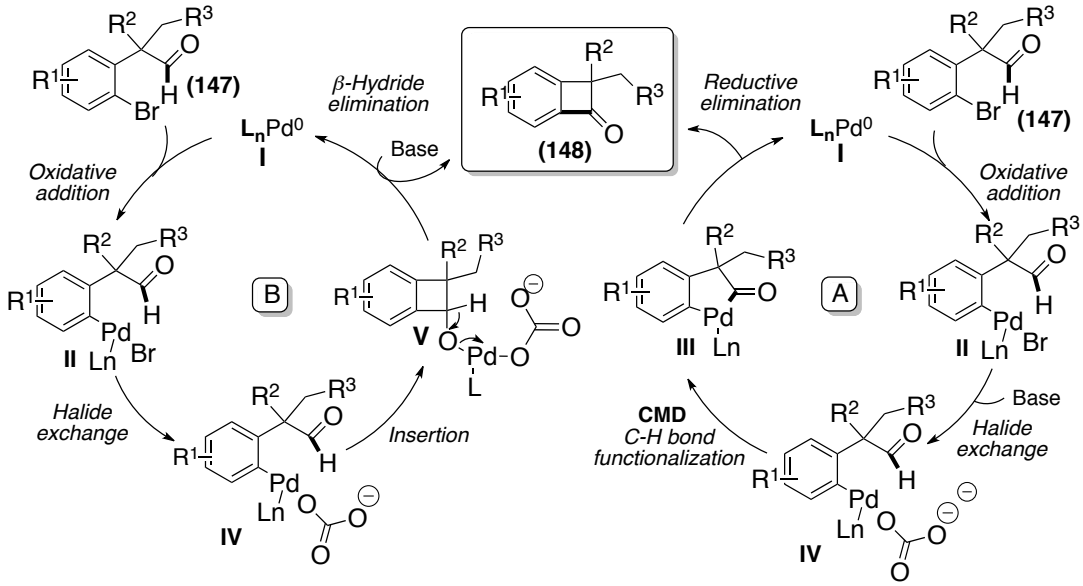


Figure 3.1

In principle, it is rather difficult to distinguish between the two catalytic scenarios depicted in Figure 3.1. We wondered whether we could gather indirect evidence by studying the reactivity of aldehyde **(150)** (Figure 3.2). If a mechanism ***A*** would be operating, one should expect that compound **(327)** would end up in a six-membered metallacycle after C-H bond-functionalization forming six membered palladacycle **VIII**; on the contrary, if mechanism ***B*** would be operating, the addition across the C=O bond in **(327)** would result in a 5-*exo*-*trig* type cyclization ending up in a five-membered ring **IX**.[178] It is expected that a 5-

[177] For selected insertions of Pd-oxidative addition complexes across the C=O bond: a) Quan, L. G.; Lamrani, M.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 4827 (ketones). b) Zhao, Y. B.; Mariampillai, B.; Candito, D. A.; Laleu, B.; Li, M. Z.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 1849 (aldehydes). c) Solé, D.; Serrano, O. *J. Org. Chem.* **2008**, *73*, 9372 (esters). d) Cacchi, S.; Fabrizi, G.; Gavazza, F.; Goggiamani, A. *Org. Lett.* **2003**, *5*, 289 (anhydrides).
[178] Gevorgyan, V.; Quan, L. G.; Yamamoto, Y. *Tetrahedron Lett.* **1999**, *40*, 4089.

exo-trig type cyclization would be predominant over the 4-*exo-trig* in **VII**. Thus, formation of **(328)** should be expected whereas formation of **(151)** should be more difficult under a catalytic regime ***B***. Interestingly, in sharp contrast to **(150)**, the use of **(327)** as substrate did not deliver the expected coupling product **(328)**. Furthermore, taking into consideration the difficulty for accessing six-membered palladacycles such **VIII** compared to the five-membered analogues **VI**, these results suggest that the mechanism might be operating via catalytic cycle ***A***. Such assumption is in analogy with the high free activation energy that is expected for compound **VII** (highly strain benzocyclobutane derivative) as compared to the five-membered palladacycle **VI**.

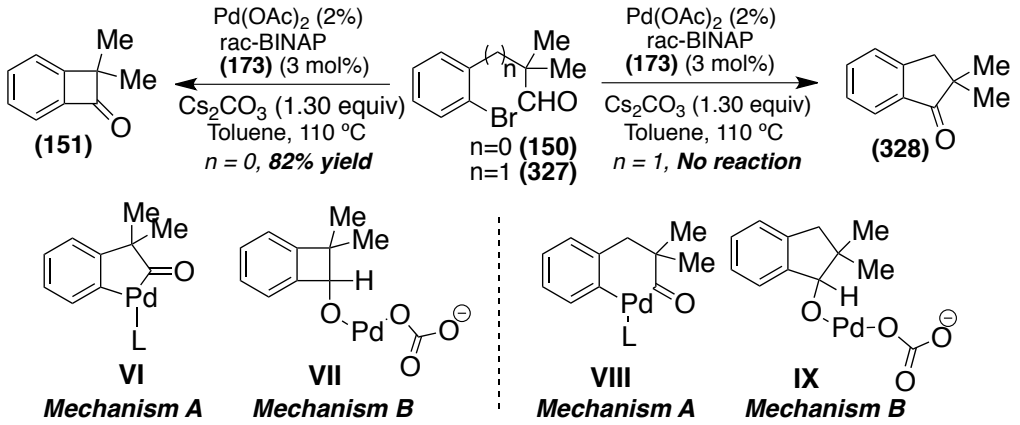


Figure 3.2

3.3.1.1 Insights into the rate-limiting step

We decided to conduct isotopically-labelled studies and compare the initial rates of **(188)** and its homologous-deuterated compound **(329)**[179]The deuterated compound **(329)** was prepared in 3 steps from commercially available methyl 2-(2-bromophenyl)acetate (Figure 3.3). Initial deprotonation with NaH followed by treatment with 1,5-dibromopentane afforded **(326)** that subsequently was

[179] a) Simmons, E. M.; Hartwig, J. F. *Angew. Chem., Int. Ed*. **2012**, *51*, 3066. b) Gómez-Gallego, M.; Sierra, M. A. *Chem. Rev*. **2011**, *111*, 4857.

reacted with $LiAlD_4$. A final oxidation in the presence of PCC/SiO_2 allowed for the preparation of **(329)** with total deuterium incorporation into the aldehydic motif.

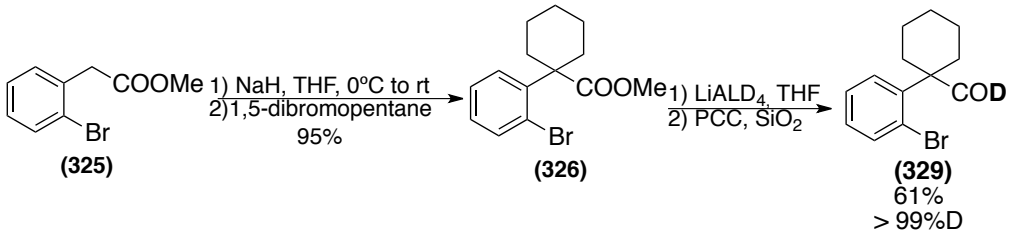
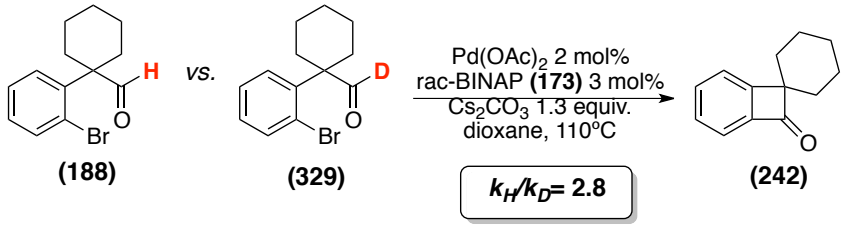


Figure 3.3

Taking into consideration the differences in the CO stretch between **(188)** (ν = 1703 cm^{-1}) and **(242)** (ν = 1749 cm^{-1}), we decided to monitor the course of the reaction by *in situ* FTIR. The spectra were collected for 20-24 hours every 10-12 minutes and the rates were calculated by linear regression fittings of product's carbonyl group absorbance *vs.* time profiles after an initial induction period where no product was generated (Figure 3.4-(A)) and the initial rates were calculated where a maximum increase in absorbance was observed for conversions lower than 25% (Figure 3.4-(B)).

As shown in Figure 3.4 (B), we observed that aldehyde **(188)** reacted at a slightly faster rate than the deuterated homologous aldehyde **(329)**. Indeed, such results can be translated into a $\boldsymbol{k_H/k_D = 2.8}$. While this value is certainly not very high for typical C-H bond-functionalization reactions, it likely suggests that C-H bond-cleavage is the rate-determining under our optimized reaction conditions.[179] While in principle mechanism ***B*** might also account for such observation if β-hydride elimination would be rate-determining, such possibility is unlikely in view of recent studies in this field as well as the expected high reactivity of intermediates of type **(188)**.[180]

[180] a) Kossoy, E.; Diskin-Posner, Y.; Leitus, G.; Milstein, D., *Adv. Synth. Catal.,* **2012**, *354*, 497. b) Prechtl, M. H. G.; Wobser, K.; Theyssen, N.; Ben-David, Y.; Milstein, D.; Leitner, W.,



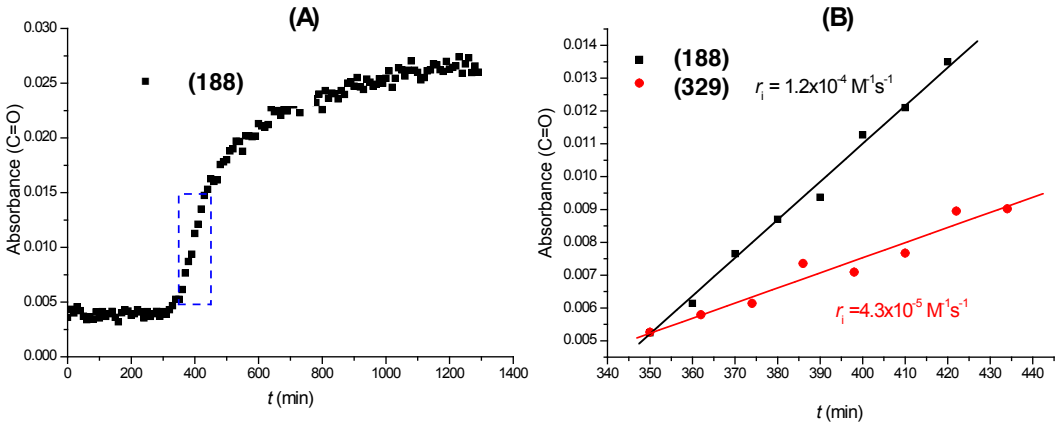


Figure 3.4

Next, we turned our attention to determine the order of all reaction components. We first examined the order of Pd/**(173)**. Reactions with different concentrations of Pd/**(173)** were run up to about 5–20% conversion by taking aliquots at different times from the reaction mixture and monitored by gas chromatography. The acquired data was plot in % product versus time and was analyzed using the initial rates method to determine the rate for each concentration. As it is shown in Figure 3.5, a plot of the initial reaction rate (M/min) versus [Pd/**(173)**] was linear, indicating a fist order dependence on the Pd/**(173)** ratio.

Catal. Sci. Technol., **2012**, *2*, 2039. c) Gnanaprakasam, B.; Ben- David, Y.; Milstein, D., *Adv. Synth. Catal.*, **2010**, *352*, 3169.

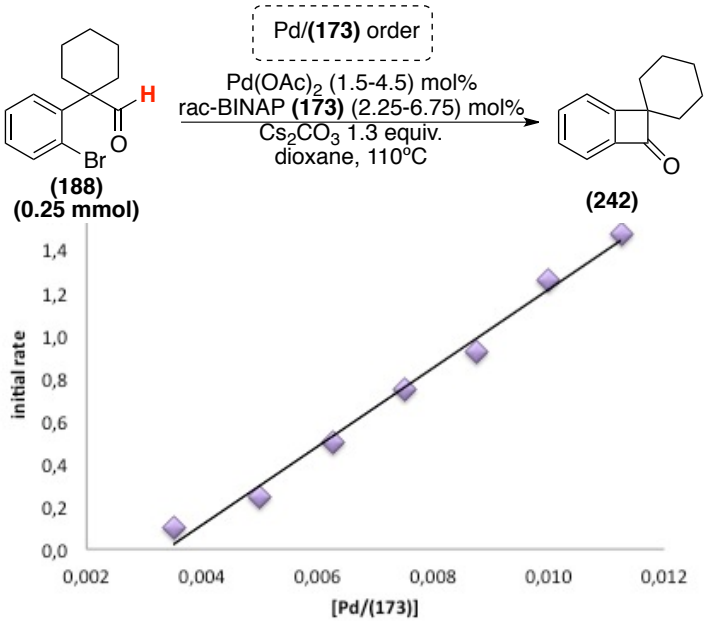


Figure 3.5

A similar behavior was observed when looking at the order dependence in [α-aryl aldehyde] and [Cs_2CO_3], indicating order 1 for both components (Figures 3.6 and 3.7).

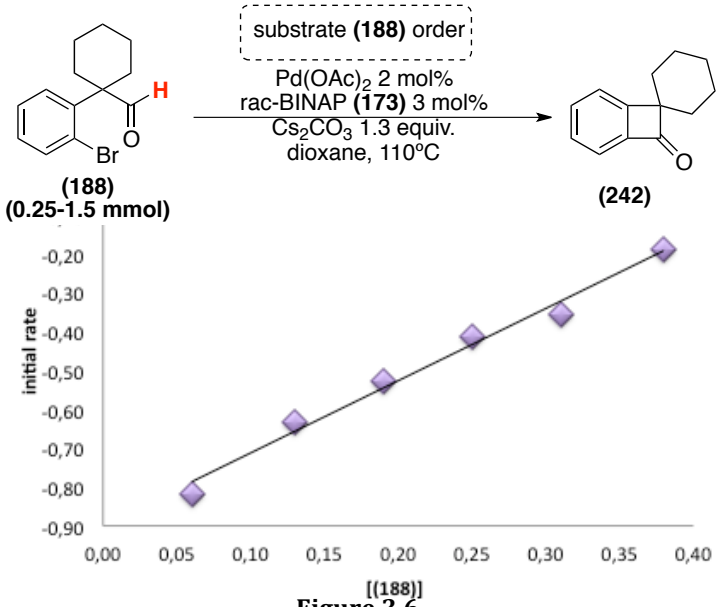


Figure 3.6

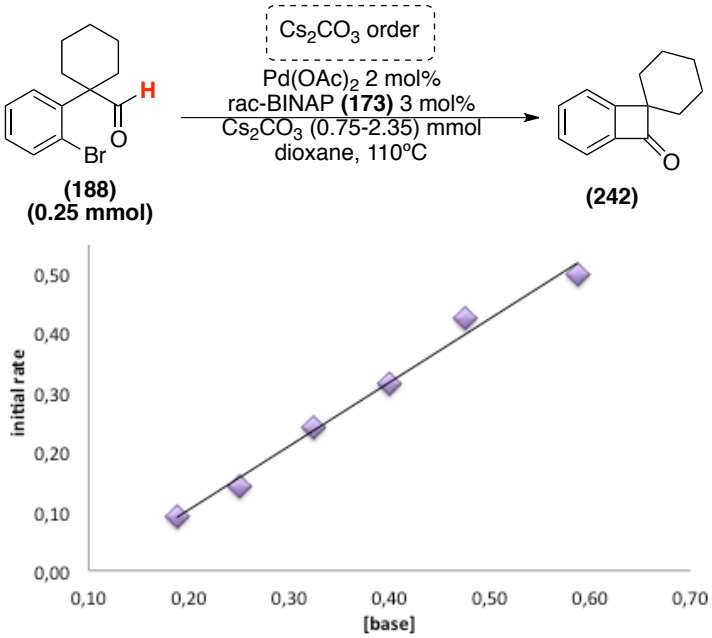


Figure 3.7

These results suggest that the [Pd/**(173)**], α-aryl aldehyde **(150)** and Cs_2CO_3 are all participating at the turnover-limiting step, thus reinforcing the notion that the C-H bond-functionalization *via* concerted metalation-deprotonation pathway (CMD) is the rate limiting step in our reaction (Figure 3.8).[27-30]

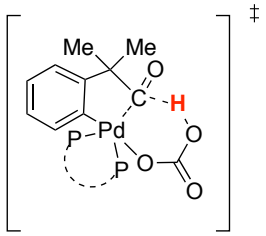


Figure 3.8

Although these results gave strong support for a catalytic cycle **A** (Figure 3.1) we decided to do a more comprehensive study via theoretical calculations to confirm whether mechanism ***A*** or ***B*** was operating under our reaction protocol.

3.3.1.2 Theoretical calculations

The basic features of the mechanism were studied on the model system of 2-(2-bromophenyl)-2-methylpropanal and *rac*-BINAP **(173)** as the supporting ligand. Experimentally, we observed that Cs_2CO_3 was the most efficient base, thus initially a CMD (concerted metallation deprotonation) mechanism for the C-H bond-functionalization event was proposed. In Figure 3.9 is presented the free energy surface (ΔG_{298}) for the competitive pathways toward the preparation of the BCB derivative **(151)**.

1) Oxidative addition. The oxidative addition of C(sp^2)-X bonds to Pd(0) has been extensively studied in many Pd-catalyzed cross-coupling reactions.[181] Generally, the reaction is considered to proceed by an initial η^2-coordination in the aryl ring forming the intermediate **Pd-BINAP+1a**, Figure 3.9. As shown, the overall activation barrier to reach **Int 1-Br** was calculated to be in 16.2 kcal mol^{-1}.

2) C-H functionalization (mechanism *A* vs. mechanism *B*). We found that the corresponding C-H bond-functionalization from the initially formed oxidative addition species bearing a Pd-Br bond was energetically unfavourable. While the substitution of Br^- by CO_3^{2-} at the coordination sphere on palladium was penalized by 8.5 kcal mol^{-1} (**Int 1-CO_3^-**), the corresponding C-H bond-functionalization was expected to be faster taking into consideration the precedents for accelerating C-H bond-functionalization reactions in the presence of carbonate bases.[25,26] Still, however, we had to consider the two pathways from **Int 1-CO_3^-**: (a) C-H bond functionalization en route to **Int 3** (Figure 3.9-blue) or (b) insertion of the Pd-C

[181] a) Lam, K. C.; Marder, T. B.; Lin, Z. *Organometallics* **2007**, *26*, 758 b) Ahlquist, M.; Norrby, P.-O. *Organometallics* **2007**, *26*, 55. c) Ahlquist, M.; Fristrup, P.; Tanner, D.; Norrby, P.-O. *Organometallics* **2006**, *25*, 2066. d) Goossen, L. J.; Koley, D.; Hermann, H. L.; Thiel, W. *Organometallics* **2005**, *24*, 2398. e) Senn, H. M.; Ziegler, T. *Organometallics* **2004**, *23*, 2980. f) Goossen, L. J.; Koley, D.; Hermann, H.; Thiel, W. *Chem. Commun.* **2004**, 2141. g) Sundermann, A.; Uzan, O.; Martin, J. M. L. *Chem.-Eur. J.* **2001**, *7*, 1703. h) de Meijere, A.; Diederich, F., *"Metal-Catalyzed Cross-Coupling Reactions"*, 2nd Edition, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, **2004**.

across the C=O bond in route to **Int 2** (Figure 3.8-red).

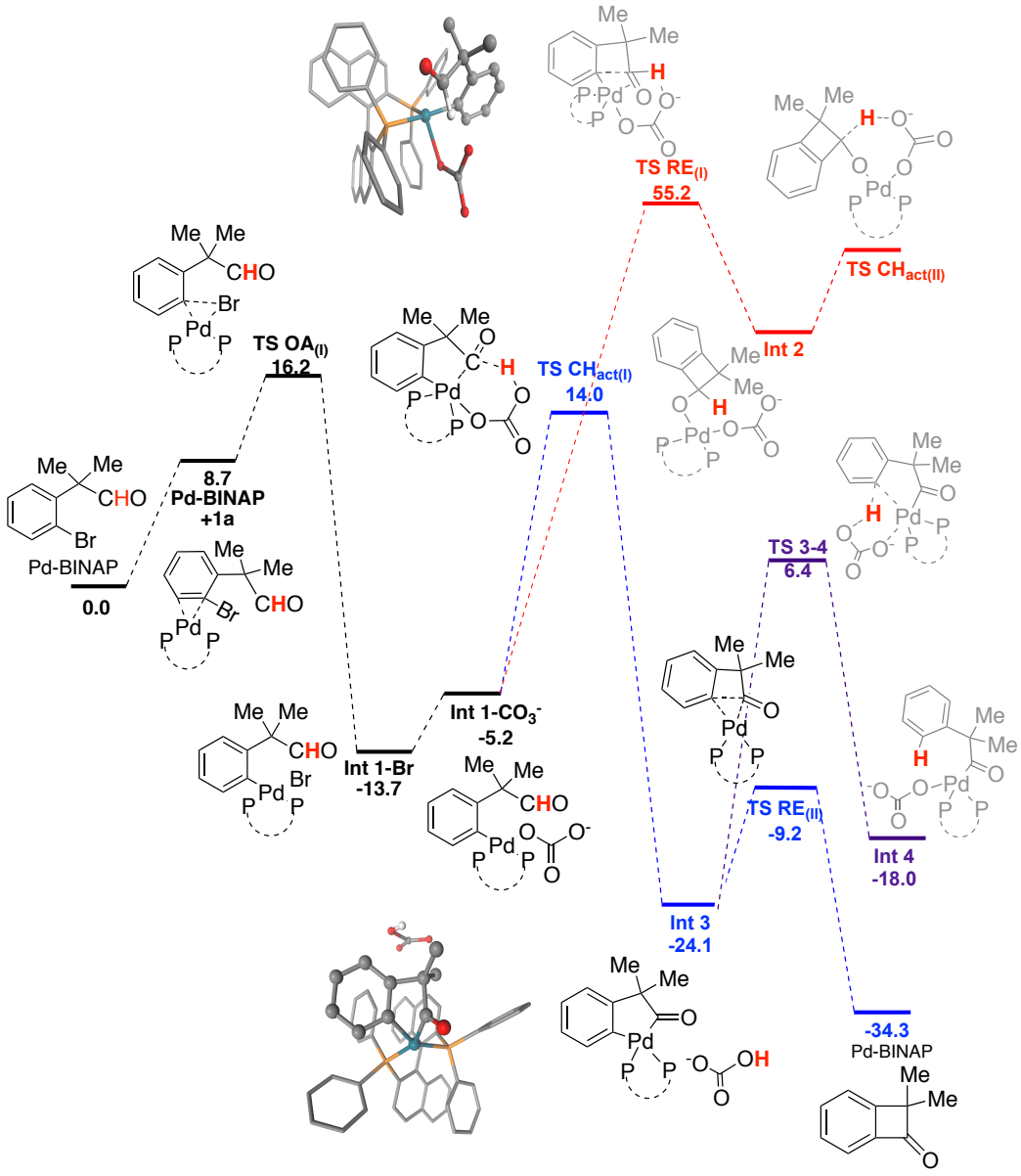


Figure 3.9

As shown in Figure 3.9 (red color) the addition of the Pd-C bond across the C-O bond trough **TS RE-2**, where the Pd centre is η^2-coordinated to the CO bond, was ruled out due to the higher barrier observed for this endothermic process (41.9

kcal mol^{-1}). In sharp contrast, the C-H functionalization event through **TS CH$_{act}$** (Figure 3.9, blue) had a significantly lower activation barrier of 27.7 Kcal mol-1, an achievable barrier at the temperatures by which our reaction operates. Such process took place by a concerted metallation deprotonation (CMD) in which there is an interaction of the CO-**H** bond with the carbonate base as well as an interaction between the forming **C···Pd** bond (2.362 Å). In this transition state, the distance aldehydic of the **C-H** bond was elongated from 1.080 Å to 1.244 Å and the agostic **H···O** was reduced to 1.499 Å**.**

Several groups have studied the proton abstraction assisted by the CO_3^{2-}.[26] For instance Echavarren and Maseras have studied the proton abstraction mechanism in the palladium catalyzed intramolecular arylations with a combined experimental and theoretical approach.[28] According to the results, the proton abstraction could take place following either intramolecular (substitution of bromide for HCO_3^-) or intermolecular (without prior coordination of the base to Pd or substitution of bromide) pathways depending on the substrates.[28] On the other hand, Fagnou have also shown that C-H functionalization can take place by the coordinated Br.[29]

3) Reductive elimination *vs.* proton transfer (selectivity of BCB over the styrene product when employing BINAP as the ligand). In **Int 4** we observed that the base was partly dissociated from the Pd coordination sphere with a **Pd···O** distance of 2.9 Å. This intermediate was the key for the selectivity observed toward BCB derivatives under BINAP **(173)** conditions. Indeed, we calculated that reductive elimination toward the benzocyclobutenone **(151)** had a surprisingly low barrier of 14.9 kcal mol^{-1}.[182] These results are quite revealing due to the fact that the formation of strained four-membered rings are typically believed to proceed with remarkably high activation barriers as compared to medium-sized rings.[182] In sharp contrast, the proton transfer from the

[182] For related reductive eliminations to afford benzocyclobutane rings, see ref. 30

hydrogencarbonate unit bound to Pd to the aryl backbone en route to the styrene derivative **1c** showed a barrier of 30.5 kcal mol^{-1} (Figure 3.9, purple). These results confirmed the observed exquisite selectivity of the reactions based upon BINAP for the formation of benzocyclobutenone cores.

3.3.2 Mechanistic studies en route to styrene derivatives.

After studying the mechanism by which α-aryl aldehydes are transformed into benzocyclobutenones we turned our attention to the formation of styrene derivatives **(291)** (Figure 3.10).[148] In principle, oxidative addition of the *in situ* formed Pd(0) species into the corresponding α-aryl aldehyde **(147)** followed by halide exchange with the exogenous cesium carbonate would result in **IV** (Figure 3.10). We anticipated that the flexibility and hemilability exerted by ligand **(293)** would allow the binding of hydrogencarbonate to the metal centre. Putative species **IV** could then follow two different pathways to obtain the styrene derivatives **(291)**. In path ***C***, an intramolecular proton transfer from **IV** would give rise to a more flexible acyl palladium complex **XI,** this transformation can be seen as a 1,4-palladium migration where the coordinated base in **X** is responsible for the proton migration[183]. Then, the acyl palladium complex **XI** can promote a decarbonylation forming **XII** followed by final β-hydride elimination to afford the styrene compound **(291)**. Alternatively, in path ***D***, C-H bond functionalization of the adehydic C-H bond in **IV** to yield palladacycle **III** and HCO_3^-, then decarbonylation from **III** would afford a rather strained palladium metallacycle

[183] For 1,4-migrations of palladium observed experimentally see: a) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685. b) Catellani, M.; Ferioli, L. *Synthesis* **1996**, 769. c) Cámpora, J.; López, J. A.; Palma, P.; Valerga, P.; Spillner, E.; Carmona, E. *Angew. Chem., Int. Ed.* **1999**, *38*, 147. d) Catellani, M.; Cugini, F.; Bocelli, G. *J. Organomet. Chem.* **1999**, *584*, 63. e) Karig, G.; Moon, M.-T.; Thasana, N.; Gallagher, T. *Org. Lett.* **2002**, *4*, 3115. f) Huang, Q.; Fazio, A.; Dai, G.; Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 7460. g) Zhao, J.; Campo, M.; Larock, R. C. *Angew. Chem., Int. Ed.* **2005**, *44*, 1873. h) Kesharwani, T.; Larock, R. C. *Tetrahedron* **2008**, *64*, 6090.

XIII that could undergo a fast β-hydride elimination yielding the styrene derivative **(291)**.

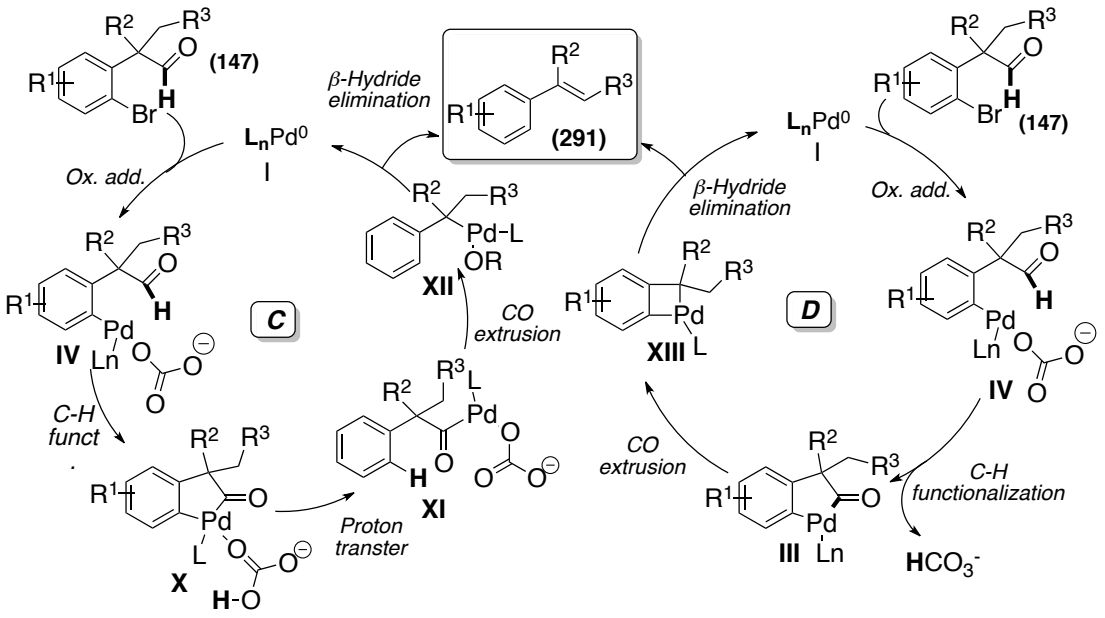


Figure 3.10

We decided to shed light into the mechanism of the reaction toward styrene derivatives via isotope-labelling studies, Figure 3.11. We hypothesized that the use of the previous synthetized deuterated aldehyde **(329)** could be highly informative. Such assumption is supported by the fact that if mechanism ***C*** would be operating, one might expect that the label would be transferred to the aromatic backbone, delivering **(330)** as the only product. On the contrary, if mechanism ***D*** would take place, one should expect that the label would be lost because there will be no proton transfer to the aromatic backbone, resulting in **(307)** (Figure 3.11).

According to our hypothesis, we also prepared **(333)** from commercially available dimethyl glutarate **(330)** in just four-step synthesis. The sequence commenced by exhaustive reduction of the aliphatic ester with $LiAlD_4$ and the

formation of the bis-tosylate derivative **(331)** that was used for preparing **(332)**. Final reduction with DIBALH at low temperatures allowed for the synthesis of **(333)** in which the four isotope labels are located in the cyclohexyl ring.

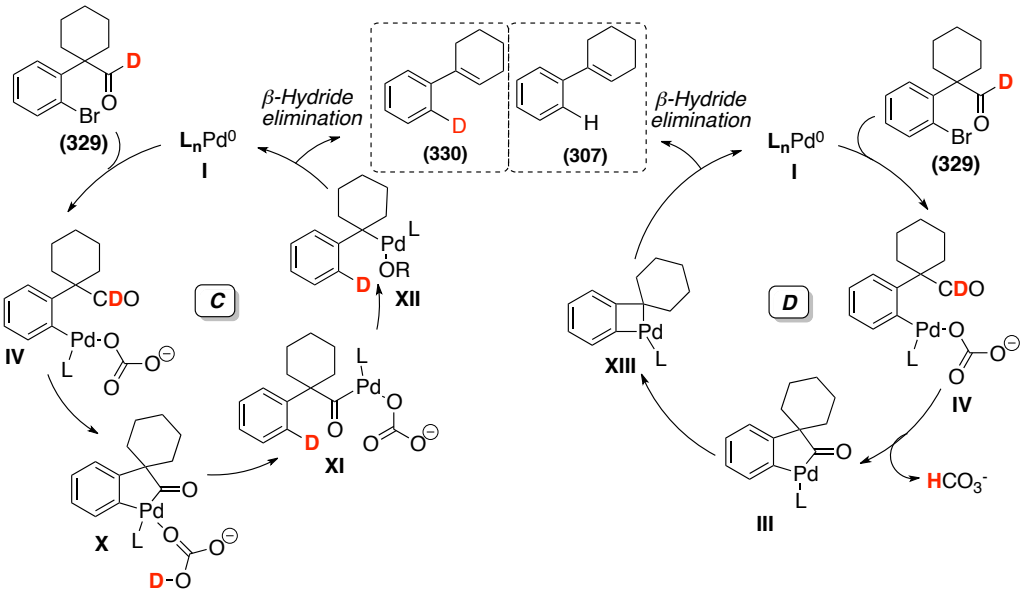


Figure 3.11

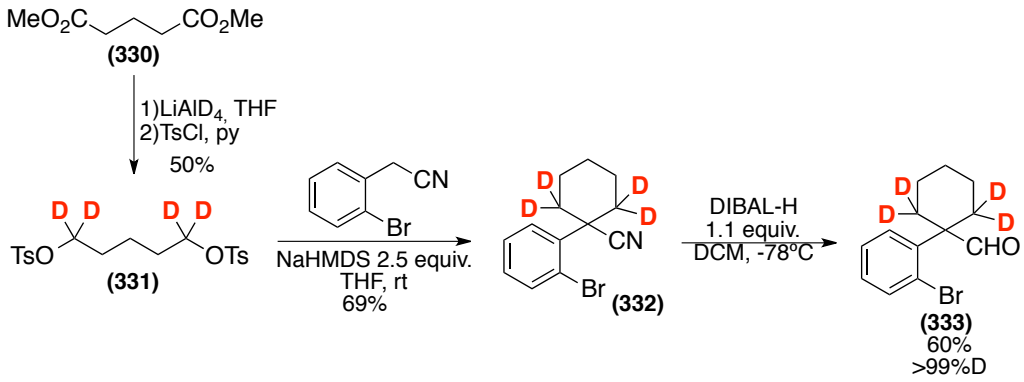


Figure 3.12

With substantial amounts of **(329)** and **(333)** in hand, we subjected these compounds to our optimized reaction conditions. Using aldehyde **(329)**, a quantitative intramolecular deuterium transfer to the aromatic motif yielding compound **(334)** was oberved,[184] Figure 3.13. On the other hand, we found that **(333)** was exclusively converted into **(335)** under the same reaction conditions (Figure 3.13). Taken together, these isotopically-labeling studies invariably suggest a mechanistic scenario based upon the catalytic cycle ***C*** depicted in Figure 3.11 in which an intramolecular proton transfer takes place.

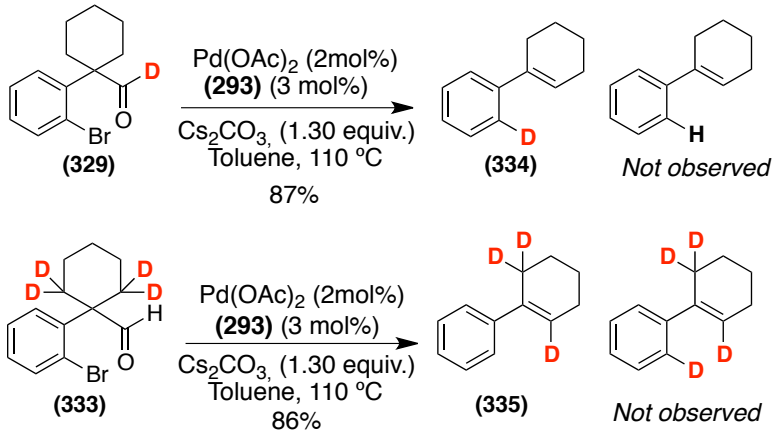


Figure 3.13

3.3.2.1 Insights into the rate-limiting step en route to styrene derivatives.

Following the same methodology as for benzocyclobutenones (Figures 3.5-3.7), we determined the order of all reactants (Pd/**(293)**, α-aryl aldehyde **(188)** and Cs_2CO_3) in the reaction toward **(307)**. Initial rates were calculated where a maximum increase in absorbance was observed for conversions up to 25%. As

[184] For 1H- and ^{13}C-NMR spectra see experimental section.

shown in Figures 3.14-3.16, we observed a first-order dependence to Pd/**(293)**, α-aryl aldehyde **(188)** and Cs_2CO_3.

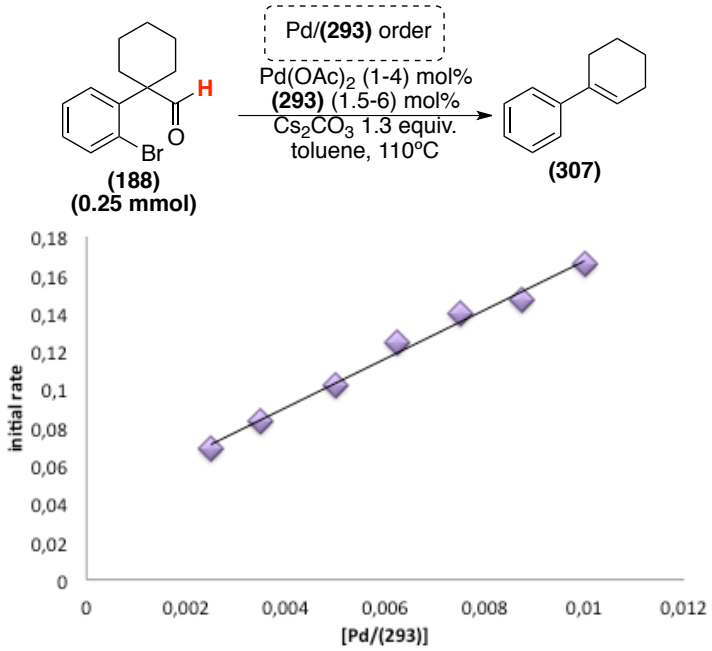


Figure 3.14

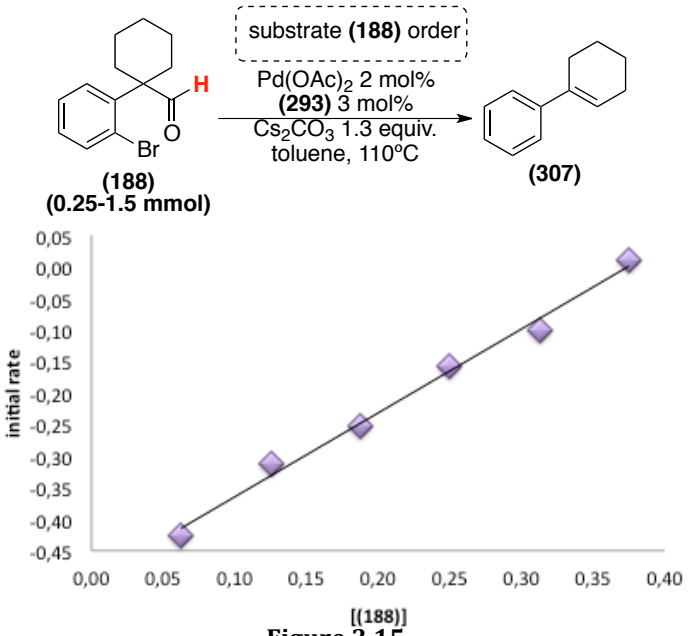


Figure 3.15

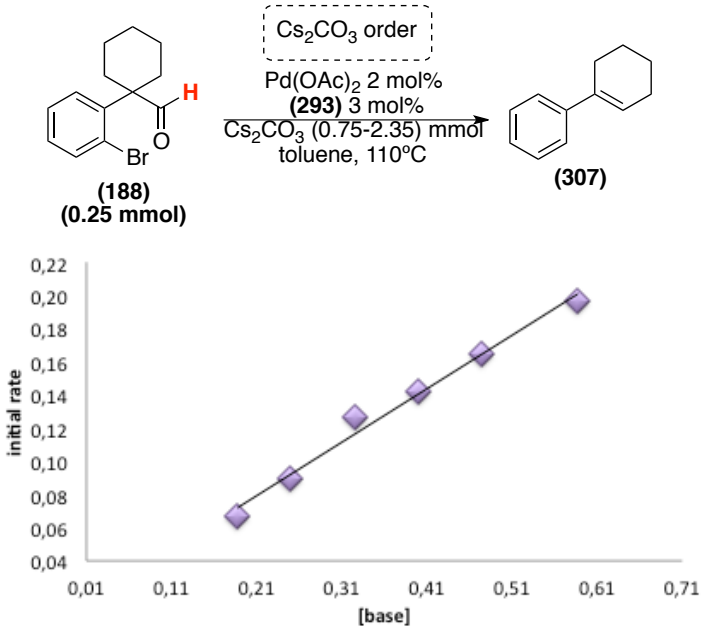


Figure 3.16

According to these results, Pd/**(293)**, Cs_2CO_3 and **(188)** participates at the rate-limiting step. However, these data do not allow us, at least in an empirical fashion, to rule out whether C-H bond-functionalization (**TS CH_{act}**) or decarbonylation from **TS CO_{ext}** are the rate-determining steps in the reaction (Figure 3.17).

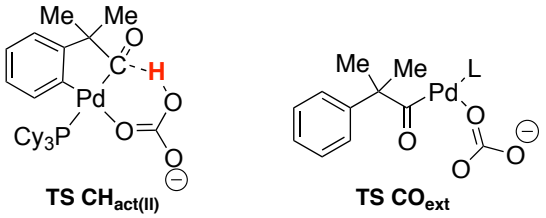


Figure 3.17

If decarbonylation was rate-determining, one should expect that the reaction would be inhibited in the presence of CO atmospheres. As anticipated, we found that very little styrene **(326)** was observed when reacting **(185)** in the presence of 20 psi CO atmospheres (Figure 3.18). These results are in sharp contrast with the 91% yield found when operating in the absence of external CO. This

experiment demonstrates that under CO atmospheres, the decarbonylation event en route to **XII** is inhibited, resulting in an increase concentration of **XI.** While one might argue that such experiment tacitly indicates that decarbonylation was rate-determining, we should be careful when making such statement. This is due to the fact that, in the presence of CO atmosphere, C-H bond-functionalization toward **(326)** would also not be favourable as CO insertion into Ar-Pd-Br bonds from the initial oxidative addition species have demonstrated to be a feasible process as well.[185] Therefore, we turned our attention to study the mechanism ***C*** en route to styrene derivatives *via* theoretical calculations.

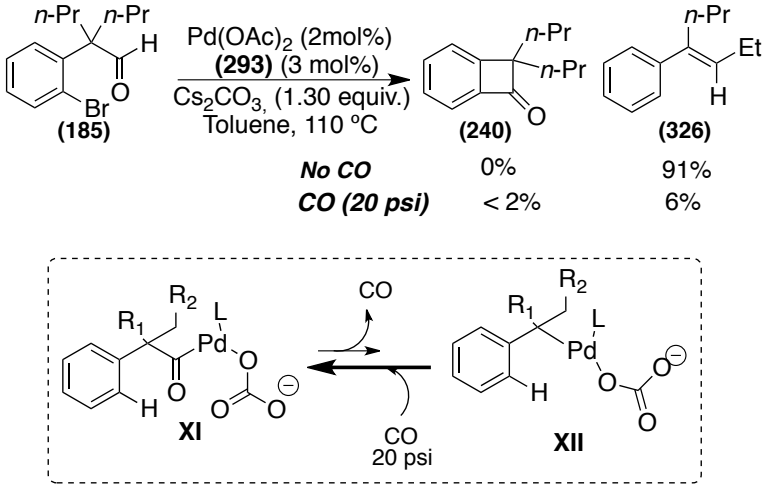


Figure 3.18

Although the available experimental data allowed us to rule out mechanism ***D***, we turned our attention to study mechanism ***C*** via theoretical calculations.

3.3.2.2 Theoretical calculations

Density functional theory (DFT) calculations have been carried out to gain more insight into mechanistic pathway for the formation of styrene **(152)** from **(150)**. We have selected the same combination of method/basis as for BCB but

[185] For a review see: Wu, X., -F.; Neuymann, H.; Beller, M., *Chem. Rev.,* **2011**, *40*, 4986.

using PCy_3 as the phosphine ligand (since both PCy_3 and ligand **(293)** gave exclusive selectivity for styrene **(152)**, we decided to carry out our calculations with PCy_3). The free energy surface (ΔG_{298}) for the competitive pathways toward alkene derivative is presented in Figures 3.19 and 3.20.

1) Oxidative addition. Our calculations suggest that the *in situ* formed $Pd(PCy_3)_2$ species initially suffers ligand dissociation to the active 12 electron species $Pd(PCy_3)$. Coordination of the metal center in a η^2-fashion to the aryl moiety formed **Pd-PCy$_3$+(150)** that facilitated the oxidative addition step. Unlike the BINAP mechanism, the halide exchange from **Int 5-Br** to **Int 5-CO$_3^-$** was exoergonic, likely due to the increased stability of the 4-coordinate Pd centre when the carbonate acts as chelating ligand in the presence of PCy_3.

2) C-H functionalization. By theoretical calculations, two pathways were considered for the C-H bond functionalization from intermediate **Int 5-CO$_3^-$**. Following mechanism ***C*** (Figure 3.19 in blue) the C-H bond functionalization occurred trough transition state **TS CH$_{act(III)}$** where the base abstracted the aldehydic proton via CMD with a barrier of 30.1 kcal mol^{-1}. Intermediate **Int 6** must then isomerize to **Int 6i** to orientate the proton in the correct position to be transfered to the phenyl ring. Alternatively, **Int 5-CO$_3^-$** would follow a mechanism ***E*** in which the aldehydic proton was activated via transition state **TS CH$_{(IV)}$** by forming a rather unstable Pd-H bond in **Int 7** (Figure 3.12 in red). The barrier for this process was 3 kcal mol^{-1} higher in energy than for mechanism ***C***. Therefore, it is rather risky to rule out a mechanism based upon such rather small energy difference and it is plausible to predict, at least computationally, that both pathways occur simultaneously under our reaction conditions.

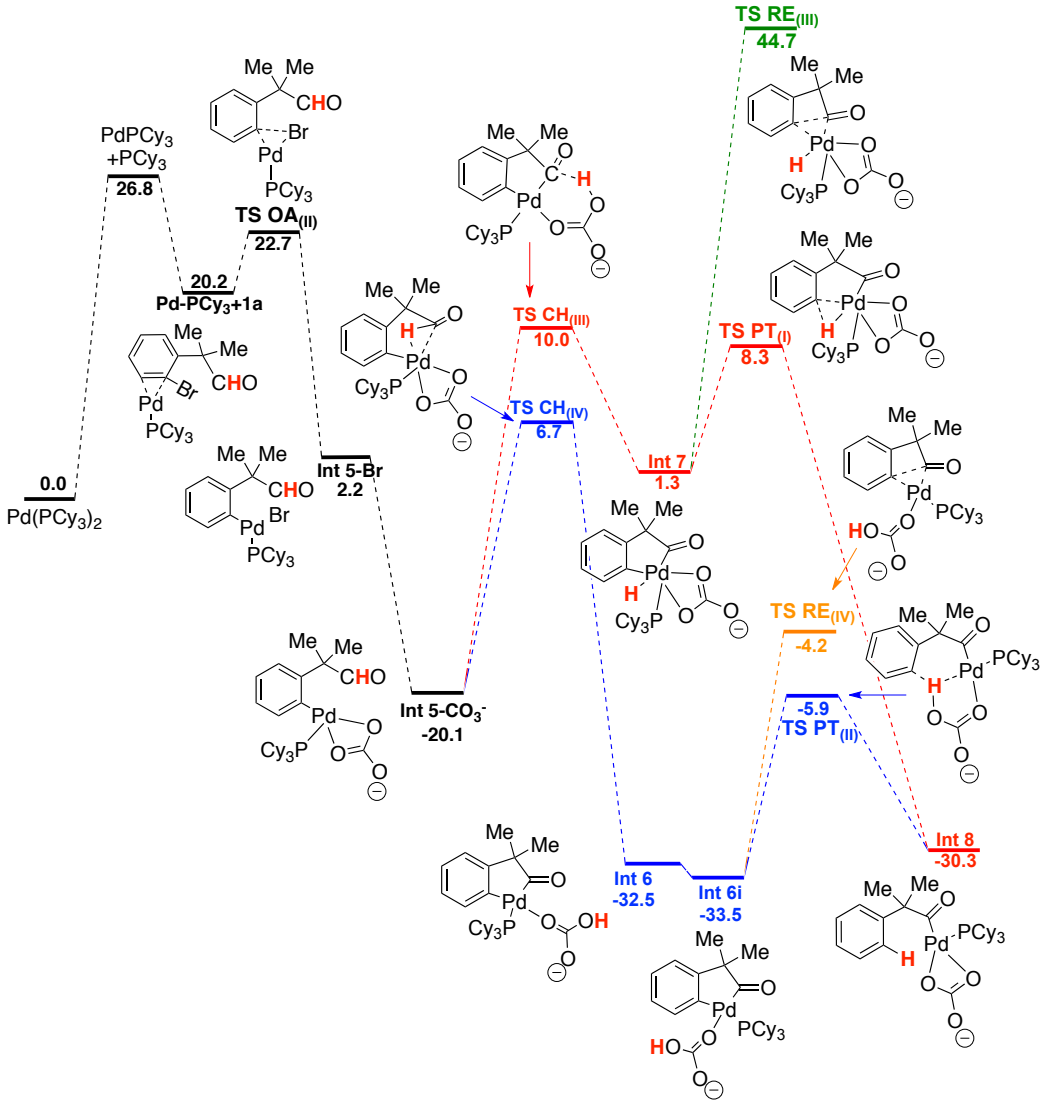


Figure 3.19

3) Proton transfer *vs.* reductive elimination (selectivity of styrene over BCB when operating with PCy_3 as the ligand). When using *rac*-BINAP **(173)** en route to benzocyclobutenone derivatives the relative energies for the reductive elimination and the proton transfer pathways were the determining factors for the selectivity in the catalytic system. As shown in Figure 3.19, the same concept applies for the mechanism based upon PCy_3. In this case, however, benzocyclobutenone could be possibly formed by reductive elimination *via* **TS**

RE$_{(III)}$ or **TS RE$_{(IV)}$** (pathways in green and orange, respectively). While the barrier of the former was 43.4 kcal mol^{-1}, the later was 29.3 kcal mol^{-1}. Since we did not detect experimentally benzocyclobutenone **(150)** when operating with PCy_3 as the ligand, it is plausible to assume that a reaction going *via* **TS RE$_{(III)}$** or **TS RE$_{(IV)}$** is highly unlikely and that the responsible for the observed selectivity goes *via* **TS PT$_{(I)}$** and **TS PT$_{(II)}$**. Indeed, we found a very little barrier for the proton migration from **Int-6** to **Int-8** (7 Kcal/mol). This low barrier together with the one observed for **Int 7i** (27.6 Kcal/mol) reinforces the perception for a mechanism proceeding *via* **Int-8**.

4) Decarbonylation. As shown in Figure 3.20, the decarbonylation event en route to **Int-7** from **Int 5** was found to have a barrier of 33.7 Kcal/mol. Such value indicates, when comparing with the values showed in Figure 3.12, that decarbonylation is the rate-limiting step of our reaction toward styrene derivatives. A subsequent loss of CO is triggered by the formation of a chelate of the carbonate base, a process that is highly exoergonic (-17.5 Kcal/mol).

5) *β*-hydride elimination. As shown in Figure 3.20, the carbonate base in **Int-10** abstracts the C(sp^3)-H bond in *β* position, setting up the stage for a *β*-hydride elimination step that has a non-neglictible barrier of 25.2 kcal mol^{-1}. Dissociation followed by ligand exchange with a new substrate allowed the formation of the corresponding styrene with a barrier of 11.1 kcal mol^{-1}.

According to our theoretical calculations, the highest barrier in the reaction pathway was attributed to the corresponding CO extrusion (33.7 kcal mol^{-1}). Such data suggest that the acylpalladium intermediate (**Int 8**) would be highly populated through the course of the reaction. Thus, in the presence of an external nucleophile, we anticipated that intermediate **Int 8** could potentially be trapped giving rise to other functionalities[121] while avoiding the formation of styrene derivatives (Figure 3.21).

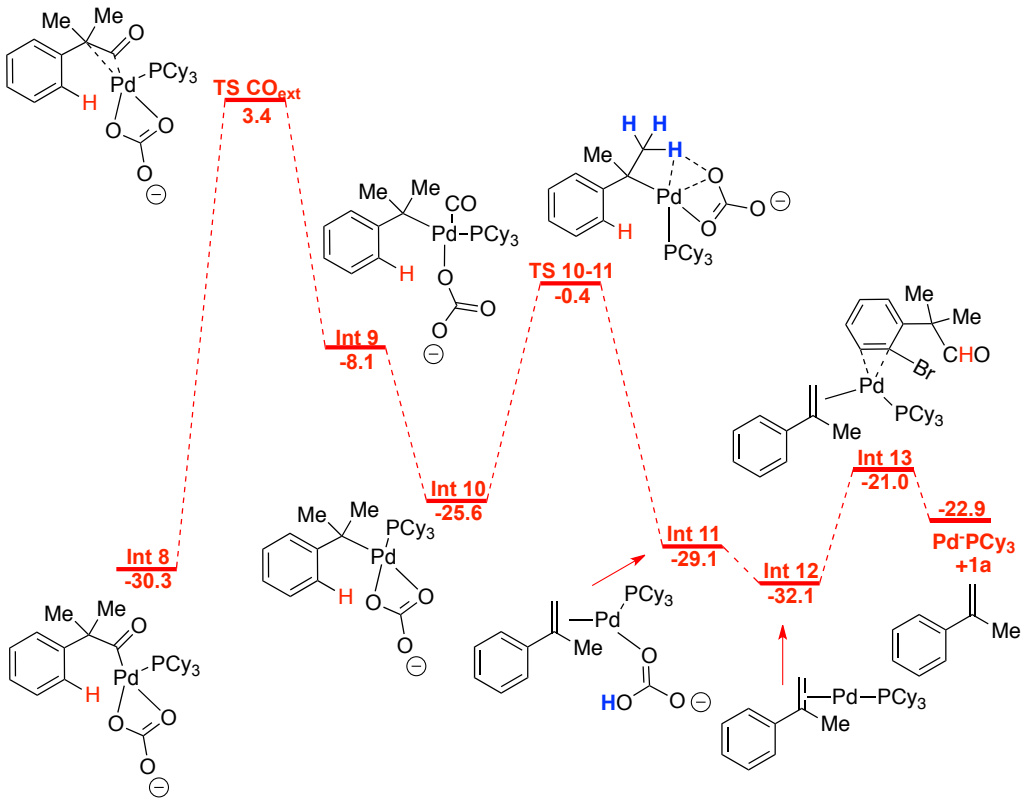


Figure 3.13

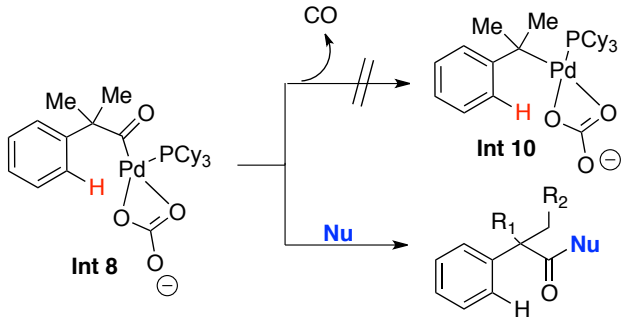
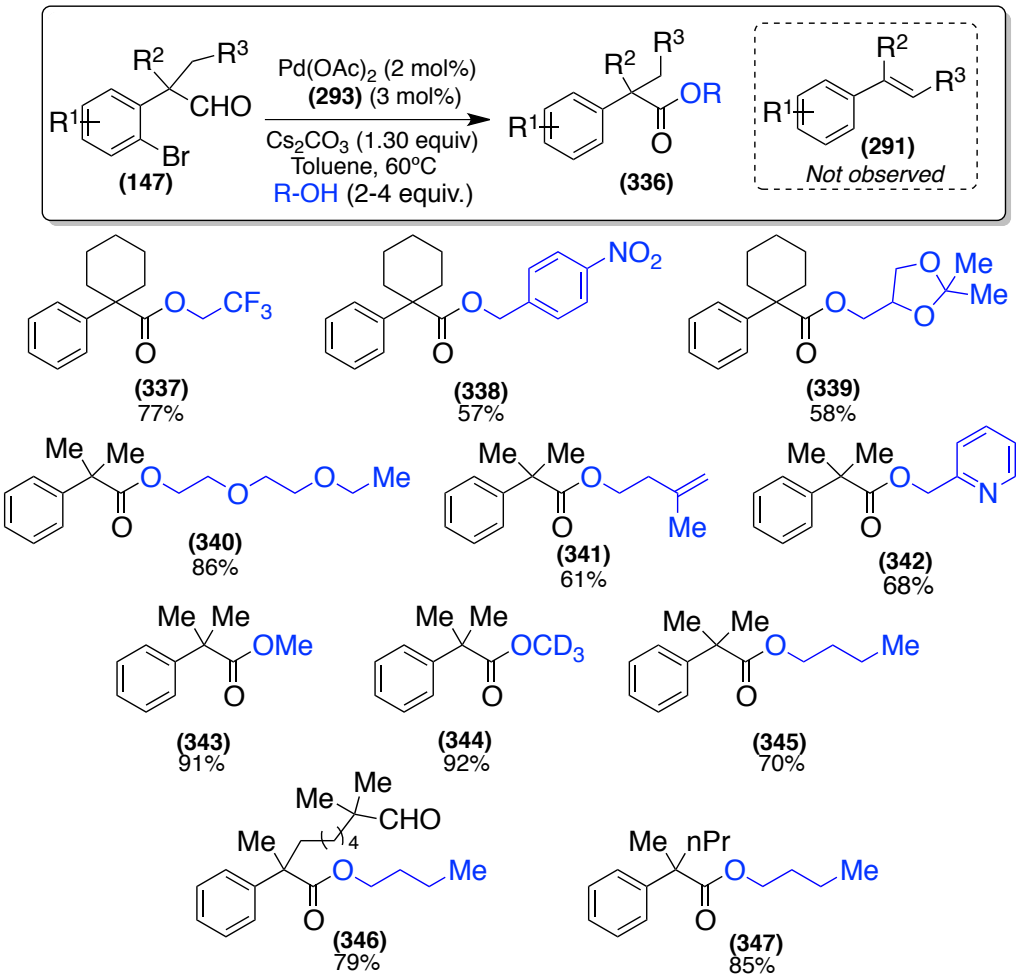


Figure 3.21

As shown in Table 18, the addition of stoichiometric amounts of alcohol derivatives under otherwise identical reaction conditions for obtaining styrenes allowed us to exclusively form the corresponding ester derivatives **(336)**. Under the limits of detection, no styrene formation was detected in the crude reaction

mixtures. These data invariably corroborated, in an indirect manner, the intermediacy of acylpalladium species as one of the key synthetic intermediates.

Table 18 Synthesis of ester derivatives.[a]



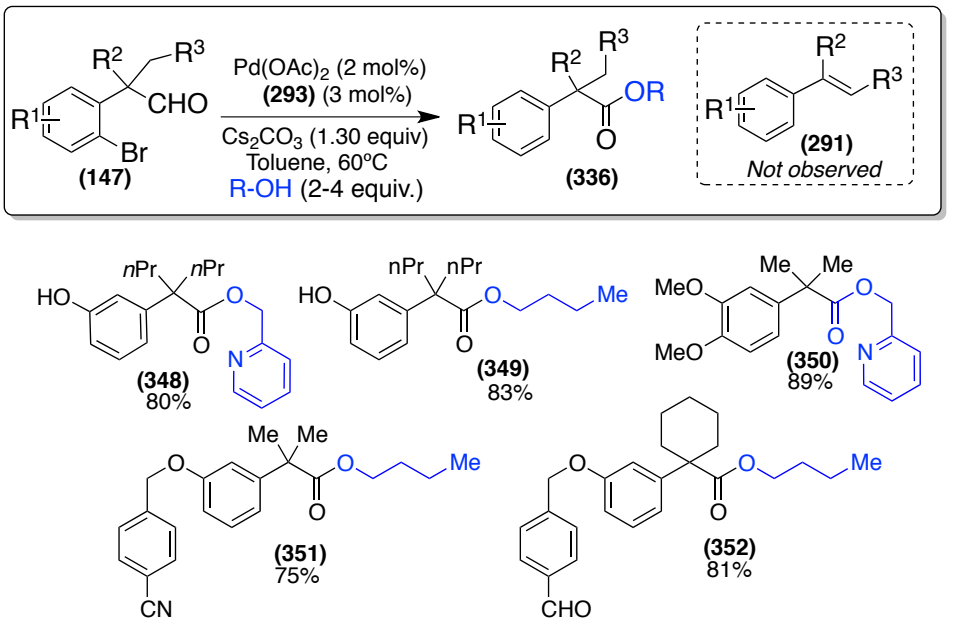
[a] Aryl bromide (0.50 mmol), $Pd(OAc)_2$ (2 mol%), **(293)** (3mol%), Cs_2CO_3 (1.30 equiv.) ROH (4 equiv.), toluene (2 mL) at 110ºC. Isolated yields, average of two runs.

The reaction shown in Table 18 tolerated a wide variety of alcohols with different functional groups, including fluorinated **(337)**, nitro **(338)**, acetals **(339)**, ethers **(340)**, alkenes **(341)** and heterocyclics **(342)** motifs. Importantly, reaction with CD_3OD afforded exclusively ester **(344)** in which no deuterium label was incorporated into the aromatic backbone, thus indicating that there was not an intermolecular proton transfer from the solvent to the *in situ* formed

palladium metallacycle. Not surprisingly, the method was not restricted to symmetrical substrates and α-aryl aldehydes with different motifs in α-position could equally be employed. Remarkably, the aldehydic motif in **(346)** remained intact in the reaction.

We also evaluated the influence of the substituents on the aromatic backbone. As shown in Figure Table 19, the reaction tolerated the presence of nitrogen-containing heterocycles, thus indicating that the presence of strong nitrogen donors does not compete with substrate binding in **(348)** and **(350)**.

Table 19 Synthesis of ester derivatives.[a]



[a] Aryl bromide (0.50 mmol), $Pd(OAc)_2$ (2 mol%), **(293)** (3mol%), Cs_2CO_3 (1.30 equiv.) ROH (4 equiv.), toluene (2 mL) at 110ºC. Isolated yields, average of two runs.

The successful preparation of **(352)** indicates that the reaction was exclusively initiated at the α-aryl aldehyde backbone, leaving the benzaldehyde unit intact. Although one might have expected that a free phenol would hinder the reaction due to competitive formation of phenolic esters, the successful preparation of **(348)** and **(349)** showed that this was not the case. Likely, the

difference in nucleophilicity between aromatic and aliphatic alcohols is the responsible for such selectivity pattern.

Although the data summarized in Tables 18 and 19 allowed us to identify acylpalladium species as the key intermediate species, we also studied the formation of methyl esters by theoretical calculations. The free energy surface (ΔG_{298}) for the methanolysis reaction using 2 and 4 equivalents is presented in Figure 3.15. As shown, we found that the addition of MeOH to **Int8** was lower in energy than the carbonyl extrusion toward intermediate **VII**. Although there are many possible mechanisms, with varying number of methanol equivalents, we only highlight two pathways, Figure 3.22.

With 2 equivalents of MeOH a stepwise mechanism was required in which the first step is the coordination of the Pd centre to a MeOH molecule forming **Int PdOMe**, This was followed by reductive elimination to form the ester product via **Int Pd-(C=O)** intermediate, where the metal atom is in η^2-coordinated to the carbonyl group. These sequence steps have barriers of 14.3 and 5.8 kcal mol^{-1}, respectively. With 4 equivalents of MeOH, we found a concerted mechanism in which the MeOH attacks the carbonyl directly. We observed that the transition state **TS-direct** was stabilized by the remaining MeOH molecules by forming a methanol proton shuttle bridge, where the base can abstract a proton from one MeOH molecule. The barrier for this mechanism is 20.1 kcal mol^{-1}. In the concerted mechanism there is no **Int Pd-(C=O)** equivalent species, with the structure optimising directly to the dissociated product.

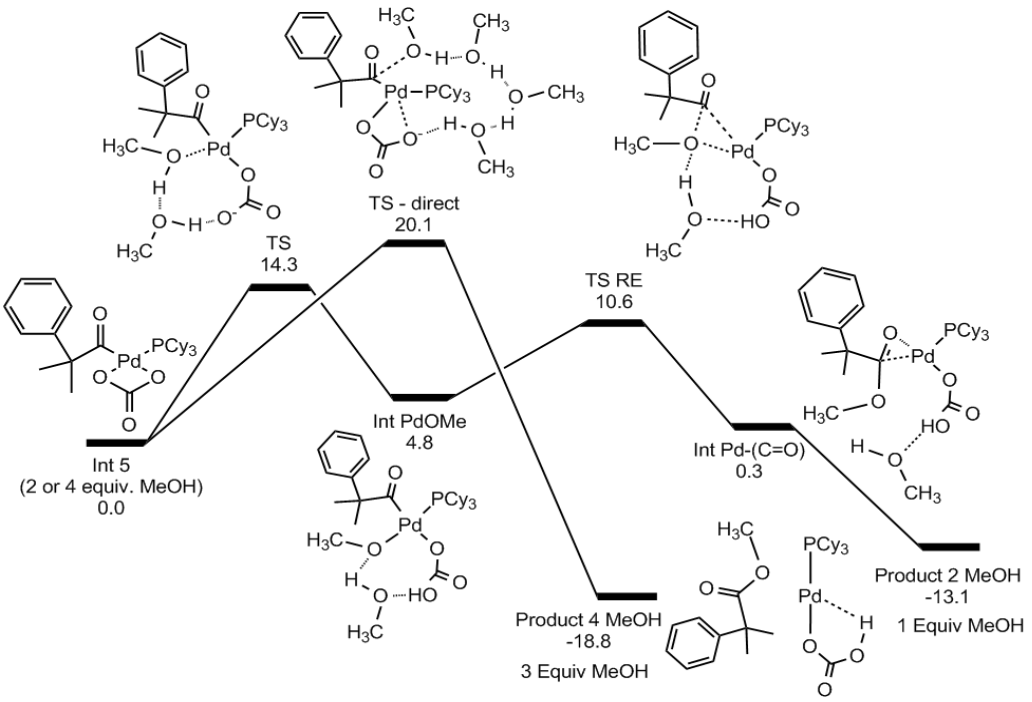


Figure 3.22

3.3.3 Other mechanistic considerations: Mechanistic reversibility

Taking into consideration the experimental and theoretical results as well as the inherent similarities of the catalytic systems for obtaining either **BCB's (148)** and **styrenes (291)** we can conclude that these pathways are somewhat linked to one another, Figure 3.23. Thus, while bidentate and therefore more rigid binaphtyl-type ligands follow a catalytic cycle ***A*** to give rise to metalacycle **III** trough the intermediate **IV**, the use of more flexible and hemilabile ligand **(293)** or monodentate PCy_3 lead to metalacycle **X** or palladium hydride species **XIV** trough intermediate **IV**. The mechanisms shown in Figure 3.23 suggest that relatively flexible ligands might not be able to end up in the corresponding metalacycle **III**. Such assumption is supported by the fact that not even traces of benzocyclobutenone was observed in the crude reaction mixtures for reactions

based on **(293)** or PCy_3. This observation is rather intriguing taking into consideration the myriad of five-membered metalacycles found in the literature with monodentate ligands.[186]

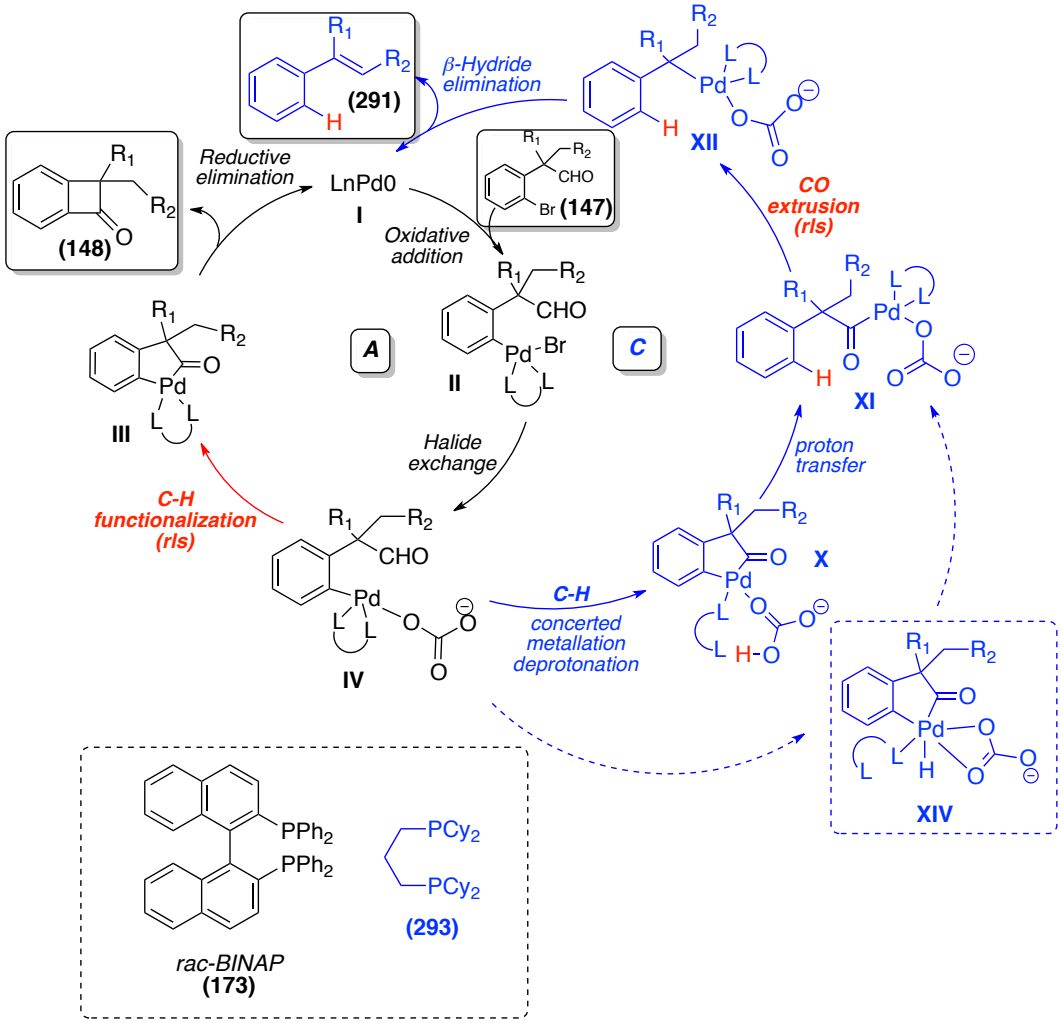
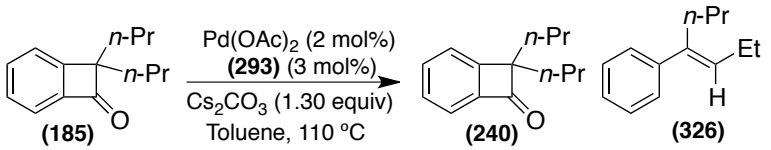


Figure 3.23

[186] a) Carfagna, C.; Gatti.; Mosca, L.; Paoli, P.; Guerri, A., *Chem. Eur. J.* **2005**, *11*, 3268. b) Fernández, A.; Uría, P.; Fernández, J. J.; López-Torres, M.; Suárez, A.; Vázquez-García, D.; Pereira, M. T.; Vila, J. M., *J. Organomet. Chem.*, **2001**, *620*, 8. c) For a review see: Mohr, F.; Privér, S. H.; Bhargava, S. K.; Bennett, M. A., *Coord. Chem. Rev.*, **2006**, *250*, 1851. d) Urriolabeitia, E. P. *"In Palladacycles, Synthesis, Characterization and Application"*; Dupont, J.; Pfeffer, M., Eds.; Wiley-VCH, Weinheim, **2008**; 35.

Thus, we wondered whether benzocyclobutenones might indeed be formed during the reaction conditions based upon the use of **(293)** or PCy3 and that these rather strain motifs undergo a fast C-C bond-cleavage en route to **III**. In other words, we hypothesized that both the formation of **III** and benzocyclobutenone might be reversible in the presence of flexible PCy_3 or hemilabile ligand such **(293)**. In order to check that possibility, we subjected the isolated benzocyclobutenone **(185)** under the catalytic conditions based upon ligand **(293)**. As shown in Figure 3.24, we observed that styrene **(326)** was formed in a non-neglictible 17% yield. Similar reactivity was found when changing Cs_2CO_3 to $CsHCO_3$. However, the formation of styrene was dramatically affected in the presence of water; while very little conversion was found in the presence of molecular sieves, the addition of 10 mol% exogeneous water afforded styrene **(326)** in 80% yield. In line with the results shown in Chapter 2, we observed that pure benzocyclobutenone **(185)** did not lead to styrene derivatives resubjecting this compound under the catalytic protocol based upon rac-BINAP **(173),** either in the presence or absence of exogeneous water**.**



No additives	83%	17%
Using $CsHCO_3$	80%	20%
4Å sieves	98%	2%
+ H_2O (10 mol%)	20%	80%
Using L1	100%	0%

Figure 3.24

According to these results, we demonstrated that C-C bond cleavage in the BCB core likely occur by forming intermediate **III,** thus formally constituting the reverse reaction of reductive elimination. In the presence of HCO_3^-, **III** forms **IV** facilitating the C-H functionalization en route to **X** or **XIV** that ultimately ends up in the corresponding styrene derivative **(291)** (Figure 3.25).

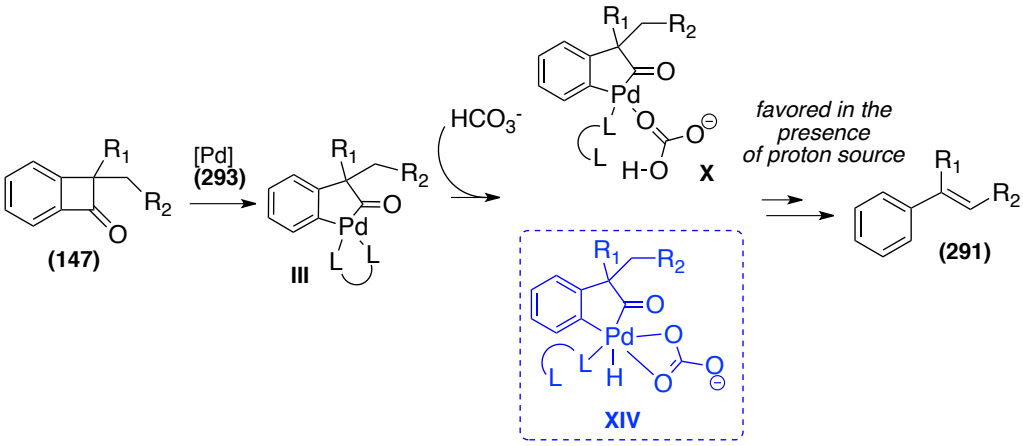

R1
R2
O
(147)
[Pd]
(293)
Pd
L
L
III
HCO3-
H-O
X
favored in the
presence
of proton source
(291)
H
XIV

Figure 3.25

3.4

Conclusions

This chapter provided experimental and computational evidence toward a better understanding of the mechanism for forming either benzocyclobutenones or styrene derivatives from common α-aryl aldehydes depending on the ligand of choice.

- Kinetic experiments, as well as computational studies univocally demonstrated that the palladium-catalyzed intramolecular C-H bond functionalization of aryl bromides en route to benzocyclobutenones using BINAP as ligand operate via the formation of a five-membered metalacycle that precedes reductive elimination.

- The C-H bond functionalization *via* concerted-metallation-deprotonation (CMD) is the rate-limiting step for the synthesis of benzocyclobutenones. Such assumption was confirmed experimentally by kinetic experimets (k_H/k_D=2.8) and by theoretical calculations.

- We demonstrated that the formation of styrene derivatives follow a catalytic cycle that is strongly related to the formation of benzocyclobutenones. The utilization of more flexible and hemilabile ligands allow for a rapid intramolecular transfer that set up the stage for a CO extrusion. Indeed, we demonstrate both experimentally and computationally that the decarbonylation event is the rate-limiting step in this reaction. We have additionally shown that a new synthesis of α-aryl esters can be performed in the presence of exogeneous nucleophiles.

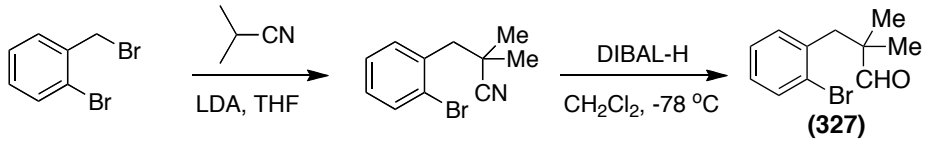
3.5

Experimental section

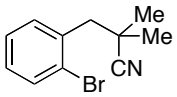
3.5.1 Computational details

All structures were optimized with the BP86-D/TZP level of theory, implemented in ADF. To obtain a better description of the energetics, single point and solvated single point energy calculations at the M06/TZP level were performed. This methodology gave excellent agreement for both the structure and energy of the system with reasonable computational expense. Full optimization with the M06/TZP level of theory for these large complexes is computationally very expensive. To verify each intermediate and transition state structure, analytical frequency calculations with model PH_3 ligands were performed. For all transition state structures the main negative frequency corresponded to the correct vibrational mode. Specific examples of frequency calculations with the full ligand system showed little deviation on the energy surface, compared to the model ligand.

3.5.2 Synthesis of miscellaneous compounds

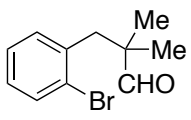


(327)

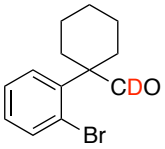


3-(2-Bromophenyl)-2,2-dimethylpropanenitrile. To a well-stirred solution of 2-methylpropanenitrile (0.90 mL, 10 mmol) in THF (40 mL) under nitrogen atmosphere was added LDA (6.0 mL, 12.0 mmol, 2M in THF) and stirred for 1 h at -78 ºC. Then, a solution of 1-bromo-2-(bromomethyl)benzene (3.0 g, 12.0 mmol) in THF (10 mL) was added dropwise

and the reaction was allowed to reach room temperature and stirred overnight. The reaction was then quenched by addition of saturated aqueous NH_4Cl solution (10 mL) and EtOAc (20 mL). The organic phase was washed twice with brine (10 mL), dried over magnesium sulfate and concentrated. The crude was then purified by column chromatography on silica gel (10:1 hexanes/ethyl acetate) to give the title compound as a colorless oil (1.59 g, 68% yield). ^{1}H-NMR ($CDCl_3$, 400 MHz) d 7.59 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.51 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.32 (td, *J* = 8.4, 1.2 Hz, 1H), 7.15 (td, *J* = 7.6, 2.0 Hz, 1H), 3.08 (s, 2H), 1.43 (s, 6H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) d 135.5, 131.8, 128.9, 127.5, 125.7, 124.6, 44.3, 34.1, 26.5 ppm. IR (neat, cm^{-1}): 3059, 2978, 2873, 2234, 1591, 1468, 1439, 1391, 1369, 1308, 1257, 1195, 1138, 1049, 1027, 946. HRMS *calcd* for ($C_{11}H_{12}BrN$+Na): 260.0051, *found* 260.0042.

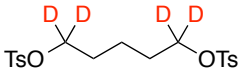


3-(2-bromophenyl)-2,2-dimethylpropanal (327). To a well-stirred solution of 3-(2-bromophenyl)-2,2-dimethyl propanenitrile (1.77 g, 7.50 mmol) in CH_2Cl_2 (20 mL) under nitrogen atmosphere was added DIBALH (8.90 mL, 8.90 mmol, 1M in hexanes) and stirred for 2 h at -78 ºC. The reaction was then quenched after 2 hours of further stirring at rt by slow addition of 2M HCl (10 mL) and ethyl acetate (20 mL). The organic phase was washed twice with brine (10 mL), dried over magnesium sulfate and concentrated. The crude was then purified by column chromatography on silica gel (10:1 hexanes/ethyl acetate) to give the title compound as a colorless oil (1.58 g, 88% yield). ^{1}H-NMR ($CDCl_3$, 400 MHz) d 9.65 (s, 1H), 7.56 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.24 (td, *J* = 7.2, 0.8 Hz, 1H), 7.16 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.08 (td, *J* = 7.2, 2.0 Hz, 1H), 3.06 (s, 2H), 1.14 (s, 6H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) d 205.3, 136.9, 133.1, 132.0, 128.3, 127.1, 125.7, 47.7, 41.7, 21.5 ppm. IR (neat, cm^{-1}): 2967, 2894, 1721, 1564, 1467, 1438, 1364, 1190, 1102, 1025, 866. HRMS *calcd* for ($C_{11}H_{13}BrO$+Na): 263.0047, *found* 263.0059.



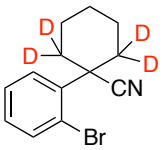
1-(2-bromophenyl)-cyclohexanecarbaldehyde (329).

To a suspension of $LiAlD_4$ (1.4 g, 30.0 mmol) in dry THF (25 mL) under argon at 0 ºC was added dropwise methyl 1-(2-bromophenyl) cyclohexanecarboxylate (**326**) (4.04 g, 15.0 mmol) in dry THF (20 mL). The mixture was stirred at room temperature for 3 hours. The reaction was then quenched by slowly addition of saturated aqueous NH_4Cl solution (30 mL) and EtOAc (40 mL). The organic phase was washed twice with brine (30 mL), dried over $MgSO_4$ and concentrated. The crude was then used directly into the next step without further purification.

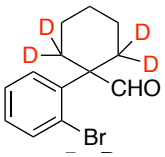


1,5-(di(4-methylbenzenesulfonate))pentane (331). A flask equipped with a magnetic stirring bar and a septum inlet was flushed with nitrogen. The flask was charged under nitrogen atmosphere with dimethyl glutarate (10.4 mmol, 1.6 mL) and 25 ml of dry THF. Then, $LiAlD_4$ (25mL, 1M in THF) was added dropwise, and the solution was stirred at rt overnight. Then, 10 mL of water and 2 mL of diluted H_2SO_4 were added to destroy the excess of hydride. The resulting mixture was extracted with dichloromethane (2 x 15 mL). The combined organic layers were washed with brine (10 mL), dried over magnesium sulfate, and finally concentrated under vacuum. The crude obtained was further purified by column chromatography on silica gel (ethyl acetate) to give the corresponding deuterated diol. Next, to a well-stirred solution of the above diol (7.4 mmol, 796 mg) in dichloromethane (15 mL) under nitrogen atmosphere was added tosyl chloride (15.5 mmol, 3.0 g) and catalytic amount of pyridine. The reaction was then quenched after 2 hours of further stirring by addition of water. The organic phase was washed twice with ethyl acetate (10 mL), dried over magnesium sulfate and concentrated. The crude was then purified by column chromatography on silica gel (hexanes/ethyl acetate, 1/1) to give 1,5-(di(4-methylbenzenesulfonate)) pentane-D as white solid; yield: 2.17 g (50% overall yield). Mp 83-85 ºC.^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 2.42 (s, 3H), 1.55 (t, *J* = 7.6 Hz, 2H), 1.38-

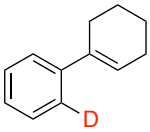
1.27(m, 1H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 144.7, 132.8, 129.8; 127.6, 69.4 (CD_2, q, *J* = 22.6 Hz), 27.8, 21.5, 21.2 ppm. IR (neat, cm^{-1}): 1346, 1173, 933, 875, 811, 660. HRMS *calc.* for [$C_{19}H_{20}D_4O_6S_2$+Na] 439.1163, *found* 439.1173.



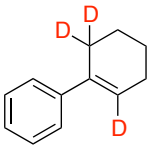
1-(2-bromophenyl)-acetonitrile (332). Following general procedure highlighted in Scheme 1, 2-bromophenylacetonitrile (1.65 mmol) and dry THF (4 mL/1.0 mmol), NaHMDS (2.5 mL, 5.0 mmol, 2M in THF), 1,5-(di(4-methylbenzene sulfonate))pentane-D (1.65 mmol. 0.69 g in 3mL THF). Column chromatography: silica gel (95:5 hexanes/ethyl acetate). White solid; yield: 0.31 g (69% yield). Mp 105-107 ºC. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.63 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.41 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.38-7.29 (m, 1H), 7.17 (dd, *J* = 7.6, 1.3 Hz, 1H), 1.95-1.71 (m, 5H), 1.26 (m, 1H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 138.1, 135.4, 129.2, 127.7, 127.2, 122.7, 120.7, 43.1, 34.0 (*CD_2*, q, *J = 20.1 Hz*), 24.6, 27.8 ppm. HRMS *calc.* for [$C_{13}H_{10}D_4NBr$] 290.0458, *found* 290.0461.



1-(2-bromophenyl)cyclohexanecarbaldehyde (333). Following general procedure highlighted in Scheme 1, 1-(2-bromophenyl)-acetonitrile-D (0.28 g, 1.05 mmol), CH_2Cl_2 (3 mL) and DIBALH (1.3 mL, 1.3 mmol, 1M in hexanes). Column chromatography, silica gel (9:1 hexanes/ethyl acetate). Colorless oil; yield: 0.19 g (60% overall yield). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 9.94 (s, 1H), 7.58 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.48 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.35 (td, *J* = 7.9, 1.3 Hz, 1H), 7.14 (td, *J* = 7.6, 1.6m, 1H), 1.79-1.57 (m, 5H), 1.52-1.37 (m, 1H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 204.2, 142.3, 134.8, 129.4, 128.7, 127.5, 123.2, 54.4, 30.7 (CD_2, *J* = 20. 1 Hz), 25.3, 22.1 ppm. IR (neat, cm^{-1}): 2927, 2858, 1698, 1586, 1561, 1423, 1337, 1120, 995, 854, 722. Anal. Calcd for [$C_{13}H_{11}D_4BrO$] C, 57.58; H, 7.06, *found*: C, 56.36; H, 7.62.



Cyclohex-1-en-1-ylbenzene (334). Following general procedure E, 1-(2-bromophenyl)-cyclohexanecarbaldehyde (329) (134 mg, 0.50 mmol) was used. Column chromatography: silica gel (20:1 hexanes/Ethyl acetate). Yellow oil; 65 mg (82% yield). ^{1}H NMR (400 MHz, CDCl3) δ 7.45-7.41 (m, 1H), 7.38-7.32 (m, 2H), 7.29-7.22 (m, 1H), 6.19-6.14 (m, 1H), 2.46 (ddd, J = 8.2, 4.1, 2.2 Hz, 2H), 2.33-2.20 (m, 2H), 1.90-1.77 (m, 2H), 1.77-1.66 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 142.6, 136.5, 128.1, 128.0, 126.5, 124.9, 124.7, 124.6 (t, *J* = 23.9 Hz), 27.4, 25.9, 23.0, 22.2. IR (neat, cm^{-1}): 3058, 3022, 2927, 2859, 2834, 1469, 1437, 1134, 1050, 921, 769, 738, 627. HRMS *calc.* for [$C_{12}H_{13}D$] 159.1158, *found* 159.1166.

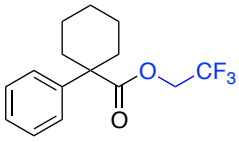


Cyclohex-1-en-1-ylbenzene (335). Following general procedure C, 1-(2-bromophenyl)-cyclohexanecarbaldehyde-D_4 (136 mg, 0.50 mmol) was used. Column chromatography: silica gel (20:1 hexanes/Ethyl acetate). Yellow oil; 67 mg (83% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.48-7.42 (m, 2H), 7.36 (t, *J* = 7.7 Hz, 2H), 7.27 (t, *J* = 7.3 Hz, 1H), 2.27 (t, *J* = 6.1 Hz, 2H), 1.88-1.81 (m, 2H), 1.77-1.67 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 142.6, 136.4, 128.1, 126.5, 124.9, 124.4 (t, *J* = 23.2 Hz), 77.3, 77.0, 76.7, 25.7, 22.9, 22.1. IR (neat, cm^{-1}): 2930, 2858, 1669, 1597, 1492, 1446, 1269, 754, 697, 630. HRMS *calc.* for [$C_{12}H_{11}D_3$] 161.1284, *found* 161.1292.

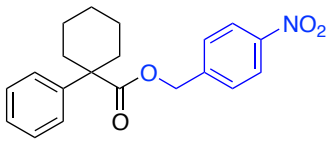
3.5.3 Synthesis of esters

General procedure F for the synthesis of trapped acyl palladium compounds. An oven-dried screw-cap test tube containing a stirring bar was charged with $Pd(OAc)_2$ (2.3 mg, 2.0 mol%), 1,3-dicyclohexyl-phosphinepropane·$2HBF_4$ (**293**) (9.2 mg, 3.0 mol%), Cs_2CO_3 (0.21 g, 0.65 mmol) and the aryl bromide (0.50 mmol), if a solid. The test tube was evacuated and back-filled with dry argon (this sequence was repeated three times). The aryl bromide (if liquid), the corresponding alcohol (4 equivalents) and toluene (2 mL)

were then added by syringe. The mixture was then placed in ultrasounds apparatus for 1 min and the mixture was then stirred in a pre-heated oil bath (110 °C) for 14 h. The mixture was then allowed to warm to room temperature, diluted with EtOAc (5 mL) and filtered through a Celite® plug, eluting with additional EtOAc (10 mL). The filtrate was concentrated and purified by column chromatography on silica gel (eluting with hexanes/ethyl acetate mixtures).

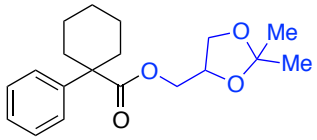


2,2,2-trifluoroethyl-1-phenylcyclohexanecarboxylate (337). Following general procedure F, 1-(2-Bromophenyl)-cyclohexane carbaldehyde (133.6 mg, 0.50 mmol) and 2,2,2-trifluoromethylmethanol (144 μL, 2.0 mmol) were used. Column chromatography: silica gel, hexanes:EtOAc 9:1,. Yellow oil; yield: 110.2 mg (77% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.41 (m, 2H), 7.37 (t, J = 7.4 Hz, 2H), 7.31–7.23 (m, 1H), 4.46 (q, $^{3}J_{H\text{-}F}$ = 8.5 Hz, 2H), 2.58 (d, J = 14.3 Hz, 2H), 1.80 (ddd, J = 14.4, 10.3, 6.8 Hz, 5H), 1.61–1.43 (m, 2H), 1.41–1.25 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6, 142.7, 128.5, 127.1, 125.9, 122.9 (q, $^{1}J_{C\text{-}F}$ = 277.6 Hz), 60.2 (q, J = 36.4 Hz), 50.9, 34.5, 25.4, 23.5. IR (neat, cm^{-1}): 2936, 2861, 1743, 1452, 1405, 1279, 1163, 1118, 975, 725, 695, 655. HRMS *calcd* for [$C_{15}H_{17}F_3O_2$+H] 287.1262, *found* 287.1259.

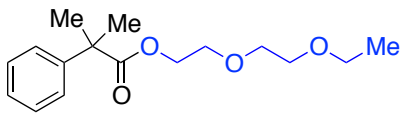


4-nitrobenzyl-1-phenylcyclohexanecarboxylate (338). Following general procedure F, 1-(2-Bromophenyl)-cyclohexane carbaldehyde (133.6 mg, 0.50 mmol) and 4-nitrobenzylalcohol (306.3 mg, 2.0 mmol) were used. Column chromatography: silica gel, hexanes:EtOAc 9:1, Yellow oil; yield: 96.7 mg (57% yield). 1H NMR (300 MHz, CDCl3) δ 8.11 (d, J = 8.3 Hz, 2H), 7.46–7.15 (m, 7H), 5.18 (s, 2H), 2.51 (s, 2H), 2.01–1.13 (m, 8H). 13C NMR (75 MHz, CDCl3) δ 174.7, 147.4, 143.5, 143.0, 128.54, 127.7, 126.9, 125.9, 123.6, 64.7, 50.8, 34.3, 25.5, 23.5. IR (neat, cm^{-1}): 2927, 2859, 1714, 1604, 1520, 1444, 1351, 1300, 1210, 1187,

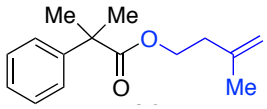
1121, 982, 843, 721, 690. HRMS *calcd* for [$C_{20}H_{21}NO_4$-H] 338.1392, *found* 338.1397.



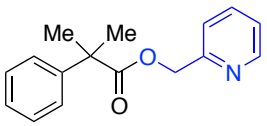
(2,2-dimethyl-1,3-dioxolan-4-yl)methyl-1-phenylcyclohexanecarboxylate (339). Following general procedure F, 1-(2-Bromophenyl)-cyclohexane carbaldehyde (133.6 mg, 0.50 mmol) and DL-1,2-isopropyideneglycerol (248.7 μL, 2.0 mmol) were used. Column chromatography: silica gel, hexanes:EtOAc 4:1, colorless oil; yield: 92.3 mg (58% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.39 (m, 2H), 7.33 (t, *J*= 7.5 Hz, 2H), 7.24 (q, *J*= 7.1, 6.0 Hz, 1H), 4.24–4.12 (m, 2H), 4.07 (dd, *J* = 10.9, 5.4 Hz, 1H), 3.89 (dd, *J* = 8.4, 6.2 Hz, 1H), 3.58 (dd, *J* = 8.4, 5.8 Hz, 1H), 2.51 (d, *J*= 14.3 Hz, 2H), 1.87–1.60 (m, 6H), 1.57–1.42 (m, 2H), 1.36 (s, 3H), 1.33 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.9, 143.5, 128.4, 126.8, 125.9, 109.5, 73.3, 66.3, 64.3, 50.9, 34.6, 34.4, 26.6 , 25.5, 25.4, 23.6, 23.6. IR (neat, cm^{-1}): 2932, 1726, 1449, 1370, 1210, 1191, 1125, 1053, 843, 697, 513. HRMS *calcd* for [$C_{19}H_{26}O_4$+Na] 341.1729, *found* 341.17163.



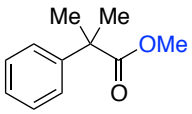
2-(2-ethoxyethoxy)ethyl 2-methyl-2-phenylpropanoate (340). Following general procedure F, 2-(2-bromophenyl)-2-methyl-propanal (113.6 mg, 0.50 mmol) and di(ethylene glycol) ethyl ether (268.6 μL, 2.0 mmol) were used. Column chromatography: silica gel, hexanes:EtOAc 4:1, colorless oil; yield: 120.6 mg (86% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41–7.28 (m, 4H), 7.22 (dd, *J* = 10.9, 4.2 Hz, 1H), 4.32–4.08 (m, 2H), 3.72–3.56 (m, 2H), 3.56–3.43 (m, 6H), 1.60 (s, 6H), 1.20 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.6, 144.6, 128.3, 126.6, 125.7, 70.6, 69.8, 68.9, 66.6, 64.0, 46.5, 26.4, 15.1. IR (neat, cm^1): 2867, 1727, 1447, 1251, 1112, 1099, 698. TOF-MS *calcd* for [$C_{16}H_{24}O_4$+Na] 303.1, *found* 303.2.



3-methylbut-3-enyl-2-methyl-2-phenylpropanoate (341). Following general procedure F, 2-(2-bromophenyl)-2-methylpropanal (113.6 mg, 0.50 mmol) and 3-methyl-3-butene-1-ol (202 μL, 2.0 mmol) were used. Column chromatography: silica gel, hexanes:EtOAc 9:1, colorless oil; yield: 71 mg (61% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41–7.30 (m, 4H), 7.29–7.20 (m, 1H), 4.71 (d, *J*= 28.5 Hz, 2H), 4.20 (t, *J* = 6.8 Hz, 2H), 2.29 (t, *J* = 6.7 Hz, 2H), 1.70 (s, 3H), 1.60 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7, 144.6, 141.6, 128.3, 126.6, 125.7, 112.3, 63.0, 46.5, 36.6, 26.5, 22.3. IR (neat, cm^{-1}): 2970, 2932, 1726, 1446, 1247, 1142, 889, 697. TOF-MS calcd for [$C_{15}H_{20}O_2$+H] 233.1, *found* 233.1.



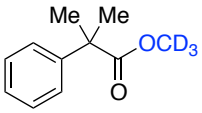
Pyridin-2-ylmethyl 2-methyl-2-phenylpropanoate (342). Following general procedure C, pyridin-2-ylmethanol (193 μL, 2.0 mmol) was used and stirring at 110ºC for 48 h. Column chromatography: silica gel, 7:3 hexanes/ethyl acetate. Colorless oil; yield: 86.5 mg (68% yield). The spectroscopic data was in full accordance with those described in the literature.[187] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (td, *J* = 7.7, 1.8 Hz, 1H), 7.49–7.41 (m, 2H), 7.41–7.33 (m, 2H), 7.30 (ddd, *J* = 7.1, 4.0, 1.3 Hz, 1H), 7.24–7.15 (m, 1H), 7.04 (d, *J* = 7.9 Hz, 1H), 5.28 (s, 2H), 1.70 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.1, 156.1, 149.0, 144.2, 136.6, 128.3, 126.7, 125.7, 122.5, 120.9, 66.7, 46.5, 26.



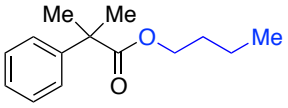
Methyl 2-methyl-2-phenylpropanoate (343). Following general procedure F, Methanol (80 μL, 2.0 mmol) was used. Column chromatography: silica gel, 95:5 hexanes/ethyl acetate. Colorless oil; yield: 80.8 mg (91% yield). The spectroscopic data was in full accordance with those described in the literature.[188] ^{1}H NMR (400 MHz, $CDCl_3$) δ

[187] Tatamidani, H., Yokota, K., Kakiuchi, F., Chatani, N., *J. Org. Chem.* **2004**, *69*, 5615.
[188] Liu, X., Hartwig, J. F. *J. Am. Chem. Soc.*, **2004**, 126, 5182.

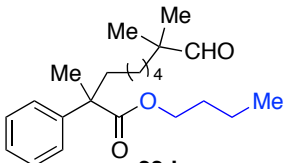
7.46–7.35 (m, 4H), 7.35–7.24 (m, 1H), 3.71 (s, 3H), 1.65 (s, 6H).^{13}C NMR (101 MHz, $CDCl_3$) δ 177.2 144.6, 128.3, 126.6, 125.5, 52.1, 46.5, 26.5.



Methyl 2-methyl-2-phenylpropanoate (344). Following general procedure F, CD_3OD (160 μL, 4.0 mmol) was used. Column chromatography: silica gel, 95:5 hexanes/ethyl acetate. Colorless oil; yield: 83.5 mg (92% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.35 (m, 4H), 7.34–7.26 (m, 1H), 1.66 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.2, 144.6, 128.3, 126.6, 125.5, 51.3 (m, *J* =22.4 Hz), 46.4, 26.5. IR (neat, cm^{-1}): 3060, 2975, 2933, 2251, 2078, 1725, 1495, 1446, 1263, 1159, 1084, 752, 697. HRMS *calc.* for [$C_{11}H_{11}D_3O_2$+Na] 204.1080, *found* 204.1088.

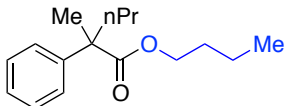


Butyl 2-methyl-2-phenylpropanoate (345). Following general procedure F, n-butanol (183 μL, 2.0 mmol) was used. Column chromatography: silica gel, 95:5 hexanes/ethyl acetate. Colorless oil; yield: 76.0 mg (70% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.30 (m, 4H), 7.29–7.20 (m, 1H), 4.07 (t, *J* = 6.6 Hz, 2H), 1.66–1.51 (m, 6H), 1.55 (s, 2H), 1.27 (dq, *J* = 14.6, 7.3 Hz, 2H), 0.87 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.8, 144.8, 128.3, 126.5, 125.6, 64.6, 46.5, 30.5, 26.5, 19.0, 13.6. IR (neat, cm^{-1}): 3025, 2975, 2950, 1729, 1599, 1496, 1366, 1254, 1100, 987, 843, 697. HRMS *calc.* for [$C_{14}H_{20}O_2$+Na] 243,1361 *found* 243,1362.

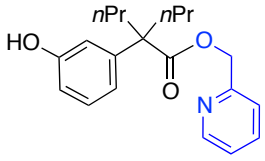


Butyl-2,8,8-trimethyl-9-oxo-2-phenylnonanoate (346). Following general procedure F, 2-(2-bromophenyl)-2,8,8-trimethylnonanedial (169.1 mg, 0.50 mmol) and 1-butanol (183 μL, 2.0 mmol) were used. Column chromatography: silica gel, hexanes:EtOAc 2:1. Colorless oil; yield: 138.8 mg (79% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.43 (s, 1H), 7.36–7.28 (m, 4H), 7.26–7.19 (m, 1H), 4.07 (t, *J*= 6.6 Hz, 2H), 1.95 (dtd, *J*= 16.1, 13.4, 6.0 Hz, 2H), 1.61–1.47 (m, 5H), 1.42 (dd, *J*= 9.7, 6.4 Hz, 2H), 1.35–1.11 (m, 8H), 1.03 (s, 6H),

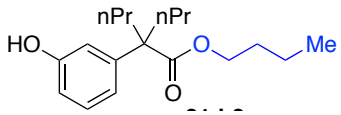
0.87 (t, *J*= 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.5, 183.6, 176.3, 160.6, 144.1, 128.2, 126.5, 125.9, 64.5, 50.3, 41.9, 40.4, 39.1, 30.5, 26.2, 24.9, 21.3, 19.0, 13.6. IR (neat, cm^{-1}): 2930, 2859, 1722, 1602, 1450, 1212, 1193, 1129, 844, 707. HRMS *calcd* for [$C_{22}H_{34}O_3$+Na] 369.2406, *found* 369.2404.



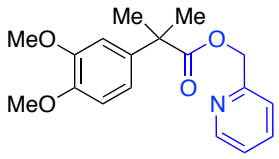
Butyl 2-methyl-2-phenylpentanoate (347). Following general procedure, 2-(2-bromophenyl)-2-methylpentanal (127.6 mg, 0.50 mmol) and 1-butanol (183 μL, 2.0 mmol) were used. Column chromatography: silica gel, hexanes:EtOAc 9:1. Colorless oil; yield: 105.6 mg (85% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (d, *J*= 4.2 Hz, 4H), 7.23 (td, *J*= 8.6, 4.5 Hz, 1H), 4.07 (t, *J*= 6.6 Hz, 2H), 2.04 (ddd, *J*= 13.5, 9.9, 6.7 Hz, 1H), 1.90 (ddd, *J* = 13.4, 10.2, 6.6 Hz, 1H), 1.62–1.48 (m, 5H), 1.36–1.12 (m, 4H), 0.90 (ddd, *J* = 14.8, 7.3, 3.7 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.3, 144.3, 128.2, 126.4, 125.9, 64.5, 50.3, 41.4, 30.5, 22.8, 19.0, 18.1, 14.6, 13.6. IR (neat, cm^{-1}): 2958, 2872, 1725, 1446, 1221, 1143, 697. HRMS *calcd* for [$C_{16}H_{24}O_2$+Na] 271.1674, *found* 271.1667.



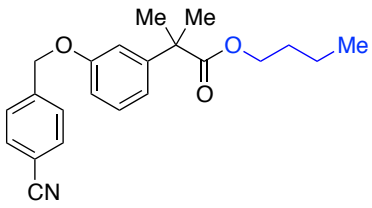
Pyridin-2-ylmethyl 2-(3-hydroxyphenyl)-2-propylpentanoate (348). Following general procedure F, 2-(2-bromo-5-hydroxyphenyl)-2-propylpentanal (149.6 mg, 0.50 mmol) and 2-pyridinemethanol (193 μL, 2.0 mmol) were used. Column chromatography: silica gel, hexanes:EtOAc 2:1. Yellow oil; yield: 131 mg (80% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 (d, *J*= 4.4 Hz, 1H), 8.05 (s, 1H), 7.61 (t, *J*= 7.7 Hz, 1H), 7.25–7.09 (m, 2H), 7.02 (d, *J*= 7.9 Hz, 1H), 6.83 (d, *J*= 7.4 Hz, 2H), 6.73 (d, *J*= 8.8 Hz, 1H), 5.21 (s, 2H), 2.15–1.77 (m, 4H), 1.25–0.98 (m, 4H), 0.87 (t, *J*= 7.2 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5, 156.5, 155.9, 148.5, 144.3, 137.3, 129.3, 122.9, 121.6, 118.1, 113.9, 113.8, 66.1, 53.9, 36.5, 17.3, 14.5. IR (neat, cm^{-1}): 2953, 2869, 2691, 1727, 1584, 1357, 1203, 1131, 1005, 746, 610. HRMS *calcd* for [$C_{20}H_{25}NO_3$+H] 328.1913, *found* 328.1906.



Butyl-2-(3-hydroxyphenyl)-2-propylpentanoate (349). Following general procedure F, 2-(2-bromo-5-hydroxyphenyl)-2-propylpentanal (149.6 mg, 0.50 mmol) and 1-butanol (183 μL, 2.0 mmol) were used. Column chromatography: silica gel, hexanes:EtOAc 2:1. Colorless oil; yield: 121.4 mg (83% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (t, *J* =7.9 Hz, 1H), 6.84 (d, *J*= 7.9 Hz, 1H), 6.81-6.76 (m, 1H), 6.71 (dd, *J* = 8.0, 2.0 Hz, 1H), 5.41 (s, 1H), 4.06 (t, *J* = 6.5 Hz, 2H), 2.07–1.83 (m, 4H), 1.59–1.46 (m, 2H), 1.35–1.19 (m, 2H), 1.17–1.02 (m, 4H), 0.96–0.83 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.3, 155.5, 145.1, 129.2, 118.9, 113.7, 113.4, 64.6, 53.9, 36.7, 30.5, 19.0, 17.4, 14.6, 13.6. IR (neat, cm^{1}): 3387, 2958, 2873, 1723, 1587, 1448, 1215, 1137, 908, 730. HRMS *calcd* for [$C_{18}H_{28}O_3$-H] 291.1960, *found* 291.1954.

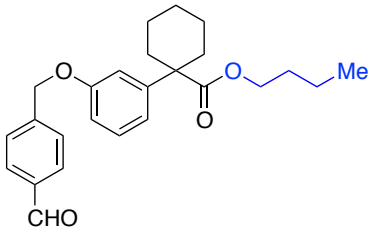


Pyridin-2-ylmethyl-2-(3,4-dimethoxyphenyl)-2-methylpropanoate (350). Following general procedure F, 2-(2-bromo-4,5-dimethoxyphenyl)-2-methylpropanal (143.6 mg, 0.50 mmol) and 2-pyridinemethanol (193 μL, 2.0 mmol) were used. Column chromatography: silica gel, hexanes:EtOAc 2:1 Yellow oil; yield: 140.3 mg (89% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (d, *J*= 4.6 Hz, 1H), 7.58 (td, *J*= 7.7, 1.7 Hz, 1H), 7.16 (dd, *J*= 7.0, 5.2 Hz, 1H), 7.01 (d, *J*= 7.9 Hz, 1H), 6.93 (dd, *J*= 8.4, 2.2 Hz, 1H), 6.87 (d, *J*= 2.1 Hz, 1H), 6.82 (d, *J*= 8.4 Hz, 1H), 5.22 (s, 2H), 3.86 (s, 3H), 3.81 (s, 3H), 1.63 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.1, 155.9, 148.9, 148.6, 147.79, 136.7, 136.6, 122.5, 120.9, 117.7, 110.8, 109.5, 66.6, 55.8, 55.8, 45.9, 26.3. IR (neat, cm^{-1}): 2971, 2834, 1728, 1590, 1517, 1255, 1133, 1025, 766, 730. HRMS *calcd* for [$C_{18}H_{21}NO_4$+H] 316.1549, *found* 316.1549.



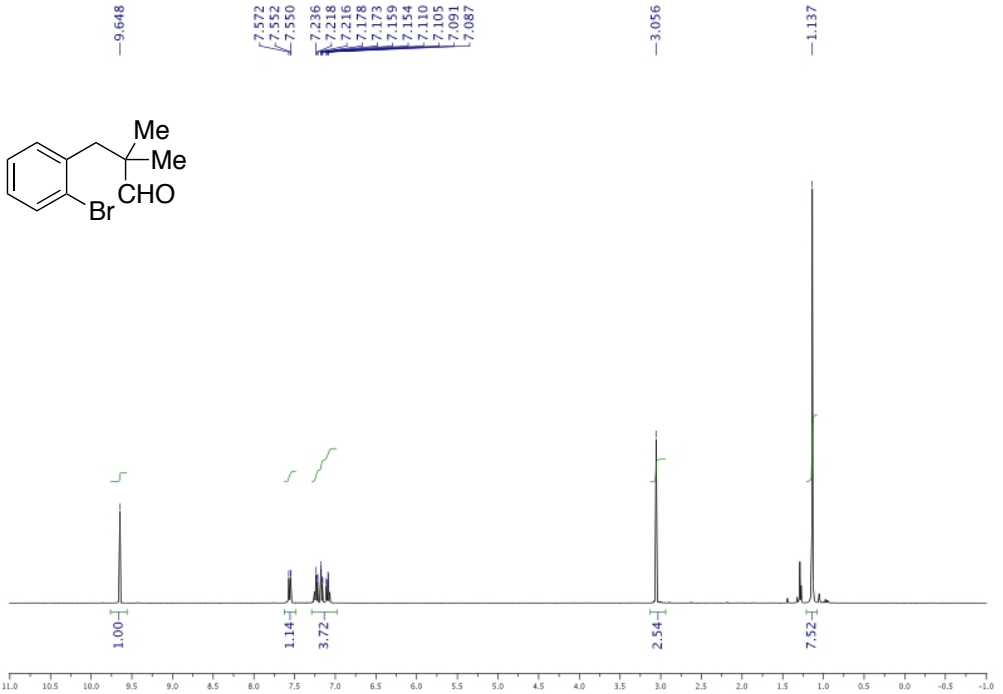
Butyl-2-(3-(4-cyanobenzyloxy)phenyl)-2-methylpropanoate (351). Following general procedure F, 4-((4-bromo-3-(2-methyl-1-oxopropan-2-yl) phenoxy)methyl) benzonitrile

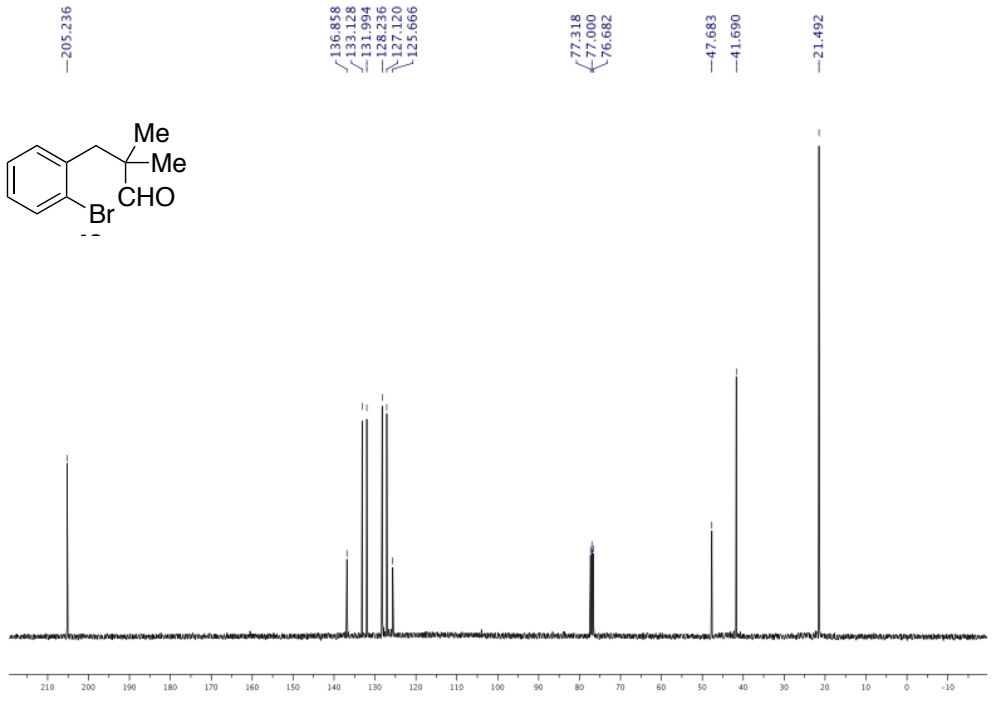
(179.1 mg, 0.50 mmol) and 1-butanol (183 μL, 2.0 mmol) were used. Column chromatography: silica gel, hexanes:EtOAc 2:1. Colorless oil; yield: 159.5 mg (75% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, *J*= 8.3 Hz, 2H), 7.56 (d, *J*= 8.2 Hz, 2H), 7.26 (t, *J*= 8.2 Hz, 1H), 7.04–6.93 (m, 2H), 6.82 (dd, *J*= 7.4, 1.8 Hz, 1H), 5.12 (s, 2H), 4.06 (t, *J*= 6.6 Hz, 2H), 1.62–1.46 (m, 8H), 1.28 (dq, *J*= 14.5, 7.3 Hz, 2H), 0.88 (t, *J*= 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.4, 158.1, 146.7, 142.5, 132.3, 129.3, 127.5, 118.9, 118.6, 112.9, 112.3, 111.6, 68.8, 64.6, 46.5, 30.5, 26.4, 18.9, 13.6. IR (neat, cm^{-1}): 2959, 2229, 1721, 1581, 1464, 1250, 1143, 1019, 818, 718, 547. HRMS *calcd* for [$C_{22}H_{25}NO_3$+Na] 374.1732, *found* 374.1721.

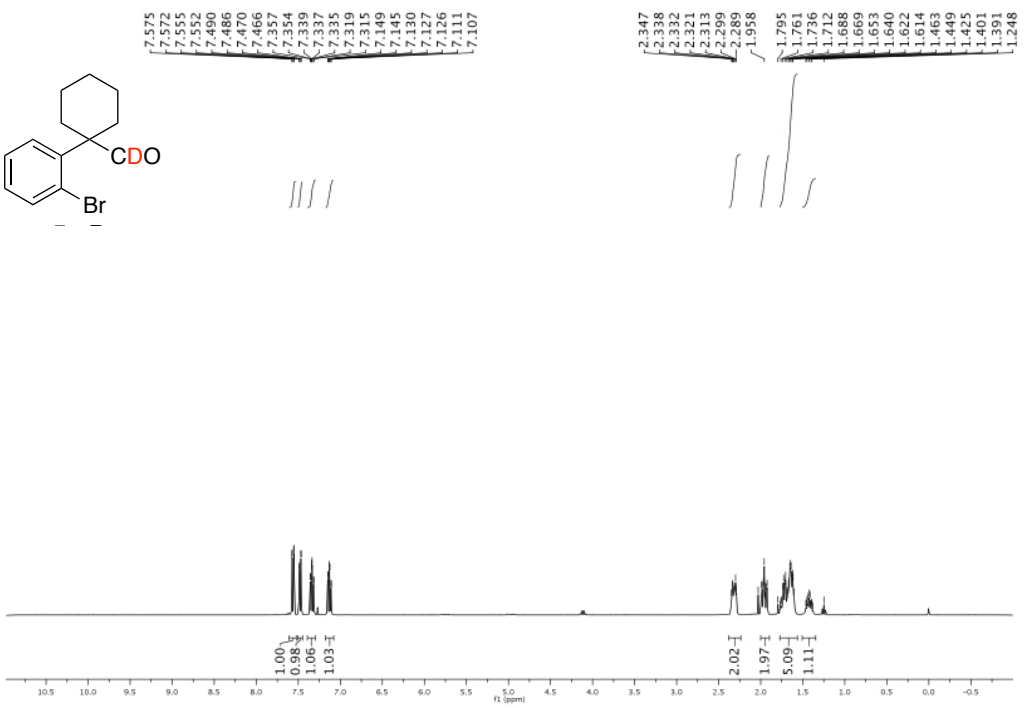


Butyl-1-(3-(4-formylbenzyloxy)phenyl) cyclohexanecarboxylate (352). Following general procedure F, 4-((4-bromo-3-(1-formylcyclohexyl) phenoxy)methyl) benzaldehyde (200.6 mg, 0.50 mmol) and 1-butanol (183 μL, 2.0 mmol) were used. Column chromatography: silica gel, hexanes:EtOAc 2:1. Colorless oil; yield: 159.8 mg (81% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.04 (s, 1H), 7.92 (d, *J*= 8.1 Hz, 2H), 7.62 (d, *J*= 8.0 Hz, 2H), 7.31–7.18 (m, 1H), 7.04 (d, *J*= 7.0 Hz, 2H), 6.88–6.79 (m, 1H), 5.15 (s, 2H), 4.05 (t, *J*= 6.6 Hz, 2H), 2.48 (d, *J*= 12.8 Hz, 2H), 1.69 (d, *J*= 11.4 Hz, 5H), 1.60–1.39 (m, 4H), 1.28 (dd, *J*= 14.9, 7.4 Hz, 3H), 0.87 (t, *J*= 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.8, 174.9, 158.4, 145.9, 144.0, 135.9, 129.9, 129.3, 127.5, 118.9, 113.2, 112.5, 69.2, 64.5, 50.9, 34.6, 30.5, 25.6, 23.6, 19.1, 13.6. IR (neat, cm^{-1}): 2932, 2860, 1720, 1699, 1606, 1579, 1451, 1298, 1209, 1129, 1054, 777, 693. HRMS *calcd* for [$C_{25}H_{30}O_4$+Na] 417.2042, *found* 417.2137.

3.5.4 Selected examples of NMR spectra



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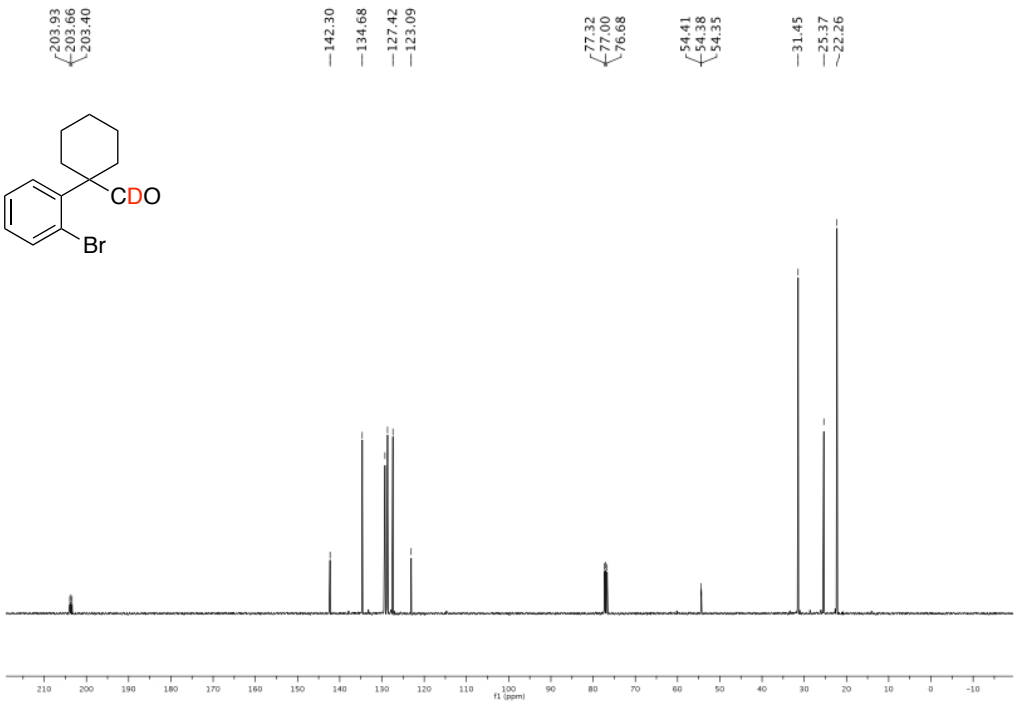
f1 (ppm)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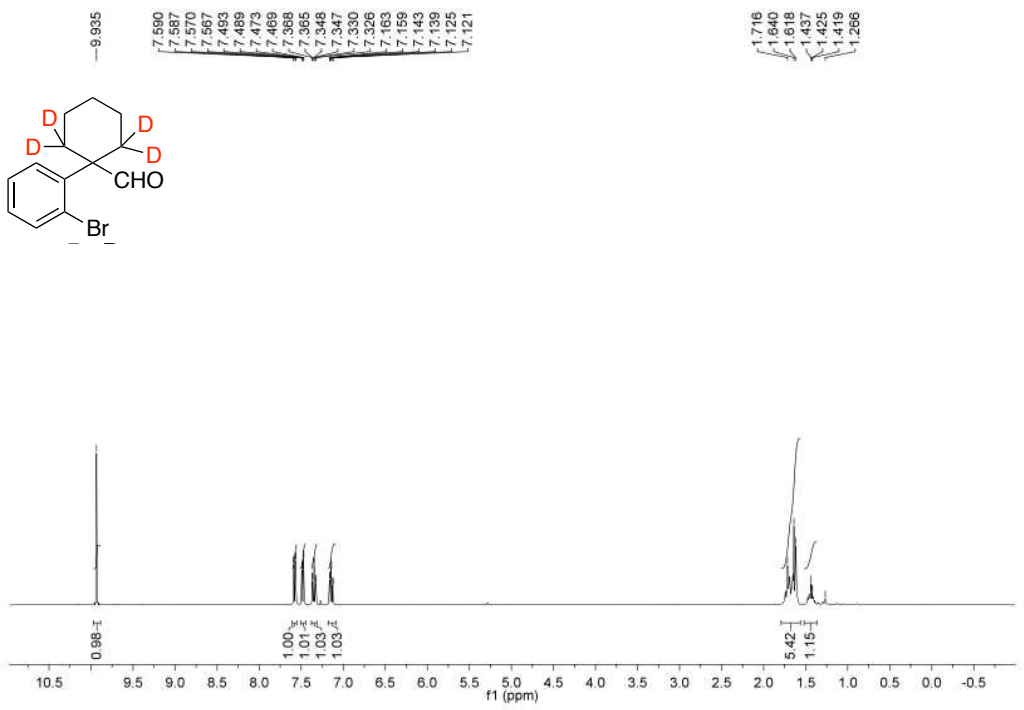
Br
f1 (ppm)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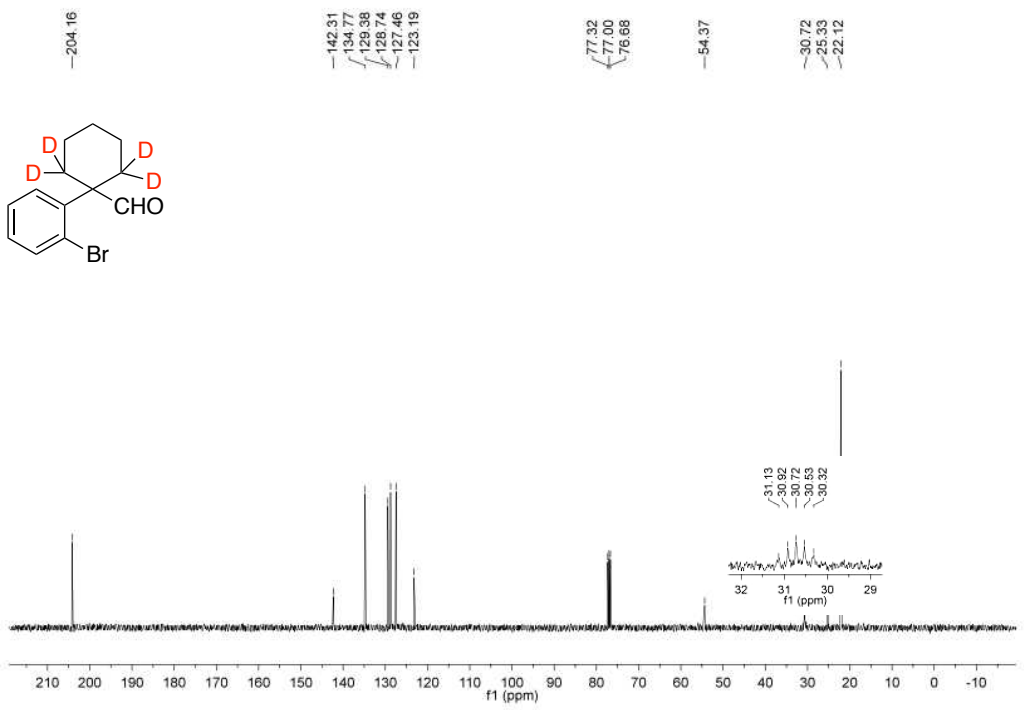
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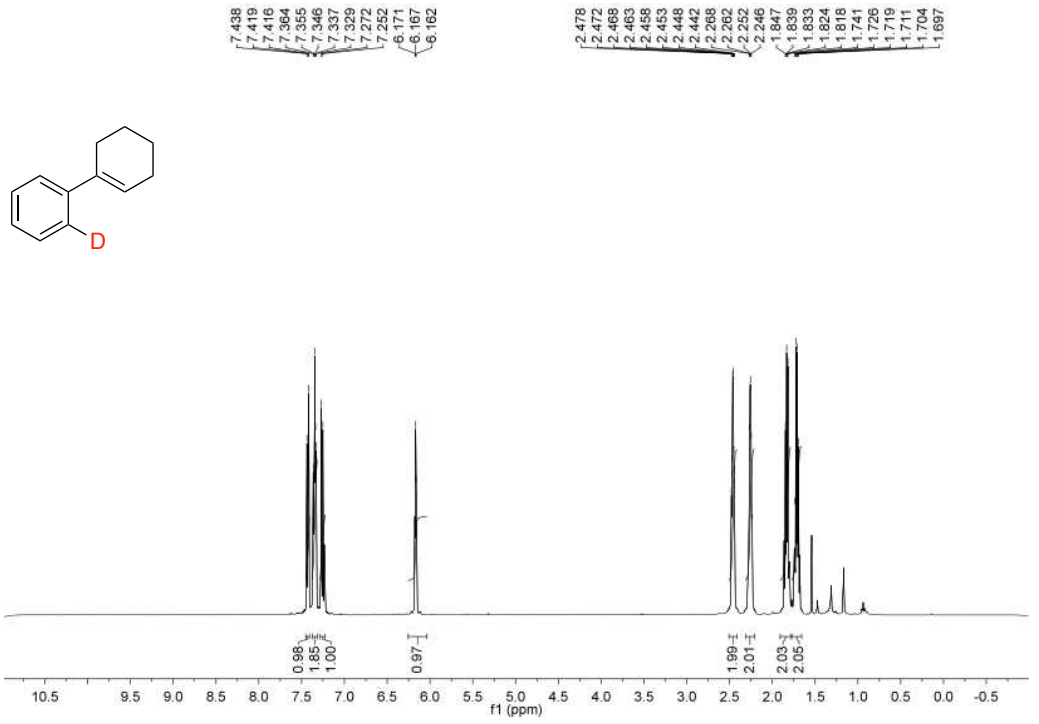
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2.468
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2.252
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1.824
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1.741
1.726
1.719
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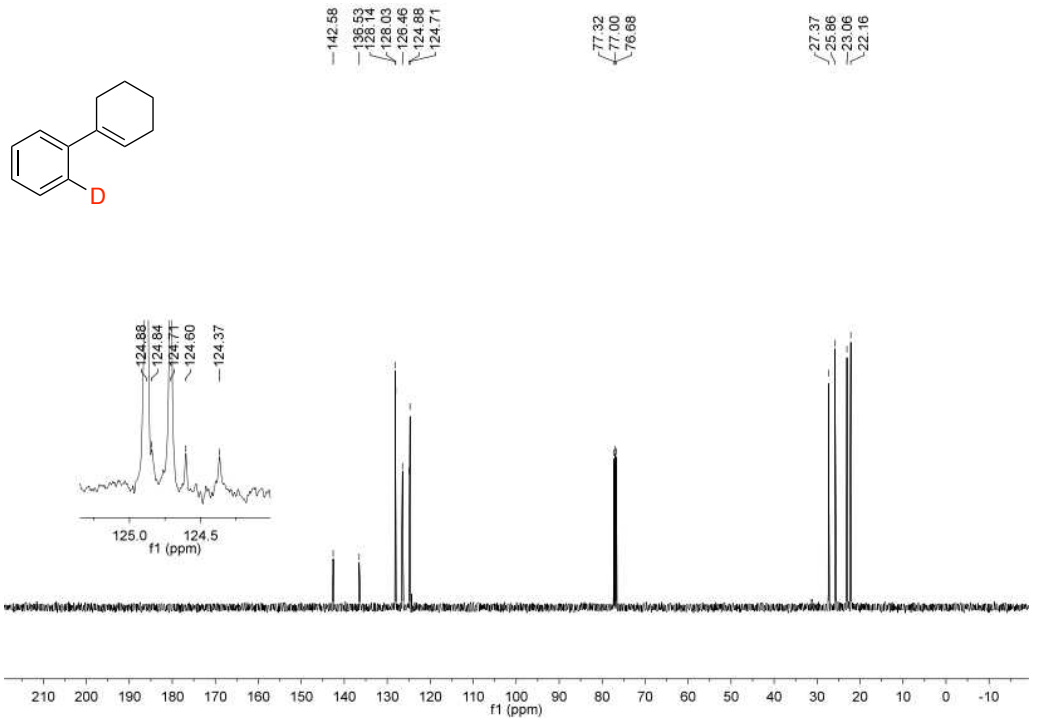
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124.71
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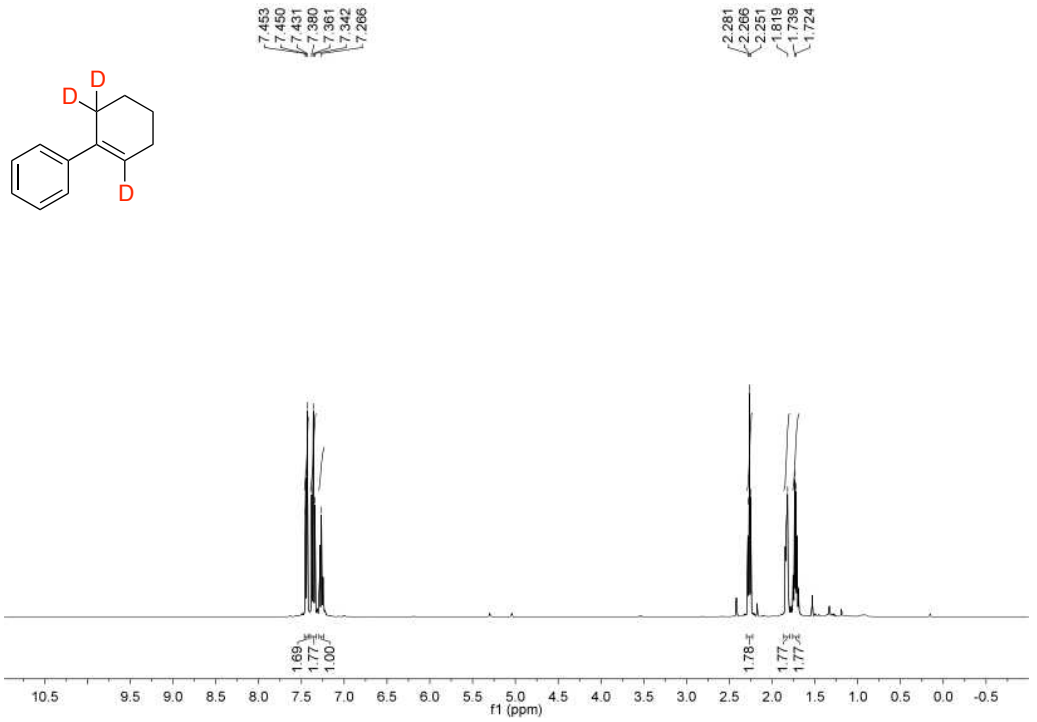
124.37
125.0
124.5
f1 (ppm)
f1 (ppm)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D
D
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1.77
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1.78
1.77
1.77
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9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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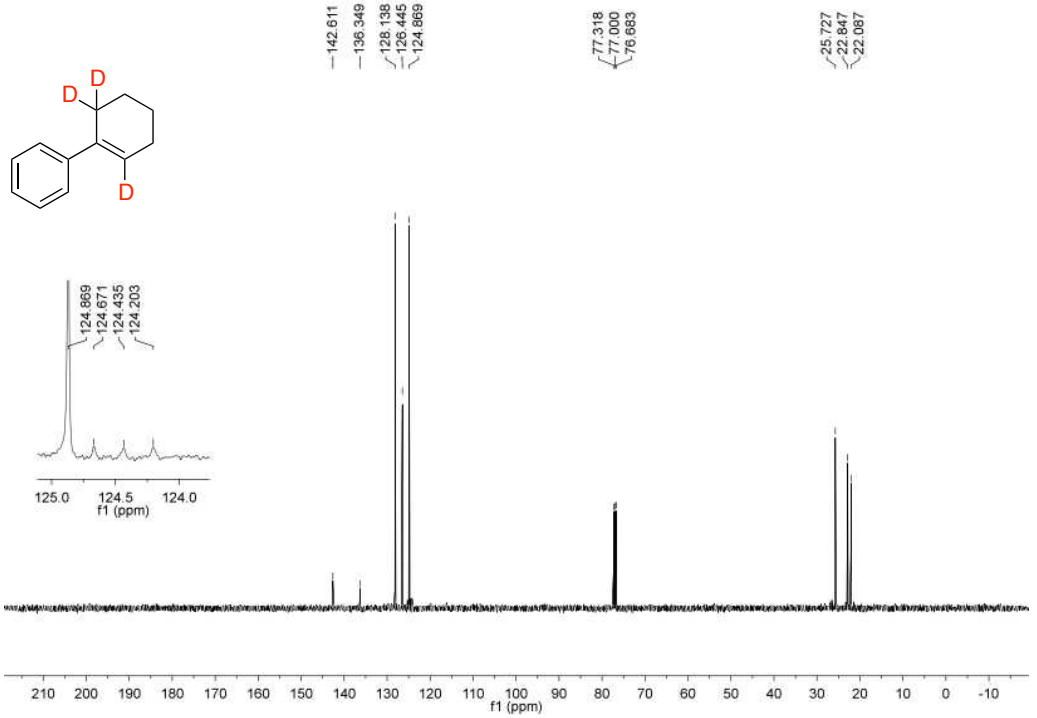
f1 (ppm)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D
D
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124.671
124.435
124.203
125.0
124.5
124.0
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200
190
180
170
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100
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70
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30
20
10
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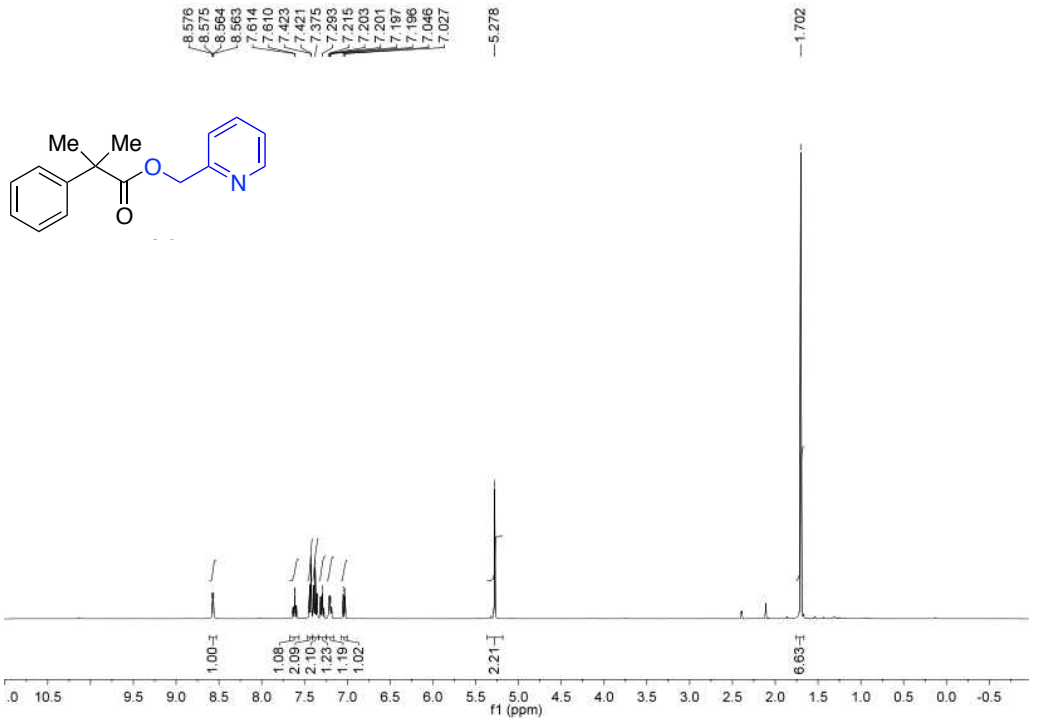
-10
f1 (ppm)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7.201
7.197
7.196
7.046
7.027
5.278
1.702
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Me
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N
O
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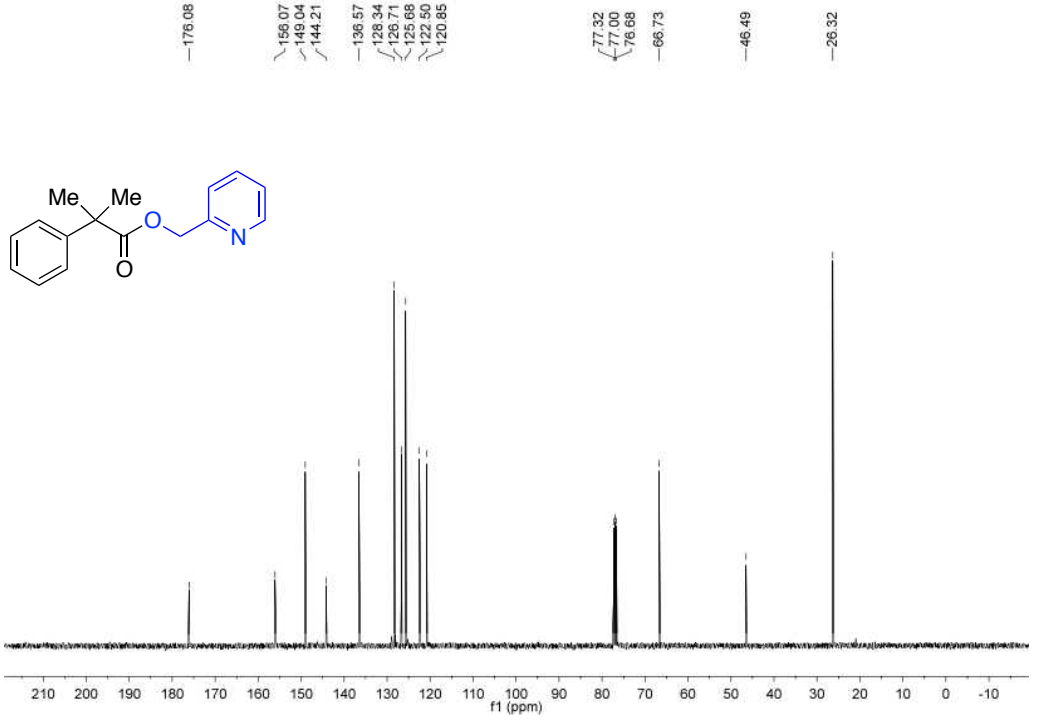
1.08
2.09
2.10
1.23
1.19
1.02
2.21
6.63
f1 (ppm)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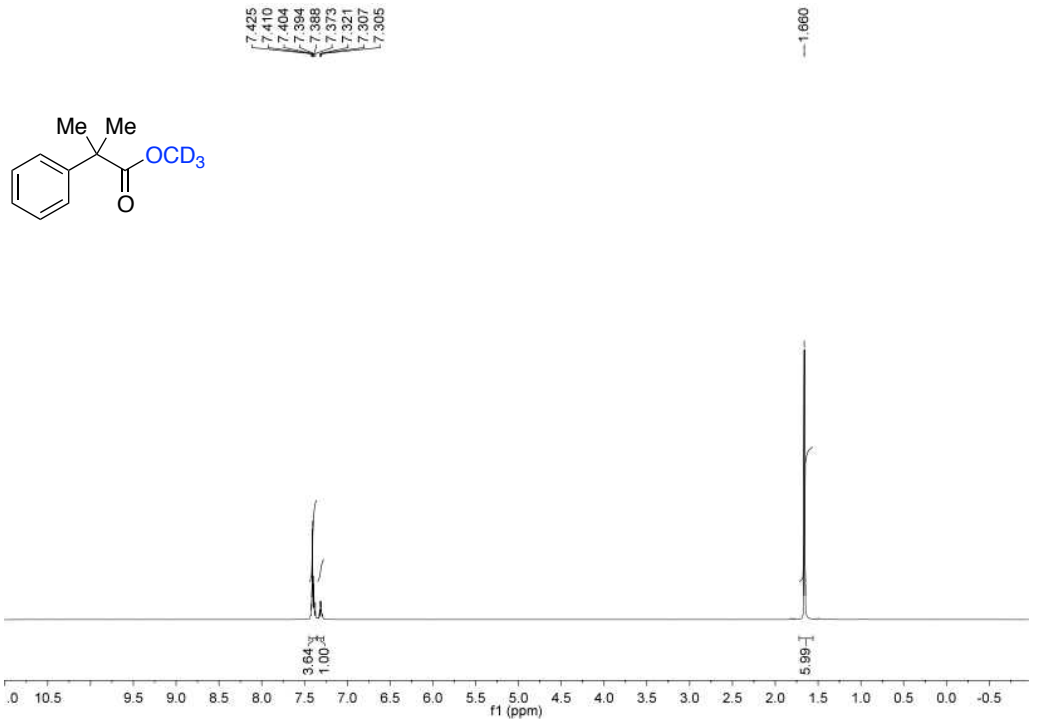
O
N
O
f1 (ppm)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OCD3
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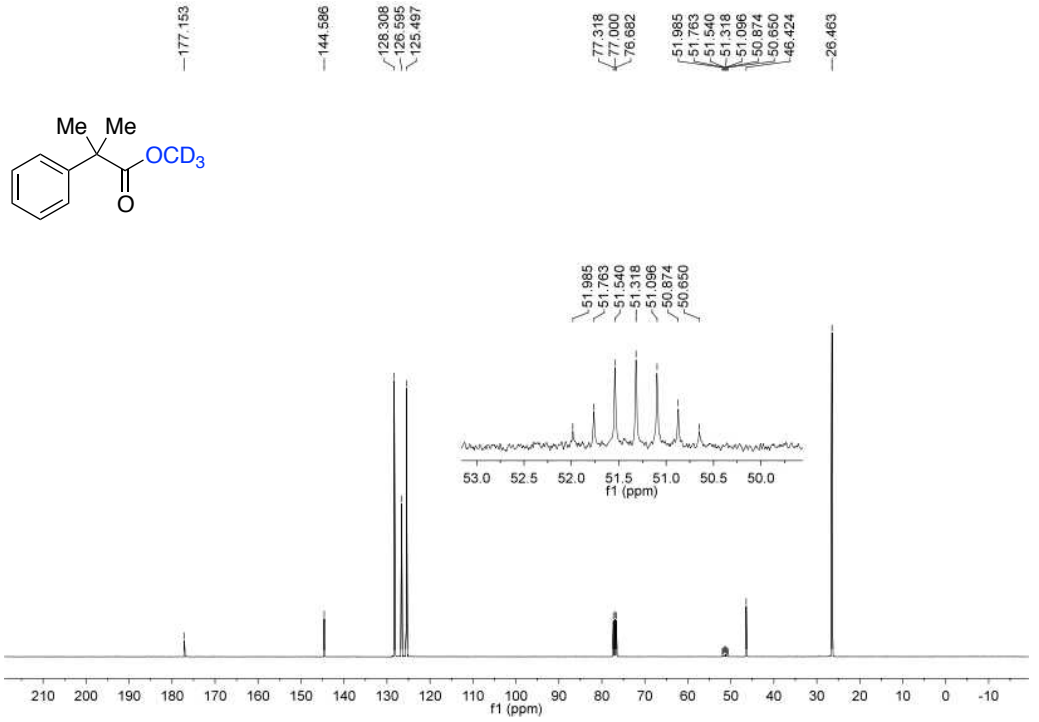
1.00
5.99
f1 (ppm)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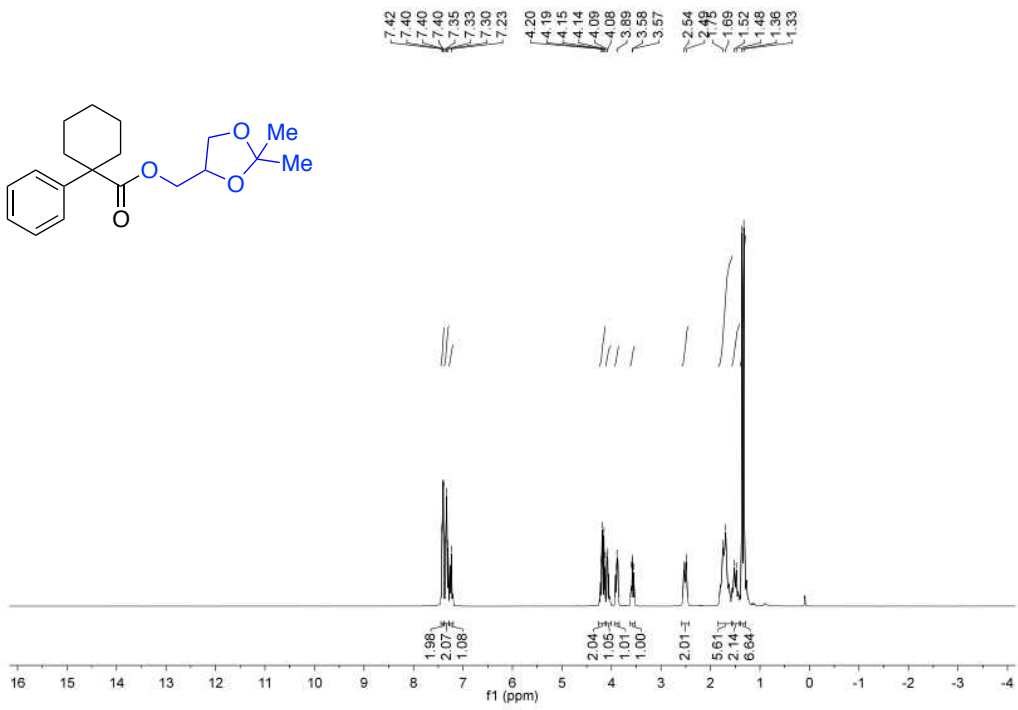
OCD3
O
f1 (ppm)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7.23
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4.08
3.89
3.58
3.57
2.54
2.49
1.69
1.52
1.48
1.36
1.33
O
Me
Me
O
O
O
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1.08
2.04
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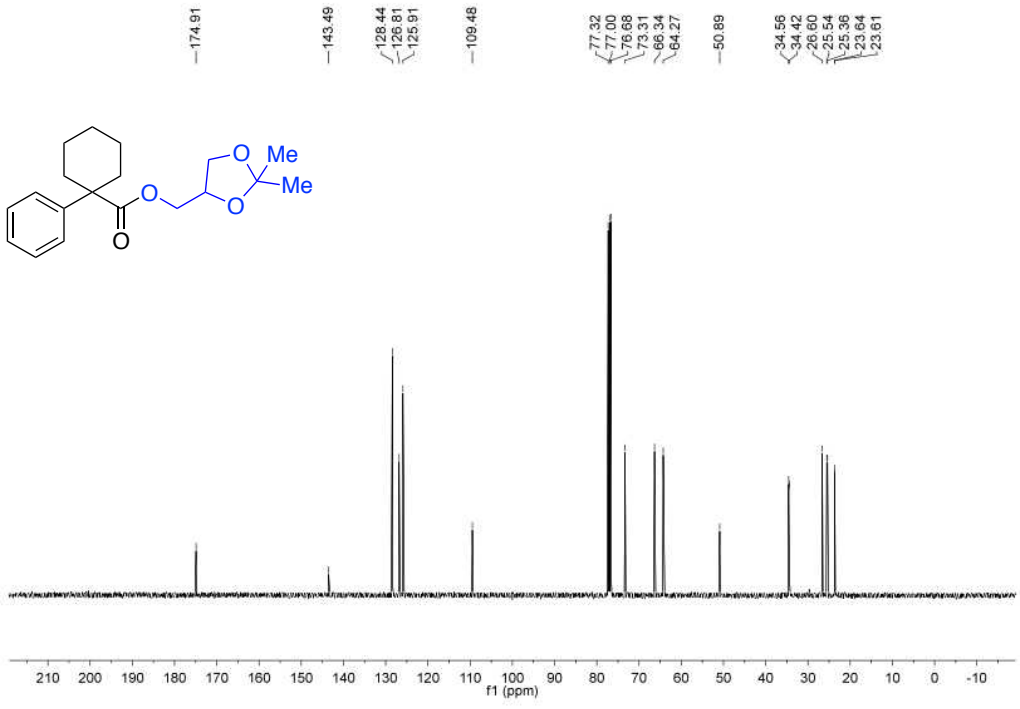
1.01
1.00
2.01
5.61
2.14
6.64
f1 (ppm)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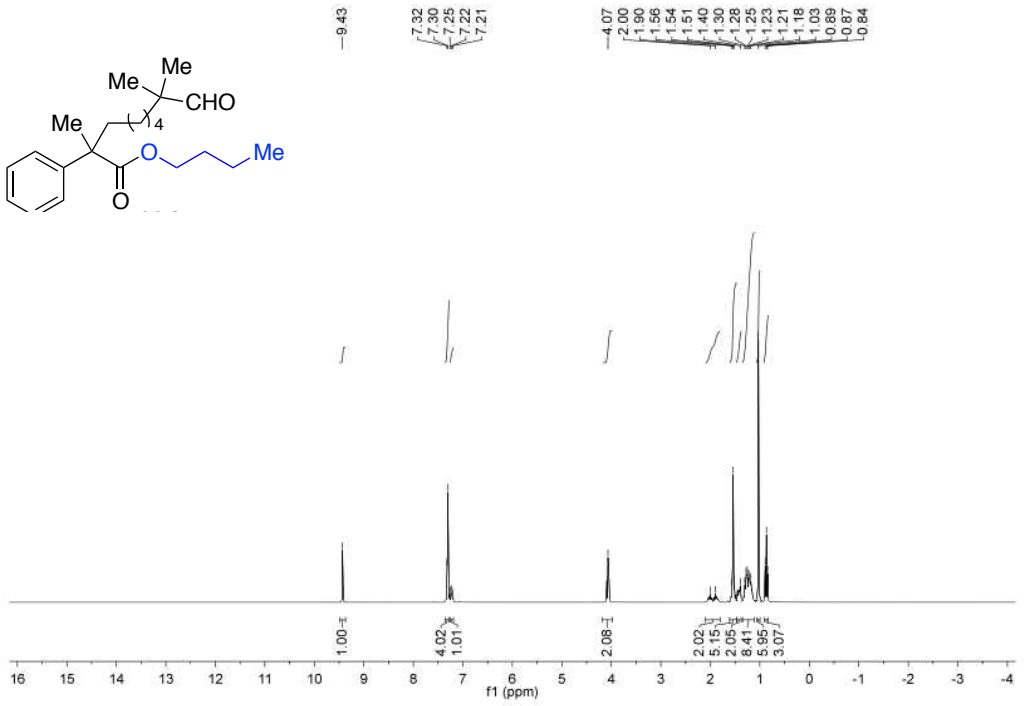
O
Me
Me
O
O
O
f1 (ppm)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1.30
1.28
1.25
1.23
1.21
1.18
1.03
0.89
0.87
0.84
Me
Me
CHO
Me
4
O
Me
O
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1.01
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2.02
5.15
2.05
8.41
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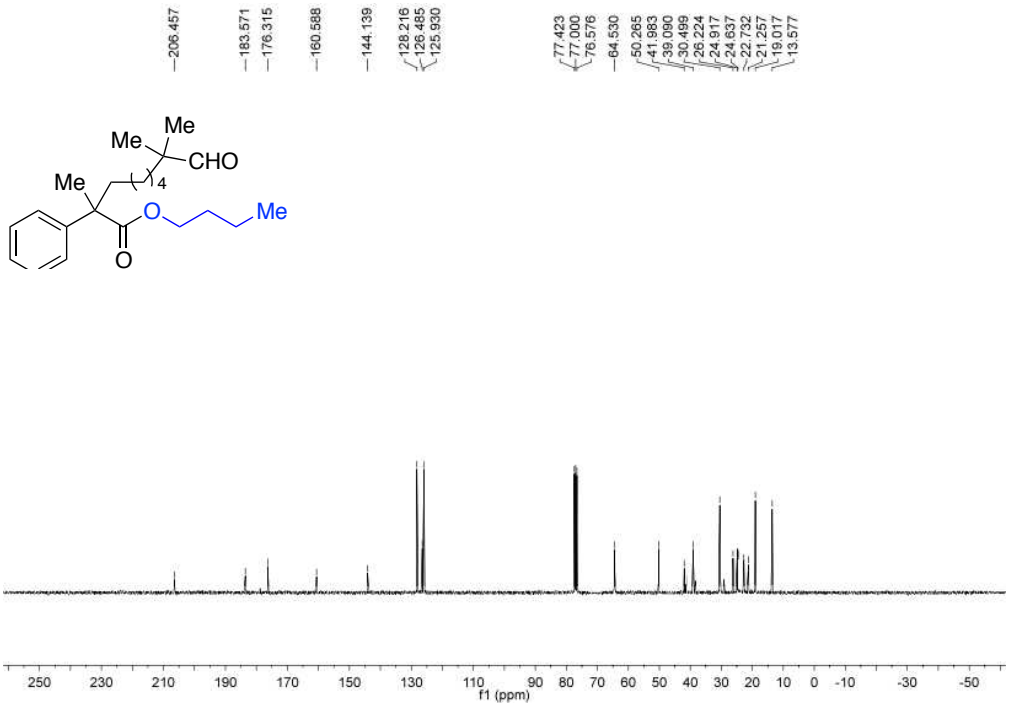
3.07
f1 (ppm)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39.090
30.499
26.224
24.917
24.637
22.732
21.257
19.017
13.577
Me
Me
CHO
Me
4
O
Me
O
f1 (ppm)

Chapter 4

Pd-Catalyzed intramolecular acylation via functionalization of aldehydic bonds with aryl chlorides as substrates

4.1

Objectives

The objectives of this chapter are the following:

- Design of a metal-catalyzed methodology for the preparation of benzocyclobutenones (BCB's) *via* functionalization of aldehydic C-H bonds with aryl chlorides as substrates.

- Study the effect of the ligand backbone for controlling the selectivity of the C-H bond-functionalization event, , ending up in benzocyclobutenones or styrenes at will.

4.2

Introduction

While the vast majority of cross-coupling reactions are still conducted with aryl iodides or aryl bromides as substrates, the employement of aryl chlorides is much more attractive, particularly from a pharmaceutical point of view where costs are an important, if not crucial, factor for implementing a process at big scale.[189] Not surprisingly, last years have witnessed a significant step forward for the implementation of efficient cross-coupling methodologies that employ aryl chlorides as subtrates.[189] The interest for such processes is primarily associated to the greater availability as well as the low cost of aryl chlorides as compared to their bromide or iodide analogues. Unfortunately the high bond strength associated to the C-Cl as compared with the corresponding C-Br and C-I bonds (Figure 4.1)[189] constitutes a serious drawback for oxidative addition, the first step within the catalytic cycle of all cross-coupling reactions. Not surprisingly, the cross-coupling of aryl chlorides is still considered a great challenge in synthetic organic chemistry. Indeed, the recent progress in this area has been intimately associated to the development of new supporting ligands that are able to tune the properties of the metal centers to overcome the natural inertness associated to the C-Cl bonds.[190]

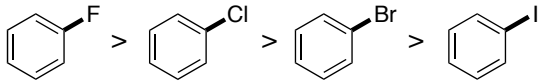


Figure 4.1

[189] a) Grushin, V.; Alper, H., *Activation of otherwise unreactive C-Cl bonds.* Topics is Organometallic Chemistry. Springer-Verlag Berin, **1999**, 194-226. b) Grushin, V. V.; Alper, H. *Chem. Re*v. **1994**, *94*, 1047.

[190] Old, D. W.; Wolfe, J. P.; Buchwald, S. L., *J. Am. Chem. Soc.,* **1998**, 120, 9722. For reviews see: a) Surry, D. S.; Buchwald, S. L. *Chem. Sci.,* **2011**, *2*, 27. b) Martin, R.; Buchwald, S. L. *Acc. Chem.* Res, **2008**, *41*, 1461.

Despite the tremendous drawbacks associated to the activation of C-Cl bonds, substantial progress has been made in the last years by employing Ni, Rh and in particular, Pd catalysts.[189, 191] An important contribution was published by Herrmann in Heck-type reactions using palladacycles **(353)** (Figure 4.2) as catalysts that were easily prepared by heating the corresponding phosphines with palladium acetate.[192] Remarkably, the activity was greatly improved by the use of different heteroatoms in the palladacycle or the use of an appropriate additive such as TBAB.[193] Subsequently, catalysts **(353)** found application in the field of Suzuki-Miyaura cross-coupling reactions as well.[194]

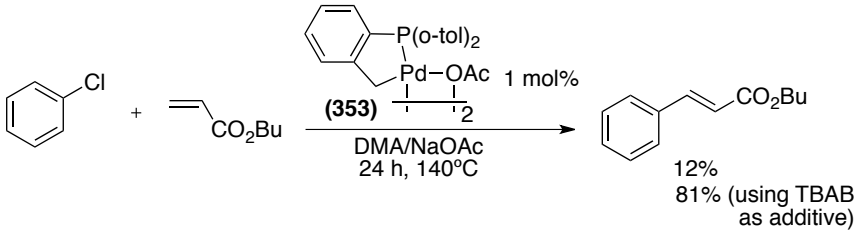
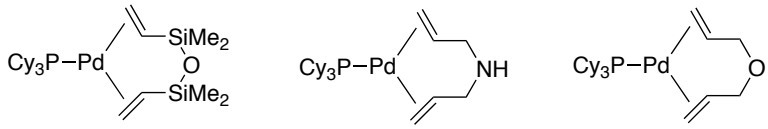


Figure 4.2

As for other cross-coupling reactions, the use of bulky ligands have demonstrated to be particularly useful when coupling aryl chlorides as a result of increasing the concentration of monoligated $L_1Pd(0)$ species that are believed to be the key propagating species in the vast majority of cross-coupling reactions.[195] Additionally, oxidative addition proceeds at a much faster rate with monoligated $L_1Pd(0)$ species than with more highly coordinated species. This is likely attributed to the smaller size of $L_1Pd(0)$ species complexes as compared to

[191] Bedford, R. B.; Cazin, C. S. J.; Holder, D. *Coord. Chem. Rev.* **2004**, 2283.
[192] M. Beller, H. Fischer, W. A. Herrmann, K. Öfele, C. Broßmer, *Angew. Chem. Int. Ed. Engl*. **1995**, 34, 1844.
[193] For reviews of Heck reaction of aryl chlorides, see: (a) Fu, G. C. *Acc. Chem. Res.* **2008**, *41*, 1555. (b) Bedford, R. B.; Cazin, C. S. J.; Holder, D. *Coord. Chem. Rev*. **2004**, *248*, 2283. (c) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176.
[194] See for example: a) Lee, D. –H.; Jin, M. –J. *Org. Lett.* **2011**, 13, 252. b) Tang, X.; Huang, Y. –T.; Liu, H., Liu, R. –Z; Shen, D. –S.; Liu, N.; Liu, F. –S. *J. Organom. Chem,* **2013**, http://dx.doi.org/10.1016/j.jorganchem.2013.01.018.
[195] a) Amatore, C.; Jutand, A.; M'Barki, M. A., *Organometallics*, **1992**, *11*, 3009. b) Christmann U., Vilar, R. *Angew. Chem., Int. Ed.,* **2005**, *44*, 366.

$L_2Pd(0)$ species, thus allowing the aryl halide to approach the metal center more closely and resulting in a faster rate. Finally, we should also take into account the fact that the rate of reductive elimination is usually faster for $L_1Pd(R^1)(R^2)$ than for $L_2Pd(R^1)(R^2)$. Following these premises, Beller showed that well-defined monoligated $L_1Pd(0)$ species **(354)**, **(355)** and **(356)** bounded to dienes resulted in a considerably higher activity for the Suzuki-Miyaura coupling of deactivated aryl chlorides than utilizing commonly employed catalysts that were formed *in situ* from a $Pd(OAc)_2$ or Pd_2dba_3 and PCy_3 under otherwise identical reaction conditions.[196]



(354) **(355)** **(356)**

Figure 4.3

Beyond any reasonable doubt, one of the biggest breakthroughs when coupling aryl chlorides came from the pioneering work of Buchwald by preparing a new family of bulky and electron-rich dialkylbiaryl phosphine ligands (Figure 4.4).[190] These ligands have dramatically improved the efficiency and selectivity of a myriad of cross-coupling reactions, ranging from C-N, C-C or C-O bond-forming reactions, among others.[197] Not surprisingly, these ligands have successfully been employed in a wide number of synthetic applications, including industrially relevant processes.

[196] Andreu, M. G.; Zapf, A.; Beller, M., *Chem. Commun.* **2000**, 2475.
[197] a) Surry, D. S.; Buchwald, S. L., *Angew. Chem., Int. Ed*., **2008**, *47*, 6338. b) Burgos, C. H.; Barder, T. E.; Huang, X. H.; Buchwald, S. L., *Angew. Chem., Int. Ed.*, **2006**, *45*, 4321. c) Vorogushin, A. V.; Huang, X. H.; Buchwald, S. L., *J. Am. Chem.Soc*., **2005**, *127*, 8146. d) Moradi W. A.; Buchwald, S. L., *J. Am. Chem. Soc*., **2001**, *123*, 7996. e) Molander, G. A.; Canturk, B., *Angew. Chem., Int. Ed.,* **2009**, *48*, 9240.

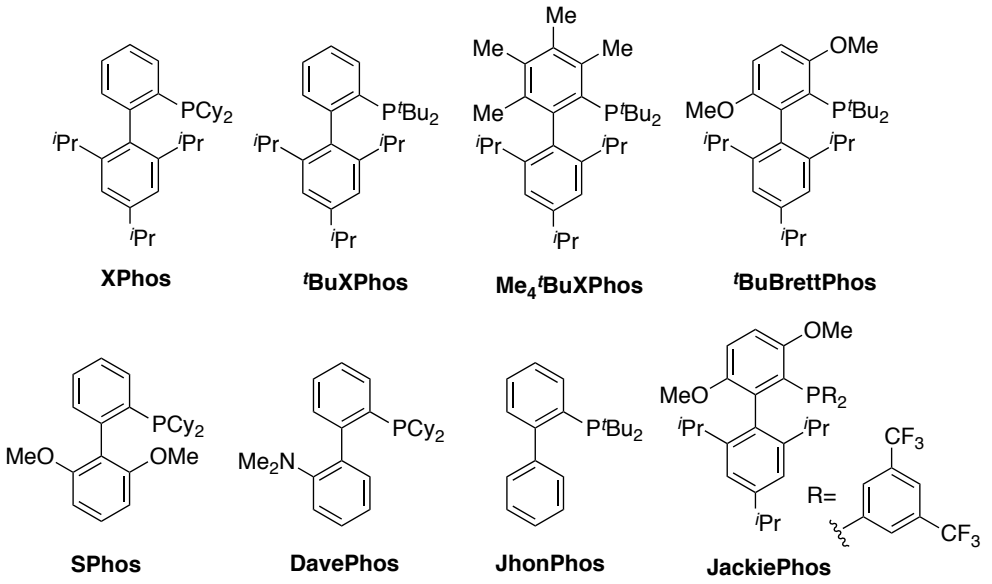


Figure 4.4

While structurally different, *N*-heterocyclic carbenes (NHC´s) have found to be a good alternative for phosphine-type ligands in many metal-catalyzed cross-coupling reactions. [198] Indeed, the utilization of such ligands have gained considerable momentum due to the following:

(i) NHC´s are strong σ-donors and very weak π-accepting ligands, thus making them particularly useful when dealing with the oxidative addition to chloroarenes;[199]

(ii) similarly to bulky phosphines, the steric bulk of NHCs greatly facilitates reductive elimination and the concentration of $L_1Pd(0)$ species;[200]

(iii) NHC´s are typically very easy to synthesize and can be employed in cross-coupling reactions as imidazolium or imidazolinium salts that can be

[198] a) Dröge, T.; Glorius, F. *Angew. Chem. Int. Ed.* **2010**, *49*, 6940. b) Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Angew. Chem. Int. Ed.* **2007**, *46*, 2768. c) Crabtree, R. H. *J. Organom. Chem.* **2005**, 690, 5451.
[199] a) Cárdenas, D. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 384. b) Luh, T.-Y.; Leung, M.-K.; Wong, K.-T. *Chem. Rev.* **2000**, *100*, 3187.
[200] a) Culkin, D. A.; Hartwig, J. F. *Organometallics* **2004**, *23*, 3398. b) Mann, G.; Shelby, Q.; Roy, A. H.; Hartwig, J. F. *Organometallics* **2003**, *22*, 2775.

deprotonated *in situ*.[201]

As for the use of bulky phosphines, Beller employed highly active monoligated Pd(0) complexes of IPr and IMes with *p*-quinone or divinyldisiloxane (DVDS), Figure 4.5.[202] These ligands were much more active than the *in situ* prepared precatalysts by combining simple Pd(II) and Pd(0) salts with the corresponding NHC carbine

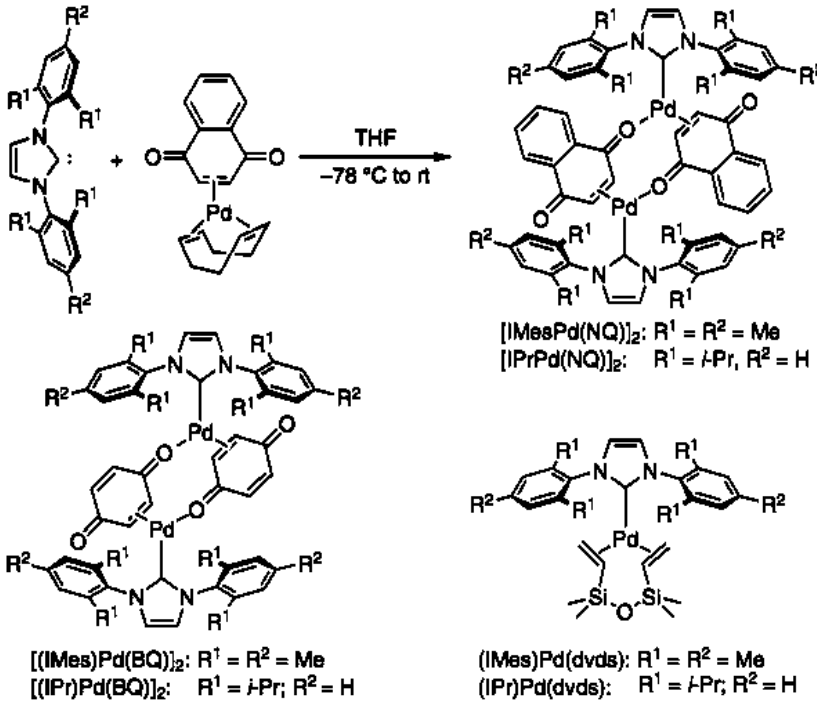


Figure 4.5

[201] a) Dorta, R.; Stevens, E. D.; Scott, N. M.; Costabile, C.; Cavallo, L.; Hoff, C. D.; Nolan, S. P. *J. Am. Chem. Soc.* **2005**, *127*, 2485. b) Chianese, A. R.; Li, X.; Janzen, M. C.; Faller, J. W.; Crabtree, R. H. *Organometallics* **2003**, *22*, 1663.

[202] a) Selvakumar, K.; Zapf, A.; Spannenberg, A.; Beller, M. *Chem. Eur. J.* **2002**, *8*, 3901. b) Frisch, A. C.; Zapf, A.; Briel, O.; Kayser, B.; Shaikh, N.; Beller, M. *J. Mol. Catal. A: Chem.* **2004**, *214*, 231. c) Jackstell, R.; Andreu, M. G.; Frisch, A.; Selvakumar, K.; Zapf, A.; Klein, H.; Spannenberg, A.; Röttger, D.; Briel, O.; Karch, R.; Beller, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 986.

In line with these complexes, Nolan has been particularly active in the area of NHCs, providing a new family of one-component NHC-Pd((η³-allyl)Cl complexes (Figure 4.6) that are applicable in many cross-coupling reactions.[203]

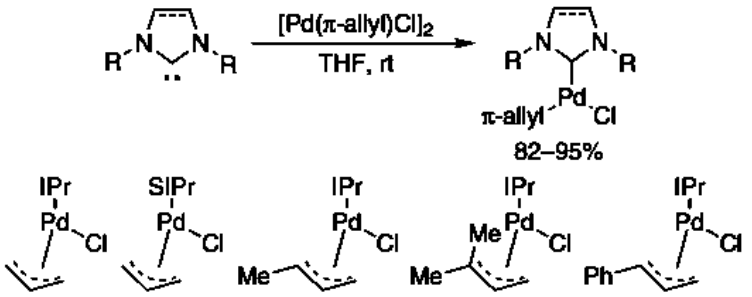


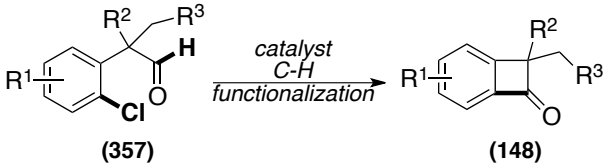
Figure 4.6

[203] a) Viciu, M. S.; Kelly, R. A., III; Stevens, E. D.; Naud, F.; Studer, M.; Nolan, S. P. *Org. Lett.* **2003**, *5*, 1479. b) Marion, N.; Navarro, O.; Mei, J.; Stevens, E. D.; Scott, N. M.; Nolan, S. P. *J. Am. Chem. Soc.* **2006**, *128*, 4101. c) Viciu, M. S.; Navarro, O.; Germaneau, R. F.; Kelly, R. A., III; Sommer, W.; Marion, N.; Stevens, E. D.; Cavallo, L.; Nolan, S. P. *Organometallics* **2004**, *23*, 1629. d) Viciu, M. S.; Germaneau, R. F.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 4053. e) Viciu, M. S.; Germaneau, R. F.; Navarro- Fernandez, O.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2002**, *21*, 5470.

4.3

Results and discussion

In order to demonstrate the full potential of our Pd-catalyzed intramolecular acylation methodology for the synthesis of benzocyclobutenone derivatives *via* C-H bond functionalization of aldehydic bonds, we envisioned the extension of this concept by using more accessible aryl chlorides as substrates **(357)**[204] (Figure 4.7). On the basis of our own findings in Chapter 2 we anticipated that the supporting ligand would play an important role to facilitate the oxidative addition into the Ar-Cl bond and to obtain benzocyclobutenone derivatives **(148)** in a selectivity fashion.



(357) **(148)**

Figure 4.7

4.3.1 Synthesis of benzocyclobutenones

4.3.1.1 Screening of the reaction conditions for synthesis of BCB.

We chose **(359)** as our model substrate. This substrate was easily prepared in high yield and in multigram scale from commercially available 2-(2-chlorophenyl) acetonitrile in essentially two-step (Figure 4.8). This sequence is essentially identical to the route followed in Chapter 2.

[204] Flores-Gaspar, A.; Gutiérrez-Bonet, A.; Martin, R., *Org. Lett.,* **2012**, *14*, 5234.

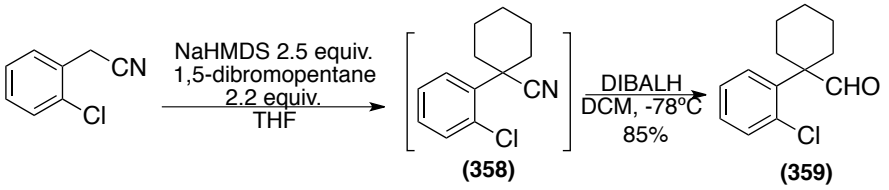


Figure 4.8

With substantial amount of **(359)** in hands, we began our screening study by examining a variety of experimental variables such as ligand, base and solvent using $Pd(OAc)_2$ as the precatalyst (Figure 4.9). Thus, a series of reactions of **(359)** (0.25 mmol) in the presence of $Pd(OAc)_2$ (4 mol%), Ligand (6 mol%), Cs_2CO_3 (1.30 equiv.) and 1,4-dioxane (0.25 M) at 110 ºC were systematically analyzed in order to find the appropriate conditions en route to obtain benzocyclobutenone **(242)** selectively.

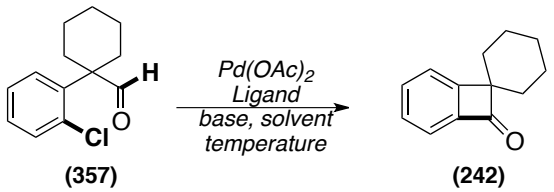
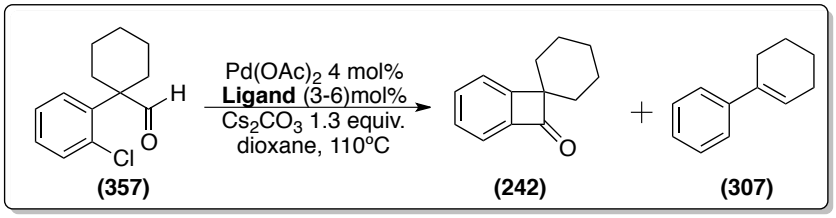


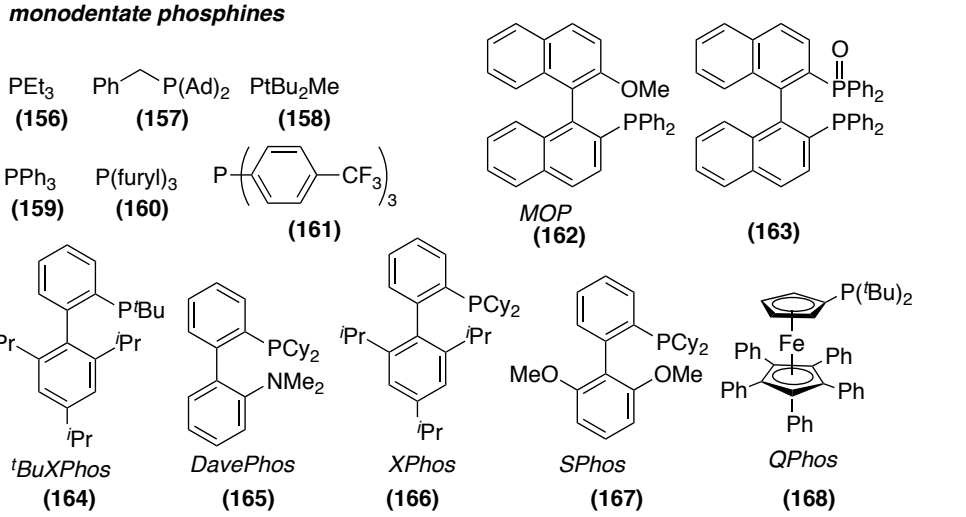
Figure 4.9

After taking a closer look into the crude reaction mixtures by GC analysis, we observed that substrate **(357)** was converted into two main products: the expected benzocyclobutenone **(242)** and the styrene derivative **(307)**. Intriguingly, we found that both monodentante showed limited reactivity in this transformation (Table 20), for instance, less than 5% of conversion was observed when using **(164)**-**(167)** monodentate ligands. On the other hand, when using bidentate phosphines no conversion or decomposition was observed in all cases (Table 20).

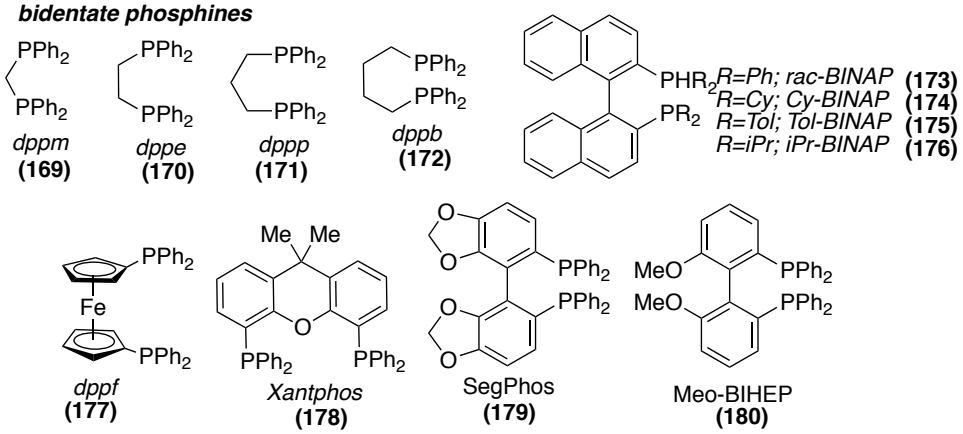
Table 20 Screening of phosphine ligands.[a],[b]



monodentate phosphines



bidentate phosphines



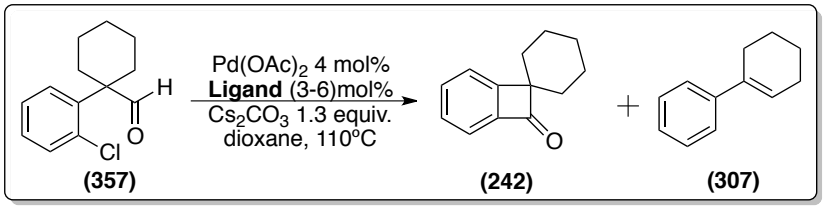
[a] Aryl chloride (0.25 mmol), $Pd(OAc)_2$ (4 mol%), Ligand (3-6 mol%), Cs_2CO_3 (1.30 equiv.), dioxane (0.50 M) at 110 ºC. [b] No conversion was observed for all cases. For (164)-(167) less than 5% of conversion was observed.

These results are in sharp contrast with the results shown in Chapter 2 in which phosphines provided the best results for obtaining benzocyclobutenones in high yields and with total selectivity. Interestingly, we found that N-heterocyclic

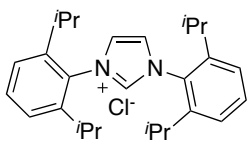
carbenes (NHC's) exhibited superior activity as compared to phosphine ligands. As shown in Table 21, **IPr·HCl** gave the best conversion of the corresponding α-aryl aldehyde (90%); however, such ligand gave exquisite selectivity toward styrene product **(307)** (BCB:styrene/1:17). Surprisingly, the use of a bigger counterion as for **IPr·HBF$_4$** resulted not only in lower conversions (77%), but also in a 1:1.3 mixture of styrene:benzocyclobutenone. At present, we do not have a rational explanation for such behavior, but it is definitely something to look after in the future. In line with these rather surprising results, we found that the use of **SIPr·HCl** gave also lower conversions and selectivities to the styrene compound. Similarly, **IMes·HCl** as well as **(362)** gave exclusively styrene **(307)**, but in 40% and 25% conversion, respectively. Unsymmetrically substituted **(361)** resulted in poor selectivities as for the use of alkyl substituted NHC's **(363)-(301)** and **(367)**[205] that yielded mixures of benzocyclobutenone and styrene products.

Taking into consideration the proposed mechanism for the preparation of benzocyclobutenones from aryl bromides (see Chapter 3), one of the key steps for controlling the selectivity in the reaction was the reductive elimination event. This step was the responsible for delivering the rather strain four-membered ring backbone while recovering back the propagating catalytic species. One way for accelerating reductive elimination is the utilization of particularly sterically-hindered ligands.[190] Thus, we checked whether the replacement of one mesityl unit in **IMes·HCl** by a more sterically-hindered motif would accelerate the rate of reductive elimination en route to benzocyclobutenone **(242)**. We observed that using **(360)** resulted in greater selectivity to benzocyclobutenone **(242)** as compared to **IMes·HCl**. Remarkably, this selectivity was enhanced when using **IAd·HBF$_4$** yielding exclusively benzocyclobutenone **(242)** over the styrene **(307)**; although in low yields the use of **IAd·HBF$_4$** represent a starting point to find the best conditions of the reaction.

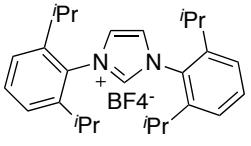
Table 21 Screening of NHC's. [a],[b]



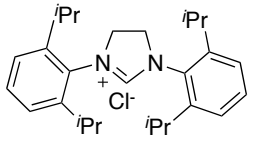
NHC Ligand



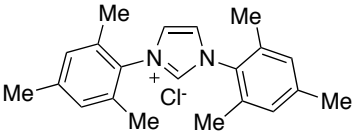
IPr·HCl
90%
1:17 (**242:307**)



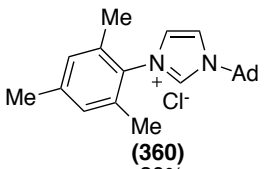
IPr·HBF$_4$
77%
1:1.3 (**242:307**)



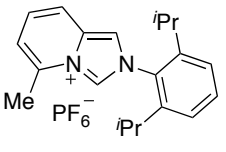
SIPr·HCl
72%
1:1.8 (**242:307**)



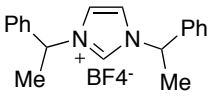
IMes·HCl
40%
1:99 (**242:307**)



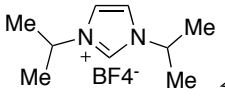
(360)
30%
1:2 (**242:307**)



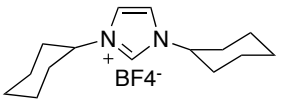
(361)
10%
5:1 (**242:307**)



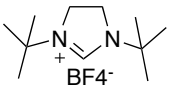
(362)
25%
1:99 (**242:307**)



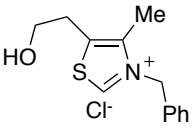
(363)
50%
1:1 (**242:307**)



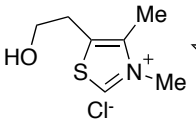
(302)
47%
3:1 (**242:307**)



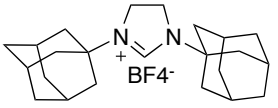
(301)
10%
1:1 (**242:307**)



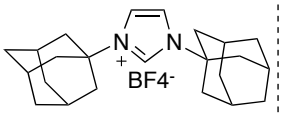
(364)
0%



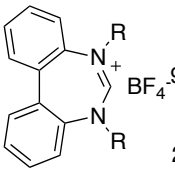
(365)
0%



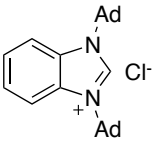
SAd·HBF$_4$
4%
99:1 (**242:307**)



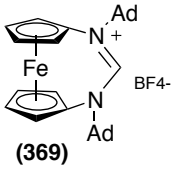
IAd·HBF$_4$
12%
99:1 (**242:307**)



R= Ad; **(366)**
5%
99:1 (**242:307**)
R= Np; **(367)**
28%
2.5:1 (**242:307**)



(368)
4%
99:1 (**242:307**)



(369)
7%
1:1 (**242:307**)

[a] Aryl chloride (0.25 mmol), $Pd(OAc)_2$ (4 mol%), Ligand (6 mol%), Cs_2CO_3 (1.30 equiv.), dioxane (0.50 M) at 110 ºC. [b] Yields and selectivities were determined by GC analysis using dodecane as internal standard.

In order to evaluate the effect of the bulky adamantly group we decided to prepare different NHC's by varying the heterocyclic backbone. Unfortunately, as shown in Table 21, although **(366)**[205] and **(368)**[206] showed exclusively formation of **(242)**, they gave very low conversions. In the case of **(369)**[207] formation of 1:1 mixture of **(242):(307)** was observed. Thus, we decided to continue the screening of the reaction using **IAd·HBF$_4$** as ligand.

Next, we investigated the effect of other palladium precatalysts in the aldehydic C-H bond-functionalization, of aryl chlorides (Table 22). We observed that other Pd(II) sources such $PdCl_2$ and $PdCl_2(MeCN)_2$ gave similar results as $Pd(OAc)_2$. Other Pd(II) sources such $Pd(acac)_2$, $Pd(OTf)_2$, $Pd(COD)Cl_2$,[208] *trans*-$Pd(SMe_2)_2Cl_2$[208] and $Pd(TMEDA)Cl_2$[209] were even less reactive than $Pd(OAc)_2$.Not surprisingly, the use of Pd(0) precatalysts such as $Pd(dba)_2$ or $Pd_2(dba)_3$ did not result in better yields of benzocyclobutenones; this is strongly related to the high binding affinity of dba to Pd(0), thus lowering down the rate of the reaction. Surprisingly, $Pd(TMEDA)Me_2$[209] gave better results than $Pd(OAc)_2$, in this case 25% of benzocyclobutenone **(242)** was observed by GC.

[205] NHC was synthetized following procedure reported by: Scarborough, C. C.; Popp, B. V.; Guzei, I. A.; Stahl, S. S., *J. Organomet. Chem.* **2005**, *690,* 6143. (**(366)** 60% overall yield and **(367)** 52% overall yield)

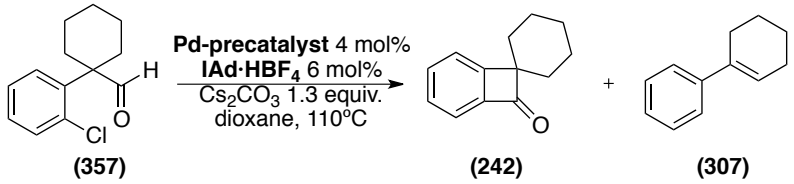
[206] Their synthesis was achieved following procedure reported by: Khramov, D. M.; Boydston, A. J.; Bielawski, C. W., *Org. Lett*., **2006**, *8*, 1831. (**(368)** 43% overall yield)

[207] **(369)** was synthetized following the reported procedures: a) Shafir, A.; Power, M. P.; Whitener, G. D.; Arnold, J., *Organometallics*, **2000**, *19*, 3978. b) Khramov, D. M.; Rosen, E. L.; Lynch, V. M.; Bielawski, C. W., *Angew. Chem., Int. Ed.*, **2008**, *47*, 2267. (45% overall yield)

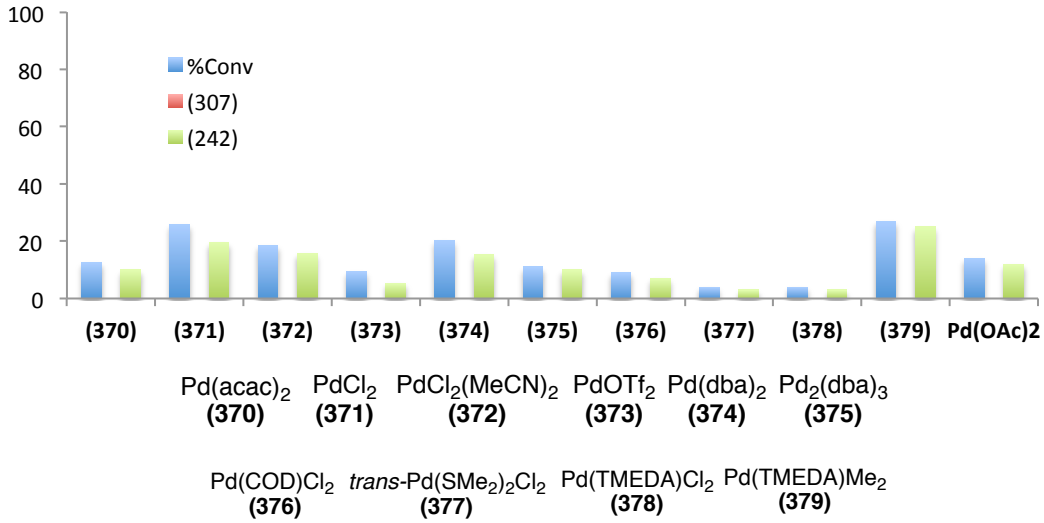
[208] $Pd(COD)Cl_2$ (87% yield) and *trans*-$Pd(SMe_2)_2Cl_2$ (90% yield) were synthetized following procedures reported by: Drew, D.; Doyle, J. R., *Inorg. Synth.* **1990**, 346.

[209] Synthesis of $Pd(TMEDA)Cl_2$ (85% yield) and $Pd(TMEDA)Me_2$ (73% yield) were performed following procedures reported by: Chatt, J.; Vallarino, L. M.; Venanzi, L. M., *J. Chem. Soc.,* **1957**, 3413.

Table 22 Screening of Pd-precatalyst. [a],[b]



(357) **(242)** **(307)**



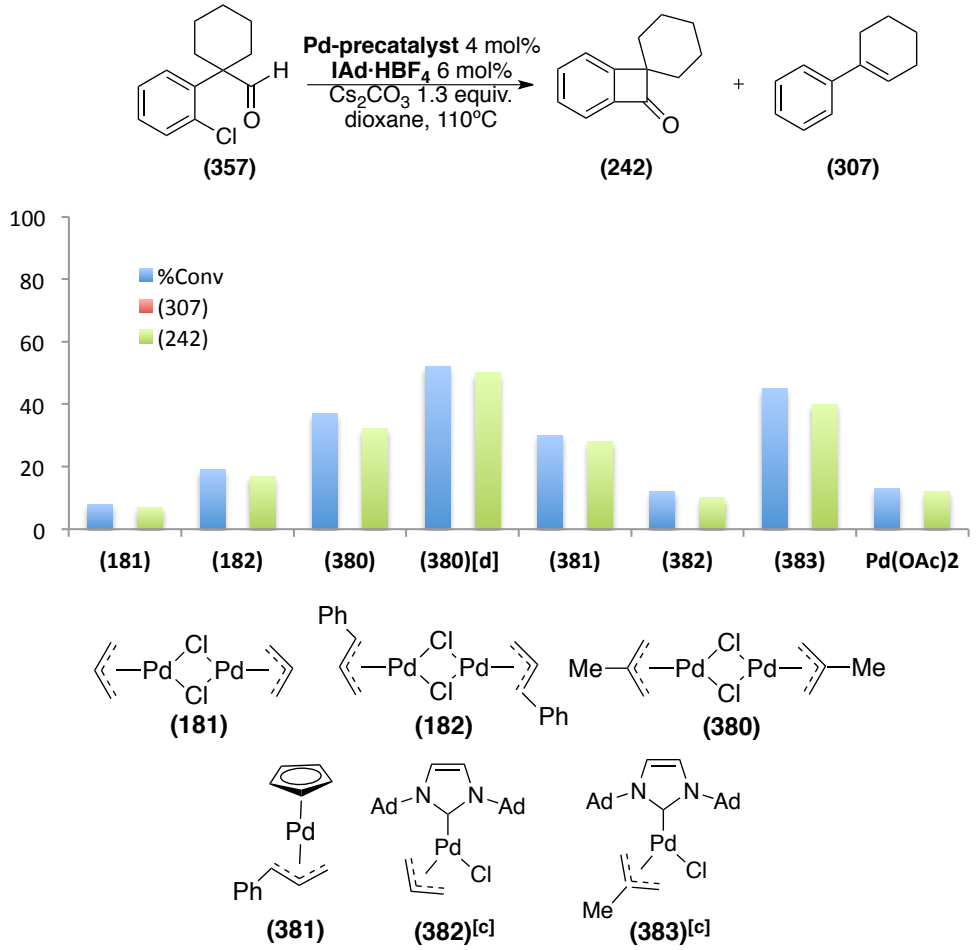
[a] Aryl chloride (0.25 mmol), Pd-precatalyst (4 mol%), Ligand (6 mol%), Cs_2CO_3 (1.30 equiv.), dioxane (0.50 M) at 110 ºC. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.

It is known that *N*-Heterocyclic carbenes react with $[(\eta^3\text{-allyl})Pd(Cl)]_2$ complexes to led the formation of monomeric species with general formula (NHC)Pd(η^3-allyl)Cl. The nucleophilic attack on the allyl moiety by a base generates the active 12-electron "NHC-Pd(0)" species that would be able to oxidatively add to aryl halides.[200] Thus, we decided to try the reactivity of homemade allyl palladium complexes such **(181)**[210], **(182)**[210] **(380)**[210] and **(381)** in combination with **IAd·HBF4**. As shown in Table 22, the best result was observed when using **(380)**, obtaining 37% yield of BCB with total selectivity. The yield could finally be increased to 51% when using 2.5 mol% of **(380)** at 140ºC. In order to evaluate if previous coordination of the NHC fragment to

[210] **(181), (182)** and **(380)** were prepared following procedure reported by: Marion, N.; Navarro, O.; Mei. J.; Stevens, E. D.; Scott, N. M.; Nolan, S. P., *J. Am. Chem. Soc.,* **2006**, *128*, 4101. (**(181),** 65% overall yield; **(182),** 57% overall yield; **(380),** 64% overal yield).

palladium center could be beneficial to enhance the reactivity toward BCB **43b** product, we also studied the activity of isolated NHC-Pd(II) complexes such as **Pd-16**[211] and **Pd-17**[211]. However we observed similar yields as their corresponding allyl palladium complexes **Pd-1** and **Pd-14** respectively, thus we decided to continue our screening by using **Pd-14** in combination with **IAd·HBF$_4$**.

Table 22 Screening of Pd-precatalyst.. [a],[b]

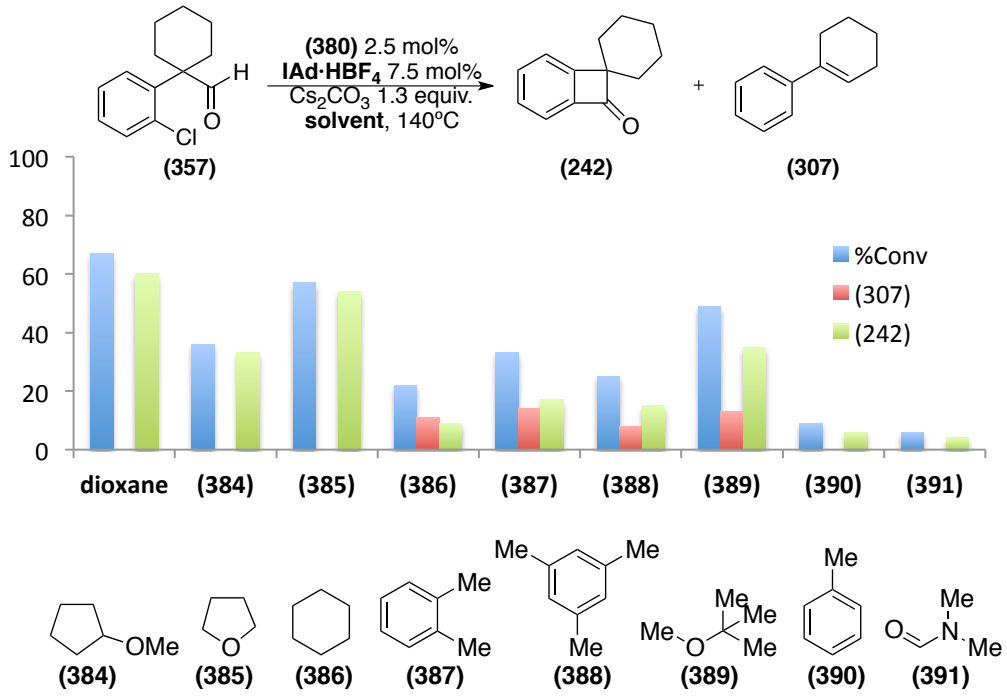


[a] Aryl chloride (0.25 mmol), Pd-precatalyst (2.5-4 mol%), Ligand (6 mol%), Cs_2CO_3 (1.30 equiv.), dioxane (0.50 M) at 110 ºC. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard. [c] Aryl chloride (0.25 mmol), Pd-precatalyst (4 mol%), Cs_2CO_3 (1.30 equiv.), dioxane (0.50 M) at 110 ºC. [d] Aryl chloride (0.25 mmol), Pd-precatalyst (2.5 mol%), Ligand (6 mol%), Cs_2CO_3 (1.30 equiv.), dioxane (0.50 M) at 140 ºC.

[211] **(382)** (30% yield) and **(383)** (34% yield) were prepared following procedure reported by: Scott, N. M.; Nolan S. P.; *Eur. J. Inorg. Chem.*, **2005**, 1815.

Having established that **(380)** gave the best results, we checked the influence of other solvents at 140ºC in the reaction outcome, Table 23. Gratifyingly, the yield to BCB product increased to 60% when using dioxane and to 54% when using THF. Other ether aprotic solvents such **(386)-(389)** gave lower yields and selectivities.

Table 23 Screening of solvents. [a],[b]



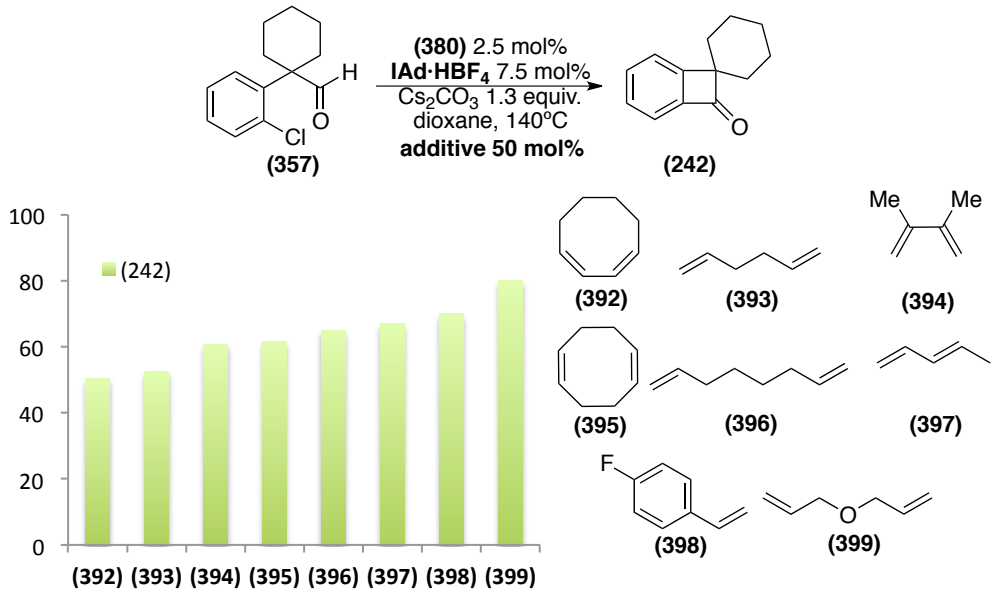
[a] Aryl chloride (0.25 mmol), **(380)** (2.5 mol%), **IAd·HBF₄** (7.5 mol%), Cs_2CO_3 (1.30 equiv.), solvent (0.50 M) at 140 ºC. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.

Although we got decent yields of the corresponding benzocyclobutenone, we decided to optimize the reaction further. It is known that the use of certain additives could be beneficial for stabilizing the transient 12 electron species "NHC-Pd(0)".[212] Thus, we decided to try different dienes as additives[212] aiming at confering stability to the *in situ* formed "IAd-Pd(0)" catalytic species. As shown in

[212] For the use of dienes to stabilize Pd(0) species see: Krause, J.; Cestaric, G.; Haack, k. –J.; Seevogel, K.; Storm, W.; Pörschke, K. –R. *J. Am. Chem. Soc.* **1999**, 121, 9807.

Table 24, this was indeed the case. We observed a significant enhancement toward **(242)** when using 50 mol% diene additives **(392)-(399)**. Among them, the use of allyl ether **(399)** as additive was particularly important, obtaining the corresponding benzocyclobutenone **(242)** in a 80% yield.

Table 24 Screening of additives.[a],[b]



[a] Aryl chloride (0.25 mmol), **(380)** (2.5 mol%), **IAd·HBF4** (7.5 mol%), Cs_2CO_3 (1.30 equiv.), solvent (0.50 M) and additive (0.5) equiv.) at 140 ºC. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.

Overall, we believe that the use of allyl ether as additive stabilizes the resting state of the catalyst by avoiding decomposition pathways, thus forming 16 electron species as shown in Figure 4.10. Most likely, the use of allyl ether makes a catalytic cycle based upon **(242)** much more robust than without such additive.

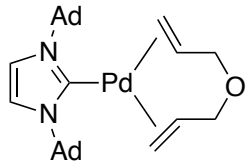


Figure 4.10

4.3.1.2 Synthesis of starting aldehydes.

After establishing the optimized reaction conditions, we set out to explore the scope of this reaction by preparing a wide variety of α-aryl aldehydes possessing a chloride in *ortho*-position.[213] As for Chapter 2, the general route for accessing the corresponding α-aryl aldehydes involved an initial alkylation of the *ortho*-chloro phenylacetonitrile using NaHMDS with the proper electrophile followed by treatment with DIBALH (Figure 4.11). A series of substrates of the type **(401)** posessing different substitution in either α-position or in the aromatic ring could be prepared in high overall yields from commercially available reagents.[214]

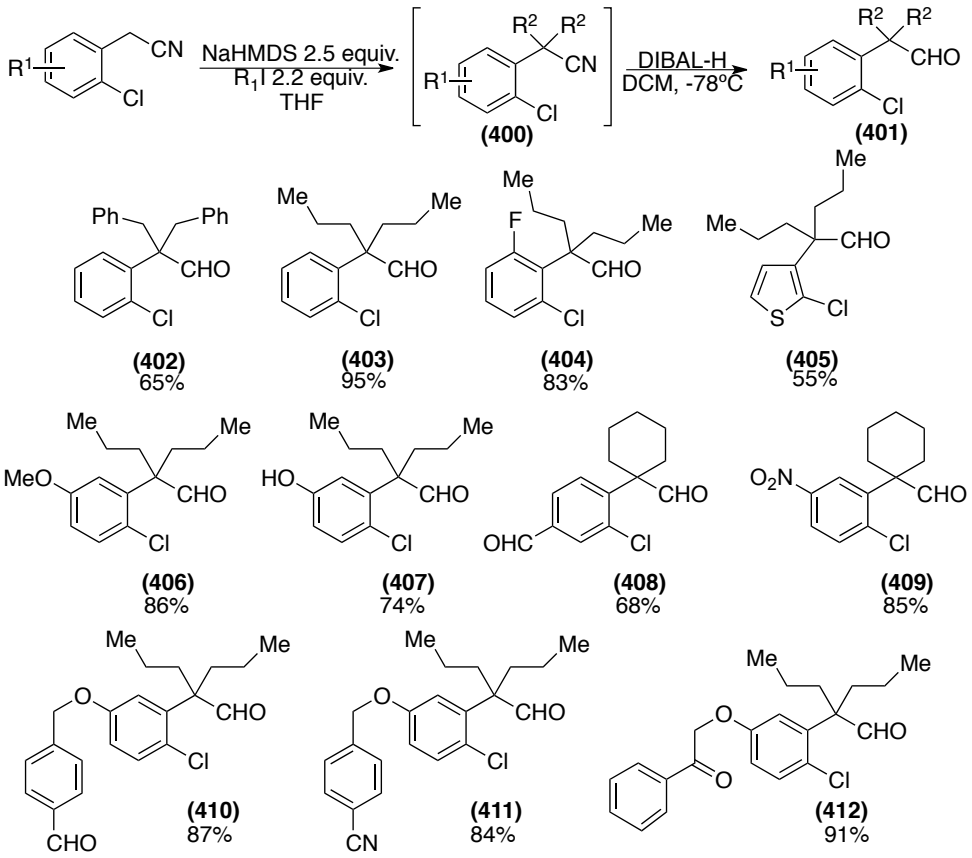


Figure 4.11

[213] The scope of the reaction was performed in collaboration with Álvaro Gutiérrez-Bonet.
[214] All aldehydes were prepared following methodologies described in Chapter 2.

Alternatively, monoalkylation of the corresponding phenylacetonitrile derivative yield compounds of the type **(413)** followed by treatment with NaHMDS and the second electrophile to yield type compounds **(414)** and a final reduction with DIBALH provided the corresponding α-aryl aldehydes **(415)**.

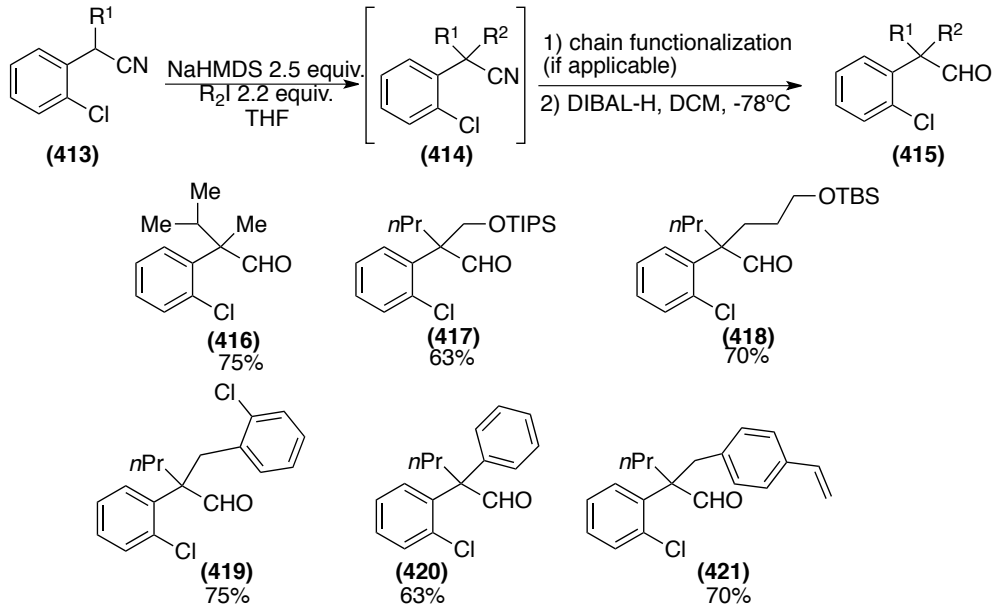


Figure 4.12[215]

In some cases, the corresponding phenylacetonitrile was not commercially available. In these cases the preparation of the corresponding 2-chloro-phenylacetonitrile derivative was achieved in an easily-scalable two-step procedure. The sequence started *via* radical bromination of the benzyl derivative followed by nucleophilic displacement of the bromine atom by NaCN in DMF as the solvent. An example is shown in Figure 4.13 in which the commercially available 1-chloro-3-methoxy-2-methylbenzene **(422)** is transformed into 2-(2-chloro-6-methoxyphenyl)acetonitrile **(424)** in two steps in good overall yield.

[215] Overall yield for the second alkylation and reduction steps.

Subsequently, this phenylacetonitrile derivative was converted into the corresponding aldehyde **(425)** following general procedure of alkylation/reduction used in Chapter 2.

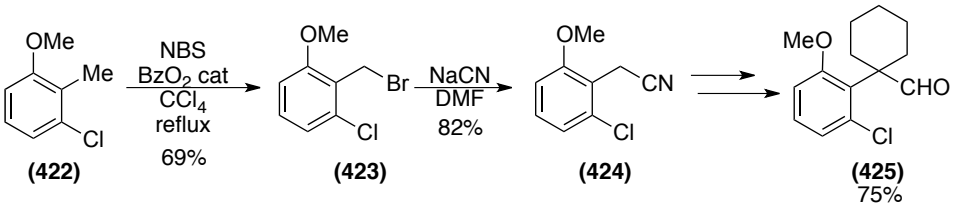


Figure 4.13

Meta-substituted *o*-chloro-phenylacetonitrile **(427)** was prepared from commercially available 4-bromo-2-chloro-1-methylbenzene **(426)** in three steps in high yield (Figure 4.13). Then, the introduction of a morpholine-backbone was accomplished *via* Pd-catalyzed C-N bond-formation followed by reduction of the nitrile motif in the presence of DIBALH at low temperatures to achieve aldehyde **(428)** in good yield (Figure 4.14-top). Similarly, pyrazole motif was introduced to yied aldehyde **(429)** in moderated yield (Figure 4.14-bottom).[216]

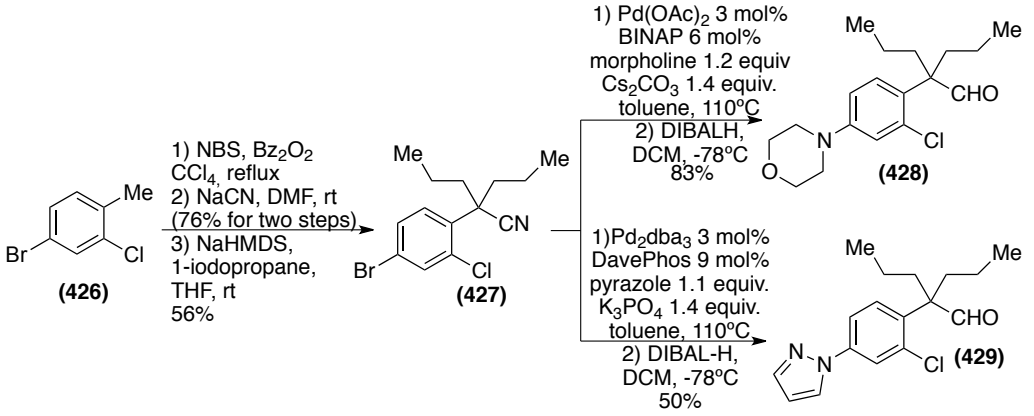


Figure 4.14

[216] Charles, M. D.; Schultz, P.; Buchwald, S. L., *Org. Lett.*, **2005**, *7*, 3965.

We also prepared a series of α-aryl aldehydes with different substituents in *para* position to the arylbromide unit. The sequence commenced with the aldehyde **(407)**, subsequently, derivatization of the phenol as triflate followed by Suzuki-Miyaura cross-coupling reaction with differently substituted boronic acids in the presence of PCy_3 as ligand[217] allowed for the formation of aldehydes of the type **(430)** from moderated to good yields, (Figure 4.15).

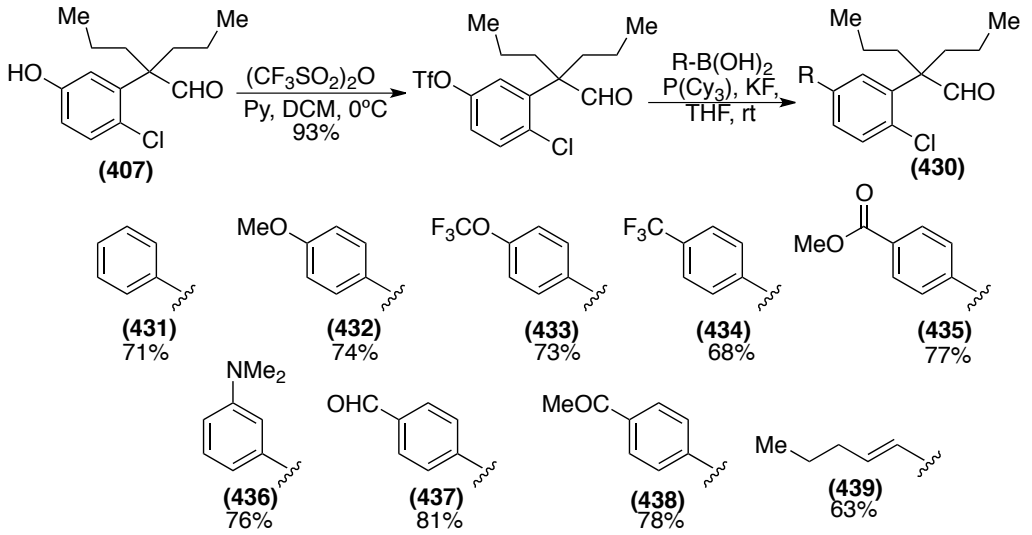


Figure 4.15

We also synthesized substrate **(440)** in two steps from commercially available 2-chloroaniline via *N*-methylation by treatment with *n*BuLi and MeI followed by *N*-formilation in moderated yield (Figure 4.16).

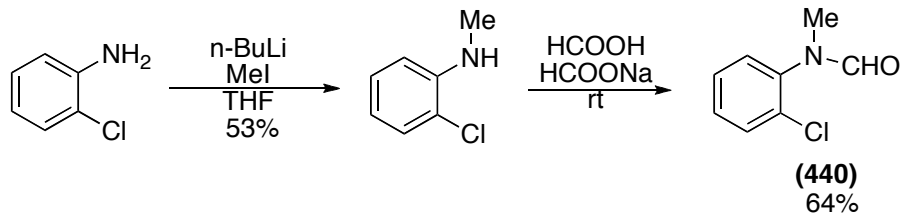


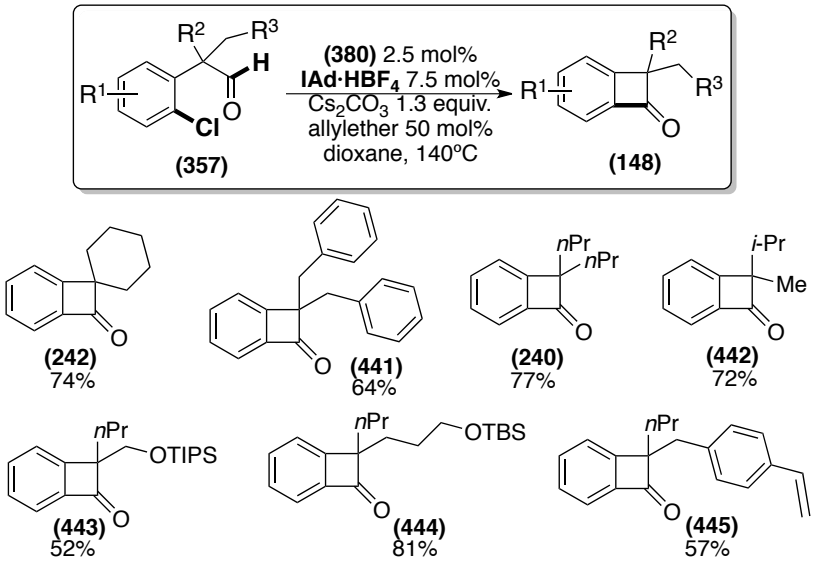
Figure 4.16

[217] Littke, A. F.; Dai, C. D.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, 122, 4020.

4.3.1.3 Scope of the reaction for the synthesis of benzocyclobutenones.

With substantial amounts of differently substituted α-aryl aldehydes, we focused our attention on exploring the preparative scope for preparing benzocyclobutenones. As shown in Table 25, the presence of both linear and cyclic chains in α-position to the aldehyde motif did not have a significant effect on the reaction. Thus, **(242)** and **(240)** were obtained with 74% and 77% yield, respectively. It is worth mentioning that, **(441)** a compound that could not be obtained from the intramolecular reaction utilizing the corresponding aryl bromide (see Chapter 2), is now within reach with this new catalytic system that employs aryl chlorides as substrates. α-aryl aldehydes possessing non-symetrical groups in -position were also tolerated, obtaining the corresponding benzocyclobutenones **(442)-(445)** in good to excellent yields. Notably, silylethers **(443)** and **(444)** as well as alkene groups in **(445)** did not have a negative impact in productive formation of the benzocyclobutenone motif.

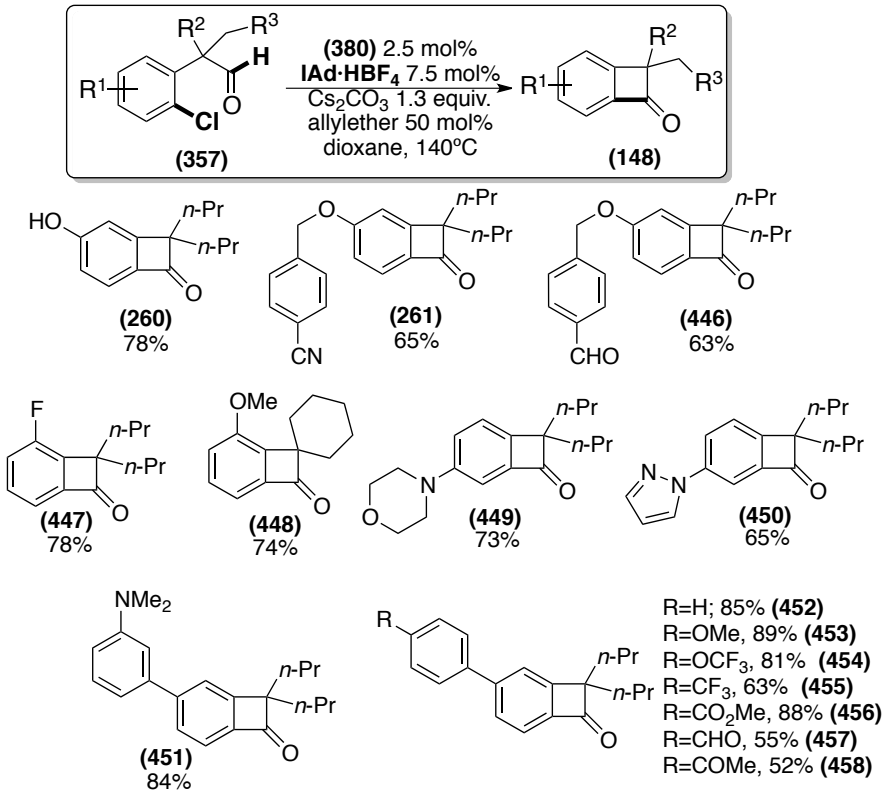
Table 25 Scope of benzocyclobutenones.[a]



[a] Aryl chloride (0.25 mmol), **(380)** (2.5 mol%), **IAd·HBF4** (7.5 mol%), Cs_2CO_3 (1.30 equiv.), solvent (0.50 M) and allyl ether (0.5 equiv.) at 140 ºC. Isolated yields, average of two runs

Next, we decided to see the influence of the substitution patterns on the aromatic moiety (Table 26). As shown for **(447)** and **(448)**, *ortho*-substitution did not hinder the reaction at all. Likewise, even unprotected alcohols **(260)** could be coupled in good yields as well; in this case, 2 equivalents of base were needed due to the acidity of the phenolic OH bond. The functional group tolerance was nicely illustrated by the fact that esters **(456)**, aldehydes **(446)** and **(457)**, ketones **(458)**, nitriles **(261)**, amines **(449)** and **(451)**, or heterocycles **(450)** were perfectly accommodated. The successful preparation of **(450)** indicates that the Pd catalytic species were not deactivated by the presence of strong nitrogen donors. In line with the same notion, no competing intermolecular acylation events were detected in the presence of other aldehydic C-H bonds, thus selectively obtaining **(446)** and **(457).**

Table 26 Scope of benzocyclobutenones.[a]



[a] Aryl chloride (0.25 mmol), **(380)** (2.5 mol%), **IAd·HBF$_4$** (7.5 mol%), Cs_2CO_3 (1.30 equiv.), solvent (0.50 M) and allyl ether (0.5 equiv.) at 140 ºC. Isolated yields, average of two runs

The proven flexibility of this method suggested that our intramolecular C-H acylation event should be applicable to site-selectivity approaches.[218] Gratifyingly, substrates possessing multiple C-H or C-Cl reactive sites could be equally employed, affording **(459)** and **(461)** exclusively (Figure 4.17); importantly, not even traces of **(460)** *via* intramolecular C-H arylation[219] or **(462)** were observed by NMR spectroscopy of the crude material.[220] These findings challenge the general perception that the preparation of strained rings is generally lower yielding than standard routes to thermodynamically more stable medium-sized rings.

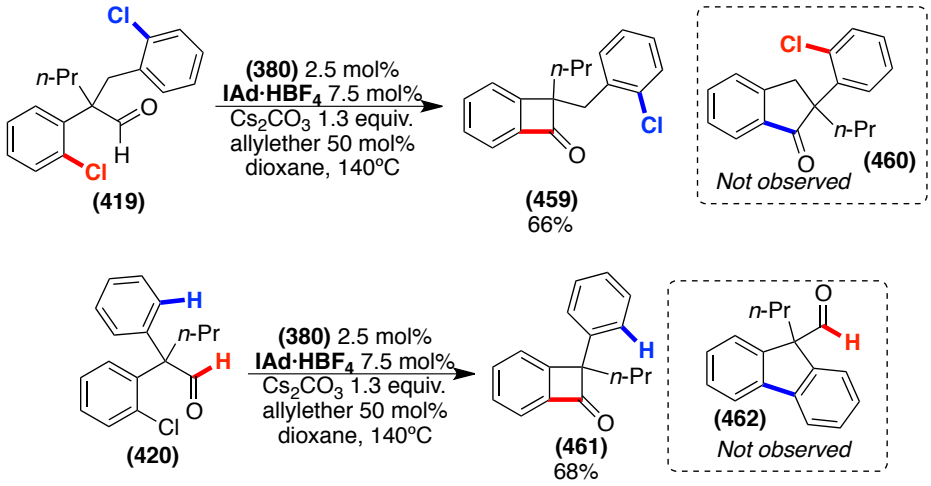


Figure 4.17

Even more important is the fact that this method allows, for the first time, the preparation of α-monosubstituted benzocyclobutenones such **(465)** when using α-silylated aryl aldehydes as precursors. In this case, immediate treatment of the crude C-H bond-functionalization reaction with TBAF for 2h gave the

[218] For a review on site-selectivity in C-H bond-functionalization: Neufeldt, S. R.; Sanford, M. S. *Acc. Chem. Res.* **2012**, *45, 936.*

[219] For selected examples of C-H intramolecular arylation with aryl chlorides, see: (a) Lafrance, M.; Lapointe, D.; Fagnou, K. *Tetrahedron* **2008**, *64*, 6015. (b) Campeau, L. –C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581

[220] Traces amounts of dechlorinated **58a** were observed in the crude reaction mixture by GC-MS.

monosubstituted BCB product in excellent overall yield (Figure 4.18). The formation of this product is particularly noteworthy because under conditions developed in Chapter 2 similar substrates could not be coupled.

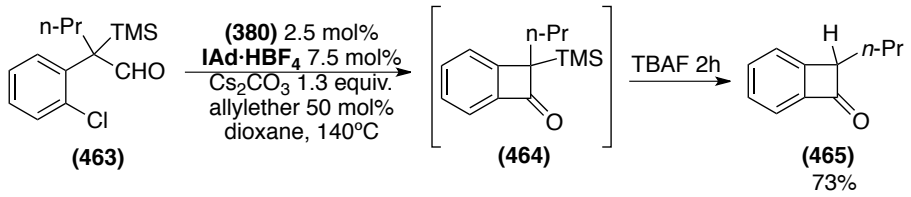


Figure 4.18

In order to shed light into the reaction mechanism, we decided to gather indirect evidence via isotope labeling, Figure 4.19. We prepared compounds **(403)** and **(466)** by a similar route to the one depicted in Chapter 2. We observed a k_H/k_D=0.93 when comparing the initial rates of **(403)** and **(466)**, suggesting that C-H bond-cleavage is not involved in the rate-determining step of the reaction. Such assumption is rather intriguing since C-H bond-functionalization was found to be indeed rate-determining when utilizing aryl bromides as substrates (see chapter 2).

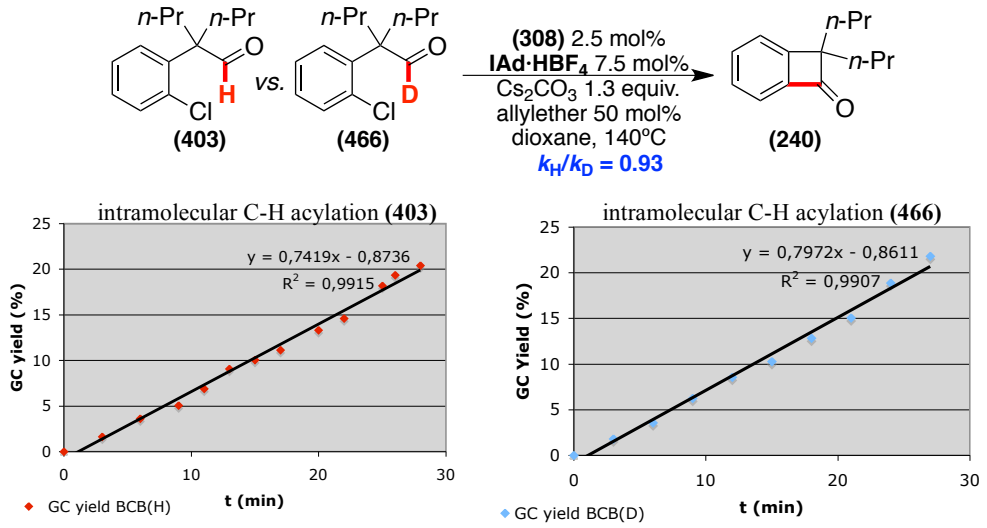


Figure 4.19

4.3.2 Mechanistic switch in Pd-catalyzed intramolecular acylation of aryl chlorides

4.3.2.1 Screening of the reaction conditions for synthesis of styrenes.

Encouraged by the selectivity toward benzocyclobutenones in a catalytic protocol based upon **IAd·HBF4**, we decided to explore whether the selectivity switch to styrene derivatives would also be general when utilizing aryl chlorides as substrates. As highlighted in Section 4.1, we observed high conversions toward styrene **(307)** with **IPr·HCl** ; however, the reaction was not 100% selective and non-neglictible amounts of benzocyclobutenone **(242)** were detected in the crude reaction mixture (1:17, **242:307**). Interestingly, we found that the use of related **IMes·HCl** provided the best selectivity toward **307** (1:99, **242:307**) but low conversions were unfortunately achieved (40%), Figure 4.20.

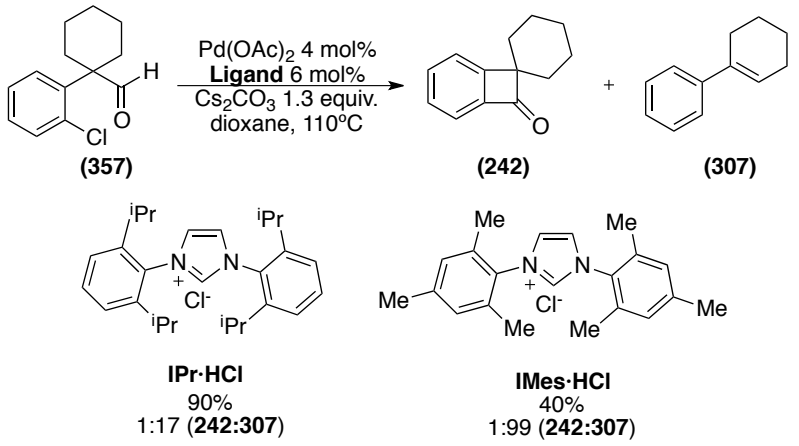
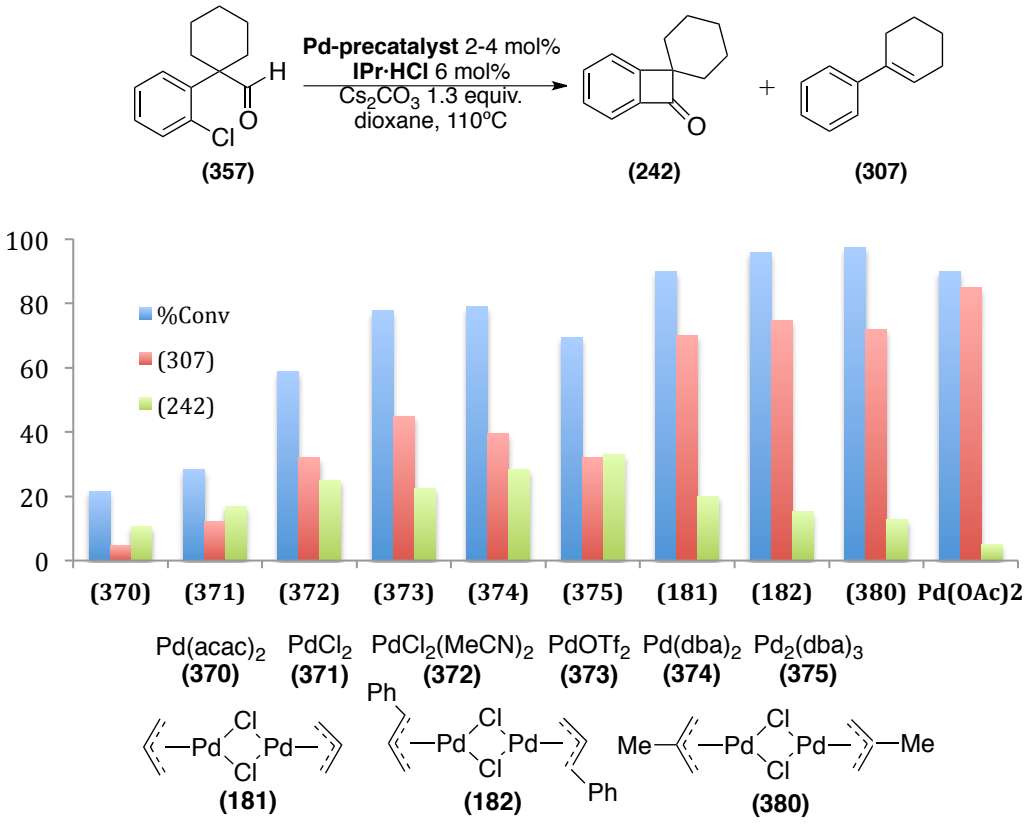


Figure 4.20

Next, we decided to explore whether other Pd precatalysts could give us better results for either a system empoying **IPr·HCl** or **IMes·HCl**, respectively. As shown

in Table 27, the use of **IPr·HCl** in combination with different Pd precatalysts gave good conversions; once again, however, the selectivity was highly compromised, observing in all cases mixtures of both **(242)** and **(307)**. In the best scenario, 85% of **(307)** and 5% of **(242)** (17:1) could be obtained when using $Pd(OAc)_2$ as precatalyst.

Table 27 Screening of Pd-precatalyst.[a],[b]

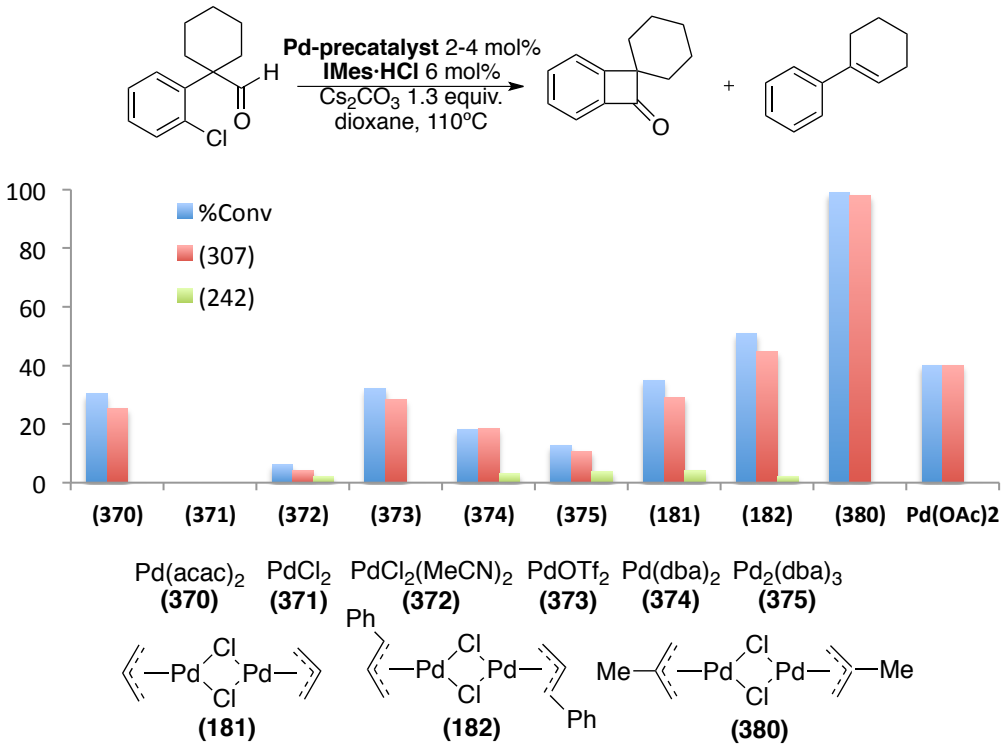


[a] Aryl chloride (0.25 mmol), Pd-precatalyst (2-4 mol%), **IPr·HCl** (6 mol%), Cs_2CO_3 (1.30 equiv.), solvent (0.50 M) at 110 ºC. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.

In sharp contrast, the nature of the Pd precatalyst had a profound impact on both yield and selectivity when using **IMes·HCl** as the catalyst, Table 4.28. For instance Pd-precatalysts **(181), (182), (370)**, **(372)** and **(373)** were higly selctive for **(307)** but much less reactive than when using **IPr·HCl** as the ligand in combination with $Pd(OAc)_2$. Remarkably, the use of **(380)** allowed us to reach full

conversion and exquisite selectivity (99% yield). Although further tests would have been necessary, apparently the substitution in the central atom of the allylic moiety of precatalyst **(380)** is the critical factor for obtaining high yields. This observation was corroborated by the fact that an otherwise similar precatalyst posessing the methyl group in the terminal position gave lower conversion to products. We tentatively attribute such observation to the ease for generating the corresponding monoligated **IMes**-Pd(0) species by *in situ* reduction of the corresponding Pd(II) precursor.

Table 28 Screening of Pd-precatalyst.. [a],[b]

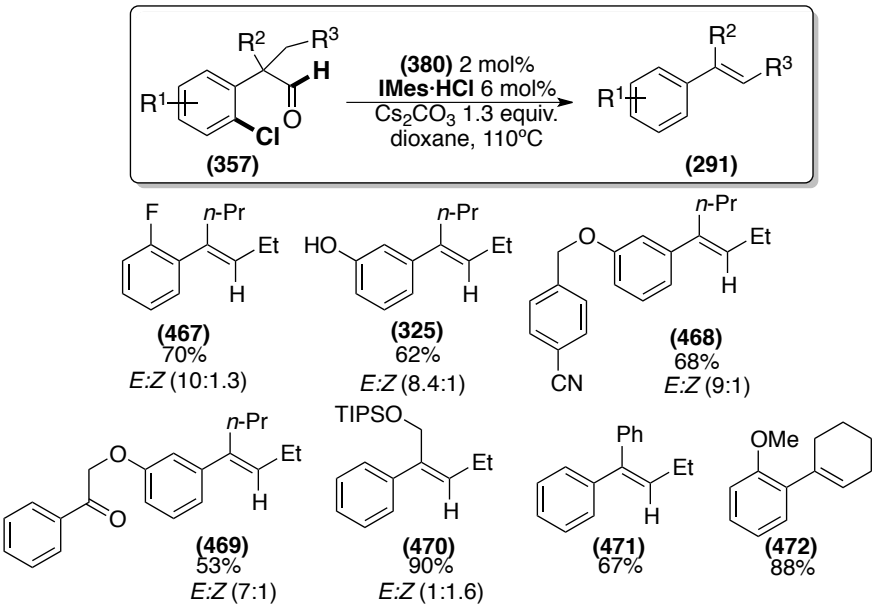


[a] Aryl chloride (0.25 mmol), Pd-precatalyst (2-4 mol%), **IMes·HCl** (6 mol%), Cs_2CO_3 (1.30 equiv.), solvent (0.50 M) at 110 ºC. [b] Conversions and yields were determined by GC analysis using dodecane as internal standard.

Having optimized the reaction for the formation of styrene derivatives from the corresponding α-aryl aldehydes possessing aryl chlorides in their structures, we went on exploring the scope of this reaction. As shown in Figure 4.28, total

regiocontrol and diastereoselectivities up to 10:1.3 were achieved. Notably, the presence of free alcohols **49c**, nitriles **71c**, ketones **72c** and silyl ethers **56c** was tolerated, delivering the final styrene derivatives in high yields.

Table 29 Synthesis of α,β-substituted styrenes. [a],[b]



[a] Aryl chloride (0.5 mmol), **(380)** (2 mol%), **IMes·HCl** (6 mol%), Cs_2CO_3 (1.30 equiv.), solvent (0.50 M) at 110 ºC. Isolated yields, average of two runs

It was also illustrative the deuterium labeling experiment shown in Figure 4.21. Under protocol based upon **IMes·HCl** as the ligand, we observed that deuterium atom in **(473)** was totally transferred to the aromatic motif in **(474)**. Thus, we believe that a similar mechanism as for the coupling of aryl bromides (see chapter 2 and 3) is operating with **IMes·HCl** as the supporting ligand.

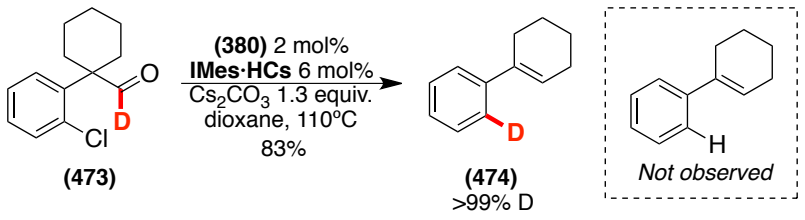


Figure 4.21

4.4

Conclusions

- We have developed the first intramolecular acylation via C-H bond-functionalization in route to benzocyclobutenones derivatives utilizing aryl chlorides as substrates.

- The use of *N*-heterocyclic carbenes as well as diene additives was critical for obtaining good conversions and selectivities toward benzocyclobutenones or styrene derivatives.

- The selectivity is completely controlled by the nature of the *N*-heterocyclic carbene, while the use of **IAd·HBF$_4$** resulted in the exclusive formation of benzocyclobutenones, the use of **IMes·HCl** results in a switch of selectivity, thus forming the corresponding styrene derivative (Figure 4.22).

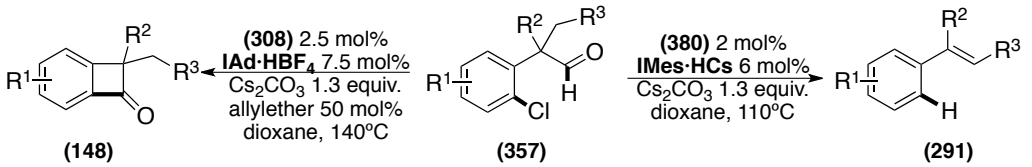
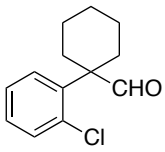


Figure 4.22

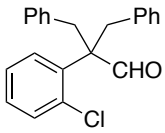
4.5

Experimental section

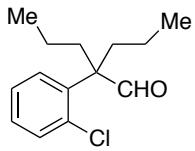
4.5.1 Synthesis of the starting materials



1-(2-chlorophenyl)cyclohexanecarbaldehyde (357). Following general procedure A, Column chromatography: silica gel, hexanes:EtOAc 9:1. (92% overall yield). 1H NMR (400 MHz, $CDCl_3$) δ 9.83 (s, 1H), 7.50 (dd, J = 7.9, 1.7 Hz, 1H), 7.38 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.31 (td, *J* = 7.6, 1.6 Hz, 1H), 7.26–7.21 (m, 1H), 2.38–2.26 (m, 2H), 2.00–1.89 (m, 2H), 1.79–1.60 (m, 5H), 1.49–1.36 (m, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.9, 140.7, 133.5, 131.2, 128.9, 128.6, 127.0, 53.9, 31.2, 25.5, 22.4 ppm. IR (neat, cm^{-1}): 2931, 2857, 1722, 1469, 1450, 1067, 1033, 753, 734, 705, 459. HRMS calcd for ($C_{13}H_{15}ClO$+H): 223.0890, found 223.0890

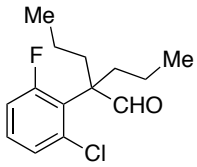


2-benzyl-2-(2-chlorophenyl)-3-phenylpropanal (402). Column chromatography: silica gel, hexanes:EtOAc 95:5. Yellow solid (mp = 97ºC). (65% overall yield) ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.93 (s, 1H), 7.46 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.33–7.24 (m, 1H), 7.24–7.09 (m, 8H), 7.01–6.88 (m, 3H), 3.41 (d, *J* = 2.9 Hz, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.3, 135.8, 131.1, 130.8, 129.1, 128.0, 126.6, 126.5, 58.8, 40.2 ppm. IR (neat, cm^{-1}): 2821, 1717, 1469, 1060, 1033, 768, 699, 528. HRMS calcd for ($C_{22}H_{19}ClO$+Na): 357.1022, found 357.1007.

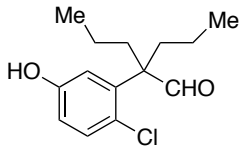


2-(2-chlorophenyl)-2-propylpentanal (403). Column chromatography: silica gel, hexanes:EtOAc 9:1. (95% overall yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (s, 1H), 7.41–7.34 (m, 2H), 7.31 (td, *J* = 7.6, 1.6 Hz, 1H), 7.27–7.22 (m, 1H), 2.06–1.88

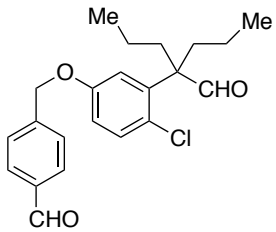
(m, 4H), 1.29–1.13 (m, 2H), 1.13–0.97 (m, 2H), 0.89 (t, J = 7.2 Hz, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.9, 138.4, 133.8, 131.1, 129.7, 128.6, 126.8, 57.5, 34.5, 16.8, 14.6 ppm. IR (neat, cm^{-1}): 2958, 2872, 1721, 1467, 1047, 753, 727. HRMS calcd for ($C_{14}H_{18}ClO$+H): 239.1203, found 239.1196.



2-(2-chloro-6-fluorophenyl)-2-propylpentanal (404). Column chromatography: silica gel, hexanes:EtOAc 95:5. Yellow pale oil. (83% overall yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.92 (d, $^5J_{H\text{-}F}$ = 4.9 Hz, 1H), 7.26–7.19 (m, 2H), 7.09–6.97 (m, 1H), 2.23–2.12 (m, 2H), 1.96–1.82 (m, 2H), 1.37–1.13 (m, 4H), 0.89 (t, J = 7.3 Hz, 6H).^{13}C NMR (126 MHz, $CDCl_3$) δ 202.2, 162.5 (d, $^1J_{C\text{-}F}$ = 249.9 Hz), 134.8 (d, $^3J_{C\text{-}F}$ = 7.6 Hz), 129.0 (d, $^3J_{C\text{-}F}$ = 11.0 Hz), 127.5 (d, $^4J_{C\text{-}F}$ = 3.0 Hz), 126.4 (d, $^2J_{C\text{-}F}$ = 14.7 Hz), 115.6 (d, $^2J_{C\text{-}F}$ = 26.9 Hz), 58.3 (d, $^3J_{C\text{-}F}$ = 4.2 Hz), 37.3, 17.7, 14.6 ppm. IR (neat, cm^{-1}): 3433, 2960, 2872, 1723, 1598, 1565, 1438, 1233, 878, 783 ppm. HRMS calcd for ($C_{14}H_{18}ClOF$+H): 257.1108, found 257,1108.

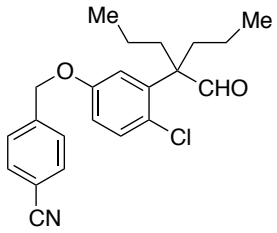


2-(2-chloro-5-hydroxyphenyl)-2-propylpentanal (407). Column chromatography: silica gel, hexanes:EtOAc 2:1. White solid (mp=83ºC). (74% overall yield) ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.75 (s, 1H), 7.34–7.12 (m, 1H), 6.89 (d, J = 2.8 Hz, 1H), 6.75 (dd, J = 8.6, 2.8 Hz, 1H), 5.39 (s, 1H), 1.96 (pd, J = 14.0, 5.0 Hz, 4H), 1.37–0.96 (m, 4H), 0.90 (t, J = 7.2 Hz, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.4, 154.5, 139.8, 131.8, 124.9, 117.0, 115.6, 57.4, 34.3, 16.7, 14.6 ppm. IR (neat, cm^{-1}): 3341, 2960, 1705, 1574, 1464, 1281, 1227, 1181, 988, 811, 745, 649, 476. HRMS calcd for ($C_{14}H_{19}O_2Cl$+Na): 277.0971, found 277.0984.

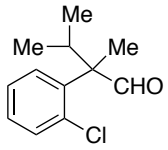


4-((4-chloro-3-(4-formylheptan-4-yl)phenoxy) methyl)benzaldehyde (410). Column chromatography: silica gel, hexanes:EtOAc 2:1. Yellow oil. (87% overall yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.05 (s, 1H), 9.74 (s,

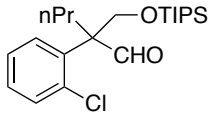
1H), 8.02–7.88 (m, 2H), 7.62 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.7 Hz, 1H), 6.97 (d, *J* = 3.0 Hz, 1H), 6.85 (dd, *J* = 8.7, 3.0 Hz, 1H), 5.17 (s, 2H), 2.08–1.80 (m, 4H), 1.27–1.10 (m, 2H), 1.10–0.94 (m, 2H), 0.88 (t, *J* = 7.2 Hz, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.6, 191.7, 157.0, 143.3, 139.9, 136.2, 131.8, 130.1, 127.6, 117.5, 114.0, 69.7, 57.5, 34.3, 16.7, 14.7 ppm. IR (neat, cm^{-1}): 2952, 2870, 1716, 1688, 1592, 1678, 1481, 1456, 1376, 1298, 1238, 1031, 985, 808, 781 515, HRMS calcd for ($C_{22}H_{25}ClO_3$+Na): 395.1390, *found* 395.1398.



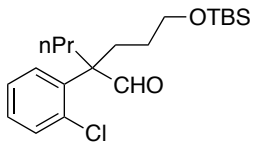
4-((4-chloro-3-(4-formylheptan-4-yl)phenoxy) methyl)benzaldehyde (411). Column chromatography: silica gel, hexanes:EtOAc 2:1. White solid (mp=102.7ºC). (84% overall yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (s, 1H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.62–7.53 (m, 2H), 7.35–7.21 (m, 1H), 6.97 (d, *J* = 3.0 Hz, 1H), 6.85 (dd, *J* = 8.7, 3.0 Hz, 1H), 5.15 (s, 2H), 2.05–1.82 (m, 4H), 1.24–1.13 (m, 2H), 1.11–0.99 (m, 2H), 0.90 (t, *J* = 7.2 Hz, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.5, 156.8, 141.8, 140.0, 132.5, 131.8, 127.6, 125.8, 118.5, 117.5, 113.9, 112.0, 69.3, 57.5, 34.3, 16.7, 14.6 ppm. IR (neat, cm^{-1}): 2955, 2870, 2223, 1716, 1592, 1455, 1295, 1234, 1181, 1116, 1034, 845, 809, 666, 546, 481. HRMS calcd for ($C_{22}H_{24}ClNO_2$+H): 370.1574, *found* 370.1581.



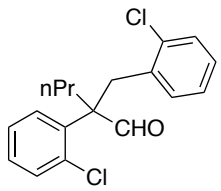
2-(2-chlorophenyl)-2,3-dimethylbutanal (416). Column chromatography: silica gel, hexanes:EtOAc 12:1. Colorless oil; (75% overall yield) ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.03 (s, 1H), 7.48-7.42 (m, 2H), 7.40 - 7.33 (m, 1H), 7.31 (d, *J* = 7.5 Hz, 1H), 2.94 (hept, *J* = 6.9 Hz, 1H), 1.45 (s, 3H), 1.17 (d, *J* = 6.9 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.5, 140.2, 133.3, 131.1, 129.7, 128.6, 126.9, 56.8, 30.8, 18.6, 18.2, 17.0 ppm. IR (neat, cm^{-1}): 2967, 2877, 2816, 1720, 1469, 1430, 1043, 754, 471. HRMS *calcd* for ($C_{12}H_{15}ClO$+H): 211.0890, *found* 211.0893.



2-(2-chlorophenyl)-2-((triisopropylsilyloxy)methyl) pentanal (417). Column chromatography: silica gel, hexanes:EtOAC 95:5. Colorless oil; (63% overall yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.87 (s, 1H), 7.38 (td, *J* = 7.7, 1.8 Hz, 2H), 7.30 (td, *J* = 7.6, 1.8 Hz, 1H), 7.27 - 7.23 (m, 1H), 4.37 (d, *J* = 9.7 Hz, 1H), 4.22 (d, *J* = 9.7 Hz, 1H), 2.22 (ddd, *J* = 13.9, 12.4, 4.8 Hz, 1H), 2.05 (ddd, *J* = 13.9, 12.3, 4.5 Hz, 1H), 1.28 - 0.95 (m, 12H), 0.91 (t, *J* = 7.2 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.4, 137.3, 133.7, 130.9, 130.5, 128.8, 126.8, 65.4, 59.6, 32.8, 18.0, 18.0, 17.2, 14.8, 12.0 ppm. IR (neat, cm^{-1}): 2962, 2866, 1721, 1465, 1102, 1043, 881, 747, 456. HRMS *calcd* for ($C_{21}H_{35}ClO_2Si$+Na): 405.1993, *found* 405.1988.

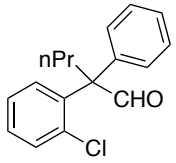


5-(*tert*-butyldimethylsilyloxy)-2-(2-chlorophenyl)-2-propylpentanal (418). Column chromatography: silica gel, hexanes:EtOAC 9:1. Colorless oil; (70% overall yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.78 (s, 1H), 7.45 - 7.36 (m, 2H), 7.33 (dd, *J* = 7.3, 1.7 Hz, 1H), 7.30 - 7.25 (m, 2H), 3.56 (t, *J* = 6.2 Hz, 2H), 2.17 - 1.88 (m, 4H), 1.51 - 1.36 (m, 1H), 1.32 - 1.16 (m, 2H), 1.14 - 1.00 (m, 1H), 0.94 - 0.83 (m, 12H), 0.03 (s, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.0, 138.4, 133.9, 131.3, 130.0, 128.8, 127.0, 63.1, 57.2, 34.6, 28.6, 27.0, 26.1, 18.4, 16.9, 14.8, -5.2 ppm. IR (neat, cm^{-1}): 2956, 2930, 2857, 1472, 1254, 1099, 1040, 832, 774. HRMS *calcd* for ($C_{20}H_{33}ClO_2Si$+H): 369.2017, *found* 369.2005.

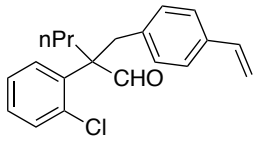


2-(2-chlorobenzyl)-2-(2-chlorophenyl)ventanal (419). Column chromatography: silica gel, hexanes:EtOAc 12:1. Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.06 (s, 1H), 7.66 (dd, *J* = 6.9, 2.4 Hz, 1H), 7.22 (m, 3H), 7.08 (td, *J* = 7.5, 1.8 Hz, 1H), 6.95 (m, 2H), 6.51 (dd, *J* = 7.5, 1.5 Hz, 1H), 3.71 (d, *J* = 13.8 Hz, 1H), 3.51 (d, *J* = 13.8 Hz, 1H), 1.98 (m, 2H), 1.34 (m, 2H), 0.91 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.7, 138.6, 135.5, 134.6, 134.5, 133.7, 132.8, 130.9, 129.5,

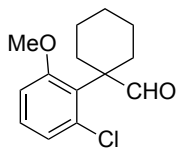
129.2, 127.8, 127.2, 125.8, 59.4, 36.7, 35.3, 17.1, 14.8 ppm. IR (neat, cm^{-1}): 3054, 2931, 1719, 1672, 1489, 1351, 1278, 1160, 981, 829.



2-(2-chlorophenyl)-2-phenylpentanal (420). Column chromatogra-phy: silica gel, hexanes:EtOAc 10:1. Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.07 (s, 1H), 7.62 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.28 (m, 8H), 2.49 (m, 2H), 1.13 (m, 2H), 0.98 (t, *J* = 6.9 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.6, 140.9, 138.9, 135.0, 133.5, 131.9, 128.9, 128.6, 128.4, 127.1, 127.0, 64.4, 34.6, 18.4, 14.5 ppm. IR (neat, cm^{-1}): 3090, 2941, 1727, 1632, 1503, 1395, 1312, 1184, 1096, 972, 809, 770. Anal Calcd for $C_{17}H_{17}ClO$: C, 74.86; H, 6.28. Found: C, 75.07; H, 6.15.

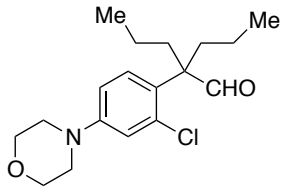


2-(2-chlorophenyl)-2-(4-vinylbenzyl)ventanal (421). Column chromatography: silica gel, hexanes:EtOAc 12:1. Colorless liquid; (70% overall yield) ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.99 (s, 1H), 7.67 (m, 1H), 7.21 (m, 2H), 7.14 (d, *J* = 8.1 Hz, 2H), 6.93 (m, 1H), 6.67 (d, *J* = 11.1 Hz, 1H), 6.59 (d, *J* = 8.1 Hz, 2H), 5.68 (d, *J* = 17.7 Hz, 1H), 5.18 (d, *J* = 17.7 Hz, 1H), 3.52 (d, *J* = 13.8 Hz, 1H), 3.32 (d, *J* = 13.8 Hz, 1H), 1.86 (t, *J* = 8.7 Hz, 2H), 1.37 (m, 2H), 0.92 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.1, 138.9, 136.5, 136.1, 135.6, 134.6, 131.0, 130.7, 129.2, 127.2, 125.5, 123.9, 113.3, 59.0, 37.8, 36.4, 16.9, 14.7 ppm. IR (neat, cm^{-1}): 3056, 2976, 2861, 1713, 1646, 1541, 1487, 1390, 1194, 978. HRMS calcd for ($C_{20}H_{21}ClO$+Na): 335.1179, found 335.1183.

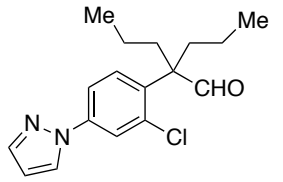


1-(2-chloro-6-methoxyphenyl)cyclohexanecarbaldehyde (425). Column chromatography: silica gel, hexanes:EtOAc 9:1. Colorless oil. (75% overall yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (s, 1H), 7.12 (t, *J* = 8.1 Hz, 1H), 7.04 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.82 (dd, *J* = 8.1, 1.4 Hz, 1H), 3.73 (s, 3H), 2.68 (d, *J* = 4.4 Hz, 2H), 2.03 (dd, *J* = 9.1, 7.7 Hz, 2H), 1.75–1.63 (m, 3H), 1.57–1.44 (m, 2H), 1.43–1.30 (m, 1H) ppm. ^{13}C NMR (101 MHz,

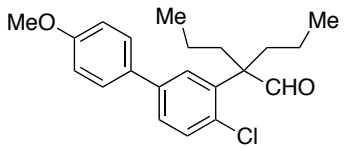
$CDCl_3$) δ ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.9, 157.9, 134.4, 131.3, 128.3, 126.2, 112.4, 56.6, 52.9, 28.5, 24.5, 22.5 ppm. IR (neat, cm^{-1}): 2920, 2853, 2708, 1718, 1693, 1585, 1565, 1448, 1425, 1246, 1010, 980, 951, 839, 732, 693. HRMS calcd for ($C_{14}H_{17}ClO_2$+H): 253.0995, *found* 253.0989.



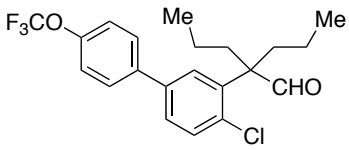
2-(2-chloro-4-morpholinophenyl)-2-propylpentanal (428). Column chromatography: silica gel, hexanes:EtOAc 9:1. Yellow solid (mp=90.7ºC). (83% overall yield) ^1H NMR (300 MHz, $CDCl_3$) δ 9.73 (s, 1H), 7.24 (d, *J* = 8.8 Hz, 1H), 6.90 (d, *J* = 2.7 Hz, 1H), 6.83 (dd, *J* = 8.8, 2.7 Hz, 1H), 3.9–3.78 (m, 4H), 3.25–3.08 (m, 4H), 2.07–1.83 (m, 4H), 1.26–0.99 (m, 4H), 0.89 (t, *J* = 7.1 Hz, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.4, 150.9, 134.5, 130.1, 128.8, 117.2, 113.4, 66.7, 56.8, 48.4, 34.5, 16.8, 14.7 ppm. IR (neat, cm^{-1}): 2955, 2870, 1719, 1602, 1494, 1447, 1382, 1234, 1118, 1039, 947, 815, 745, 648, 609, 514 ppm. HRMS calcd for ($C_{18}H_{26}ClNO_2$): 324.1730, found 324.1733.



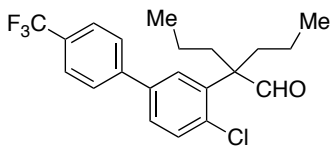
2-(2-chloro-4-(1*H*-pyrazol-1-yl)phenyl)-2-propylpentanal (429). Column chromatography: silica gel, hexanes:EtOAc 9:1. White solid (mp=77.5ºC); (50% overall yield). ^1H NMR (300 MHz, $CDCl_3$) δ 9.77 (s, 1H), 7.93 (d, *J* = 2.6 Hz, 1H), 7.79 (d, *J* = 2.4 Hz, 1H), 7.74 (d, *J* = 1.8 Hz, 1H), 7.65 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.44 (d, *J* = 8.7 Hz, 1H), 6.50 (t, *J* = 2.2, 2.2 Hz, 1H), 2.11–1.89 (m, 4H), 1.32–0.97 (m, 4H), 0.91 (t, *J* = 7.1 Hz, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.5, 141.6, 139.9, 136.3, 134.6, 130.6, 126.6, 121.4, 117.0, 108.2, 57.3, 34.5, 16.8, 14.6 ppm. IR (neat, cm^{-1}): 2956, 2870, 1749, 1603, 1476, 1449, 1377, 1260, 1228, 1121, 921, 896, 823, 557. HRMS calcd for ($C_{17}H_{21}ClN_2O$+Na): 327.1240, *found* 327.1248.



2-(4-chloro-4'-methoxy-[1,1'-biphenyl]-3-yl)-2-propylpentanal (432). Column chromatography: silica gel, hexanes:EtOAc 2:1. White solid (mp=67.5ºC). (74% overall yield) ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.81 (s, 1H), 7.50 (dd, *J* = 6.6, 2.1 Hz, 3H), 7.43 (s, 2H), 7.02 (d, *J* = 8.7 Hz, 2H), 3.88 (s, 3H), 2.17–1.88 (m, 4H), 1.35–1.19 (m, 2H), 1.17–1.02 (m, 2H), 0.92 (t, *J* = 7.1 Hz, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.9, 159.5, 139.6, 138.6, 132.7, 132.2, 131.4, 128.2, 128.1, 126.9, 114.4, 57.6, 55.4, 34.5, 16.9, 14.7 ppm. IR (neat, cm^{-1}): 2955, 2870, 1720, 1605, 1514, 1463, 1441, 1248, 1179, 1038, 817, 746, 487, 448. HRMS calcd for ($C_{21}H_{25}ClO_2$+Na): 367.1441, found 367.1433.

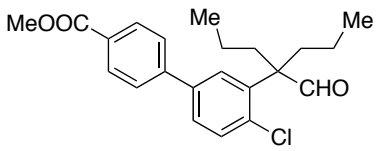


2-(4-chloro-4'-(trifluoromethoxy)-[1,1'-biphenyl]-3-yl)-2-propylpentanal (433). Column chromato-graphy: silica gel, hexanes:EtOAc 9:1. Yellow pale solid (mp=50.5ºC). (73% overall yield) ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.82 (s, 1H), 7.58 (d, *J* = 8.7 Hz, 2H), 7.54–7.40 (m, 3H), 7.34 (d, *J* = 8.1 Hz, 2H), 2.21–1.86 (m, 4H), 1.35–1.01 (m, 4H), 0.93 (t, *J* = 7.2 Hz, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.6, 149.0 (d, $^{3}J_{C\text{-}F}$ = 1.8 Hz), 139.1, 138.9, 138.7, 133.3, 131.6, 128.5, 127.3, 121.4, 120.5 (d, $^{1}J_{C\text{-}F}$ = 257.4 Hz), 57.6, 34.4, 16.9, 14.7 ppm. IR (neat, cm^{-1}): 2960, 2872, 1720, 1511, 1466, 1250, 1206, 1153, 1051, 1016, 922, 853, 809, 739, 739, 654. HRMS calcd for ($C_{21}H_{22}ClF_3O_2$+Na): 421.1158, found 421.1148.

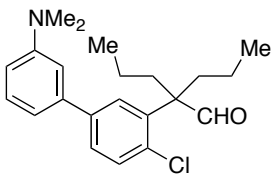


2-(4-chloro-4'-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-2-propylpentanal (434). Column chromatography: silica gel, hexanes:EtOAc 9:1. White solid (mp=74.6ºC). (68% overall yield) ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.82 (s, 1H), 7.71 (dd, *J* = 21.8, 8.3 Hz, 4H), 7.58–7.46 (m, 3H), 2.26–1.91 (m, 4H), 1.38–1.04 (m, 4H), 0.93 (t, *J* = 7.2 Hz, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.5, 143.7, 139.2, 138.6, 133.9, 131.7, 128.7, 127.4, 126.0, 124.1, 57.6,

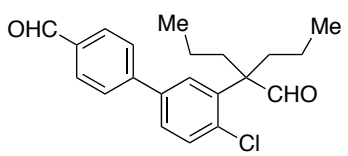
34.4, 16.9, 14.6 ppm. IR (neat, cm^{-1}): 2965, 2875, 1719, 1615, 1465, 1321, 1160, 1109, 1069, 1014, 844, 817, 744, 677, 625, 486. HRMS calcd for ($C_{21}H_{22}OClF_3$+H): 383.1390, *found* 383.1389.



Methyl 4'-chloro-3'-(4-formylheptan-4-yl)-[1,1'-biphenyl]-4-carboxylate (435). Column chro-matography: silica gel, hexanes:EtOAc 2:1. White solid (mp=101.8ºC). (77% overall yield) ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.8 (s, 1H), 8.23–8.06 (m, 2H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.59–7.53 (m, 1H), 7.49 (d, *J* = 1.3 Hz, 2H), 3.96 (s, 3H), 2.17–1.90 (m, 4H), 1.38–1.01 (m, 4H), 0.92 (t, *J* = 7.2 Hz, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.6, 166.8, 144.5, 139.1, 138.8, 133.8, 131.6, 130.3, 129.4, 128.6, 127.4, 127.1, 57.6, 52.2, 34.4, 16.9, 14.7 ppm. IR (neat, cm^{-1}): 2961, 2872, 1711, 1608, 1432, 1285, 1189, 1109, 1050, 1034, 1016, 973, 865, 830, 768, 653, 474. HRMS calcd for ($C_{22}H_{25}ClO_3$+Na): 395.1390, *found* 395.1402.

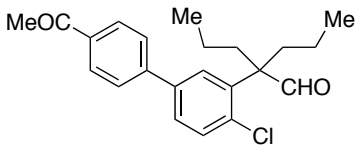


2-(4-chloro-3'-(dimethylamino)-[1,1'-biphenyl]-3-yl)-2-propylpentanal (436). Column chromatography: silica gel, hexanes:EtOAc 2:1. Yellow pale solid (113.5ºC). (76% overall yield) ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.83 (s, 1H), 7.55 (d, *J* = 1.9 Hz, 1H), 7.52–7.42 (m, 2H), 7.35 (t, *J* = 7.9, 7.9 Hz, 1H), 6.93–6.84 (m, 2H), 6.79 (ddd, *J* = 8.3, 2.7, 0.9 Hz, 1H), 3.03 (s, 6H), 2.04 (dd, *J* = 11.0, 5.9 Hz, 4H), 1.35–1.23 (m, 2H), 1.18–1.02 (m, 2H), 0.91 (t, *J* = 7.2 Hz, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.1, 151.0, 141.2, 141.1, 138.4, 132.6, 131.2, 129.6, 128.8, 127.4, 115.6, 111.9, 111.3, 57.6, 40.6, 34.7, 16.9, 14.7 ppm. IR (neat, cm^{-1}): 3130, 2957, 2871, 1722, 1600, 1498, 1465, 1354, 1215, 1141, 1040, 993, 822, 773, 696, 527. HRMS calcd for ($C_{22}H_{28}ClNO$+H): 358.1938, *found* 358.1925.

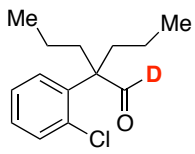


4'-chloro-3'-(4-formylheptan-4-yl)biphenyl-4-carbaldehyde (437). Column chromatography: silica gel, hexanes:EtOAc 2:1. Yellow solid

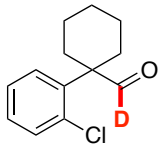
(mp=74.5ºC). (81% overall yield) ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.09 (s, 1H), 9.82 (s, 1H), 8.00 (d, *J* = 8.3 Hz, 2H), 7.73 (d, *J* = 8.2 Hz, 2H), 7.58 (s, 1H), 7.51 (d, *J* = 1.1 Hz, 2H), 2.13–1.97 (m, 4H), 1.32–1.20 (m, 2H), 1.19–1.04 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 6H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.5, 191.7, 146.0, 139.3, 138.6, 135.6, 134.1, 131.8, 130.4, 128.7, 127.7, 127.5, 57.6, 34.4, 16.9, 14.7 ppm. IR (neat, cm^{-1}): 2958, 2870, 1720, 1683, 1604, 1461, 1358, 1264, 1049, 960, 844, 739, 654, 617, 469. HRMS calcd for ($C_{21}H_{23}ClO_2$+H): 343.1465, *found* 343.1469.



2-(4-chloro-4'-ethanoylbiphenyl-3-yl)-2-propylpentanal (438). Column chromatography: silica gel, hexanes:EtOAc 9:1. White solid (mp=89.5ºC). (78% overall yield) ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.81 (s, 1H), 8.07 (d, *J* = 8.4 Hz, 2H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.57 (s, 1H), 7.50 (s, 2H), 2.66 (s, 3H), 2.17–1.92 (m, 4H), 1.34–1.21 (m, 2H), 1.21–1.04 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 6H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.6, 197.5, 144.6, 139.2, 138.7, 136.3, 133.9, 131.7, 129.1, 128.6, 127.4, 127.3, 57.6, 34.4, 26.7, 16.9, 14.7 ppm. IR (neat, cm^{-1}): 2957, 2870, 1720, 1683, 1604, 1462, 1377, 1264, 1049, 960, 813, 739, 617, 589, 469. HRMS calcd for ($C_{22}H_{25}ClO_2$+H): 357.1621, *found* 357.1607.



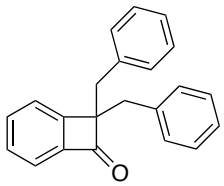
2-(2-chlorophenyl)-2-propylpentanal (466). Column chromato-graphy: silica gel, hexanes:EtOAc 9:1. Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 - 7.35 (m, 2H), 7.35 - 7.28 (m, 1H), 7.26 (dd, *J* = 7.5, 2.0 Hz, 1H), 2.10 - 1.88 (m, 4H), 1.32 - 1.14 (m, 2H), 1.13 - 0.98 (m, 2H), 0.89 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.7 (t, *J* = 26.8 Hz), 138.6, 133.9, 131.2, 129.8, 128.8, 126.9, 57.4 (t, *J* = 2.9 Hz), 34.7, 16.9, 14.8. IR (neat, cm^{-1}): 2959, 2873, 2064, 1714, 1467, 1041, 753. HRMS *calcd* for ($C_{14}H_{18}DClO$+H): 240.1265, *found* 240.1268. IR (neat, cm^{-1}): 2932, 2855, 2048, 1704, 1450, 1063, 774, 628, 514. HRMS *calcd* for ($C_{13}H_{14}DClO$+H): 224.0952, *found* 224.0954.



1-(2-chlorophenyl)cyclohexanecarbaldehyde (473). Column chromatography: silica gel, hexanes:EtOAc 9:1. Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.35 (td, *J* = 7.2, 1.6 Hz, 1H), 7.28 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.22 (td, *J* = 7.4, 1.6 Hz, 1H), 2.31 (dt, *J* = 13.3, 4.2 Hz, 2H), 1.93 (ddd, *J* = 13.3, 8.9, 3.4 Hz, 2H), 1.77 - 1.60 (m, 5H), 1.49 - 1.36 (m, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.7 (t, *J* = 26.7 Hz), 140.8, 133.5, 131.3, 129.0, 128.7, 127.2, 53.9 (t, *J* = 3.2 Hz), 31.3, 25.6, 22.5 ppm.

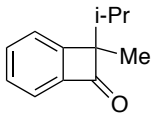
4.5.2 Pd-catalyzed intramolecular acylation of aryl chlorides.

General procedure F for the synthesis of benzocyclobutenones *via* Pd-catalyzed intramolecular acylation of aryl chlorides. An oven-dried screw-cap test tube containing a stirring bar was charged with **(357)** (4.9 mg, 2.5 mol%), **IAd·HBF$_4$** (21.2 mg, 10 mol%), Cs_2CO_3 (209 mg, 0.65 mmol) and the aryl chloride (0.50 mmol), if a solid. The test tube was evacuated and back-filled with dry argon (this sequence was repeated three times). The aryl chloride (if liquid) and dioxane (2 mL) were then added by syringe. The mixture was then placed in ultrasounds apparatus for 1 min and the mixture was then stirred in a pre-heated oil bath (140 ^{o}C) for 14 h. The mixture was then allowed to warm to room temperature, diluted with ethyl acetate (5 mL) and filtered through a Celite® plug, eluting with additional ethyl acetate (10 mL). The filtrate was concentrated and purified by column chromatography on silica gel (eluting with hexanes/ethyl acetate mixtures). Only new BCB are described (different to ones described in Chapter 2)

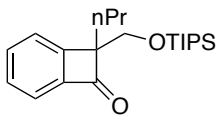


8,8-dibenzylbicyclo[4.2.0]octa-1,3,5-trien-7-one (441). Following general procedure 2-benzyl-2-(2-chlorophenyl)-3-phenylpropanal, (167 mg, 0.50 mmol) was used. Column chromatography: silica gel, hexanes. Yellow pale solid

(mp=89ºC); yield: 98.5 mg (66% yield).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.1 Hz, 1H), 7.27 (dd, *J* = 7.3, 2.6 Hz, 2H), 7.22–7.10 (m, 7H), 7.09–6.99 (m, 4H), 3.19 (q, *J* = 13.7 Hz, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.7, 158.1, 145.9, 137.1, 134.6, 130.1, 129.2, 128.5, 128.0, 126.3, 124.4, 120.8, 75.4, 41.3 ppm. IR (neat, cm^{-1}): 3028, 1747, 1581, 1494, 1453, 1265, 1142, 1079, 913, 760, 735, 700, 519. HRMS calcd for ($C_{22}H_{18}O$+Na): 321.1255, found 321.1260.

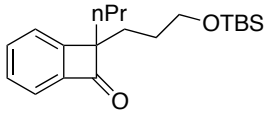


2-isopropyl-2-methylcyclobutabenzen-1(2*H*)-one (442). Following general procedure, 2-(2-chlorophenyl)-2,3-dimethylbutanal (105.4 mg, 0.50 mmol) was used. The benzocyclobutenone was dissolved under argon atmosphere in methanol (5 mL) and cooled to 0ºC. Then, $NaBH_4$ was added (5.0 mmol, 10.0 equiv.) and the reaction was stirred at rt for 12 h. The crude was then quenched by addition of water, followed by addition of HCl 2M. After extractions with ethyl acetate (3 x 5 mL) and brine (3 x 5 mL) it was dried over magnesium sulfate, filtered and concentrated. A mixture of diastereoisomers in a 2.3:1 ratio was obtained as a white solid mixture (63.1 mg, 72%, two steps). Purification on silica gel chromatography column (9:1 hexanes/ethyl acetate) allowed us to characterize the minor diastereoisomer (judged by NOESY experiments): mp: 51.4 – 52.6. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 - 7.24 (m, 3H), 7.18 - 7.13 (m, 1H), 4.82 (d, *J* = 8.9 Hz, 1H), 2.15 (d, *J* = 9.6 Hz, 1H), 1.99 (hept, *J* = 6.8 Hz, 1H), 1.26 (s, 3H), 1.09 (dd, *J* = 8.2, 6.7 Hz, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.4, 144.5, 129.3, 127.8, 123.5, 122.6, 80.5, 58.6, 31.5, 18.5, 18.1, 17.2 ppm. IR (neat, cm^{-1}): 3231, 2954, 2870, 1454, 1193, 1056, 740, 477. HRMS *calcd* for ($C_{12}H_{16}O$-OH): 159.1174, *found* 159.1179.

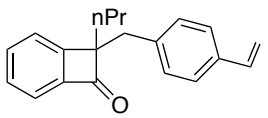


2-propyl-2-((triisopropylsilyloxy)methyl) cyclobuta-benzen-1(2*H*)-one (443). Following general procedure F, 2-(2-chlorophenyl)-2-(((triisopropyl-silyl)oxy) methyl)pentanal (191.5 mg, 0.50 mmol) was used. Column chromatography: silica gel,

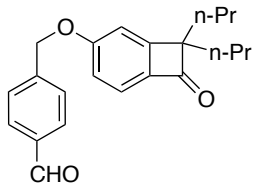
hexanes/ethyl acetate 98/2. Colorless oil; yield: 90 mg (52% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 - 7.48 (m, 2H), 7.45 - 7.38 (m, 1H), 7.38 - 7.34 (m, 1H), 4.05 (d, *J* = 10.0 Hz, 1H), 3.98 (d, *J* = 10.0 Hz, 1H), 1.79 (dd, *J* = 9.6, 7.2 Hz, 1H), 1.36-1.23 (m, 3H), 1.08-0.84 (m, 23H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.1, 158.8, 147.2, 134.9, 129.2, 123.46, 120.4, 76.3, 65.6, 33.8, 19.1, 18.0, 17.9, 14.7, 12.0 ppm. IR (neat, cm^{-1}): 2941, 2865, 1757, 1461, 1113, 1068, 881, 755, 680. HRMS *calcd* for ($C_{21}H_{34}O_2Si$+Na): 369.2226, *found* 369.2218.



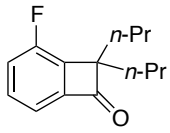
2-(3-(*tert*-butyldimethylsilyloxy)propyl)-2-propyl-cyclobutabenzen-1(2*H*)-one (444). Following general procedure 5-(*tert*-butyldimethylsilyloxy)-2-(2-chlorophenyl)-2-propylpentanal (184 mg, 0.50 mmol) was used. Column chromatography: silica gel, hexanes/ethyl acetate 18:1. Colorless liquid; yield: 133 mg (81% yield). The spectroscopical data correspond to tose previously reported in the literature.[2] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (m, 4H), 3.60 (t, *J* = 6.6 Hz, 2H), 1.87 (m, 4H), 1.50 (m, 2H), 1.29 (m, 2H), 0.91 (t, *J* = 6.6 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.9, 160.6, 146.2, 135.3, 129.3, 123.3, 121.1, 73.8, 63.5, 37.3, 31.4, 29.1, 26.2, 19.2, 18.5, 14.7, -5.5 ppm.



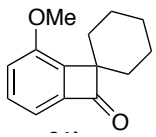
2-propyl-2-(4-vinylbenzyl)cyclobutabenzen-1(2*H*)-one (445). Following general procedure 2-(2-chlorophenyl)-2-(4-vinylbenzyl)ventanal (157 mg, 0.50 mmol) was used. Column chromatography: silica gel, hexanes. Yellow pale solid (mp=89ºC); yield: 79 mg (57% yield).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 6H), 7.05 (d, *J* = 8.1 Hz, 2H), 6.65 (dd, *J* = 17.7, 10.8 Hz, 1H), 5.67 (d, *J* = 17.7 Hz, 1H), 5.18 (d, *J* = 17.7 Hz, 1H), 3.11 (s, 2H), 1.81 (m, 2H), 1.28 (m, 2H), 0.87 (t, *J* = 7.5 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.9, 159.3, 145.8, 137.0, 136.5, 135.6, 134.8, 130.2, 129.2, 125.8, 123.7, 120.9, 113.2, 74.5, 41.2, 36.7, 19.0, 14.4 ppm. IR (neat, cm^{-1}): 3028, 1751, 1618, 1566, 1387, 1295, 1092, 1011, 885, 704. HRMS calcd for ($C_{20}H_{20}O$+Na): 299.1412, found 299.1419.



4-((1-oxo-2,2-dipropyl-1,2-dihydrocyclobutabenzen-4-yloxy)methyl) benzaldehyde (446). Following general procedure 4-((4-chloro-3-(4-formylheptan-4-yl)phenoxy) methyl)benzaldehyde, (186 mg, 0.50 mmol) was used. Column chromatography: silica gel, hexanes:EtOAc 2:1. Colorless oil; yield: 107.6 mg (64% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.02 (s, 1H), 7.89 (d, *J* = 8.2 Hz, 2H), 7.62 (d, *J* = 8.0 Hz, 2H), 7.46 (dd, *J* = 8.2, 7.2 Hz, 1H), 6.96 (dd, *J* = 13.8, 7.7 Hz, 2H), 5.56 (s, 2H), 1.84–1.66 (m, 4H), 1.32–1.13 (m, 4H), 0.85 (t, *J* = 7.3 Hz, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.8, 191.9, 160.0, 151.9, 143.6, 137.7, 135.9, 130.5, 129.8, 127.7, 116.6, 114.8, 72.9, 72.6, 37.1, 18.8, 14.5 ppm. IR (neat, cm^{-1}): 2957, 1753, 1701, 1597, 1571, 1471, 1269, 1207, 1123, 1046, 1013, 780. HRMS calcd for ($C_{22}H_{24}O_3$+H): 337.1804, found 337.1794.

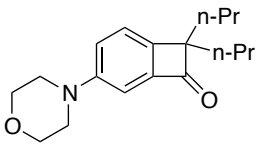


2-fluoro-8,8-dipropylbicyclo[4.2.0]octa-1,3,5-trien-7-one (447). Following general procedure 2-(2-chloro-6-fluorophenyl)-2-propylpentanal, (128 mg, 0.50 mmol) was used. Column chromatography: silica gel, hexanes:EtOAc 9:1. Yellow pale oil; yield: 84.8 mg (77% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (ddd, *J* = 8.2, 7.4, 4.1 Hz, 1H), 7.23–7.12 (m, 2H), 1.87–1.77 (m, 4H), 1.33–1.19 (m, 4H), 0.88 (t, *J* = 7.3 Hz, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.2 (d, $^{4}J_{C\text{-}F}$ = 2.2 Hz), 158.0 (d, $^{1}J_{C\text{-}F}$ = 255.6 Hz), 148.8 (d, $^{3}J_{C\text{-}F}$ = 7.1 Hz), 144.2 (d, $^{2}J_{C\text{-}F}$ = 19.0 Hz), 131.2 (d, $^{3}J_{C\text{-}F}$ = 5.1 Hz), 121.7 (d, $^{2}J_{C\text{-}F}$ = 21.3 Hz), 116.8 (d, $^{4}J_{C\text{-}F}$ = 4.6 Hz), 75.2 (d, $^{3}J_{C\text{-}F}$ = 2.4 Hz), 36.8, 19.2, 14.6, 14.4 ppm. IR (neat, cm^{-1}): 2959, 1768, 1590, 1476, 1240, 1207, 1018, 967, 805. HRMS calcd for ($C_{14}H_{17}FO$+H): 221,1342, found 221,1334.

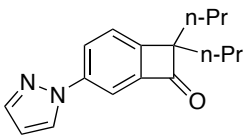


5-methoxyspiro[bicyclo[4.2.0]octa[1,3,5]triene-7,1'-cyclohexan]-8-one (448). Following general procedure 1-(2-chloro-6-methoxyphenyl)cyclohexane carbonitrile, (126 mg, 0.50 mmol) was used. Column chromatography: silica gel, hexanes:EtOAc 9:1. Colorless oil; yield: 81 mg (75% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 8.0, 7.5 Hz, 1H),

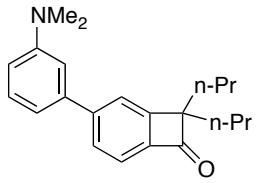
6.97 (dd, *J* = 7.8, 2.1 Hz, 2H), 3.89 (s, 3H), 1.99–1.86 (m, 4H), 1.85–1.69 (m, 4H), 1.57 (dd, *J* = 11.6, 5.7 Hz, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.8, 155.3, 149.4, 146.1, 130.6, 116.7, 113.2, 71.0, 55.4, 32.8, 25.7, 23.7 ppm. IR (neat, cm^{-1}): 2929, 2854, 1719, 1586, 1565, 1485, 1447, 1249, 1012, 794, 732. HRMS calcd for ($C_{14}H_{16}O_2$+H): 217.1229, *found* 217.1219.



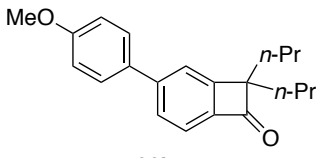
4-morpholino-8,8-dipropylbicyclo[4.2.0]octa-1,3,5-trien-7-one (449). Following general procedure 2-(2-chloro-4-morpholinophenyl)-2-propylpentanal (163 mg, 0.50 mmol) was used. Column chromatography: silica gel, hexanes:EtOAc 9:1. Colorless oil; yield: 103.5 mg (73% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.1 Hz, 1H), 7.14 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.84 (d, *J* = 1.5 Hz, 1H), 3.91–3.79 (m, 4H), 3.22–3.07 (m, 4H), 1.85–1.62 (m, 4H), 1.35–1.12 (m, 4H), 0.86 (t, *J* = 7.3 Hz, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.9, 152.8, 152.4, 146.9, 124.3, 123.5, 106.2, 72.9, 66.8, 49.7, 37.3, 19.0, 14.5 ppm. IR (neat, cm^{-1}): 2956, 2870, 1749, 1603, 1476, 1449, 1377, 1476, 1449, 1260, 1228, 1121, 896, 557. HRMS calcd for ($C_{18}H_{25}NO_2$+H): 288.1964, *found* 288.1957.



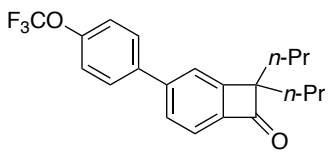
8,8-dipropyl-4-(1*H*-pyrazol-1-yl)bicyclo[4.2.0]octa-1,3,5-trien-7-one (450). Following general procedure 2-(2-chloro-4-(1*H*-pyrazol-1-yl)phenyl)-2-propylpentanal, (152.4 mg, 0.50 mmol) was used. Column chromatography: silica gel, hexanes:EtOAc 9:1. Colorless oil; yield: 88.6 mg (65% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.91 (d, *J* = 2.5 Hz, 1H), 7.73 (d, *J* = 1.8 Hz, 1H), 7.61–7.58 (m, 1H), 7.53 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.51–6.46 (m, 1H), 1.85–1.74 (m, 4H), 1.37–1.14 (m, 4H), 0.88 (t, *J* = 7.2 Hz, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.9 , 158.2, 146.9, 141.5, 141.3, 126.9, 126.7, 124.0, 110.8, 108.1, 73.8, 37.1, 18.9, 14.5 ppm. IR (neat, cm^{-1}): 2957, 2872, 1755, 1520, 1477, 1391, 1334, 1142, 1044, 1020, 946, 835, 744, 611, 549. HRMS calcd for ($C_{17}H_{20}N_2O$+H): 269.1654, found 269.1641.



3-(3-(dimethylamino)phenyl)-8,8-dipropylbicyclo [4.2.0] octa-1,3,5-trien-7-one (451). Following general procedure 2-(4-chloro-3'-(dimethylamino)-[1,1'-biphenyl]-3-yl)-2-propylpentanal (179 mg, 0.50 mmol) was used. Column chromatography: silica gel, hexanes:EtOAc 9:1. Colorless oil; yield: 130.2 mg (81% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69–7.58 (m, 2H), 7.44–7.30 (m, 2H), 7.02–6.88 (m, 2H), 6.83–6.76 (m, 1H), 3.04 (s, 6H), 1.88–1.76 (m, 4H), 1.39–1.22 (m, 4H), 0.90 (t, *J* = 7.3 Hz, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.5, 160.8, 151.0, 149.4, 144.4, 141.8, 129.6, 128.9, 121.5, 120.9, 116.0, 112.5, 111.5, 73.5, 40.7, 37.1, 19.0, 14.5 ppm. IR (neat, cm^{-1}): 2955, 2928, 2870, 1748, 1585, 1499, 1456, 1353, 1164, 1113, 1094, 1060, 879, 773, 691. HRMS calcd for ($C_{22}H_{27}NO$+H): 322.2147, *found* 322.2156.

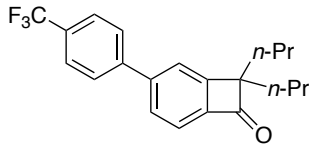


3-(4-methoxyphenyl)-8,8-dipropylbicyclo[4.2.0] octa-1,3,5-trien-7-one (453). Following general procedure 2-(4-chloro-4'-methoxy-[1,1'-biphenyl]-3-yl)-2-pro-pylpentanal (172.4 mg, 0.50 mmol) was used. Column chromatography: silica gel, hexanes:EtOAc 9:1. Colorless oil; yield: 135.7 mg (88% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (t, *J* = 7.3 Hz, 4H), 7.40 (d, *J* = 8.5 Hz, 1H), 7.02 (d, *J* = 8.8 Hz, 2H), 3.88 (s, 3H), 1.87–1.76 (m, 4H), 1.42–1.21 (m, 4H), 0.90 (t, *J* = 7.3 Hz, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.3, 160.9, 160.0, 147.8, 143.9, 133.0, 128.7, 128.2, 121.1, 120.7, 114.4, 73.4, 55.3, 37.1, 18.9, 14.5 ppm. IR (neat, cm^{-1}): 2956, 2871, 1749, 1587, 1456, 1094, 887, 835, 758, 695. HRMS calcd for ($C_{21}H_{24}O_2$+H): 309.1855, found 309.1867.

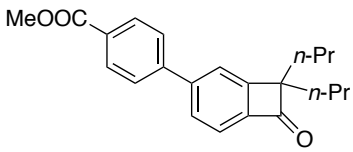


8,8-dipropyl-3-(4-(trifluoromethoxy)phenyl) bicyclo[4.2.0]octa-1,3,5-trien-7-one (454). Following general procedure 2-(4-chloro-4'-(trifluoromethoxy) -[1,1'-biphenyl]-3-yl)-2-propylpentanal, (199 mg, 0.50 mmol) was used. Column chromatography: silica

gel, hexanes:EtOAc 9:1. Colorless oil; yield: 141.3 mg (78% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69–7.57 (m, 4H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.38–7.30 (m, 2H), 1.94–1.72 (m, 4H), 1.46–1.17 (m, 4H), 0.90 (t, *J* = 7.3 Hz, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.2, 161.1, 149.4 (d, $^{3}J_{C\text{-}F}$ = 1.8 Hz), 146.7, 145.0, 139.4, 129.0, 128.6, 121.5, 121.3, 121.3, 120.5 (d, $^{1}J_{C\text{-}F}$ = 257.6 Hz), 73.8, 37.1, 19.0, 14.5 ppm. IR (neat, cm^{-1}): 2959, 2931, 1750, 1590, 1512, 1458, 1253, 1207, 1159, 1010, 923, 827, 677. HRMS calcd for ($C_{21}H_{21}F_3O_2$+Na): 385.1391, *found* 385.1379.

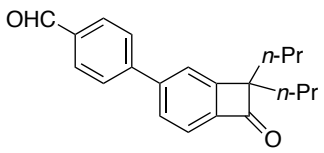


8,8-dipropyl-3-(4-(trifluoromethyl)phenyl)bicyclo[4.2.0]octa-1,3,5-trien-7-one (455). Following general procedure 2-(4-chloro-4'-(trifluoromethyl)-[1,1'-bi-phenyl]-3-yl)-2-propylpentanal (191 mg, 0.50 mmol) was used. Column chromatography: silica gel, hexanes:EtOAc 9:1. Colorless oil; yield: 104 mg (60% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80–7.70 (m, 4H), 7.71–7.62 (m, 2H), 7.47 (d, *J* = 8.3 Hz, 1H), 1.94–1.75 (m, 4H), 1.43–1.18 (m, 4H), 0.91 (t, *J* = 7.3 Hz, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) 196.2, 161.1, 146.6, 145.5, 135.5, 128.8, 128.0, 125.9 (d, $^{2}J_{C\text{-}F}$ = 3.8 Hz), 124.1 (d, $^{1}J_{C\text{-}F}$ = 272.2 Hz), 122.4, 121.7, 121.3, 73.9, 37.1, 19.0, 14.5 ppm. IR (neat, cm^{-1}): 2959, 2873, 1752, 1590, 1465, 1322, 1165, 1123, 1068, 1012, 851, 825, 615. HRMS calcd for ($C_{21}H_{21}F_3O$+Na): 369.1442, *found* 369.1430.

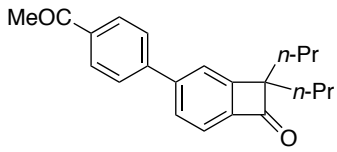


Methyl 4-(7-oxo-8,8-dipropylbicyclo[4.2.0]octa-1,3,5-trien-3-yl)benzoate (456). Following general procedure methyl 4'-chloro-3'-(4-formylheptan-4-yl)-[1,1'-biphenyl]-4-carboxylate, (186 mg, 0.50 mmol) was used. Column chromatography: silica gel, hexanes:EtOAc 9:1. Colorless oil; yield: 141.3 mg (84% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21–8.07 (m, 4H), 7.79 (d, *J* = 7.8 Hz, 1H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.44 (d, *J* = 7.2 Hz, 1H), 3.96 (s, 3H), 1.90–1.74 (m, 4H), 1.35–1.24 (m, 4H), 0.90 (t, *J* = 7.3 Hz, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.8, 166.8, 161.0, 142.9, 139.7, 135.4, 135.1, 130.3, 130.2, 127.5, 126.4, 122.3, 73.0, 52.2, 37.1, 18.9, 14.5 ppm. IR (neat,

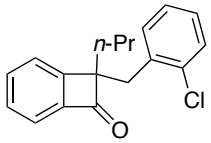
cm^{-1}):2954, 2927, 2869, 1751, 1726, 1556, 1435, 1274, 1187, 1099, 1010, 811, 794, 697. HRMS calcd for ($C_{22}H_{24}O_3$+Na): 359.1623, *found* 359.1625.



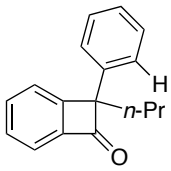
4-(1-oxo-2,2-dipropyl-1,2-dihydrocyclobutabenzen-4-yl)benzaldehyde (457). Following general procedure 4'-chloro-3'-(4-formylheptan-4-yl)biphenyl-4-carbaldehyde (171.4 mg, 0.50 mmol) was used. Column chromatography: silica gel, hexanes:EtOAc 9:1. Colorless oil; yield: 84.3 mg (55% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.08 (s, 1H), 7.99 (d, *J* = 8.2 Hz, 2H), 7.79 (d, *J* = 8.2 Hz, 2H), 7.67 (d, *J* = 6.6 Hz, 2H), 7.45 (d, *J* = 8.4 Hz, 1H), 1.91–1.75 (m, 4H), 1.42–1.19 (m, 4H), 0.88 (t, *J* = 7.3 Hz, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.1, 191.6, 161.0, 146.5, 146.5, 145.6, 135.8, 130.2, 128.8, 128.2, 121.7, 121.2, 73.8, 37.0, 18.9, 14.4 ppm. IR (neat, cm^{-1}): 2958, 2870, 1720, 1683, 1604, 1461, 1358, 1264, 1049, 813, 739, 617, 589. HRMS calcd for ($C_{21}H_{22}O_2$+H): 307.1674, found 307.1685.



4-(4-ethanoylphenyl)-2,2-dipropylcyclobutabenzen-1(2H)-one (458). Following general procedure 2-(4-chloro-4'-ethanoylbiphenyl-3-yl)-2-propylpenta-nal, (178 mg, 0.50 mmol) was used. Column chromatography: silica gel, hexanes:EtOAc 9:1. Colorless oil; yield: 93 mg (58% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12–8.06 (m, 2H), 7.77–7.72 (m, 2H), 7.68 (dd, *J* = 4.4, 2.3 Hz, 2H), 7.47 (dd, *J* = 8.3, 0.5 Hz, 1H), 2.68 (s, 3H), 1.84 (td, *J* = 6.6, 1.4 Hz, 4H), 1.40–1.26 (m, 4H), 0.91 (t, *J* = 7.3 Hz, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.5, 196.2, 161.0, 146.8, 145.5, 145.2, 136.7, 129.0, 128.8, 127.8, 121.6, 121.3, 73.8, 37.1, 26.7, 19.0, 14.5 ppm. IR (neat, cm^{-1}): 2957, 2933, 1720, 1683, 1604, 1462, 1377, 1264, 1049, 1016, 813, 739, 617, 589. HRMS calcd for ($C_{22}H_{24}O_2$+Na): 343.1674, found 343.1657.

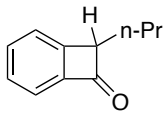


8-(2-chlorobenzyl)-8-propylbicyclo[4.2.0]octa-1,3,5-trien-7-one (459). Following general procedure 2-(2-chlorobenzyl)-2-(2-chlorophenyl)pentanal, (152.4 mg, 0.50 mmol) was used. Column chromatography: silica gel, hexanes:EtOAc 12:1. Colorless oil; yield: 93 mg (66% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50–7.36 (m, 2H), 7.35–7.26 (m, 1H), 7.25–7.13 (m, 3H), 7.10–6.98 (m, 2H), 3.43 (d, J = 13.9 Hz, 1H), 3.26 (d, J = 13.9 Hz, 1H), 2.01–1.79 (m, 2H), 1.41–1.13 (m, 2H), 0.89 (t, J = 7.2, 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.66, 158.76, 145.88, 135.57, 134.68, 134.34, 131.72, 129.32, 129.15, 127.73, 126.37, 124.12, 120.38, 74.66, 37.51, 37.38, 18.95, 14.40. IR (neat, cm^{-1}): 2957, 2929, 1749, 1581, 1461, 1440, 1274, 1051, 1037, 890, 752, 680, 536, 514. HRMS calcd for ($C_{18}H_{17}ClO$+Na): 307.0866, *found* 307.0876.



2-phenyl-2-propylcyclobutabenzen-1(2*H*)-one (461).

Following general procedure 2-(2-chlorophenyl)-2-phenylpentanal (158 mg, 0.50 mmol) was used. Column chromatography: silica gel, hexanes:EtOAc 10:1. Colorless oil; yield: 80.1 mg (68% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 6.3 Hz, 1H), 7.64 (td, *J* = 7.2, 1.5 Hz, 1H), 7.47 (m, 4H), 7.34 (t, *J* = 6.0 Hz, 2H), 7.25 (d, *J* = 7.2 Hz, 1H), 2.14 (m, 2H), 1.28 (m, 2H), 0.88 (t, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.2, 158.5, 145.7, IR (neat, cm^{-1}): 2997, 2891, 1751, 1511, 1424, 1340, 1298, 1110, 984, 911, 823. HRMS calcd for ($C_{17}H_{16}O$+H): 237.1279, found 237.1281.

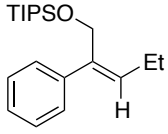


8-propylbicyclo[4.2.0]octa-1,3,5-trien-7-one (465). Following general procedure 2-(2-chlorophenyl)-2-(trimethylsilyl)pentanal (134 mg, 0.50 mmol) was used. Once the reaction was finished as judged by TLC (13 h), TBAF (2 mL, 2 mmol, 1M in THF) was added and the reaction was stirred for an additional 2 h. Filtration through Celite and evaporation of the solvent afforded a crude that was purified by flash column

chromatography in silica gel (hexanes/ethyl acetate 16:1). Colorless liquid; yield: 58 mg (73% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (m, 2H), 7.41 (m, 1H), 7.35 (td, *J* = 7.5, 1.2 Hz, 1H), 4.23 (t, *J* = 7.2 Hz), 1.87 (m, 1H), 1.73 (m, 1H), 1.51 (m, 2H), 0.97 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.9, 156.5, 146.6, 134.9, 128.9, 123.3, 120.7, 64.8, 32.4, 20.6, 13.9 ppm. IR (neat, cm^{-1}): 2958, 2872, 1757, 1581, 1461, 1142, 768, 753, 738. HRMS calcd for ($C_{11}H_{12}O$): 160.0888, found 160.0891

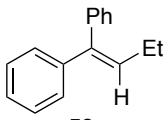
4.5.3 Pd-catalyzed synthesis of styrenes via C-H bond-functionalization

General procedure G for the synthesis of α-aryl styrenes. An oven-dried screw-cap test tube containing a stirring bar was charged with **(357)** (3.9 mg, 2.0 mol%), **IMes·HCl** (10.2 mg, 6.0 mol%), Cs_2CO_3 (209 mg, 0.65 mmol) and the aryl chloride (0.50 mmol), if a solid. The test tube was evacuated and back-filled with dry argon (this sequence was repeated three times). The aryl chloride (if liquid) and dioxane (2 mL) were then added by syringe. The mixture was then placed in a pre-heated oil bath (110 °C) for 14 h. The mixture was then allowed to warm to room temperature, diluted with ethyl acetate (5 mL) and filtered through a Celite® plug, eluting with additional ethyl acetate (10 mL). The filtrate was concentrated and purified by column chromatography on silica gel (eluting with hexanes/ethyl acetate mixtures).

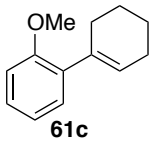


(*Z*)-triisopropyl((2-phenylpent-2-en-1-yl)oxy)silane (470). Following the general procedure, 2-(2-chlorophenyl)-2-(((triisopropylsilyl)oxy)methyl)pentanal (191.5 mg, 0.5 mmol) was used. Column chromatography: silica gel, hexanes/ethyl acetate 9:1. Colorless oil; yield: 144.1 mg (90% yield, 1:1.6 *E:Z*). The next data corresponds to the mayor isomer E: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.5 Hz, 1H), 7.39 - 7.25 (m, 2H), 7.21 (t, *J* = 6.5 Hz, 1H), 5.81 (t, *J* = 7.3 Hz, 1H), 4.67 (s, 2H), 2.32 (p, *J* = 7.4

Hz, 2H), 1.24 ? 0.84 (m, 25H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.3, 139.3, 138.6, 133.2, 128.9, 128.0, 126.8, 126.6, 60.8, 21.9, 18.2, 14.6, 12.2 ppm. IR (neat, cm^{-1}):2942, 2866, 1459, 1064, 1014, 881, 755, 681, 657. HRMS *calcd* for ($C_{20}H_{34}OSi$+H): 319.2457, *found* 319.2472.



But-1-ene-1,1-diyldibenzene (471). Following the general procedure, 2-(2-chlorophenyl)-2-phenylpentanal (136.4 mg, 0.50 mmol) was used at 140 ºC. Column chromatography: silica gel, hexanes/ethyl acetate 9:1. Colorless oil; yield: 63.1 mg (61% yield). The spectroscopical data correspond to those previously reported in the literature.[221] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 - 7.32 (m, 3H), 7.30 - 7.20 (m, 7H), 6.11 (t, *J* = 7.5 Hz, 1H), 2.16 (p, *J* = 7.5 Hz, 2H), 1.08 (t, *J* = 7.5 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.0, 141.1, 140.4, 131.9, 130.0, 128.3, 128.2, 127.4, 127.0, 126.9, 23.4, 14.7 ppm.

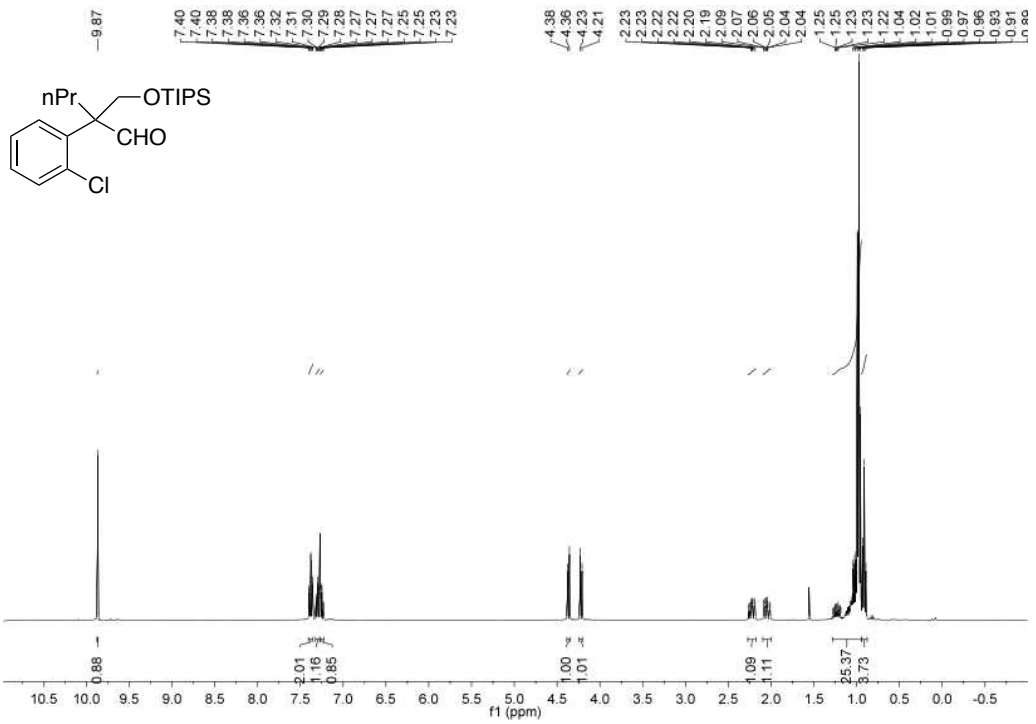


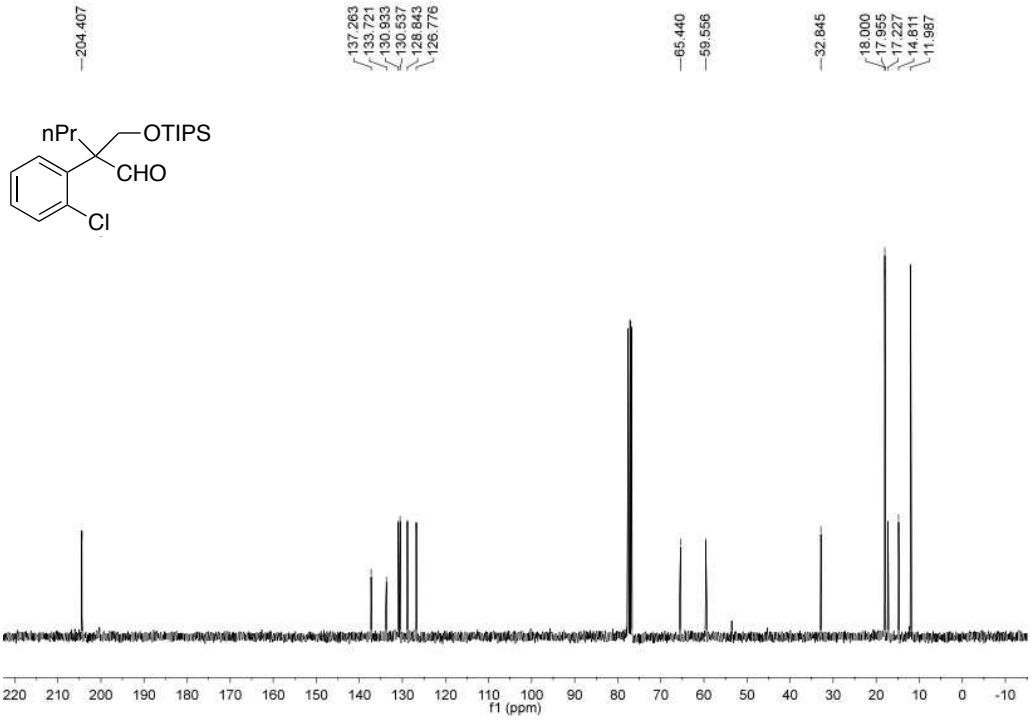
61c

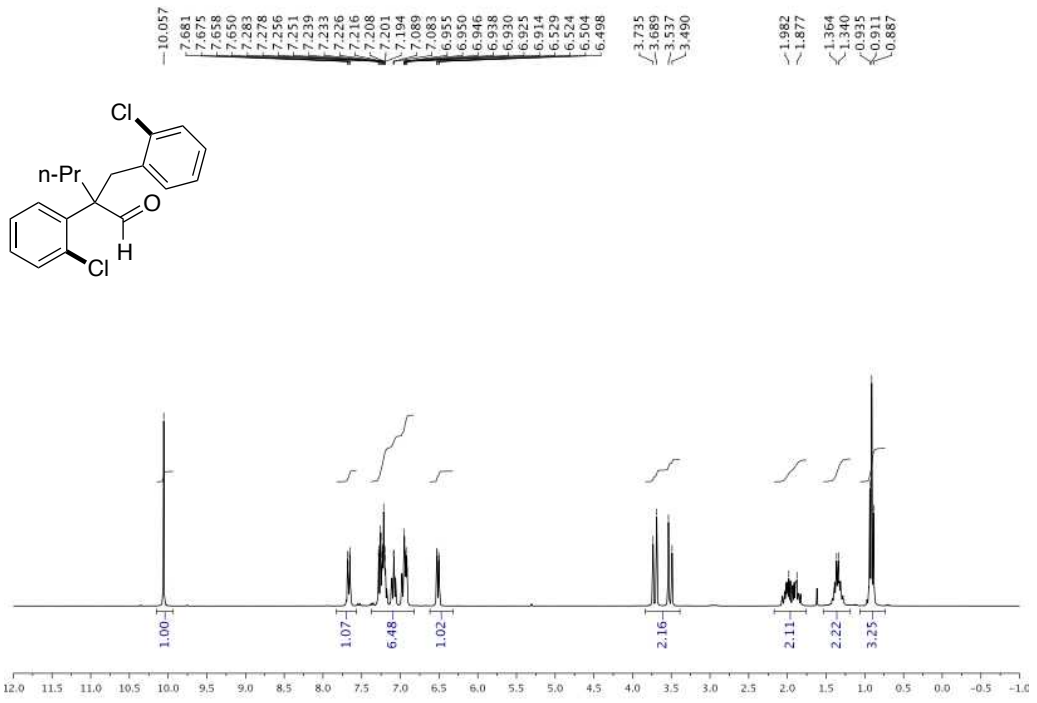
1-Cyclohexenyl-2-methoxybenzene (472). Following general procedure 1-(2-chloro-6-methoxyphenyl)cyclohexanecarbonitrile, (126 mg, 0.50 mmol) was used. Column chromatography: silica gel, hexanes:EtOAc 9:1. Colorless oil; yield: 75.3 mg (80% yield).. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (ddd, *J* = 8.2, 7.4, 1.8 Hz, 1H), 7.22–7.17 (m, 1H), 6.97 (td, *J* = 7.4, 1.1 Hz, 1H), 6.92 (dd, *J* = 8.2, 0.9 Hz, 1H), 5.83 (tt, *J* = 3.7, 1.7 Hz, 1H), 3.87 (s, 3H), 2.53–2.37 (m, 2H), 2.32–2.20 (m, 2H), 1.87–1.69 (m, 4H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.7 , 137.5, 133.8, 129.5, 127.7, 126.1, 120.5, 110.7, 67.1, 55.4, 28.8, 25.7, 23.1, 22.2 ppm.

[221] Wang, T.; Hu, Y.; Zhang, S. *Org. Biomol. Chem.* **2010**, *8*, 2312.

4.5.3 Selected examples of NMR spectra



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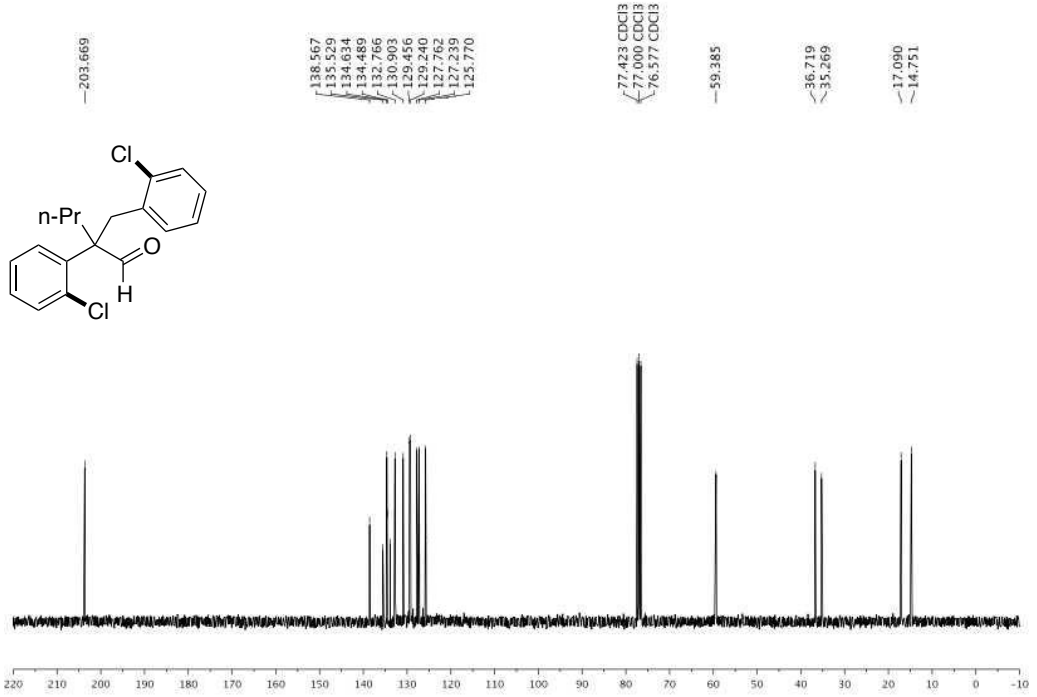
7.675
7.658
7.650
7.283
7.278
7.256
7.251
7.239
7.233
7.226
7.216
7.208
7.201
7.194
7.089
7.083
6.955
6.950
6.946
6.938
6.930
6.925
6.914
6.529
6.524
6.504
6.498
3.735
3.689
3.537
3.490
1.982
1.877
1.364
1.340
0.935
0.911
0.887
Cl
n-Pr
O
H
Cl
1.00
1.07
6.48
1.02
2.16
2.11
2.22
3.25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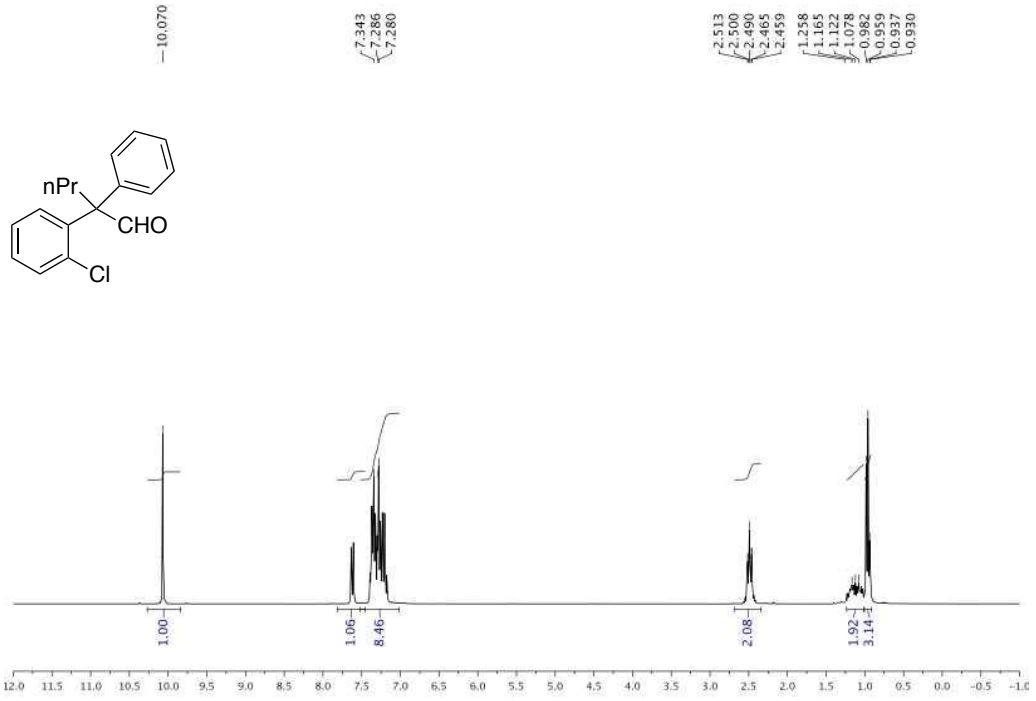
138.567
135.529
134.634
134.489
132.766
130.903
129.456
129.240
127.762
127.239
125.770
77.423 CDCl3
77.000 CDCl3
76.577 CDCl3
59.385
36.719
35.269
17.090
14.751
Cl
n-Pr
O
H
Cl


10.070
7.343
7.286
7.280
2.513
2.500
2.490
2.465
2.459
1.258
1.165
1.122
1.078
0.982
0.959
0.937
0.930
nPr
CHO
Cl
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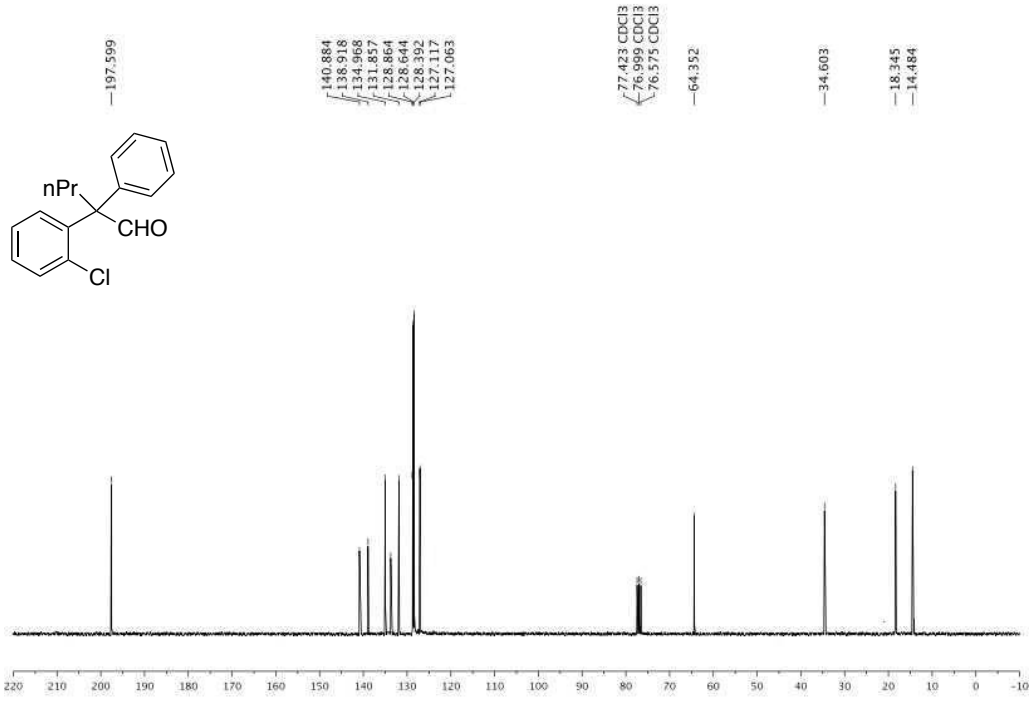
1.06
8.46
2.08
1.92
3.14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140.884
138.918
134.968
131.857
128.864
128.644
128.392
127.117
127.063
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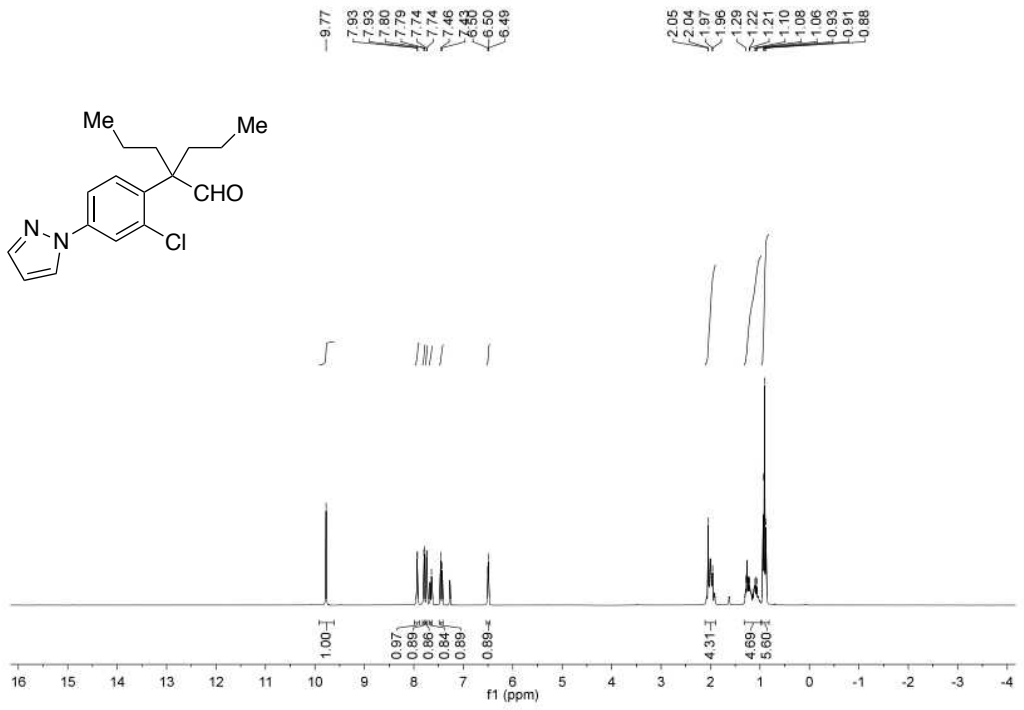
76.999 CDCl3
76.575 CDCl3
64.352
34.603
18.345
14.484
nPr
CHO
Cl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7.93
7.93
7.80
7.79
7.74
7.74
7.46
7.43
6.50
6.50
6.49
2.05
2.04
1.97
1.96
1.29
1.22
1.21
1.10
1.08
1.06
0.93
0.91
0.88
Me
Me
CHO
N
N
Cl
1.00
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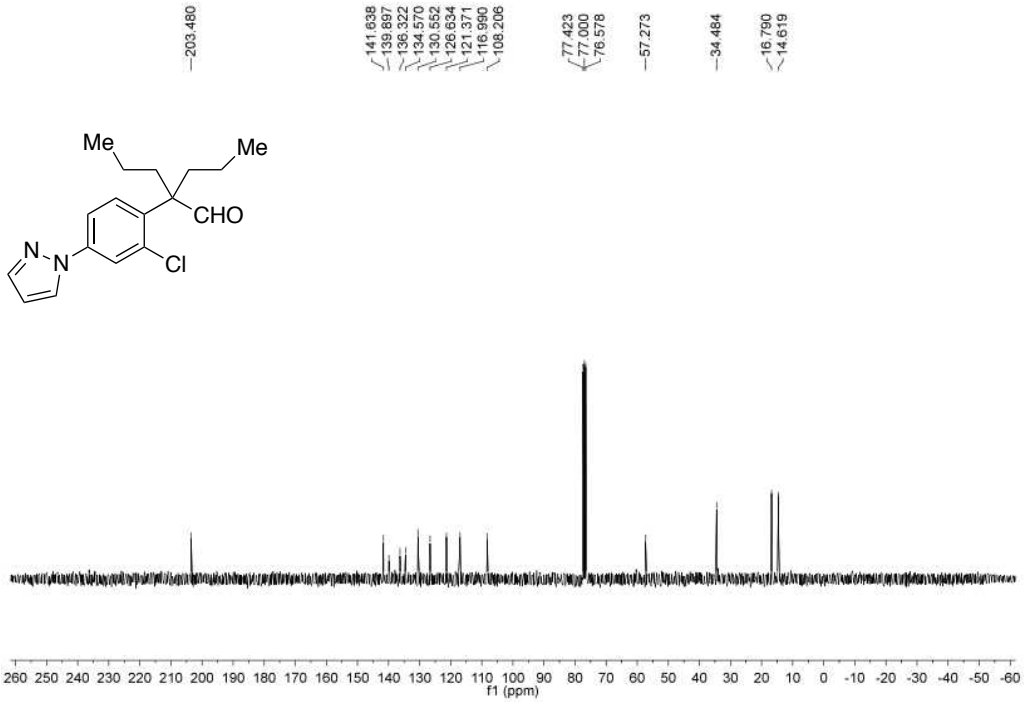
0.89
0.86
0.84
0.89
0.89
4.31
4.69
5.60
f1 (ppm)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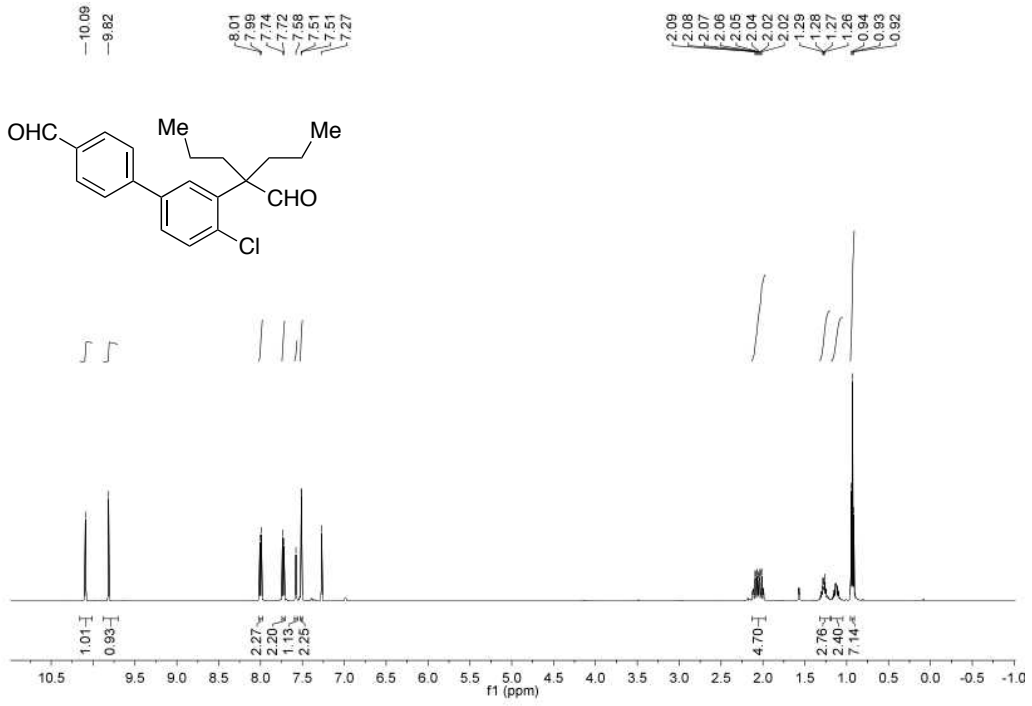
136.322
134.570
130.552
126.634
121.371
116.990
108.206
77.423
77.000
76.578
57.273
34.484
16.790
14.619
Me
Me
CHO
N
N
Cl
f1 (ppm)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9.82
8.01
7.99
7.74
7.72
7.58
7.51
7.51
7.27
2.09
2.08
2.07
2.06
2.05
2.04
2.02
2.02
1.29
1.28
1.27
1.26
0.94
0.93
0.92
OHC
Me
Me
CHO
Cl
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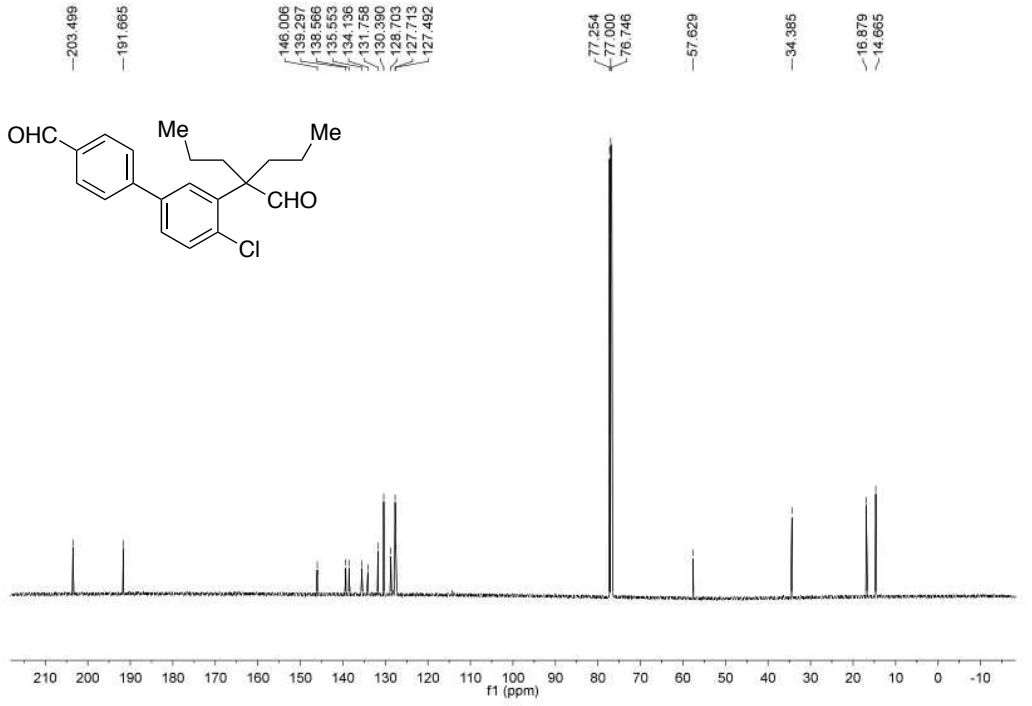
1.13
2.25
4.70
2.76
2.40
7.14
f1 (ppm)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191.665
146.006
139.297
138.566
135.553
134.136
131.758
130.390
128.703
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127.492
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76.746
57.629
34.385
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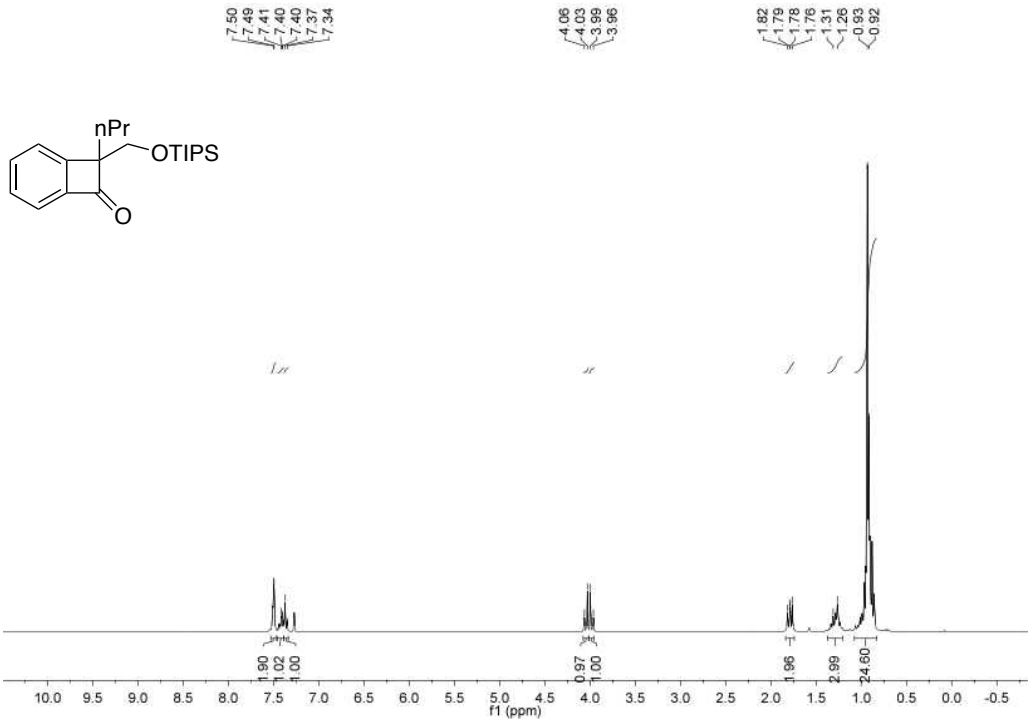
OHC
Me
Me
CHO
Cl
f1 (ppm)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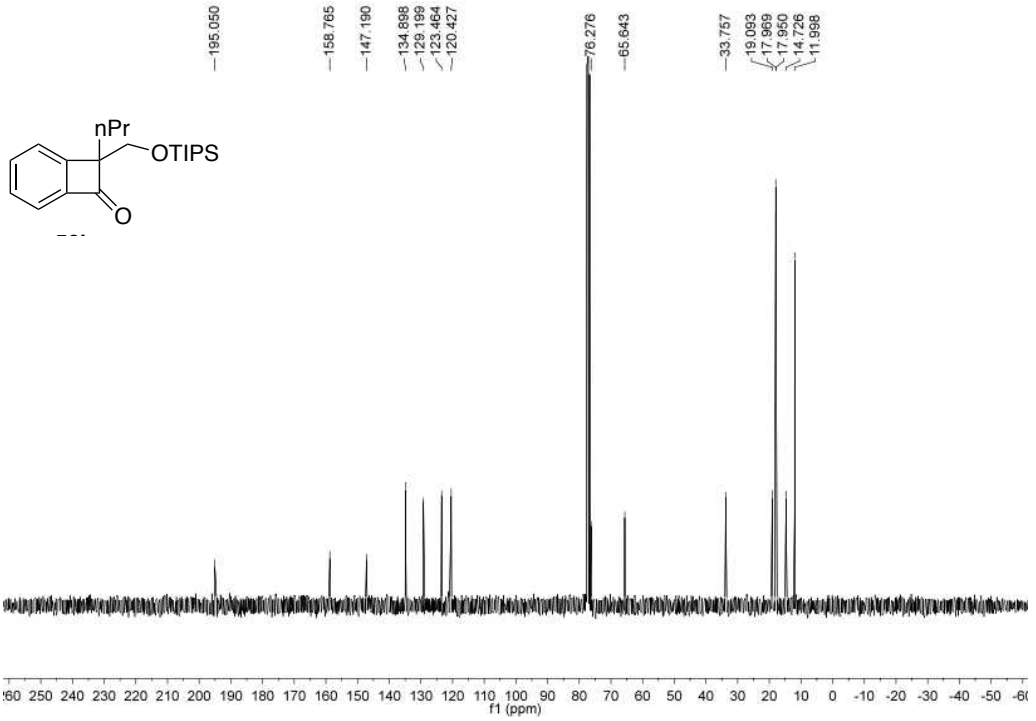
7.49
7.41
7.40
7.40
7.37
7.34
4.06
4.03
3.99
3.96
1.82
1.79
1.78
1.76
1.31
1.26
0.93
0.92
nPr
OTIPS
O
1.90
1.02
1.00
0.97
1.00
1.96
2.99
24.60
f1 (ppm)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158.765
147.190
134.898
129.199
123.464
120.427
76.276
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33.757
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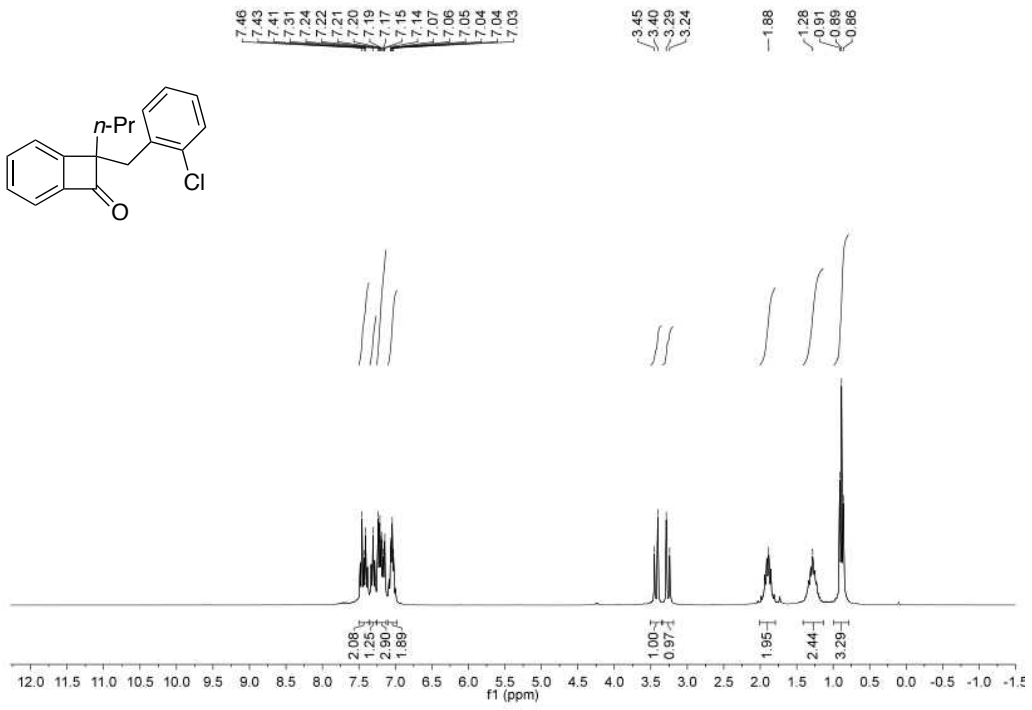
17.950
14.726
11.998
nPr
OTIPS
O
f1 (ppm)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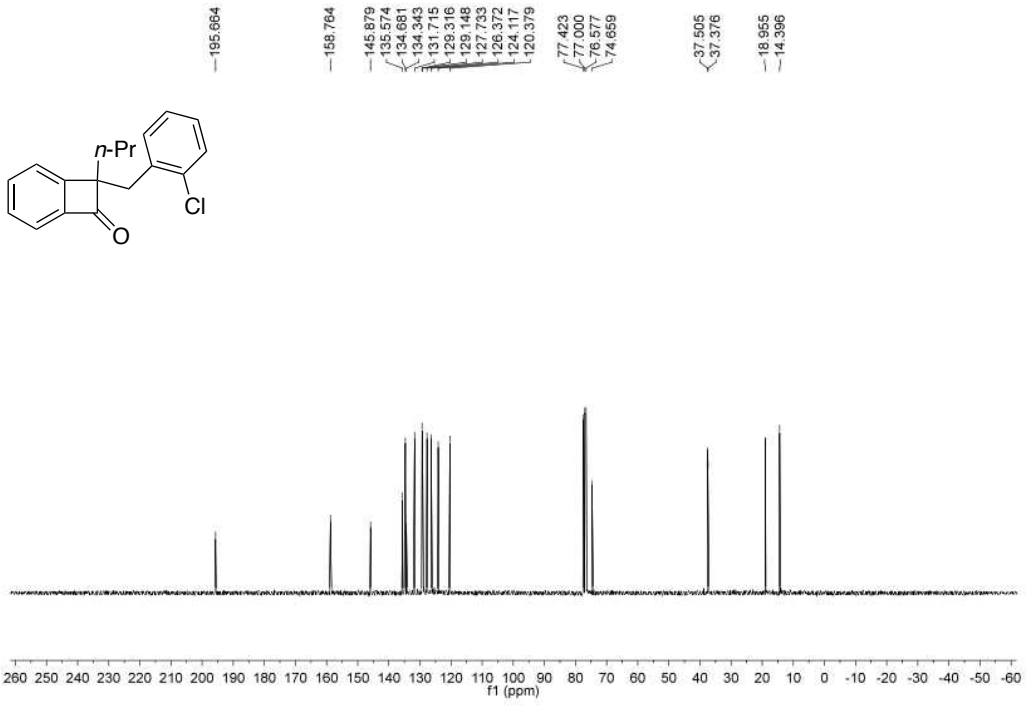
7.06
7.05
7.04
7.04
7.03
3.45
3.40
3.29
3.24
1.88
1.28
0.91
0.89
0.86
n-Pr
Cl
O
2.08
1.25
2.90
1.89
1.00
0.97
1.95
2.44
3.29
f1 (ppm)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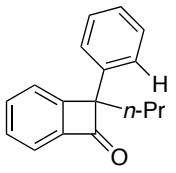
n-Pr
Cl
O
f1 (ppm)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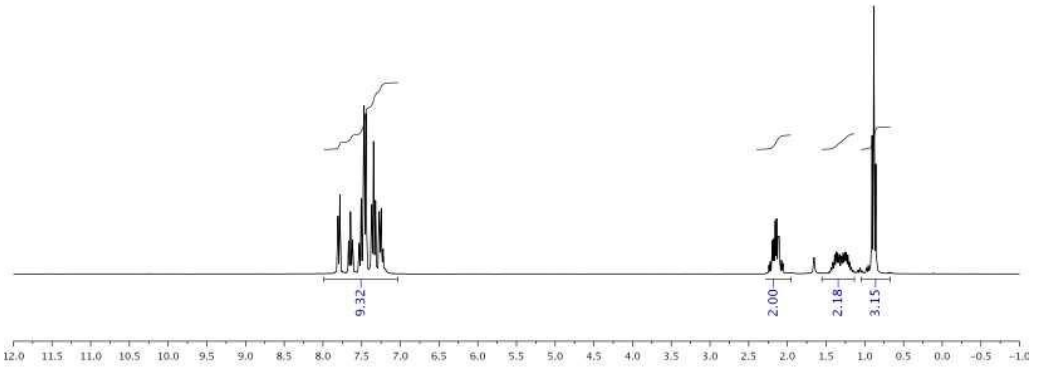
n-Pr
O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3.15
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193.192
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145.699
140.434
135.302
129.504
128.354
126.708
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121.646
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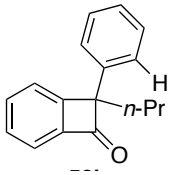
14.188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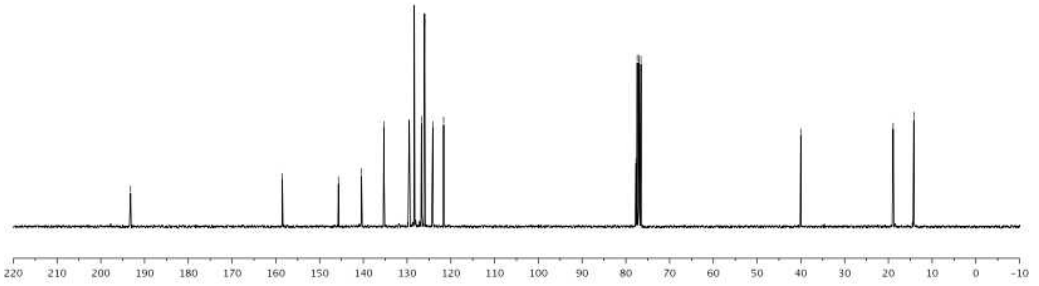
O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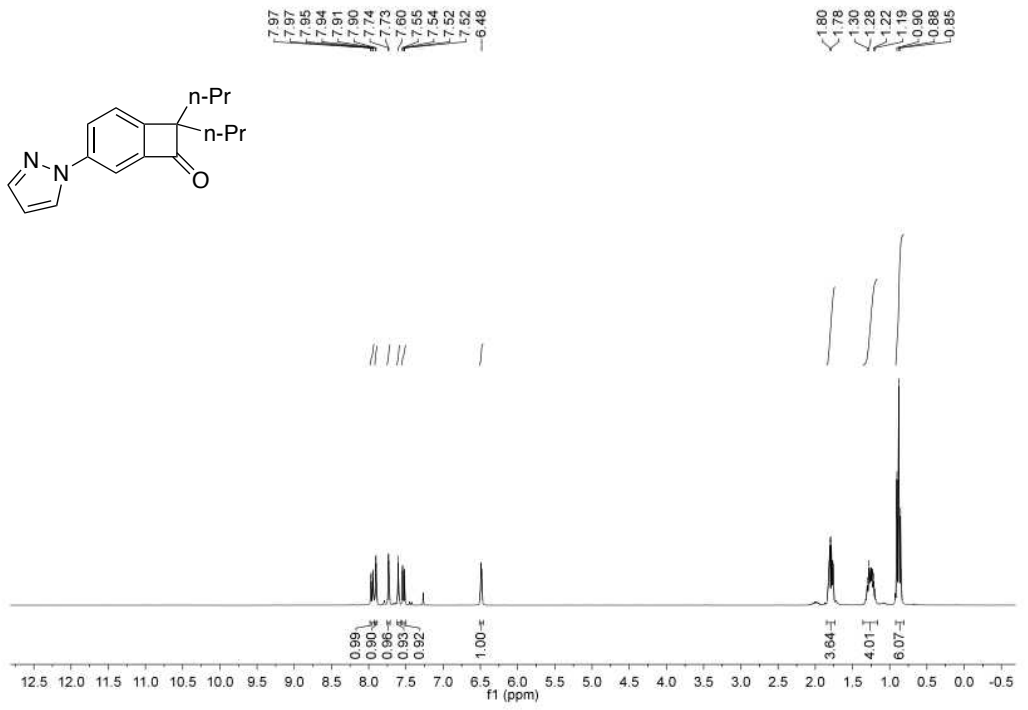
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7.55
7.54
7.52
7.52
6.48
1.80
1.78
1.30
1.28
1.22
1.19
0.90
0.88
0.85
n-Pr
n-Pr
N
N
O
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0.93
0.92
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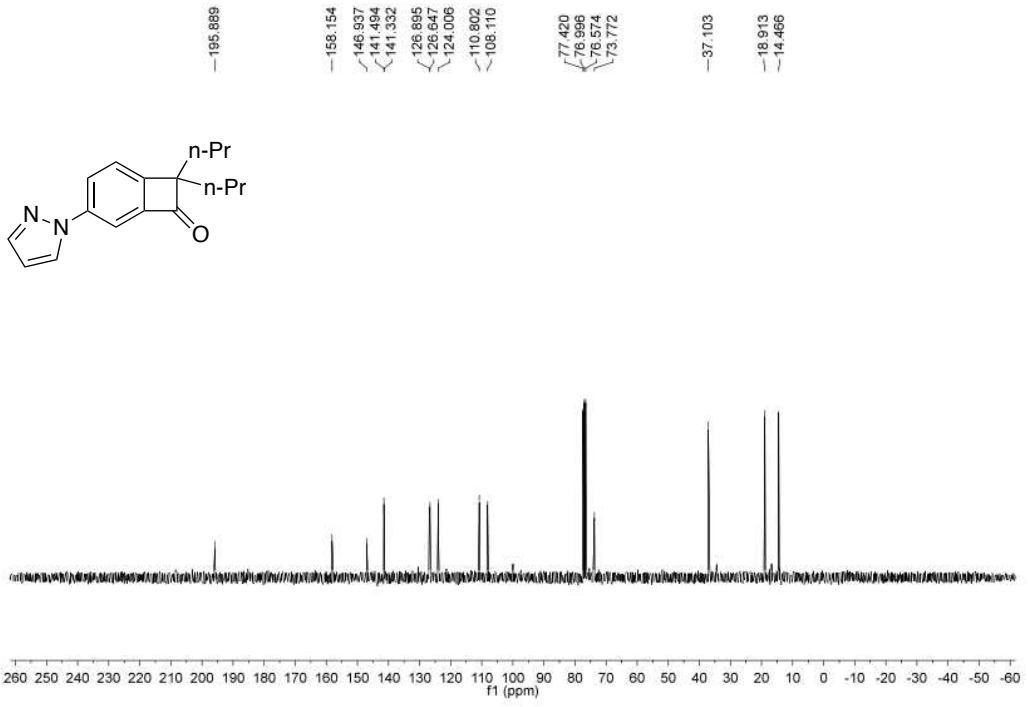
6.07
f1 (ppm)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18.913
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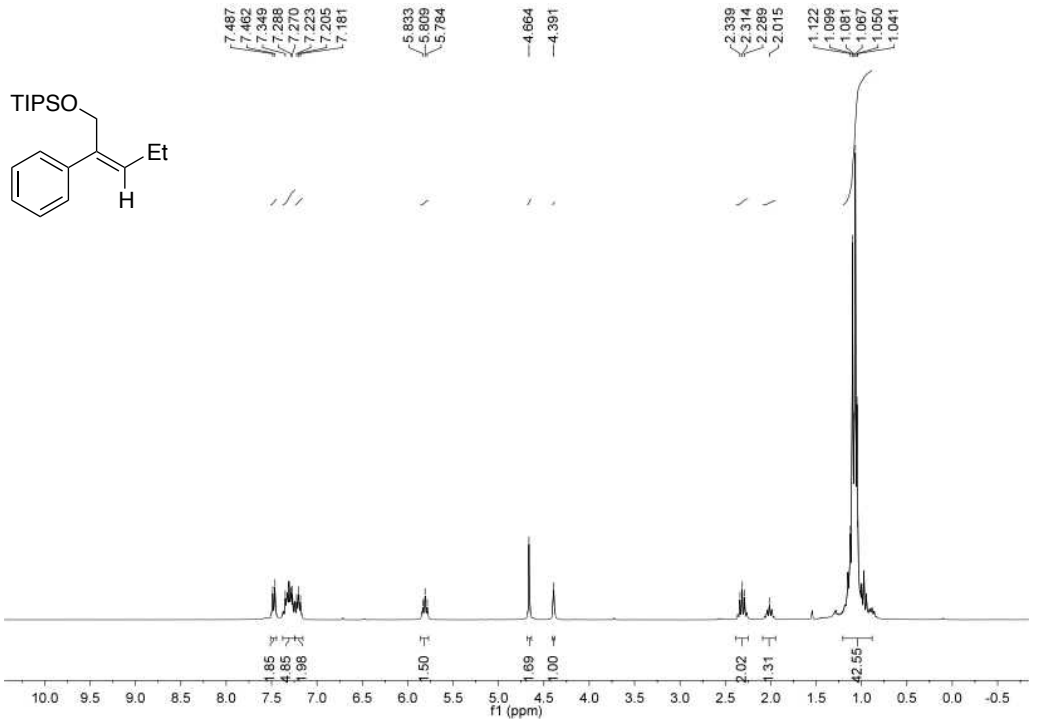
n-Pr
n-Pr
N
N
O
f1 (ppm)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H
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7.349
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7.223
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7.181
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5.784
4.664
4.391
2.339
2.314
2.289
2.015
1.122
1.099
1.081
1.067
1.050
1.041
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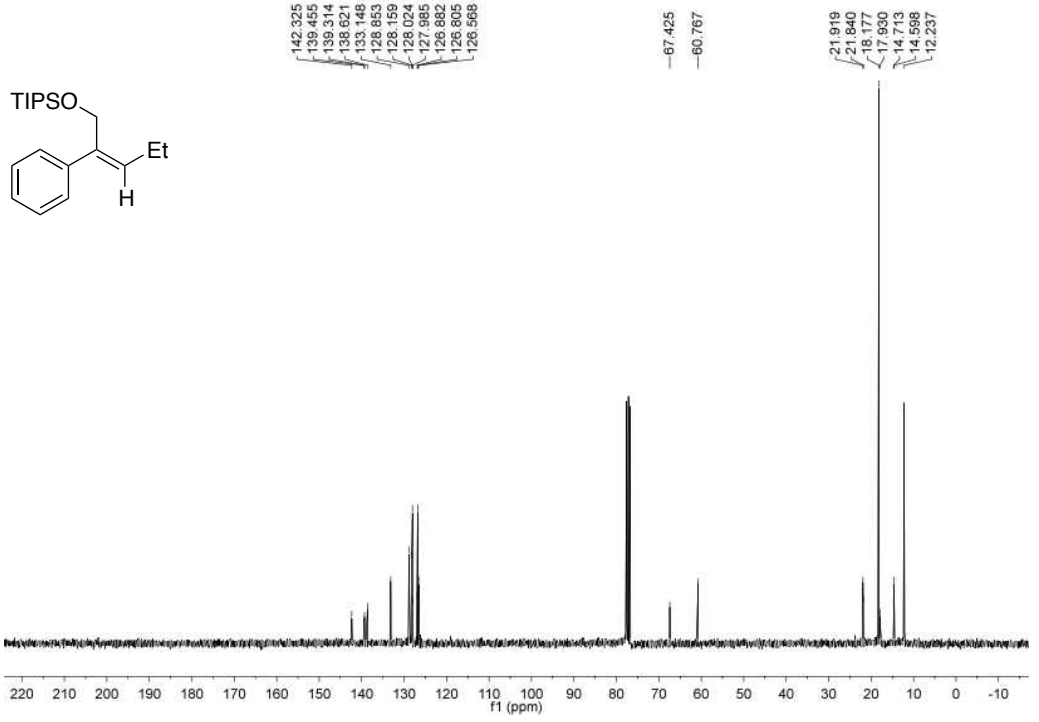
1.00
2.02
1.31
42.55
f1 (ppm)


TIPSO
Et
H
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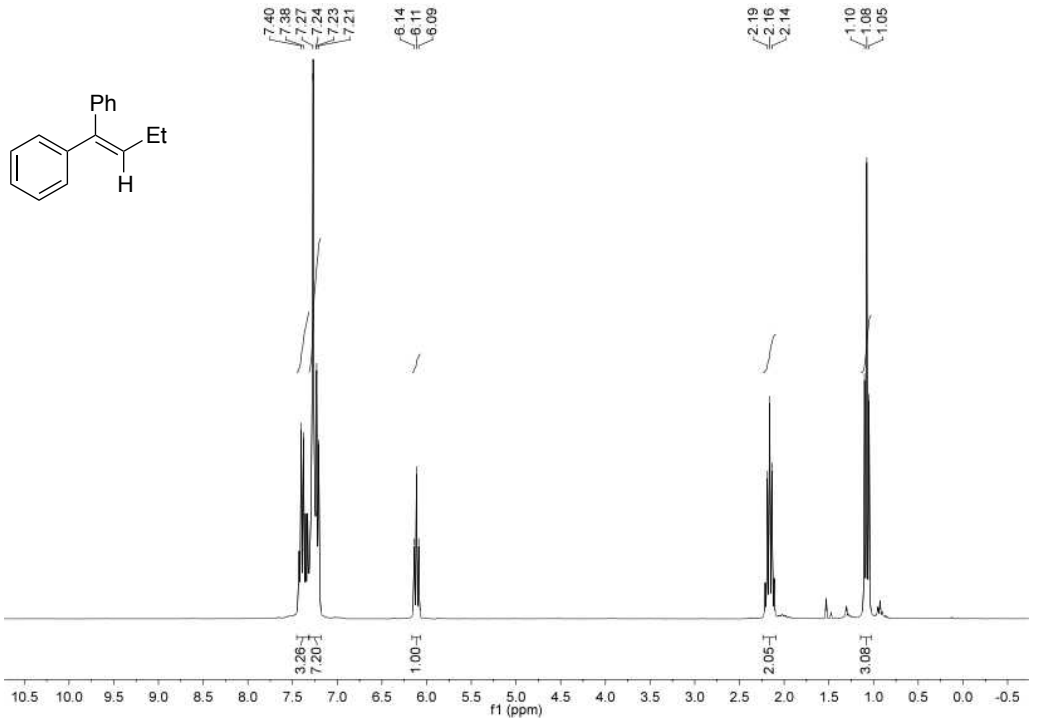
139.455
139.314
138.621
133.148
128.853
128.159
128.024
127.985
126.882
126.805
126.568
67.425
60.767
21.919
21.840
18.177
17.930
14.713
14.598
12.237
f1 (ppm)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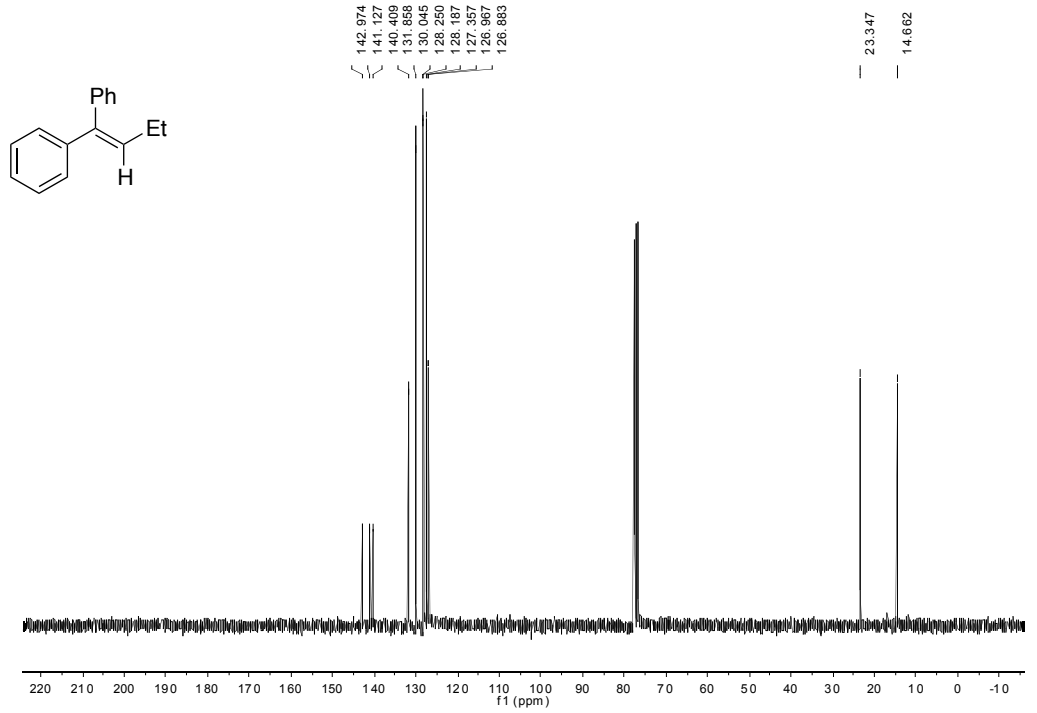
7.38
7.27
7.24
7.23
7.21
6.14
6.11
6.09
2.19
2.16
2.14
1.10
1.08
1.05
Ph
Et
H
3.26
7.20
1.00
2.05
3.08
f1 (ppm)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131.858
130.045
128.250
128.187
127.357
126.967
126.883
23.347
14.662
Ph
Et
H
f1 (ppm)

General Conclusions and Outlook

We have developed a new protocol for *selectively* preparing benzocyclobutenones through intramolecular acylation of aryl bromides *via* palladium catalyzed C-H bond functionalization (Figure 5.1-right). The reaction proceeded with a vast array of functionalized substrates with a diverse substitution patterns. The use of Cs_2CO_3 as the inorganic base was critical for success, likely indicating that a concerted-metalation-deprotonation mechanism (*CMD)* was operating in our protocol. Experimental and theoretical studies concluded that the C-H bond-functionalization was the rate-determining step of the reaction. The exquisite selectivity observed in the reaction was attributed to the formation of a five-membered metalacycle in which *rac*-BINAP is coordinated to the palladium center.

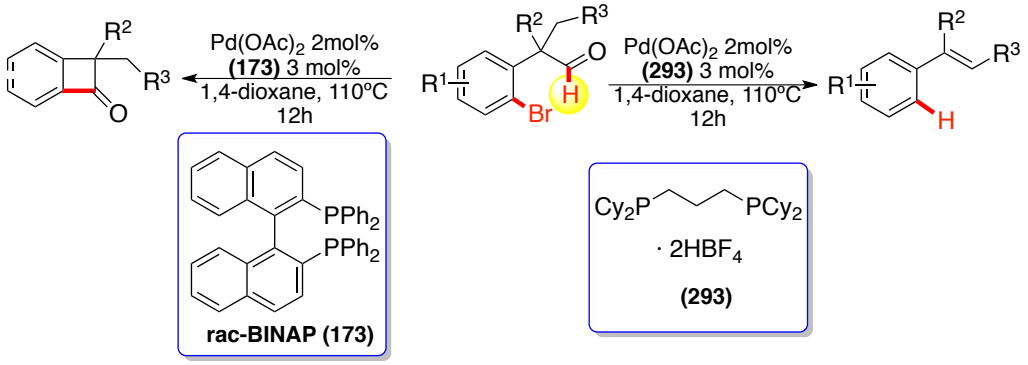

Figure 5.1

We found that a subtle modification on the ligand backbone lead to a new catalytic manifold for preparing configurationally-pure styrene derivatives *via* palladium catalyzed C-H bond-functionalization (Figure 5.1-left). We determined that the use more flexible and hemilabile ligands allowed for a rapid intramolecular proton transfer that set up the stage for a CO extrusion. Indeed, we demonstrated both experimentally and computationally that the decarbonylation event is the rate-determining step in this reaction. We have additionally shown that a new synthesis of α-aryl esters can be performed in the presence of exogeneous alcohol nucleophiles.

In Chapter 4 we extended our catalytic intramolecular C-H bond functionalization for preparing benzocyclobutenones or styrenes at will utilizing aryl chlorides as substrates. In this particular case, the nature of the *N*-heterocyclic carbenes (NHC´s) was critical, thus dictating the selectivity pattern. Thus, while IAd·HBF_4 yielded selectively benzocyclobutenone products, the use of IMes·HCl resulted in a selectivity switch, ending up in styrene derivatives (Figure 5.2). The presence of allylether as an additive allowed for the stabilization of the active 12 electron NHC-Pd(0) species, thus increasing the overall yield of the reaction.

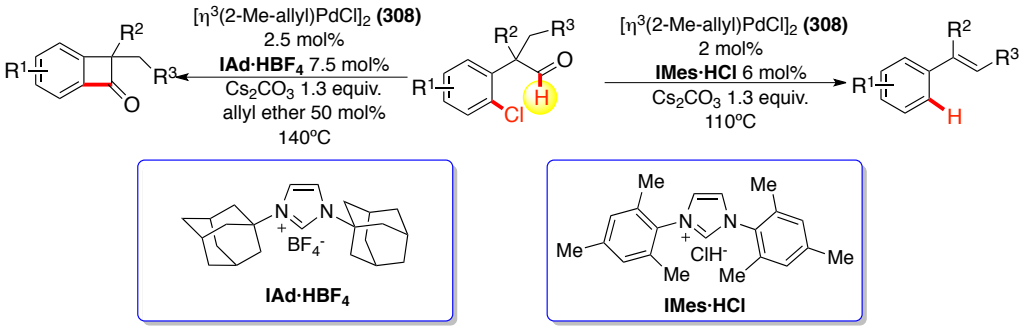

Figure 5.2

We believe that our catalytic protocol for preparing benzocyclobutenones via intramolecular C-H bond functionalization can be considered as a straightforward alternative to existing methodologies for synthesizing rather strained rings. Taking into consideration the potential of benzocyclobutenones as intermediates, we anticipate that our method could be applied for preparing heavily functionalized compounds in the context of total synthesis of natural products. Additionally, the means to selectively prepare benzocyclobutenones or styrenes at will depending on the ligand of choice will likely bring new knowledge in catalyst design.

Future work will primarily be devoted toward the discovery of new reactivity based upon the use of α-aryl aldehydes as substrates from an atom- and step-economical fashion. Currently a new transformation involving Fe-catalyzed aldehyde-ketone from α-aryl aldehydes is being studied in our group (Figure 5.3-bottom). Additionally, we are also interested in the study the enantioselective version of the Pd-catalyzed intramolecular C-H acylation en route to benzocyclobutenone derivatives.

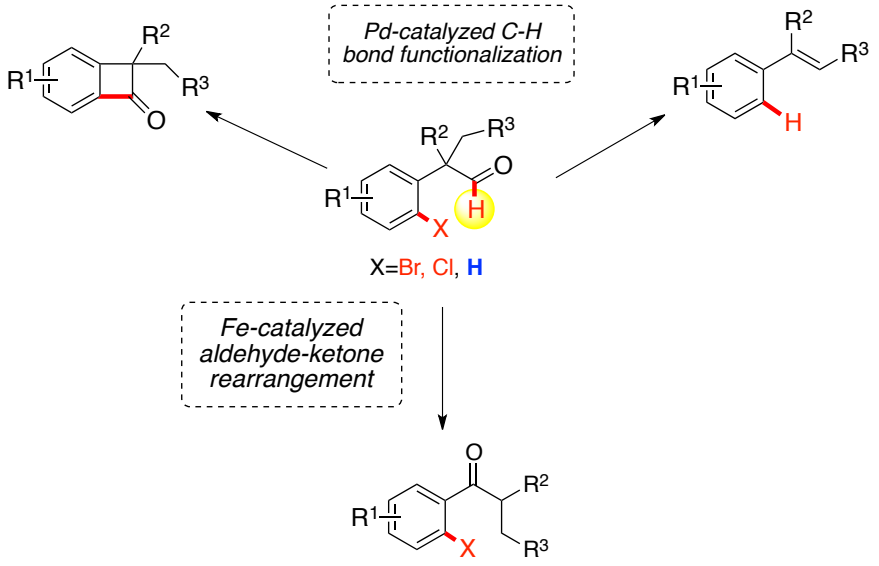

Figure 5.3

Appendix 1

X-Ray Chrystallography of (260)

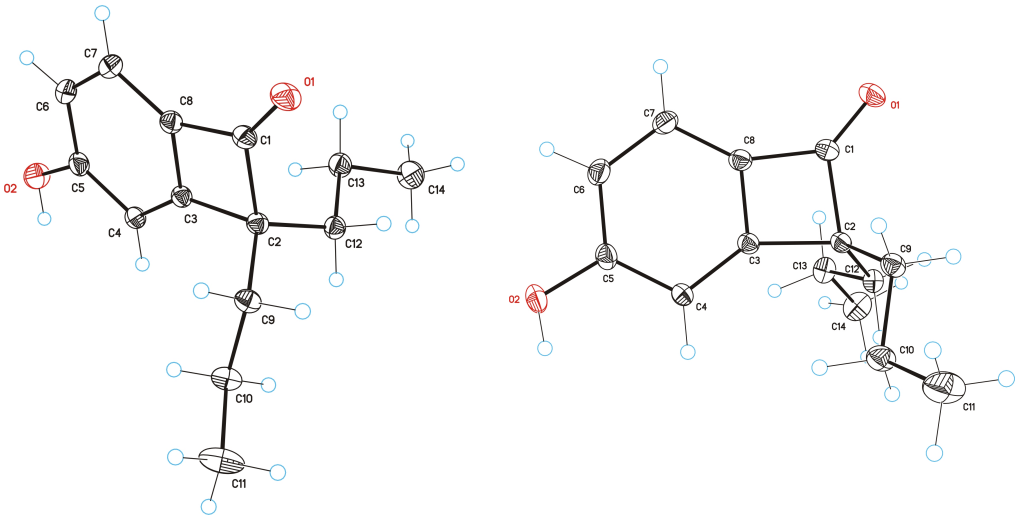

Table 1. Crystal data and structure refinement for (260)_0m.

Identification code	33b_0m
Empirical formula	C14 H18 O2
Formula weight	218.28
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	P2(1)2(1)2(1)
Unit cell dimensions	a = 8.7295(3) Å a= 90.00 ° b = 9.1322(4) Å b = 90.00 ° c = 15.4663(6) Å g = 90.00 °
Volume	1232.97(8) $Å^3$
Z	4
Density (calculated)	1.176 Mg/m^3
Absorption coefficient	0.077 mm^{-1}
F(000)	472
Crystal size	0.50 x 0.20 x 0.07 mm^3
Theta range for data collection	2.59 to 35.03 °.
Index ranges	-14 <=h<=14 ,-14 <=k<=14 ,-24 <=l<=20
Reflections collected	5372

Independent reflections	4883 [R(int) = 0.0681]
Completeness to theta =35.03 °	0.988 %
Absorption correction	Empirical
Max. and min. transmission	0.9946 and 0.9625
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5372 / 0 / 148
Goodness-of-fit on F^2	1.072
Final R indices [I>2sigma(I)]	R1 = 0.0439 , wR2 = 0.1109
R indices (all data)	R1 = 0.0495 , wR2 = 0.1146
Largest diff. peak and hole	0.465 and -0.167 e.Å^{-3}

Table 2. Bond lengths [Å] and angles [°] for 33b_0m.

Bond lengths----		C12-C2-C3	116.48(7)
C1-O1	1.2182(12)	C9-C2-C1	112.74(7)
C1-C8	1.4630(13)	C12-C2-C1	113.95(7)
C1-C2	1.5659(11)	C3-C2-C1	82.72(6)
C2-C9	1.5336(12)	C4-C3-C8	122.44(8)
C2-C12	1.5355(11)	C4-C3-C2	142.88(8)
C2-C3	1.5405(12)	C8-C3-C2	94.60(7)
O2-C5	1.3461(12)	C3-C4-C5	115.48(8)
C3-C4	1.3797(13)	O2-C5-C4	122.29(8)
C3-C8	1.3982(12)	O2-C5-C6	115.68(8)
C4-C5	1.4088(12)	C4-C5-C6	122.02(9)
C5-C6	1.4151(13)	C7-C6-C5	121.74(8)
C6-C7	1.3767(15)	C6-C7-C8	116.06(8)
C7-C8	1.4016(12)	C3-C8-C7	122.25(9)
C9-C10	1.5241(13)	C3-C8-C1	91.66(7)
C10-C11	1.5185(13)	C7-C8-C1	145.95(8)
C12-C13	1.5231(12)	C10-C9-C2	113.76(7)
C13-C14	1.5248(13)	C11-C10-C9	111.94(8)
		C13-C12-C2	114.94(7)
Angles----------		C12-C13-C14	111.74(8)
O1-C1-C8	136.16(8)		
O1-C1-C2	132.82(8)		
C8-C1-C2	91.01(7)		
C9-C2-C12	111.80(7)		
C9-C2-C3	116.19(7)		

Table 3. Torsion angles [°] for 33b_0m.

O1-C1-C2-C9	66.07(13)
C8-C1-C2-C9	-114.93(7)
O1-C1-C2-C12	-62.74(13)
C8-C1-C2-C12	116.26(7)
O1-C1-C2-C3	-178.53(10)
C8-C1-C2-C3	0.46(6)
C9-C2-C3-C4	-72.21(13)
C12-C2-C3-C4	62.81(14)
C1-C2-C3-C4	175.99(11)
C9-C2-C3-C8	111.32(8)
C12-C2-C3-C8	-113.66(8)
C1-C2-C3-C8	-0.49(6)
C8-C3-C4-C5	0.82(12)
C2-C3-C4-C5	-175.01(10)
C3-C4-C5-O2	177.62(8)
C3-C4-C5-C6	-1.07(12)
O2-C5-C6-C7	-178.02(9)
C4-C5-C6-C7	0.75(14)
C5-C6-C7-C8	-0.10(13)
C4-C3-C8-C7	-0.23(13)
C2-C3-C8-C7	177.24(8)
C4-C3-C8-C1	-176.96(8)
C2-C3-C8-C1	0.52(7)
C6-C7-C8-C3	-0.15(13)
C6-C7-C8-C1	174.00(12)
O1-C1-C8-C3	178.43(11)
C2-C1-C8-C3	-0.51(7)
O1-C1-C8-C7	3.4(2)
C2-C1-C8-C7	-175.56(13)
C12-C2-C9-C10	-72.58(10)
C3-C2-C9-C10	64.46(10)
C1-C2-C9-C10	157.50(8)
C2-C9-C10-C11	176.59(9)
C9-C2-C12-C13	172.66(8)
C3-C2-C12-C13	35.76(11)
C1-C2-C12-C13	-58.05(11)
C2-C12-C13-C14	-179.26(9)

Appendix 2

J|A|C|S COMMUNICATIONS

Published on Web 12/28/2009

Pd-Catalyzed Intramolecular Acylation of Aryl Bromides via C−H Functionalization: A Highly Efficient Synthesis of Benzocyclobutenones

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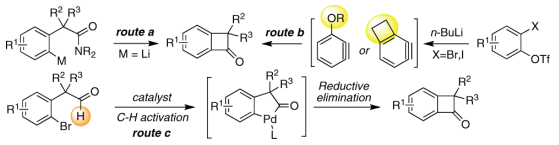
Benzocyclobutenones (BCBs) are an intriguing class of four-membered-ring ketones.[1] Their large ring strain and the great electrophilicity of their carbonyl unit make them highly susceptible to further manipulation. As a result, they have been successfully used as powerful intermediates in a wide variety of remarkable synthetic transformations,[1a,2] even in the context of the total synthesis of complex molecules.[3] Surprisingly, however, a limited number of methods have been developed for the selective formation of BCBs. Indeed, their synthesis is usually accomplished by intramolecular cyclization of stochiometric organolithium reagents (route a, Scheme 1)[4] or [2 + 2] cycloadditions (route b, Scheme 1).[1a,5] In the latter, the regioselectivity can be nicely controlled by the elegant approach of Suzuki using either proximal ring strain[5a] or α-alkoxybenzynes.[5b,c] However, the need for such *ortho*-directing groups as well as the use of highly reactive organolithium species might become important issues when preparing backbones with sensitive functional groups. Therefore, more general and direct routes to BCBs, particularly the design of regioselective strategies with the metal source being catalytic, would be highly desirable.

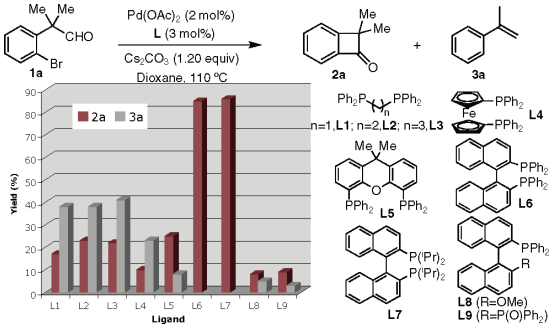
Scheme 1



In recent years, metal-catalyzed acylation of π systems such as alkenes and alkynes have become powerful tools in organic synthesis.[6] Despite the advances realized,[7−9] particularly the Heck-type process recently reported by Xiao,[10,11] direct acylation of aldehydes with aryl halides via metal-catalyzed C−H bond functionalization remains less explored.[12,13] As part of our investigations into Pd chemistry,[14] we present herein a versatile intramolecular acylation of aryl bromides via a C−H bond-functionalization event for the synthesis of BCBs (route c, Scheme 1).[15,16] The protocol is distinguished by its wide scope, thus opening access to functionalized BCB cores with a diverse set of substitution patterns that are beyond reach otherwise.

We began our study using readily available **1a** as the model substrate (Table 1).[17] A variety of experimental variables, such as the Pd precatalyst, ligand, base, and solvent, were systematically examined. After several rounds of optimization, we found that the best results were accomplished using $Pd(OAc)_2$, Cs_2CO_3, and a bidentate diarylphosphine in dioxane at 110 °C. Under these reaction conditions, we obtained variable amounts of **2a** and **3a**. While low conversions to **2a** were found for commonly employed **L1**−**L5**, the use of the binaphthyl-type ligands **L6** and **L7** *exclusively* afforded **2a** with *not even a trace* of **3a** detected in the crude reaction mixtures. At present, we have no explanation for this

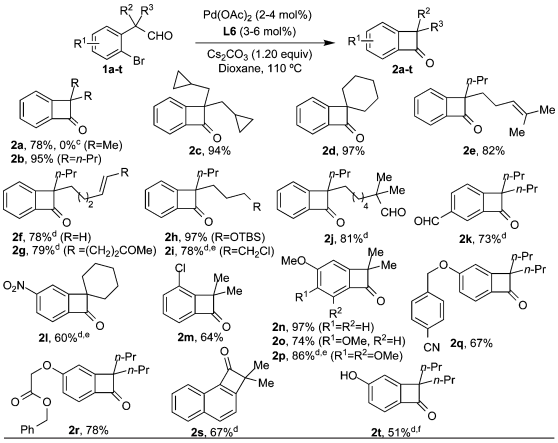
Table 1. Optimization of Reaction Conditions



behavior. Importantly, **L8** and **L9** gave low conversions to either **2a** or **3a**, thus indicating that the nature of the diarylphosphine backbone is crucial to the reactivity of the catalyst system. It is worth mentioning that at the same time we conducted our work, Larock reported the synthesis of styrene derivatives **3a** in modest yields;[18] interestingly, **2a** was not formed under their reaction conditions.

Having established the optimized reaction conditions, we set out to explore the scope of this reaction. As shown in Table 2, a host of aryl bromides with *ortho*, *meta*, or *para* electron-donating or electron-withdrawing substituents reacted with good to excellent

Table 2. Pd-Catalyzed Synthesis of Benzocyclobutenones[a,b]



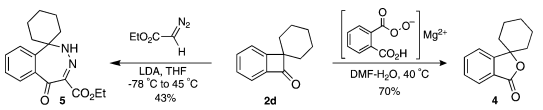
[a] Conditions: ArBr (0.5 mmol), $Pd(OAc)_2$ (2 mol %), **L6** (3 mol %), Cs_2CO_3 (0.6 mmol), dioxane (2 mL), 110 °C. [b] Isolated yields, average of two runs. [c] From ArCl. [d] $Pd(OAc)_2$ (4 mol %). [e] Using **L7**. [f] Cs_2CO_3 (2.40 equiv).

10.1021/ja909811t

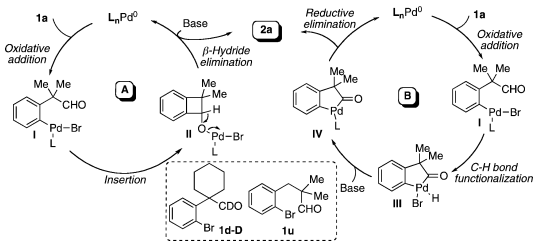
yields. Unlike other [2 + 2] cycloaddition approaches, the regioselectivity is totally controlled for unsymmetrical substrates, thus avoiding the need for directing-group methodologies.[5] Particularly significant is the chemoselectivity profile of this new protocol, as alkenes (**2e**, **2f**), esters (**2r**), nitriles (**2q**), aldehydes (**2j**, **2k**), ketones (**2g**), free hydroxy (**2t**), silyl groups (**2h**), alkyl halides (**2i**), and nitro groups (**2l**) all were perfectly accommodated. These results are noteworthy, as classical methods are not suitable for highly functionalized substrates.[1] As clearly shown by the formation of **2s**, this protocol could be extended to naphthyl derivatives as well. Furthermore, aryl chlorides were found to be inert (**2m**), thus providing a convenient functional handle for further functionalization. Although *o*-methoxy substituents did not hinder the reaction (**2p**), it was necessary to use the more bulky and electron-rich ligand **L7**. Gratifyingly, the acidic α-protons in **1g** and **1r** did not interfere with productive formation of **2g** and **2r**, respectively.[19] Finally, although the overall NMR data unambiguously identified the BCB core, we independently confirmed it by X-ray analysis of **2t**.[17]

Next, we turned our attention to the synthetic applicability of the resulting BCBs obtained using our method. As shown in Scheme 2, lactone **4** and benzodiazepine **5** could be easily obtained in one step by Baeyer−Villiger oxidation[2g] and diazomethylene insertion[2b] from **2d** in 70 and 43% yield, respectively.

Scheme 2. Synthetic Applicability of Benzocyclobutenones



Scheme 3. Proposed Catalytic Cycles



In principle, two mechanisms are conceivable for the results highlighted in Table 2 (Scheme 3): (1) 4-*exo*-trig-type insertion across the C═O bond from the oxidative addition complex **I**[20] followed by *β*-hydride elimination (mechanism **A**) or (2) C−H functionalization, loss of HBr from Pd(IV) intermediate **III**,[21] and a *challenging reductive elimination* from the five-membered metallacycle **IV** (mechanism **B**). As the available data do not allow us to distinguish between these two mechanisms, we reasoned that we could gather indirect evidence by studying the cyclization of **1u**. While **1u** would be expected to react faster via a 5-*exo*-trig-type cyclization in mechanism **A**,[22] a mechanism of type **B** would deal with a less favorable six-membered palladacycle. We found that **1u** did not cyclize under our optimized protocol; although this is not conclusive, we believe this experiment supports mechanism **B**. More interestingly, a kinetic isotope effect ($k_H/k_D = 2.8$) was observed when comparing the reaction rates of **1d** and the monodeuterated substrate **1d-D** (Scheme 3). This result implies that C−H bond cleavage is rate-limiting, thus providing further experimental evidence for mechanism **B**.[23]

In summary, we have developed a new protocol for the intramolecular acylation of aryl bromides via C−H functionalization. The practicality of the method, as well as the vast array of functionalized substrates with diverse substitution patterns that can be accessed, renders this method a powerful alternative to other approaches for the synthesis of BCBs. Further investigations of related processes are ongoing in our laboratories.

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Supporting Information Available: Experimental procedures, spectral data for all compounds, and crystallographic data for **2t** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) At present, we cannot rule out the intermediacy of acyl palladium intermediates via 1,4-palladium migration (see ref 18).

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Mechanistic Switch *via* Subtle Ligand Modulation: Palladium-Catalyzed Synthesis of α,β-Substituted Styrenes *via* C–H Bond Functionalization

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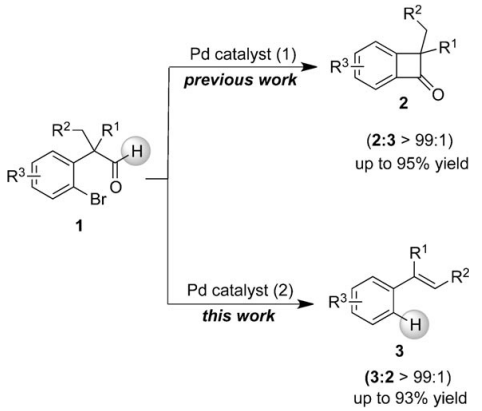
Abstract: A new catalyst system able to efficiently perform the synthesis of styrenes *via* C–H bond functionalization and a subtle ligand modification are described. The high level of activity achieved allows for the synthesis of highly functionalized α,β-substituted styrenes, even the elusive *E*-configured trisubstituted olefins, in a regio- and stereoselective manner. Mechanistic experiments allowed for the identification of the corresponding synthetic intermediates.

Keywords: aryl halides; catalyst design; C–H activation; palladium; P ligands



Scheme 1. Mechanistic switch in Pd-catalyzed intramolecular acylation of aryl bromides.

Metal-catalyzed reactions have arguably expanded the organic chemist's arsenal, allowing the development of innovative tactics for the construction of complex structures in few synthetic steps.[1] Critical for achieving high levels of reactivity, efficiency, practicality and reliability has been the use of ancillary ligands capable of modulating the properties of the catalytic species of such reactions.[2] Indeed, in recent years a myriad of operationally simple and highly efficient transformations has been described in the literature in this regard.[2] Particularly intriguing are recent metal-catalyzed strategies for generating multiple compounds from common building blocks as a result of a subtle modulation of the active catalyst.[3]

As part of our studies in the field of inert bond functionalization,[4] we have recently found that benzocyclobutenones (BCB) could be prepared *via* Pd-catalyzed intramolecular acylation of α-aryl aldehydes *via* C–H bond-activation (Scheme 1, upper pathway).[4b,5] In 2009, as part of their pioneering work on Pd-catalyzed migrations,[6] the Larock group reported a related procedure using aldehydes of type **1**;[7] intriguingly, this method did not lead to BCB, but rather to styrenes.[7] Despite the inherent interest of the latter method, however, this procedure resulted in low yields, and seemed to be limited to unfunctionalized aryl iodides at relatively high catalyst loadings. Additionally, only a single example using an aryl bromide was reported. In view of the importance of α,β-substituted styrene derivatives as synthetic intermediates in organic synthesis,[8] we wish to report herein the development of a general and highly efficient method for preparing related compounds when employing aryl bromides as substrates.[9] We demonstrate that subtle changes on the ancillary ligand lead to a dramatic mechanistic switch, resulting in the discovery of a C–H bond functionalization manifold capable of converting α-aryl aldehydes into BCB or α,β-substituted styrenes at will, depending on the judicious choice of the ligand employed.

We started our work by studying the reactivity of our model substrate **1a** (Figure 1) with several Pd pre-

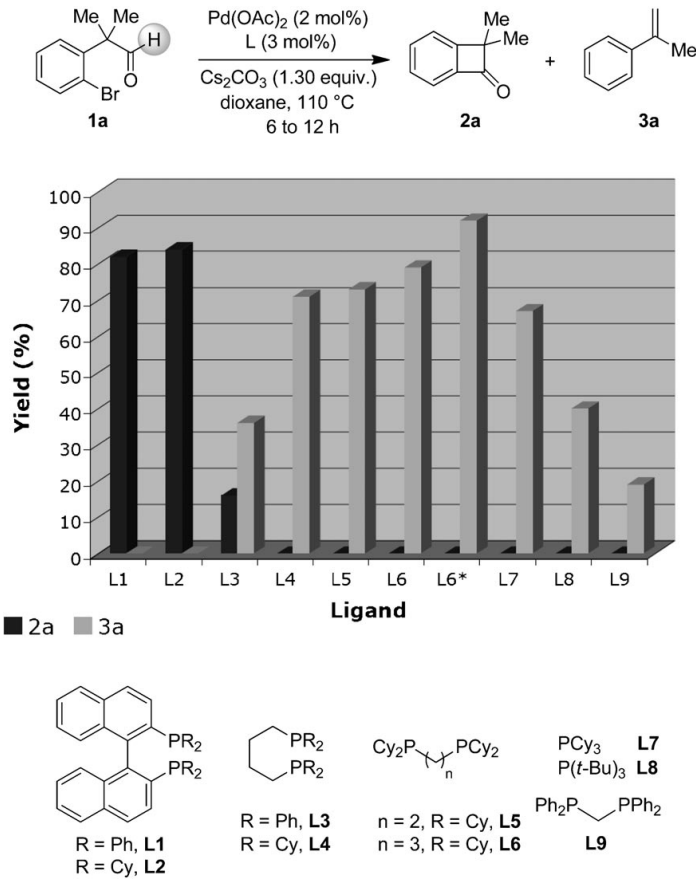
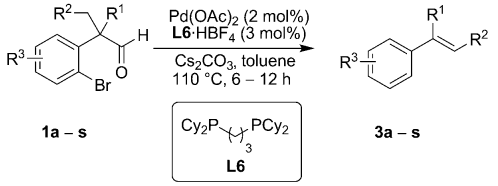


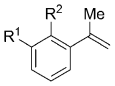
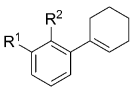
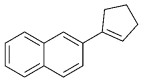
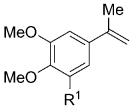
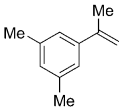
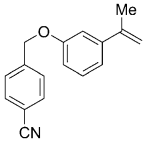
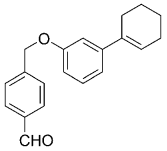
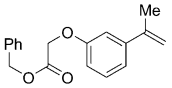
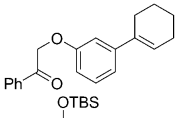
Figure 1. Screening of reaction conditions.[a–d] [a] **1a** (0.50 mmol), $Pd(OAc)_2$ (2 mol%), **L** (3 mol%), Cs_2CO_3 (1.30 equiv.), dioxane (0.50 M) at 110 °C. [b] GC yields using dodecane as internal standard. [c] **L6*** = **L6** was used in toluene as the solvent. [d] **L9** was used following the conditions reported in ref.[7]

catalysts, ligands, bases, solvents and temperatures. As expected,[4b] the use of either **L1** or **L2** afforded exclusively benzocyclobutenone **2a**, thus indicating that electronic factors on the phosphine binaphthyl backbone do not play a critical role. As a result, we hypothesized that the naphthyl moiety could exert an influence on the reaction outcome. Thus, we wondered whether a more flexible bisphosphine backbone with a similar bite angle[10] would have a deleterious effect on both reactivity and/or selectivity. Gratifyingly, this was indeed the case, as structurally related **L3** and **L4** had a different chemical behaviour; thus, while **L3** afforded mixtures of both **2a** and **3a**, the use of a more electron-rich ligand **L4** gave access to **3a**, with no **2a** being detected by NMR spectroscopy of the crude reaction mixture.

These results provide us with a unique opportunity to turn the flexibility exerted by these ligands into a strategic advantage, suggesting that *subtle differences on the ligand backbone lead to a dramatic switch on selectivity*.[3,11] After some experimentation,[12] we found that **L6** in toluene provided the best results.[13] At present we believe that ligands of type **L6** might act as a monodentate or hemilabile ligands. Although in lower yields, the ability of PCy_3 (**L7**) or $P(t\text{-}Bu)_3$ (**L8**) to selectively furnish **3a** clearly supports this working hypothesis. Gratifyingly, the formation of **3a** could also be accomplished at only 0.5–1 mol% catalyst loading; note, however, that in this particular case, longer reaction times were generally required.[12] In order to put these results into perspective, we performed a control experiment with the conditions previously described by Larock (Figure 1, **L9**);[7] only 19% yield was formed in this case, thus indicating the superior activity of the catalyst system based upon **L6**.

Table 1. Scope for the synthesis of α-styrene derivatives.[a,b]



Entry	Product	R^n	Yield [%][b]
1		$R^1=R^2=H$	77% (**3a**)
2		$R^1=OMe$; $R^2=H$	93% (**3b**)
3		$R^1=H$; $R^2=Cl$	65% (**3c**)
4		$R^1=R^2=H$	88% (**3d**)
5		$R^1=F$; $R^2=H$	52% (**3e**)
6		$R^1=NO_2$; $R^2=H$	91% (**3f**)
7			60% (**3g**)
8		$R^1=H$	66% (**3h**)
9		$R^1=OMe$	80% (**3i**)
10			80% (**3j**)
11			70% (**3k**)
12			61% (**3l**)
13			90% (**3m**)
14			75% (**3n**)
15			68% (**3o**)

[a] Aryl bromide (0.50 mmol), $Pd(OAc)_2$ (2 mol%), **L6** (3 mol%), Cs_2CO_3 (1.30 equiv.), toluene (0.50 M) at 110 °C.

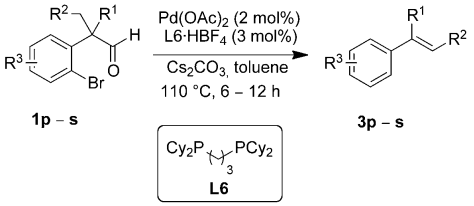
[b] Isolated yields, average of at least two runs.

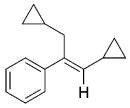
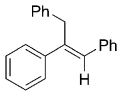
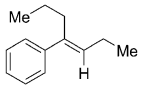
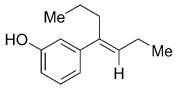
Encouraged by our initial findings, we sought to examine the preparative scope of this reaction. As become apparent from the results compiled in Table 1, a host of electron-deficient and electron-donating aryl bromides with different substitution patterns reacted with good to excellent yields. An illustrative example is the preparation of **3b** and **3f** in 93% and 91% yield, indicating that electronic factors do not play a prominent role in this reaction Notably, the method showed a strong preference for the coupling of aryl bromides as aryl chlorides (**3c**) and aryl fluorides (**3e**) remained inert. Furthermore, the presence of *ortho* substituents did not hinder the reaction, as **3i** and **3j** could be efficiently prepared in 80% yield, respectively. Particularly noteworthy is the chemoselectivity profile of our method as substrates containing nitro groups (**3f**), nitriles (**3k**), aldehydes (**3l**), esters (**3m**) and ketones (**3n**) were perfectly accommodated. Interestingly, our protocol was also amenable for the synthesis of silyl enol ethers (**3o**).

As highlighted in a recent review, the preparation of configurationally pure trisubstituted olefins in a regio- and diastereoselective manner, particularly with substituents possessing similar electronic or steric environments is still considered a great synthetic challenge.[14] Indeed, classic Wittig-type olefinations[15] or alkyne hydroarylation[16] are still ineffective in terms of regio- and diastereoselectivity. Similarly, the use of metal-catalyzed cross-coupling reactions is still problematic when preparing geometrically defined alkenyl metal (halide) species having similar substituents over the alkene backbone.[14,17] Remarkably, our new protocol based upon **L6** allows for the preparation of trisubstituted olefins in high yields with total regiocontrol and diastereoselectivities up to 22.2:1, hence providing a rapid and modular access to a variety of *E*-configured olefins (Table 2; **3p**, **3q**, **3r** and **3s**). Importantly, even unprotected phenols (**3s**) were tolerated. This example illustrates that nucleophilic attack of OH to the palladium(II) intermediates within the catalytic cycle does not compete with the efficacy of this reaction.

The data summarized above advocate the notion that both BCB **2** and α,β-styrenes **3** might share common synthetic pathways. As a result, we next turned our attention to unravel the mechanistic dichotomy when using ligands of type **L6**. We recently proposed that Pd(IV)[18] intermediates **II**[19] and **III**, respectively (mechanism A, Scheme 2);[4b] accordingly, there are in principle two conceivable mechanisms for the preparation of α,β-styrene derivatives: (a) reductive elimination of **II** *via* 1,4-palladium migration[6] affording an acylpalladium(II) intermediate (**IV**) followed by CO extrusion and a final reductive elimination (mechanism B, Scheme 2) or (b) CO extrusion from **III** leading to **VI** followed by β-hydride elimination and a final reduc-

Table 2. Scope for the synthesis of α-styrene derivatives in a regio- and diastereoselective manner.[a,b]



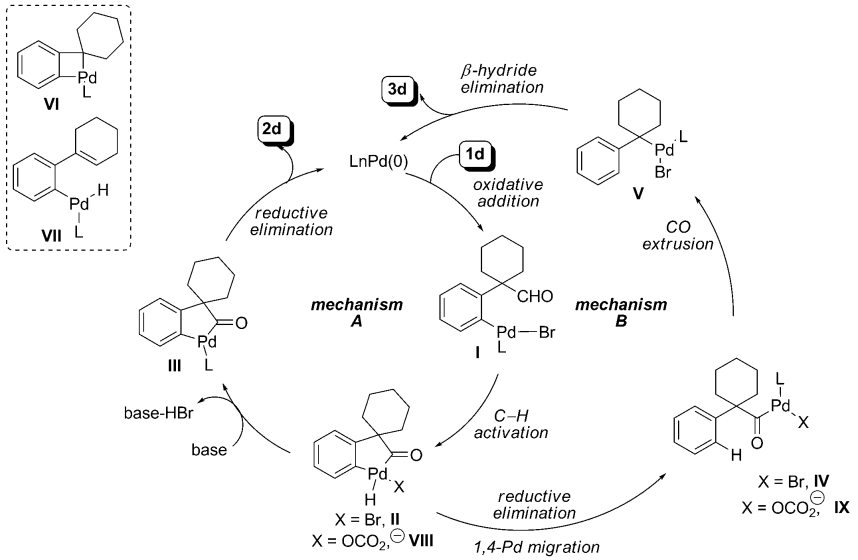
Entry	Product	Yield [%][b]
1		71% (**3p**), 16.5:1 (*E*:*Z*)
2		92% (**3q**), 22.2:1 (*E*:*Z*)
3		87% (**3r**), 10:1 (*E*:*Z*)
4		74% (**3s**),[c] 14.3:1 (*E*:*Z*)

[a] As for Table 1.
[b] Isolated yields, average of at least two runs.
[c] Cs_2CO_3 (2.60 equiv.) was used.

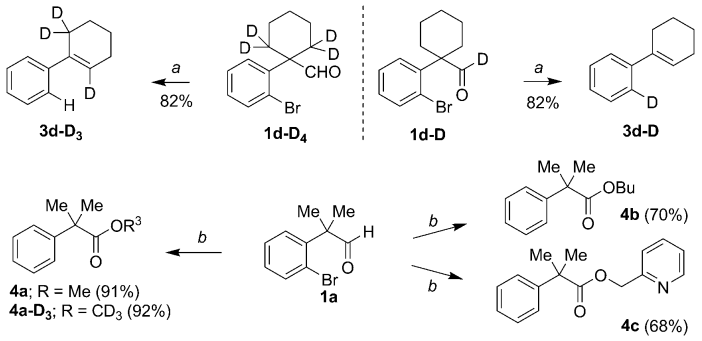
tive elimination from an intermediate of type **VII**. At present we cannot rule out intermediates **VIII** or **IX** *via* concerted metalation-deprotonation mechanisms promoted by carbonate bases.[20]

Although acylpalladium species have been postulated by Larock,[6] their prominent role for the synthesis of α-styrenes **3** still needs to be clarified.[7] As a result, we decide to gather indirect evidence through deuterium-labelling experiments (Scheme 3). If a mechanism *via* **VI** would be operating, we hypothesized that the reaction of **1d-D** would result in a loss of the deuterium label; on the contrary, in mechanism B, the deuterium label would be transferred to the aryl moiety. Experimentally, we found that the reaction of **1d-D** gave styrene **3d-D** as the only product in 85% isolated yield (Scheme 3). Notably, **1d-D$_4$** exclusively afforded **3d-D$_3$**, thus suggesting that only the hydrogen (or deuterium) from the aldehyde motif migrated to the aryl backbone.[21] While these experiments might not be taken as a definitive proof, we believe they provide a strong evidence for mechanism B (Scheme 3).

Additionally, we hypothesized that acylpalladium intermediate **IV** (or **IX**) could be trapped by addition of nucleophiles in the reaction mixture. Gratifyngly, the reaction of **1a** in the presence of CH_3OH, CD_3OD, *n*-BuOH or pyridinylmethanol at 60 °C afforded the corresponding esters **4a**, **4a-D$_3$**, **4b** and **4c** in good yields, respectively;[22] not even traces of styrene **3a** were identified in the crude reaction mixtures. We believe these experiments additionally support



Scheme 2. Possible mechanistic scenarios.



Scheme 3. Mechanistic considerations.

the intermediacy of acylpalladium intermediates of type **IV** (or **IX**).

In summary, we have found that a subtle modification on the phosphine ligand backbone leads to a new mechanistic manifold for the preparation of configurationally pure α,β-substituted styrenes *via* C–H bond-functionalization. This procedure is distinguished by its excellent chemoselectivity and wide scope. Further investigations to investigate the preparative scope of related reactions as well as the isolation of the reaction intermediates are currently underway in our laboratories.

Experimental Section

General Procedure for the Synthesis of α-Arylstyrenes (Table 1, entry 1)

An oven-dried screw-cap test tube containing a stirring bar was charged with $Pd(OAc)_2$ (2.3 mg, 2.0 mol%), 1,3-dicyclohexylphosphinepropane·2 HBF_4 (**L6**) (9.2 mg, 3.0 mol%), Cs_2CO_3 (0.21 g, 0.65 mmol) and 2-(2-bromophenyl)-2-methylpropanal (113.6 mg, 0.5 mmol). The test tube was evacuated and back-filled with dry argon (this sequence was repeated three times). The mixture was then placed in ultrasounds apparatus for 1 min and the mixture was then stirred in a pre-heated oil bath (110 °C) for 14 h. The mixture was then allowed to cool to room temperature, diluted with EtOAc (5 mL) and filtered through a Celite® plug, eluting with additional EtOAc (10 mL). The filtrate was concentrated and purified by column chromatography on silica gel eluting with hexanes to afford **3a** as a colourless oil; yield: 44.9 mg (76%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.59–7.53 (m, 2H), 7.41 (t, J = 7.5 Hz, 2H), 7.35 (dd, J = 8.2, 6.3 Hz, 1H), 5.46 (s, 1H), 5.18 (d, J = 1.4 Hz, 1H), 2.25 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.3, 141.2, 128.2, 127.4, 125.5, 112.4, 21.8.

Acknowledgements

We thank the ICIQ Foundation, Consolider Ingenio 2010 (CSD2006-0003) and MICINN (CTQ2009-13840) for financial support. Dr. Arkaitz Correa is gratefully acknowledged for preliminary results. Johnson Matthey, Umicore and Nippon Chemical Industrial are acknowledged for gifts of metal and ligand sources. R.M. and A.-F.G. thank MICINN for a RyC predoctoral fellowship (FPU).

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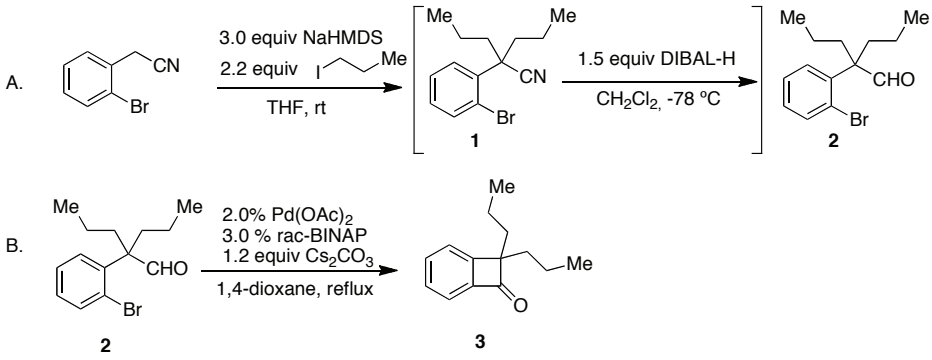
Synthesis of 8,8-Dipropylbicyclo[4.2.0]octa-1,3,5-trien-7-one via Pd-catalyzed Intramolecular C-H Bond-Acylation



Submitted by Ruben Martin and Areli Flores-Gaspar.[1]
Checked by Hongqiang Liu and Mark Lautens.

1. Procedure

A. *2-(2-Bromophenyl)-2-propylpentanenitrile* (**1**). An oven-dried, 500-mL, round-bottomed flask containing 2-bromophenylacetonitrile (8.0 g, 40.8 mmol, 1.0 equiv) (Note 1) is equipped with an oval magnetic stirring bar (32 mm x 15 mm), argon inlet, and a rubber septum. An argon atmosphere is maintained throughout the reaction using an argon manifold system. The flask is charged through the septum via syringe with anhydrous THF (150 mL) (Note 2) and NaHMDS (122.4 mL, 122.4 mmol, 3.0 equiv) (Note 3) is added dropwise over a 4 min period, which results in the solution becoming brown. After stirring for 20 min, the flask is immersed in a room temperature water bath and 1-iodopropane (8.8 mL, 89.8 mmol, 2.2 equiv) (Note 4) is added dropwise over a 3 min period, resulting in a pale brown slurry. The reaction is followed by TLC analysis (Note 5). After stirring for 2.5 h, the septum is removed and saturated NH_4Cl solution (100 mL) is added (Note 6). The organic layer is separated using a 500-mL separatory funnel and the aqueous solution is extracted with diethyl ether (3 x 20 mL) (Note 7). The combined organic layers are dried over $MgSO_4$ (10 g) (Note 8), filtered and concentrated by rotary evaporation (from 760 mmHg to 26 mmHg, 40 °C). The residue is transferred to a 500-mL round-bottomed flask and dried for 4 h under vacuum (10 mmHg). The crude compound **1**

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thus obtained is used directly in the next step without further purification (Note 9).

2-(2-Bromophenyl)-2-propylpentanal (**2**). The previous 500-mL round-bottomed flask with the crude 2-(2-bromophenyl)-2-propylpentanenitrile (**1**) is equipped with an oval stirring bar (32 mm x 15 mm), argon inlet and a rubber septum. An argon atmosphere is maintained throughout the reaction using an argon manifold system. The flask is charged through the septum (*via* syringe) with anhydrous CH_2Cl_2 (150 mL) (Note 10) and immersed in a previously cooled dry ice/acetone bath at –78 ºC (internal temperature) (Note 11). Then, DIBAL-H (45 mL, 45.0 mmol, 1.1 equiv) is added dropwise via syringe over a 15 min period (Note 12), resulting in a pale orange solution. The reaction progress is followed by TLC analysis (Note 13) or GC analysis (Note 14). After 2 h reaction time, additional DIBAL-H (20.4 mL, 20.4 mmol, 0.5 equiv) is added dropwise via syringe; after stirring for an additional 1 h, no more starting material is observed by TLC analysis (Note 15). The flask is removed from the cooled bath, and the reaction is then quenched by slow addition of ethyl acetate (150 mL) (Note 16) and 2M HCl (100 mL) (Note 17) over a 10 min period. The organic phase is separated using a 1-L separatory funnel and the aqueous solution is extracted with ethyl acetate (2 x 50 mL). The combined organic layers are dried over magnesium sulfate (8 g) and concentrated by rotary evaporation (from 760 mmHg to 26 mmHg, 40 °C). The residue is purified by column chromatography on silica gel (Note 18). The title compound is thus obtained as a yellow oil (8.00–8.09 g, 69–70% yield) (Note 19).

B. *8,8-Dipropylbicyclo[4.2.0]octa-1,3,5-trien-7-one* (**3**). An oven-dried 500-mL Schlenk flask equipped with a reflux condenser and a stirring bar (32 mm x 15 mm) is charged with $Pd(OAc)_2$ (134.7 mg, 2.0 mol%) (Note 20), *rac*-BINAP (560.4 mg, 3.0 mol%) (Note 21), Cs_2CO_3 (11.73 g, 36.01 mmol, 1.2 equiv) (Note 22). The Schlenk flask is evacuated and back-filled with argon (this sequence was repeated three times over a period of 3 min). Under an argon atmosphere, the 1,4-dioxane (150 mL) solution of *2-(2-bromophenyl)-2-propylpentanal* (**2**) (8.50 g, 30.01 mmol), (Note 23) is then added by syringe. The mixture is then placed in a pre-heated oil bath (Note 24) at 110 °C for 22 h under argon atmosphere, resulting in a black slurry. The mixture is then allowed to cool to room temperature, diluted with EtOAc (3 x 50 mL) and filtered through a Celite® plug (19.4 g, 50 mL) (Note 25) eluting with additional EtOAc (2 x 30 mL). The filtrate is

concentrated and purified by column chromatography on silica gel (Note 26), obtaining 4.24 g (20.96 mmol, 70% yield) of the title compound as a yellow oil (Notes 27 and 28).

2. Notes

1. 2-Bromophenylacetonitrile (97%) was purchased from Alfa Aesar and used as received.

2. THF was distilled from Na/benzophenone ketyl. Submitters used THF anhydrous (content in H_2O <10 ppm) that was dried from an Instrument Solvent Purification System (MBraun-SPS).

3. NaHMDS (1.0 M in THF) was purchased from Aldrich and used as received.

4. 1-Iodopropane (99%) was purchased from Aldrich and used as received.

5. TLC analysis (performed using EMD TLC silica gel 60 F254 plates thin-layer chromatography) using hexanes:EtOAc (95:5) as the eluent; visualization with $KMnO_4$ stain; 2-bromophenylacetonitrile: R_f= 0.49, mono-alkylated product: R_f=0.79 and compound **1**: R_f=0.89

6. NH_4Cl was purchased from ACP; the solution was prepared using 110 g of NH_4Cl and 100 mL of distilled water.

7. Diethyl ether (stabilized with ~1 ppm of 2,6 di-*tert* butyl-*p*-cresol) was purchased from Caledon and used as received.

8. Magnesium sulfate anhydrous was purchased from ACP and used as received.

9. Crude compound **1** has the following properties: Brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.92 (t, *J* = 7.2 Hz, 6 H), 1.06–1.19 (m, 2 H), 1.39–1.52 (m, 2 H), 1.97 (ddd, *J* = 14.0, 12.4, 4.4 Hz, 2 H), 2.61 (ddd, *J* = 14.0, 12.0, 4.4 Hz, 2 H), 7.16 (ddd, *J* = 8.0, 7.2, 1.2 Hz, 1 H), 7.32 (ddd, *J* = 8.0, 7.2, 1.2 Hz, 1 H), 7.61 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.72 (dd, *J* = 8.0, 1.6 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.9, 18.9, 39.3, 50.9, 120.3, 123.0, 127.6, 129.2, 131.5, 135.3, 135.9.

The pure compound **1** was prepared following the procedure *A* using 2-bromophenylacetonitrile (1.46 g, 7.44 mmol, 1.0 equiv), 20 mL of anhydrous THF, NaHMDS (22 mL, 22 mmol, 3.0 equiv), 1-iodopropane (1.60 mL, 16.4 mmol, 2.2 equiv). Column chromatography was performed on 75 mL of Silica gel 230-400 mesh SiliaFlash®P60, purchased from Silicycle. It was wet packed in a 3 cm diameter column using hexanes/ethyl

Acetate: 90/10 and the crude material was directly loaded to the column (the remaining residue was loaded in the minimal amount of hexanes/ethyl acetate 90/10). 10 mL fractions were collected at 0.15 mL/s rate, eluting with hexanes/ethyl Acetate: 90/10. All the fractions (9 to 18) containing the desired product were combined and concentrated by rotary evaporation (from 760 mmHg to 26 mmHg, 40 °C), and dried under high vacuum (10 mmHg), to yield 1.77 g (9.23 mmol, 85% yield) of the title compound as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.92 (t, *J* = 7.2 Hz, 6 H), 1.04–1.21 (m, 2 H), 1.37–1.54 (m, 2 H), 1.97 (ddd, *J* = 16.8, 12.0, 4.5 Hz, 2 H), 2.61 (ddd, *J* = 16.8, 12.3, 4.5 Hz, 2 H), 7.16 (ddd, *J* = 8.7, 7.5, 1.5 Hz, 1 H), 7.32 (ddd, *J* = 8.7, 7.5, 1.2 Hz, 1 H), 7.60 (dd, *J* = 7.8, 1.2 Hz, 1 H), 7.71 (dd, *J* = 7.8, 1.5 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.9, 18.9, 39.2, 50.8, 120.2, 123.0, 127.5, 129.2, 131.5, 135.2, 135.9. IR (neat, cm^{-1}): 2961, 2932, 2874, 2359, 2233, 1629, 1470, 1391, 1021, 758. HRMS calcd. for ($C_{14}H_{18}BrN+NH_4$): 297.0966, Found 297.0953. Anal. calcd. for $C_{14}H_{18}BrN$: C, 60.01; H, 6.47; N, 5.00 Found: C, 59.80; H, 6.46; N, 4.89.

10. Dichloromethane anhydrous (content in H_2O <10 ppm) was dried from an Instrument Solvent Purification System (MBraun-SPS).

11. Submitter used an immersion cooler HAAKE EK90 with methanol bath for –78 ºC.

12. Diisobutyl aluminiumhydride (DIBAL-H), 1M solution in hexane, Sureseal ™ was purchased from Aldrich and used as received. Submitters used DIBAL-H, 1M solution in hexane, Acroseal™ that was purchased from Acros Organics and titrated before use with the following procedure: Hoye, T. R.; Aspaas, A. W.; Eklov, B. M.; Ryba, T. D. *Org. Lett.* **2005**, *7*, 2205.

13. TLC is run twice using a mixture of Hexanes:EtOAc (40:1) as eluent (compound **1**: R_f= 0.50, compound **2** R_f=0.46), using a $KMnO_4$ stain.

14. Submitters also used GC to monitor the reaction progress. Compounds **1** and **2** are easily distinguished by GC: $t_{r\mathbf{1}}$=5.04 min; $t_{r\mathbf{2}}$=5.24 min.

GC-method (Agilent 19091J-413): Initial Temp: 70ºC; Maximum Temp: 300ºC; Initial Time: 1.0 min, Equilibration Time: 3.0 min; Ramp: Rate = 50.0 °/min; Final Temp = 250 °C, Final Hold Time= 1.50 min; Run Time: 6.10 min; Pressure: 10.10 psi; Split flow: 97.1 mL/min; Gas type: Helium; Capillary column: HP-5, 5% phenyl methyl siloxane

15. Addition of DIBAL-H at the start of experiment rather than semi-batch addition led to incomplete reduction in a 3 h period.

16. Ethyl acetate was purchased from Fisher Scientific and used as received.

17. HCl (37-38%) was purchased from Fisher Scientific; a 2M HCl solution is preparing by adding 16.7 mL of HCl (37-38%) to a 250-mL volumetric flask containing 83.3 mL of distilled water.

18. Column chromatography was performed on 260 mL of silica gel (230-400 mesh SiliaFlash®P60), purchased from Silicycle. It was wet packed in a 5-cm diameter column using hexanes/ethyl acetate (96/4) and the crude material was directly loaded to the column (The remaining residue was loaded in the minimal amount of hexanes/ethyl acetate (96/4)). Fractions of 30 mL were collected at 0.5 mL/s rate, eluting with hexanes/ethyl acetate (96/4). All fractions (10-18) containing the desired product were combined, concentrated by rotary evaporation (from 760 mmHg to 26 mmHg, 40 ºC), and dried overnight at 10 mmHg. In order to avoid any decomposition, compound **2** was kept under argon atmosphere.

19. Compound **2** has the following physical properties: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.88 (t, *J* = 7.2 Hz, 6 H), 0.97–1.11 (m, 2 H), 1.16–1.30 (m, 2 H), 2.00 (ddd, *J* = 26.0, 12.0, 4.8 Hz, 4 H), 7.13–7.19 (m, 1 H), 7.33–7.38 (m, 2 H), 7.60 (d, *J* = 8.0 Hz, 1 H), 9.86 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.9, 17.0, 35.1, 58.6, 123.9, 127.5, 129.1, 130.4, 135.0, 140.2, 204.4. IR (neat, cm^{-1}): 2957, 2872, 1716, 1564, 1466, 1432, 1380, 1264, 1167, 1113, 1067, 1029, 971. HRMS calcd. for ($C_{14}H_{19}BrO+NH_4$): 300.0963, Found 300.0959. Anal. calcd. for $C_{14}H_{19}BrO$: C, 59.37; H, 6.76. Found: C, 59.42; H, 6.91**.** Submitters also determined the purity of **2** using GC analysis. The range of yield for different runs is from 63% to 70%.

20. $Pd(OAc)_2$ (min. 98%; 99.9% Pd) was purchased from Strem Chemicals and used as received. Submitters noted that $Pd(OAc)_2$ (99.98% (metal basis); Pd 47% min) purchased from Alfa-Aesar gave similar efficiency.

21. Racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl 98% was purchased from Strem Chemicals and used as received. Submitters noted that racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl 98% from Atomax chemicals gave similar efficiency.

22. Cs_2CO_3 99.9% [metal basis] was purchased from Aldrich and was stored in the glove box. The exact amount of cesium carbonate was weighed out inside the glove box and then added to the reaction mixture under an

argon stream outside the glove box. Submitters used Cs_2CO_3 99% [metal basis] purchased from Alfa Aesar.

23. 1,4-Dioxane was distilled over sodium, and used directly without degassing. Submitters used dioxane anhydrous, 99.8% that was purchased from Sigma Aldrich. Instead of the addition of a dioxane solution of 2-(2-bromophenyl)-2-propylpentanal (**2**), submitters added **2** to the flask at the start of experiment followed by air exclusion and addition of dioxane.

24. Oil Bath: silicone oil δ=0.97, was purchased from Fisher Scientific and used as received (working temperature from –40 ºC to +200 ºC).

25. Celite® 545 coarse was purchased from Sigma-Aldrich and used as received.

26. Column chromatography was performed on 500 mL of silica gel 230-400 mesh SiliaFlash®P60, purchased from Silicycle. The column was wet packed in a 8-cm diameter column with hexanes and the crude material was directly loaded to the column (The remaining residue was loaded in the minimal amount of hexanes/ethyl acetate (10/1)). Fractions of 30 mL were collected at 0.8 mL/s rate eluting with the following gradient: 500 mL hexane, 850 mL hexanes/ethyl acetate: 30/1, 300 mL hexanes/ethyl acetate: 20:1, 400 mL hexanes/ethyl acetate: 10/1, 300 mL hexanes/ethyl acetate: 5/1. The fractions (10-17) containing compound **3** (R_f=0.65; hexanes:EtOAc (90:10)) are collected, combined and concentrated by rotary evaporation (from 760 mmHg to 26 mmHg, 40 ºC). In order to avoid any decomposition, compound **3** was kept under argon atmosphere.

27. Compound **3** has the following physical properties: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.83 (t, *J* = 7.2 Hz, 6 H), 1.13–1.30 (m, 4 H), 1.74 (ddd, *J* = 8.8, 6.4, 2.4 Hz, 4 H), 7.32 (dt, *J* = 6.8, 0.8 Hz, 1 H), 7.37 (td, *J* = 6.8, 0.8 Hz, 1 H), 7.42 (dt, *J* = 6.8, 0.8 Hz, 1 H), 7.48 (td, *J* = 6.8, 0.8 Hz, 1 H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 14.7, 19.1, 37.4, 74.2, 120.9, 123.2, 129.2, 135.1, 146.1, 160.6, 197.1. IR (neat, cm^{-1}): 3064, 2958, 2873, 2845, 1754, 1582, 1461, 1441, 1379, 1274, 1142, 1092, 926. HRMS calcd. for ($C_{14}H_{19}O+NH_4$): 203.1436, Found 203.1433. Anal. calcd. for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 82.97; H, 8.79**.** The range of yields for different runs is from 67% to 71%.

28. The only by-product generated in the reaction is [(1*E*)-1-propylbut-1-enyl]benzene (**4**) as a mixture of diastereoisomers (16:1, favoring *E* isomer, as judged by NOESY) in 9.0% yield. This by-product elutes prior to the main fraction in the column chromatography and is readily removed (R_f=0.90; hexanes:EtOAc (90:10)). Compound **4** has the following physical

properties: Colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.06 (t, J = 7.6 Hz, 3 H), 1.23 (t, J = 7.6 Hz, 3 H), 1.51–1.60 (m, 2 H), 2.38 (q, J = 7.2 Hz, 2 H), 2.65 (t, J = 7.2 Hz, 2 H), 5.83 (t, J = 7.2 Hz, 1 H), 7.33–7.37 (m, 1 H), 7.42–7.46 (m, 2 H), 7.49–7.52 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.9, 14.4, 21.8, 21.9, 31.6, 126.32, 126.34, 128.1, 130.9, 139.4, 143.4. IR (neat, cm^{-1}): 3058, 2930, 2871, 1599, 1491, 1457, 1443, 1377, 1074, 1030, 754, 697. HRMS Calcd for ($C_{13}H_{19}$): 175.14868, Found 175.14834. Anal. Calcd for $C_{13}H_{18}$: C, 89.59; H, 10.41. Found: C, 89.39; H, 10.33.

Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995

3. Discussion

Benzocyclobutenones are an intriguing class of four-membered ring ketones that have been used extensively as powerful synthetic intermediates in organic synthesis[2]. The reactivity of benzocyclobutenones is primarily associated to their unique high electrophilicity of the carbonyl unit, allowing

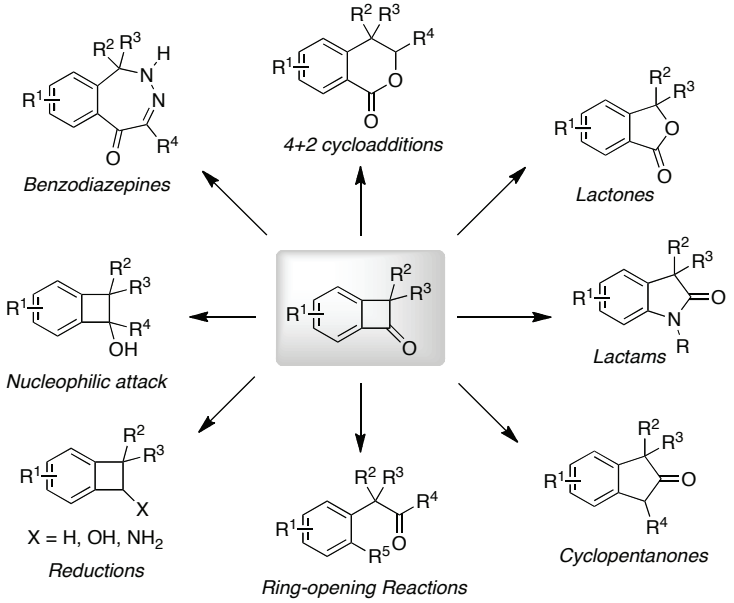

Figure 1. Benzocyclobutenones in Organic Synthesis

a myriad of different transformations, ranging from classical 1,2-additions, ring-expansion, ring-opening reactions, cycloadditions, heterocycle synthesis or preparation of complex benzocyclobutanes via reduction of the carbonyl backbone, among many others (Figure 1).

Despite their potential as synthetic intermediates, benzocyclobutenones are elusive compounds to prepare in a straightforward and general fashion. To the best of our knowledge, the synthesis of benzocyclobutenones is usually accomplished via two different routes: (1) intramolecular addition of organolithium or Grignard reagents to Weinreb amides (route 1, Figure 2)[3] or (2) [2+2]-cycloaddition of silyl enol ethers and benzyne (route 2, Figure 2),[4] as elegantly described by Suzuki and coworkers. The application profile of these methods, unfortunately, is quite limited, as only a limited set of substitution patterns can be accessed; additionally, these procedures do not tolerate the presence of functional groups, as stochiometric amounts of organolithium derivatives are required.

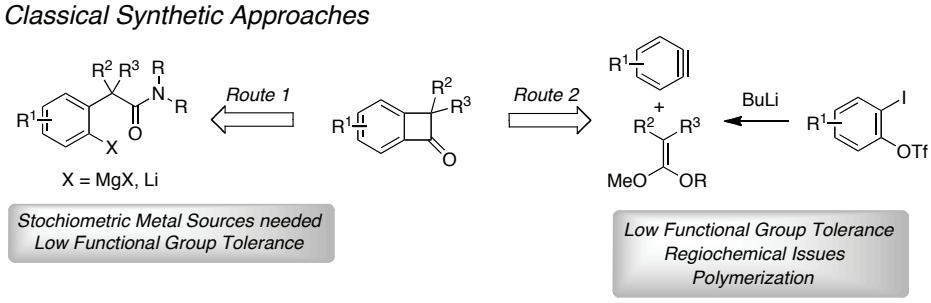

Figure 2. Alternative Pathways to Benzocyclobutenones

In recent years, metal-catalyzed C-H bond-functionalization strategies have become one of the most popular areas of research in organic (organometallic) chemistry.[5] The attractiveness of such methodologies is based on the ability to build up molecular complexity from rather inert and abundant C-H bonds, thus allowing unconventional and elegant bond disconnection strategies for assembling valuable organic structures. Our group has recently reported that benzocyclobutenones can be prepared by intramolecular Pd-catalyzed acylation via C-H bond-functionalization.[6] Such an approach has the advantage of using readily available precursors and controlling the substitution pattern over the aryl backbone; additionally, the method tolerates a wide range of functional groups, allowing for the first

time, the preparation of highly complex benzocyclobutenones in a straightforward manner. The scope of this procedure is illustrated in Table 1.

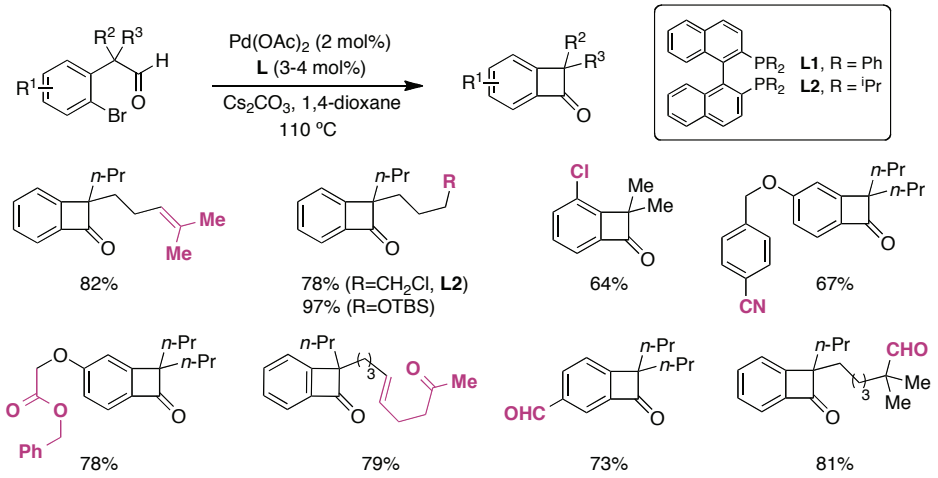

Table 1. Pd-catalyzed Synthesis of Benzocyclobutenones via C-H Bond-Functionalization

Herein, we describe the preparation of the model compound [8,8-dipropylbicyclo[4.2.0]octa-1,3,5-trien-7-one], thus illustrating the simplicity of our new protocol for the direct conversion of commonly employed and readily available α-aryl aldehydes into benzocyclobutenones. This user-friendly methodology nicely complements the existing routes to benzocyclobutenones in the literature.[3,4] Given the practicality and flexibility, it is expected that this method will find immediate application in advanced organic synthesis.

1. Institute of Chemical Research of Catalonia (ICIQ), AV. Països Catalans 16, 43007 Tarragona, Spain, E-mail: rmartinromo@iciq.es; We thank ICIQ Foundation, Consolider Ingenio 2010 (CSD2006-0003) and MICINN (CTQ2009-13840) for financial support. Johnson Matthey, Umicore, and Nippon Chemical Industrial are acknowledged for gifts of metal and ligand sources. R. M and A. F-G thank MICINN for RyC and FPU fellowships.

2. (a) Sadana, A. K.; Saini, R. K.; Billups, W. E. *Chem. Rev.* **2003**, *103*, 1539. (b) Bellus, D.; Ernst, B. *Angew. Chem., Int. Ed.* **1988**, *27*, 797.

3. Aidhen, I. S.; Ahuja, J. R. *Tetrahedron Lett.* **1992**, *33*, 5431.

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5. For reviews, see: (a) Daugulis, O.; Do, H. –Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (b) Chen, X.; Engle, K. M.; Wang, D. –H.; Yu, J. –Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (c) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 9792. (d) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624.

6. Álvarez-Bercedo, P.; Flores-Gaspar, A.; Correa, A.; Martin, R. *J. Am. Chem. Soc.* **2009**, *132*, 466.

Appendix
Chemical Abstracts Nomenclature; (Registry Number)

2-Bromophenylacetonitrile: Benzeneacetonitrile, 2-bromo-; (19472-74-3)

NaHMDS: Silanamine, 1,1,1-trimethyl-N-(trimethylsilyl)-, sodium salt (1:1); (1070-89-9)

1-Iodopropane: Propane, 1-iodo-; (107-08-4)

DIBAL-H: Aluminum, hydrobis(2-methylpropyl)-; (1191-15-7)

$Pd(OAc)_2$: Acetic acid, palladium (2+) salt (2:1); (3375-31-3)

Rac-BINAP: Phosphine, 1, 1'-[1,1'binaphthalene]-2,2'-diylbis[1,1-diphenyl-; (98327-87-8)

Cs_2CO_3: Carbonic acid, cesium salt (1:2); (534-17-8)

2-(2-Brommophenyl)-2-propylpentanal: Benzeneacetaldehyde, 2-bromo-α,α-dipropyl-; (1206450-98-7)

[8,8-Dipropylbicyclo[4.2.0]octa-1,3,5-trien-7-one]: Bicyclo[4.2.0]octa-1,3,5-trien-7-one, 8,8-dipropyl-; (1206451-50-4)

[(1*E*)-1-Propylbutyl-1-enyl]benzene: Benzene, [(1*E*)-1-propyl-1-buten-1-yl]-; (1151654-13-5)

Ruben Martin was born in 1976. He received his Ph.D in 2003 at the Universitat de Barcelona with Prof. Antoni Riera. After two postdoctoral stages at the Max-Planck-Institut für Kohlenforschung with Prof. Alois Fürstner and at the Massachusetts Institute of Technology with Prof. Stephen L. Buchwald, he initiated his independent career in 2008 at the Institute of Chemical Research of Catalonia (ICIQ). His interests are primarily focused on the metal-catalyzed activation of inert bonds.

Areli Flores-Gaspar was born in Mexico, City. She did her Bachelor studies and a M.Sc. at the Universidad Nacional Automoma de México. She is currently a Ph.D. student in Dr. Ruben Martin's group at Institut Català d'Investigació Química in Tarragona, Spain. Her work is focused on the development of novel synthetic transformations based upon C-H bond-activation protocols.

Hongqiang Liu was born in China. He did his B. Sc. and M. Sc, at Peking University and Peking Union Medical College respectively. He finished his Ph.D. degree in 2010 under supervision of Dr. John Vederas at the University of Alberta. He is currently a postdoctoral fellow at Dr. Mark Lautens group at the University of Toronto. His work is focused on molecular motor synthesis using palladium-catalyzed and norbornene-mediated domino reactions.

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N-Heterocyclic Carbene Dichotomy in Pd-Catalyzed Acylation of Aryl Chlorides via C−H Bond Functionalization

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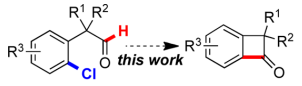
ABSTRACT



Ligand-controlled selectivity
Chemo- and site-selectivity
Aryl chlorides as substrates
No decarbonylation events

The first Pd-catalyzed intramolecular acylation of aryl chlorides via C−H bond functionalization is presented. The method allows for the synthesis of a variety of elusive benzocyclobutenones with a wide range of functional groups and substitution patterns. We demonstrate that a change in the ligand backbone dictates the selectivity pattern.

Metal-catalyzed C−H arylation protocols are now widely recognized as powerful synthetic tools in organic synthesis.[1] Despite the utility of aldehydes, perhaps the most versatile synthon in organic synthesis, an arylation event via C−H functionalization of the aldehyde motif, is underrepresented in the C−H arylation arena.[2] A close survey of the existing methodologies shows that directing groups are generally required and that the control of selectivity still represents a major concern;[2,3] however, the cleavage of directing groups is notoriously difficult under mild reaction conditions, thus limiting the application profile of these methodologies and enforcing a change in strategy. In this regard, the use of aryl halides constitutes an excellent alternative for increasing molecular complexity while lowering the overall cost for producing fine chemicals.[4]

In order to demonstrate the potential of the intramolecular acylation techniques via C−H functionalization, we envisioned the synthesis of benzocyclobutenones (BCBs), unique scaffolds with great significance due to their versatility as synthetic intermediates.[5] Such logic unravels readily accessible α-aryl aldehydes[6] as the key building blocks (Scheme 1). This transformation is quite remarkable, as one C−C bond must be formed while generating a rather strained ring. Recently, we reported the preparation of BCBs via C−H functionalization with aryl bromides as coupling counterparts.[7] Unfortunately, this protocol was not yet satisfactory, since (a) the less reactive and more accessible aryl chlorides were totally inert;[4] (b) the method showed low selectivity with multiple reaction sites, and (c) the reaction was restricted to α,α-disubstituted benzocyclobutenones. Although one might anticipate that

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(2) For reviews in C−H hydroacylation using alkynes or alkenes as coupling partners: (a) Leung, J. C.; Krische, M. J. *Chem. Sci.* **2012**, *3*, 2202. (b) Willis, M. C. *Chem. Rev.* **2010**, *110*, 725.

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(4) *Metal-catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998.

(5) For selected references: (a) Takahashi, N.; Kanayama, T.; Okuyama, K.; Kataoka, H.; Fukaya, H.; Suzuki, K.; Matsumoto, T. *Chem.—Asian. J.* **2011**, *6*, 1752. (b) Mori, K.; Ohmori, K.; Suzuki, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 5633. (c) Hamura, T.; Suzuki, T.; Matsumoto, T.; Suzuki, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 6294. (d) Ohmori, K.; Mori, K.; Ishikawa, Y.; Tsuruta, H.; Kuwahara, S.; Harada, N.; Suzuki, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 3167. (e) Hosoya, T.; Kuriyama, Y.; Suzuki, K. *Synlett* **1995**, 635.

(6) (a) Martin, R.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 4561. (b) Vo, G. D.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2008**, *47*, 2127. (c) Martin, R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 7236.

(7) Álvarez-Bercedo, P.; Flores-Gaspar, A.; Correa, A.; Martin, R. *J. Am. Chem. Soc.* **2010**, *132*, 466.

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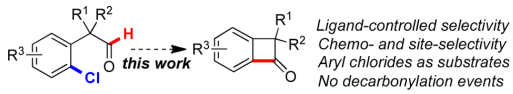
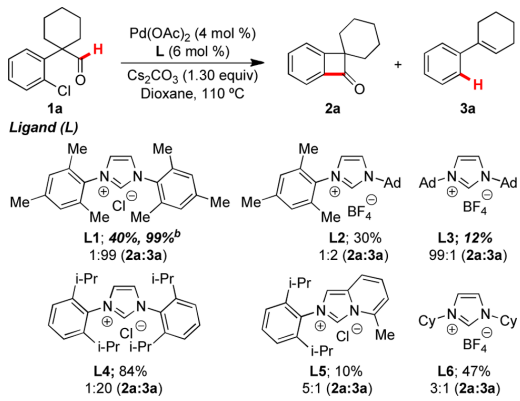
Heck-type processes could also be utilized for similar purposes,[8] the inherent rigidity of the four-membered ring makes such a scenario highly unlikely.[9] Despite the simple structure of BCBs, the drawbacks imparted by classical methods in terms of functional group tolerance and substitution patterns[10] contribute to the perception that our approach in Scheme 1 represents a straightforward alternative to these compounds. Herein, we describe the first successful intramolecular acylation of aryl chlorides via C−H functionalization as a means to access BCBs that are beyond reach otherwise. In addition to the preparative aspects, our results reveal exquisite selectivity control depending on the chosen ligand.

Scheme 1. Synthetic Approach to BCBs Using Aryl Chlorides



We began our study with **1a** as the model substrate (Scheme 2). On the basis of our own findings,[11] we anticipated that the supporting ligand would play an important, if not crucial, role in the route to **2a**. Among all the ligands examined, N-heterocyclic carbenes (NHCs), showed superior activity as compared to phosphine ligands.[12] It is noteworthy that, unlike other aldehyde C−H functionalization reactions,[2] competitive decarbonylation of **1a** was not observed in the crude reaction mixtures. Intriguingly, while **L1** afforded **3a** exclusively,[13] *the presence of a bulky adamantyl group in* ***L2*** *had a deleterious impact on selectivity*, with **2a** in a 1:2 ratio (**2a:3a**). Gratifyingly, we found that **L3**, readily available on large scale from cheap commercial sources,[14] produced **2a** as the only product, albeit in lower yields. Other related NHCs such as **L4**−**L6** afforded mixtures of both **2a** and **3a**, thus showing the subtleties of the catalytic system.[15]

Scheme 2. Striking NHC Effects on Selectivity[a]



[a] GC yields using dodecane as internal standard. [b] Using **5** (2 mol %).

The observed selectivity switch by catalyst tuning allows us to distinguish between different mechanistic scenarios.[16] At present, we suggest that the higher buried volume of **L3** is critical for achieving selectivity.[17,18] Subsequently, the effects of palladium precatalysts, solvents, bases, and temperatures were systematically examined (Table 1). While typically employed $Pd(OAc)_2$ resulted in lower yields (entry 1), the use of allyl chloride palladium dimers **5**−**6** gave better results (entries 3−4), with a catalyst based upon **5** being the most active (entry 5). At this stage, we hypothesized that the presence of additives could accelerate the C−H functionalization event; as shown in entries 8−12, this was indeed the case. After some optimization, we found that *the synergistic use of* ***L3*** *and allyl ether* (**9**) allowed for the preparation of **2a** in 80% yield (entry 10). We currently support the notion that allyl ether might be crucial for stabilizing monoligated **L3**−Pd(0) species.[19,20]

Next, we set out to explore the preparative scope of this reaction. As shown in Scheme 3, the functional group tolerance is nicely illustrated by the fact that differently substituted silyl ethers (**2d** and **2e**), alkenes (**2g**), esters (**2l**), aldehydes (**2m** and **2q**), ketones (**2n**), nitriles (**2p**), amines (**2o** and **2r**), fluorides (**2t**), or heterocycles (**2s**) are perfectly

(8) For Heck-type acylation approaches using aryl halides not involving C−H bond-activation protocols, see: (a) Colbon, P.; Ruan, J.; Purdie, M.; Xiao, J. *Org. Lett.* **2010**, *12*, 3670. (b) Ruan, J.; Saidi, O.; Iggo, J. A.; Xiao, J. *J. Am. Chem. Soc.* **2009**, *130*, 10510.

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(15) For the use of other NHC ligands, see Supporting Information.

(16) For recent examples of this concept: (a) Shareet, A.-R.; Sherman, D. H.; Montgomery, J. *Chem. Sci.* **2012**, *3*, 892. (b) Kwak, J.; Kim, M.; Chang, S. *J. Am. Chem. Soc.* **2011**, *133*, 3780. (c) Urban, S.; Ortega, N; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 3803. (d) Malik, H. A.; Sormunen, G. J.; Montgomery, J. *J. Am. Chem. Soc.* **2010**, *132*, 6304.

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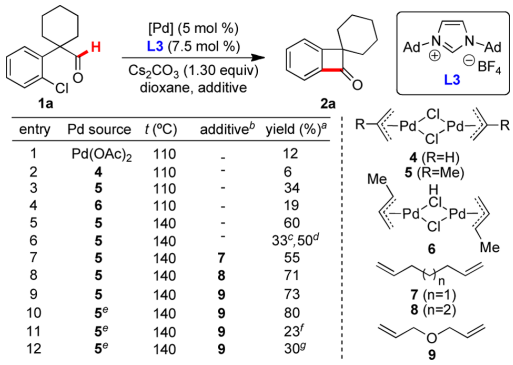
(18) According to ref 12, the calculated buried volumes in $Ni(CO)_3L$ are the following: $\%V_{bur}$(IMes) = 26, $\%V_{bur}$(IPr) = 29, $\%V_{bur}$(ICy) = 23, and $\%V_{bur}$(IAd) = 37.

(19) (a) Selvakumar, K.; Zapf, A.; Spannenberg, A.; Beller, M. *Chem.—Eur. J.* **2002**, *8*, 3901. (b) Jackstell, R.; Andreu, M. G.; Frisch, A. C.; Selvakumar, K.; Zapf, A.; Klein, H.; Spannenberg, A.; Röttger, D.; Briel, O.; Karch, R.; Beller, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 986.

(20) Christmann, U.; Vilar, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 366.

Table 1. Optimization of Reaction Conditions[a]



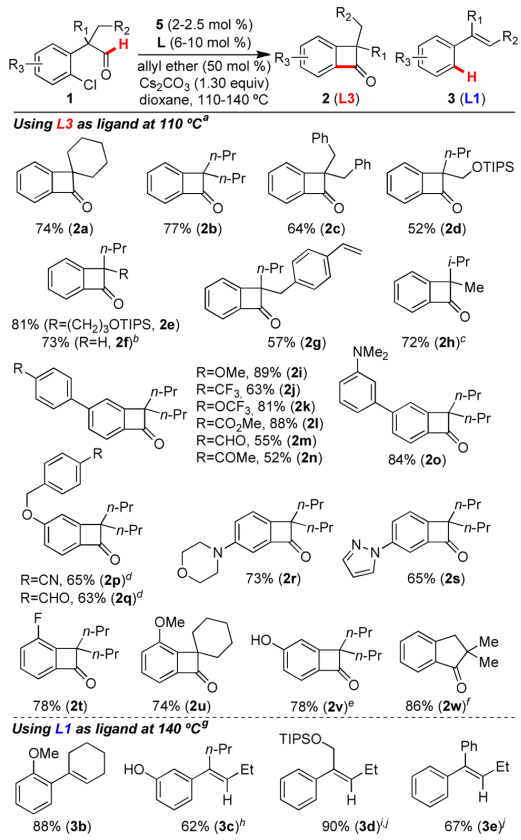
entry	Pd source	t (°C)	additive[b]	yield (%)[a]
1	$Pd(OAc)_2$	110	-	12
2	**4**	110	-	6
3	**5**	110	-	34
4	**6**	110	-	19
5	**5**	140	-	60
6	**5**	140	-	33[c],50[d]
7	**5**	140	**7**	55
8	**5**	140	**8**	71
9	**5**	140	**9**	73
10	**5**[e]	140	**9**	80
11	**5**[e]	140	**9**	23[f]
12	**5**[e]	140	**9**	30[g]

[a] **1a** (0.50 mmol), Pd (5 mol %), **L3** (7.5 mol %), Cs_2CO_3 (1.30 equiv), dioxane (0.25 M); GC yield using dodecane as internal standard. [b] 50 mol %. [c] THF as solvent. [d] Cyclpentylmethyl ether as solvent. [e] Pd/**L3** = 1:2. [f] K_2CO_3 (1.30 equiv). [g] NaO*t*BuO (1.30 equiv).

accommodated, thus providing an additional handle for further manipulation. The successful preparation of **2s** indicates that the Pd catalytic species are not deactivated by the presence of strong nitrogen donors. Likewise, even unprotected alcohols (**2v**) could be coupled in good yields as well. As shown for **2t** and **2u**, *ortho*-substitution did not hinder the reaction at all. Even more important is the fact that this method allows, for the first time, the preparation of a monosubstituted BCB (**2f**) when using α-silylated aryl aldehydes as precursors. This is particularly noteworthy in view of the inability of aryl bromides to promote an otherwise identical reaction.[7,21] In striking contrast to the previous use of aryl bromides,[7] the method could also be extended to the preparation of five-membered rings (**2w**). Notably, no competing intermolecular acylation events were detected by spectroscopy of the crude reaction mixtures, thus selectively obtaining **2m** and **2q**. Overall, we believe these results not only show the exceptional activity and functional group compatibility but also the robustness of C−H functionalization catalysts based on **L3**.[22] Encouraged by the selectivity switch in Scheme 2 when utilizing **L1**, a further extension of the scope of styrene derivatives was envisaged. As shown in Scheme 4 (bottom), the protocol based on **L1** allows for the preparation of trisubstituted olefins **3b**, **3c**, **3d**, and **3e** with total regiocontrol and diastereoselectivities up to 8.4:1, even in the presence of free alcohols (**3c**).

The proven flexibility of this method suggested that our intramolecular C−H acylation event should be applicable to site-selectivity approaches.[23] Gratifyingly, substrates

Scheme 3. Reaction Scope



[a] As for Table 1 (entry 10); isolated yields, average of two independent runs. [b] The 2-(trimethylsilyl)pentanal derivative was used followed by TBAF treatment. [c] Due to its volatility, the product was isolated as the benzocyclobutanol by treatment with $NaBH_4$ in MeOH. [d] **5** (5.0 mol %) was used. [e] Cs_2CO_3 (2.60 equiv) was used. [f] **5** (3.0 mol %), **L3** (12 mol %), allyl ether (60 mol %). [g] **5** (2 mol %) and **L1** (6.0 mol %); isolated yields. [h] E/Z = 8.4:1. [i] E/Z = 1:1.6. [j] 140 °C.

possessing multiple C−H or C−Cl reactive sites could be equally employed, affording **2x** and **2y** exclusively (Scheme 4); importantly, not even traces of **10** via intramolecular C−H arylation[24] or **11** were observed by NMR spectroscopy of the crude material.[25] These findings challenge the general perception that the preparation of smaller and more strained rings are lower yielding than standard routes to thermodynamically more stable medium-sized rings.

The exceptional reactivity and versatility of BCBs is illustrated in Scheme 5. Exposure of **2b** to $NaBH_4$ followed

(21) No monosubstituted benzocyclobutenones were obtained under the reaction conditions reported in ref 7.

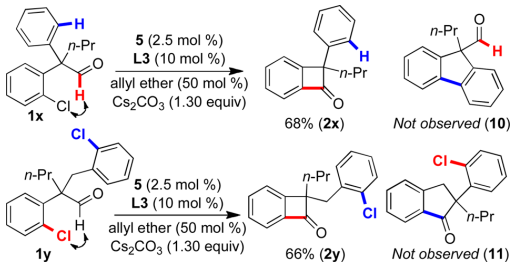
(22) The protocol based upon **L3** could also be utilized with similar yields when utilizing aryl bromides as substrates (ref 7).

(23) For a review on site selectivity in C−H bond functionalization: Neufeldt, S. R.; Sanford, M. S. *Acc. Chem. Res.* **2012**, *45*, 936.

(24) For selected examples of C−H intramolecular arylation with aryl chlorides, see: (a) Lafrance, M.; Lapointe, D.; Fagnou, K. *Tetrahedron* **2008**, *64*, 6015. (b) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581.

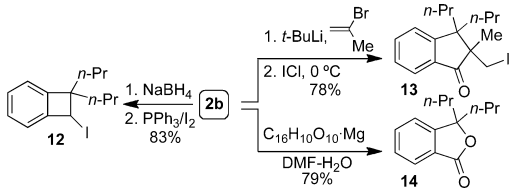
(25) Trace amounts of dechlorinated **2y** were observed in the crude reaction mixture by GC-MS.

Scheme 4. Site Selectivity with Multiple Reaction Sites



by PPh_3/I_2 treatment cleanly afforded synthetically attractive **12** in high overall yield. Likewise, indanone **13** possessing two contiguous quaternary centers or phthalide **14** could easily be obtained via ring expansion promoted by ICl[5c] or regioselective Baeyer–Villiger oxidation with magnesium monoperphthalate.[5e]

Scheme 5. Synthetic Applicability

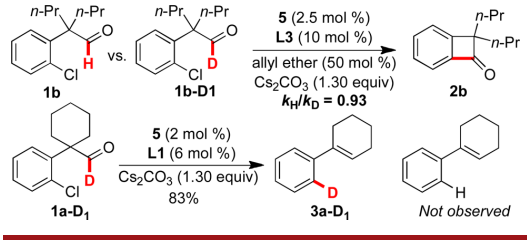


In order to gain more insight into the mechanism, we decided to gather indirect evidence via isotope labeling (Scheme 6). We observed $k_H/k_D = 0.93$ when comparing the initial rates of **1b** and **1b-D$_1$**. This experiment suggests that C–H cleavage is not rate determining, an intriguing

(26) (a) Rousseaux, S.; Davi, M.; Sofack-Kreutzer, J.; Pierre, C.; Kefalidis, C. E.; Clot, E.; Fagnou, K.; Baudoin, O. *J. Am. Chem. Soc.* **2010**, *132*, 10706. (b) Chaumontet, M.; Piccardi, R.; Audic, N.; Hitce, J.; Peglion, J.-L.; Clot, E.; Baudoin, O. *J. Am. Chem. Soc.* **2008**, *130*, 15157. (c) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848.

(27) We cannot rule out a mechanism consisting of an addition of the C—Pd bond across the C=O bond. For selected insertions of Pd oxidative addition complexes across the C=O bond, see: (a) Solé, D.; Fernández, I.; Sierra, M. A. *Chem.—Eur. J.* **2012**, *18*, 6950. (b) Fernández, I.; Solé, D.; Sierra, M. A. *J. Org. Chem.* **2011**, *76*, 1592. (c) Quan, L. G.; Lamrani, M.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 4827.

Scheme 6. Mechanistic Studies



observation given the known literature data for related processes.[3b,7] Quite illustrative, the deuterium label in **1a-D$_1$** was totally transferred to the aromatic motif in **3a-D$_1$** using **L1** as the ligand. At present, we support a mechanistic scenario in which the initial oxidative addition species undergoes a C–H functionalization via a concerted metalation deprotonation pathway (CMD)[26] and, in the presence of **L3**, final reductive elimination to afford the desired BCB **2** while recovering the active species.[7,27] We propose that the less-sterically encumbered **L1** facilitates an intramolecular proton transfer followed by CO extrusion and β-hydride elimination, thus affording the olefin **3**.[13]

In summary, the first intramolecular acylation of aryl chlorides via C–H bond functionalization en route to benzocyclobutenones has been developed. The protocol is characterized by its broad scope and exceptional site selectivity in which *the ligand backbone dictates the selectivity pattern*. We believe such a transformation will bring new knowledge in catalyst design. In further studies, we aim to explore the asymmetric reaction and the potential of this and related transformations.

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Supporting Information Available. General procedures and spectral data for all new compounds (**2a**–**2y**, **3a**–**3f**, and **12**–**14**). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

Recent Advances in the Synthesis and Application of Benzocyclobutenones and Related Compounds

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Abstract: Benzocyclobutenones are an intriguing class of four-membered-ring ketones that have been used extensively as powerful synthetic intermediates in organic synthesis. Their high reactivity is primarily attributed to the unique high electrophilicity of the carbonyl unit and the ability to generate *o*-quinone dimethides, allowing a myriad of different transformations. However, the synthesis of benzocyclobutenones still represents a great challenge. This review provides an overview of the preparation, use and impact of benzocyclobutenones in organic synthesis. Selected applications in the synthesis of natural products are also described, in order to illustrate the utility of these compounds.

Key words: benzocyclobutenones, cycloaddition, C–C bond cleavage, *o*-quinone dimethides, fused π-aromatic systems, ring expansion

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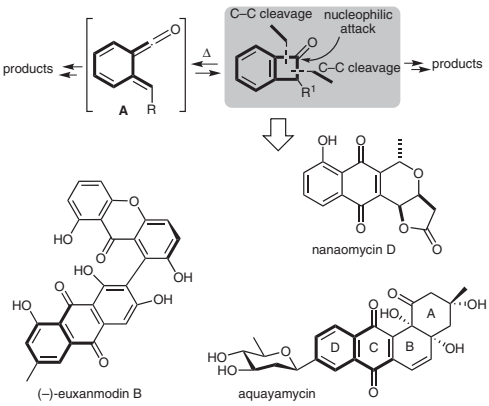
1 Introduction

The interest that organic chemists have in strained molecules has been gaining considerable momentum in recent years.[1] While some may see the ring strain as a rather difficult problem to deal with, others have seen this as an opportunity to devise new methods for their synthesis and to discover new reactivity within this area of expertise. Indeed, challenges are no doubt the main driving force for innovation, allowing creative thinking and breaking new ground not apparent at first sight. Quite clearly, the preparation and utilization of strained molecules has opened up new prospects and horizons in preparative chemistry, changing the landscape of organic synthesis for creative thinking for devising new carbon–carbon or carbon–heteroatom bond-forming reactions.[1]

Benzocyclobutenones are an intriguing class of four-membered-ring ketones with a particularly high ring strain.[2] While esthetically beautiful, these organic compounds have distinctive reactivity patterns that have inspired chemists to study in more detail such strained structures. Benzocyclobutenones in organic synthesis have evolved from structures of mere curiosity to indispensable tools for building up a high degree of molecular complexity.[2] The observed reactivity is primarily attributed to the torsional and angle strain of the corresponding carbon–carbon bonds, allowing for the development of carbon–carbon bond-cleavage reactions, in some cases even in a regioselective manner (Scheme 1).[2] On the other hand, such ring strain has a remarkable influence on the carbonyl group electrophilicity; indeed, these compounds are much more susceptible to nucleophilic attack than regular aliphatic or cyclic ketones. Not surprisingly, the high ring strain of the four-membered ring allows for a thermal conrotatory retro-4π cyclization, leading to vinyl ketene type intermediates (Scheme 1, **A**) that can participate in many synthetic transformations, mainly cycloaddition approaches.[2]



Scheme 1 Synthetic applicability of benzocyclobutenones

The scope of the reactions using benzocyclobutenones or their derivatives, as well as the high yields achieved in these processes, makes them exceptionally practical when dealing with complex synthetic sequences. The scope is tremendously wide, ranging from ring-expansion or ring-opening reactions to the preparation of synthetically attractive heterocyclic scaffolds. Not surprisingly, these unique compounds have been employed as platforms for natural product synthesis (Scheme 1, bottom; see also section 3.4).

As witnessed by recent literature data (vide infra), the preparation and utilization of benzocyclobutenones has been garnering considerable attention from the scientific community. Indeed, these methodologies have been recognized as powerful tools in the organic synthesis chemist's arsenal, and are becoming attractive transformations in both academic and pharmaceutical laboratories. This is particularly true when taking a closer look into the recent developments in this area, as they now allow levels of sophistication, efficiency and applicability that were beyond the reach of traditional and classical methods in which benzocyclobutenones or their derivatives were used.

Given the preparative potential of these rather unique building blocks, we identified a need to review the most recent advances in this field. It is worth noting that other reviews have been published highlighting the importance of related four-membered rings;[2] unlike these disclosures, however, the purpose of this article is to focus on the most important advances for preparing benzocyclobutenones, including synthetic applications and mechanistic considerations when appropriate.

2 Synthetic Methods for Preparing Benzocyclobutenones

At first glance, one might assume that the synthetic pathways to benzocyclobutenones would not differ that much from those known in the literature for preparing much

Biographical Sketches

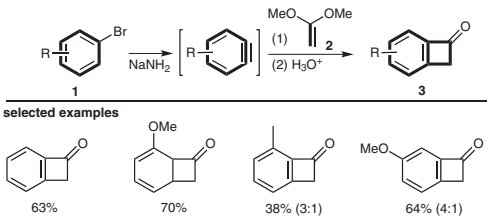
Areli Flores-Gaspar was born in Mexico City. She received her MSc at the Universidad Nacional Autónoma de México in 2008 working with Prof. Juventino García on the development of nickel-catalyzed isomerization reactions of unsaturated nitrile derivatives as well as nickel-catalyzed reduction of carbonyl compounds. She began her PhD studies in 2009 under the supervision of Dr. Ruben Martin at ICIQ (Tarragona, Spain). Her current research involves the discovery of new synthetic transformations based upon C–H bond-functionalization reactions.

Ruben Martin was born in 1976 in Barcelona (Spain). He received his PhD in 2003 at the Universitat de Barcelona with Prof. Antoni Riera, working on the total synthesis of glycosidase inhibitors. He then moved to the Max-Planck-Institut für Kohlenforschung (Mülheim, Germany) as a Humboldt postdoctoral fellow with Prof. Alois Fürstner, where he worked on the application of novel iron catalysts for cross-coupling and Alder–ene-type reactions. In 2005 he undertook further postdoctoral studies at the Massachusetts Institute of Technology with Prof. Stephen L. Buchwald where he developed new synthetic strategies for metal-catalyzed C–C and C–N bond-forming reactions. In September 2008 he joined the ICIQ (Tarragona, Spain) as a group leader. His current research interests concern the discovery and development of synthetically useful organometallic methodologies. During his time at ICIQ, he has received an RSEQ Young Investigator Award (2010), a Thieme Chemistry Journal Award (2011), an Eli Lilly Young Research Investigator Award (2011) and an ERC Starting Grant awarded by the European Research Council (2011).

simpler cyclobutenone motifs.[2] A close literature survey indicates, however, that this is clearly not the case. While there are a myriad of methods to prepare cyclobutenone derivatives,[2] the chemist's arsenal does not yet include a general and robust method for preparing benzocyclobutenones with high chemoselectivity and with a diverse set of substitution patterns. Most likely, the high ring strain of the four-membered ring, as well as the presence of the fused aromatic ring in the benzocyclobutenone core, makes the development of a universal method for their synthesis a rather challenging task. The purpose of this section is not to summarize all synthetic methods available, but rather to highlight the methodologies with greater potential for preparing benzocyclobutenones.

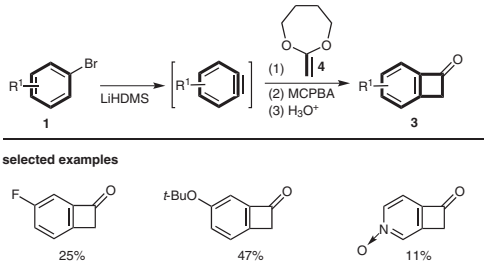
2.1 [2+2]-Type Cycloadditions

The [2+2] cycloaddition of in situ generated benzynes and olefins is probably the most direct and utilized synthetic route to benzocyclobutenones.[3] The high reactivity of benzyne makes such a route thermodynamically feasible;[4] however, the natural tendency for retro-4π cyclization of benzocyclobutenones requires that these cycloaddition approaches be conducted at low temperatures.[2] In 1982, Bisacchi and Stevens developed a procedure for preparing the rather elusive benzocyclobutenones from readily available aryl bromides (Scheme 2).[5] Deprotonation of the *ortho* carbon–hydrogen bond in **1** upon treatment with sodium amide triggers the formation of the benzyne derivative that reacts with the olefin through a thermal [2+2] cycloaddition. A final hydrolysis ultimately affords the corresponding benzocyclobutenone **3**. While other olefins could also be used, the employment of 1,1-dimethoxyethylene **2** was critical for obtaining good yields and regioselectivities of the [2+2]-cycloaddition reaction. Good selectivities were found with *o*-methoxy or *o*-chloro substituents; unfortunately, however, low selectivities were obtained for *o*-methyl derivatives or for those with substituents in *meta* or *para* positions.



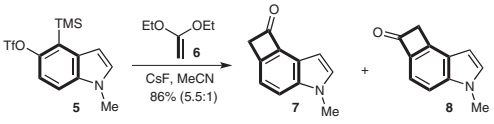
Scheme 2 Synthesis of benzocyclobutenones via [2+2] cycloaddition by in situ generation of benzyne and subsequent reaction with vinyl ethers

The regioselectivity issues found for *meta*- and *para*-substituted aryl bromide derivatives prompted chemists to study whether electronic effects on these remote positions of the aryl backbone might exert some influence on the reaction outcome. Santelli and co-workers found that a high regioselectivity could be achieved when coupling 2-methylene-1,3-dioxepane (**4**) and aryl bromides **1** bearing *p*-fluoro or *p*-*tert*-butoxy substituents, although in low yields (Scheme 3).[6] Additionally, it was discovered that benzocyclobutenones fused to heteroarynes proceeded equally well by reaction with 1,1-dimethoxyethylene (**2**), giving access to scaffolds with great synthetic potential (Scheme 3, bottom right).[7]



Scheme 3 Synthesis of benzocyclobutenone rings with substituents in the *para* position

Recently, Garg and co-workers reported that an otherwise analogous [2+2] cycloaddition can be performed using indolyne precursors **5** (Scheme 4).[8] Interestingly, electronic effects dominated over steric effects and the corresponding benzocyclobutenone could be obtained in good yields and moderate regioselectivities. Importantly, this strategy for generating highly reactive indolyne intermediates could also be employed for the preparation of interesting scaffolds bearing an indole heterocycle by reaction with nucleophiles other than 1,1-dimethoxyethylene derivatives.

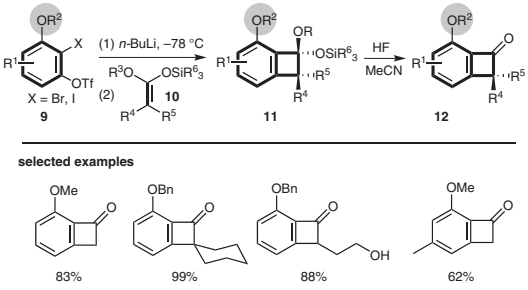


Scheme 4 Regioselectivity in [2+2]-cycloaddition approaches for indolyne intermediates

Despite the advances realized, the [2+2] cycloaddition of benzynes with activated olefins has several limitations: (a) harsh reaction conditions are typically required for the generation of benzyne;[4] (b) reproducibility issues; (c) limited amount of olefins that can be employed; and (d) low yields are generally observed using these protocols. Convinced of the relevance of the [2+2]-cycloaddition approach, Suzuki and co-workers turned their attention to the development of a new procedure for generating the corresponding arynes via halogen–metal exchange of aryl triflates possessing *o*-halogen substituents **9**, using ketene silyl acetals **10** as the olefin coupling partner (Scheme 5).[9] Treatment with hydrofluoric acid in acetonitrile at 0 °C delivered the final benzocyclobutenones **12**. This modified procedure allowed for the synthesis of benzocyclo-

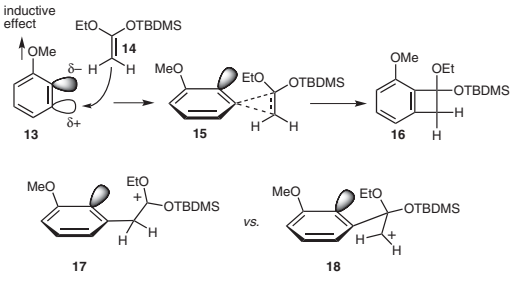
butenones in higher yields, particularly when utilizing *o*-alkoxy groups.

The scope of the reaction included the preparation of benzocyclobutenones with different substitution patterns. The method was robust enough to accommodate α,α′-substituents on the four-membered ring as well. It is worth noting that in all cases, the presence of an *o*-alkoxy group was required for obtaining good regioselectivities (Scheme 5).



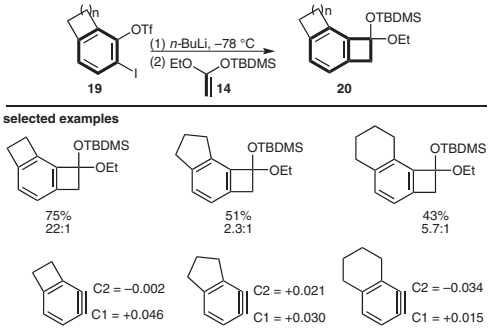
Scheme 5 Synthesis of benzocyclobutenones, via in situ generated benzynes, from aryl triflates with *ortho*-halogens and subsequent reaction with ketene silyl acetals

As for Bisacchi's experiments,[5] the rationale behind the observed regioselectivity could be attributed to the inductive effect of the *o*-methoxy group in **13**. Thus, the polarization of the in situ generated benzyne directs the nucleophilic attack of the β-carbon of the ketene silyl acetal **14** at the *meta* position, triggering an intramolecular attack that ultimately affords the final four-membered ring in **16** (Scheme 6).[10] The preference for the β-carbon of the ketene silyl acetal is likely due to the greater stabilization of the canonical form **17**, in which the carbocation is further stabilized by the two geminal oxygen moieties.



Scheme 6 Rationale for the regioselectivity observed in the [2+2] cycloaddition of unsymmetrical benzyne derivatives and ketene silyl acetals

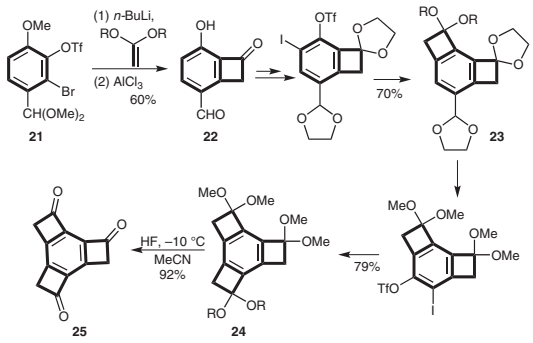
The results shown in Scheme 5 demonstrated that an *o*-alkoxy group played an important, if not critical, role in the [2+2]-cycloaddition reaction. Suzuki and co-workers studied in more detail whether other substituents might exert a similar effect. Interestingly, their investigations showed that the presence of fused strained rings, such as in **19**, gave comparable regioselectivities (Scheme 7).[11] The striking influence of the contiguous four-membered ring was demonstrated by the fact that low regioselectivities were obtained with larger rings in the *ortho* position. Thus, the authors hypothesized that the key for success was the high ring-strain associated with the four-membered ring. This assumption was supported by theoretical calculations in which C2 was bound to an orbital of higher electronegativity, thus rendering C1 more electron-deficient and therefore more susceptible to nucleophilic attack. As shown in Scheme 7, the differences were much less pronounced when arenes with fused five- or six-membered rings were used as coupling counterparts.



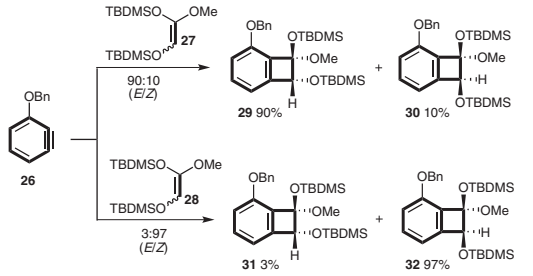
Scheme 7 Striking effect on regioselectivity by proximal substituents with ring strain in the [2+2]-cycloaddition reaction of benzynes and ketene silyl acetals

The directing ability of the alkoxy group and the strain-controlled nucleophilic attack could be combined in a synergistic manner. Indeed, Suzuki and co-workers showed that poly-oxygenated tricyclobutabenzenes such as **25** were within reach by using an iterative [2+2]-cycloaddition approach involving the reaction of in situ generated benzynes with ketene silyl acetals (Scheme 8).[12] Interestingly, the regioselectivity was controlled perfectly by the proximal four-membered ring, thus giving access to poly-fused aromatic compounds with exceptional ring strain.

Taking into consideration the concerted nature of the [2+2] cycloaddition,[3] the frontier molecular orbital theory predicts that the coupling reaction with olefins might also proceed in a stereospecific manner. As shown in Scheme 9, this was indeed the case and the coupling of geometrically defined ketene silyl acetals **27** and **28** proceeded with total stereoselectivity.[13]



Scheme 8 Iterative [2+2] cycloaddition of benzyne derivatives with ketene silyl acetals for the preparation of poly-oxygenated tricyclobutabenzenes

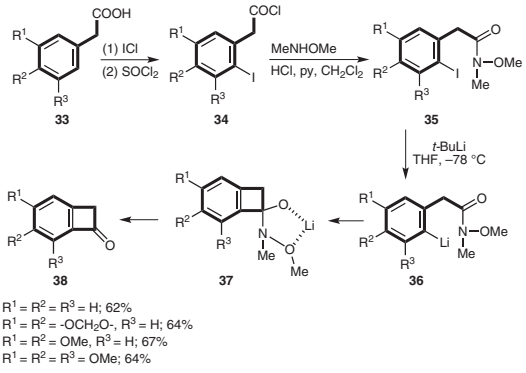


Scheme 9 Control of the stereoselectivity in [2+2]-cycloaddition reactions of benzynes with configurationally well-defined ketene silyl acetals

While benzyne routes[4] are no doubt widely applicable and are still, in many instances, the route of choice for preparing benzocyclobutenones, the need for *ortho* substituents as well as the special electronic requirements for obtaining good regioselectivities are serious drawbacks to be overcome.[14] Additionally, these methodologies do not tolerate a wide range of functional groups, possibly owing to the need for stoichiometric amounts of highly reactive organolithium derivatives. Furthermore, a synthetic challenge remains in the preparation of advanced intermediates en route to the benzyne motif, an issue that lowers the application profile of these methodologies. These matters reinforce the notion that other pathways for preparing benzocyclobutenone motifs would be appreciated at the synthetic community level.

2.2 Metal-Mediated Intramolecular Reactions

While [2+2]-cycloaddition reactions provide a rapid and modular entry to benzocyclobutenones, alternatives have been investigated. Among these, the method described by Ahuja and Aidhen is particularly remarkable in that an in situ generated organolithium reagent **36** attacks, intramolecularly, the Weinreb amide functionality leading to the formation of lithium chelate **37** (Scheme 10).[15] While moderate yields were generally obtained, it represents an excellent alternative to the [2+2]-cycloaddition reactions, particularly when electronic or steric effects are not in play. Still, the need for stoichiometric amounts of highly reactive organolithium derivatives might have a deleterious impact when applying this methodology to molecules possessing particularly sensitive functional groups.



Scheme 10 Synthesis of benzocyclobutenones via intramolecular attack of organolithium derivatives to Weinreb amides

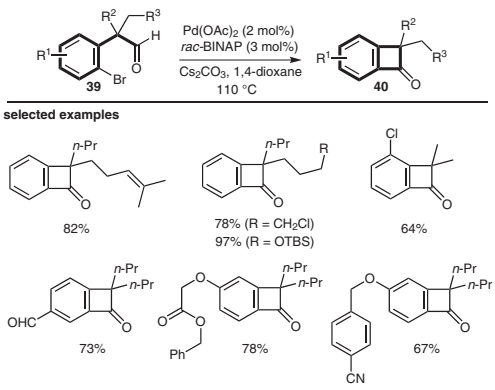
2.3 Metal-Catalyzed Cross-Coupling Reactions

The rapidly developing and ever-growing importance of palladium-catalyzed carbon–carbon bond-forming reactions has inspired chemists to initiate a quest for the discovery of new catalytic processes, thus opening up new prospects in preparative organic chemistry.[16] Within few years, these methodologies have become routine tools in modern organic synthesis, allowing for their implementation in many areas of expertise ranging from polymers, agrochemicals and pharmaceuticals to natural products.[16]

2.3.1 Carbon–Hydrogen Bond-Functionalization Events

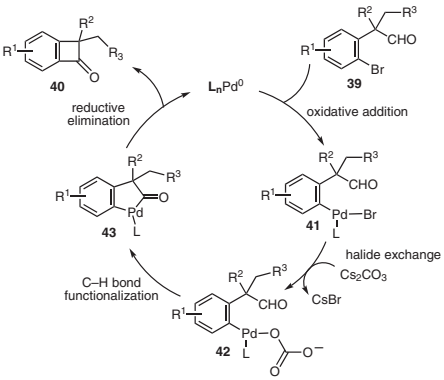
Martin and co-workers recently reported that readily available α-aryl aldehydes **39**[17] can be used as intermediates to access benzocyclobutenones (Scheme 11).[18] The methodology could be visualized as a formal intramolecular carbon–hydrogen bond acylation of an aryl bromide motif.[19,20] The key for success was the use of BINAP as the ligand in combination with cesium carbonate, and with 1,4-dioxane as the solvent. Regarding the substrate scope, a wide variety of electron-rich, electron-neutral as well as electron-deficient aryl bromides were well tolerated, including hindered substrate combinations. This new route to benzocyclobutenones via carbon–hydrogen bond functionalization is distinguished by its wide scope, resulting in the preparation of densely functionalized backbones with a diverse set of substitution patterns that are otherwise beyond reach.[18] Of additional significance was the ability to conduct reactions at up to 40 mmol scale in

high yields, thus becoming practical solutions when applied at industrial scale.[21]



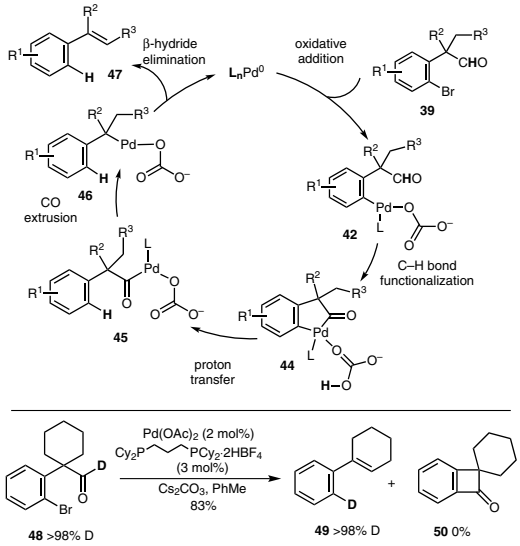
Scheme 11 Palladium-catalyzed intramolecular carbon–hydrogen bond acylation of α-aryl aldehydes as a means to access substituted and heavily functionalized benzocyclobutenones

Mechanistically, this reaction is somewhat related to the well-established palladium-catalyzed cross-coupling reactions.[16] It is believed that initial oxidative addition of an aryl bromide to a palladium(0) complex and halide substitution by cesium carbonate leads to **42** (Scheme 12). Carbon–hydrogen bond functionalization[22] then occurs to form the relatively stable five-membered palladacycle **43** and reductive elimination delivers the target benzocyclobutenone **40** while regenerating the catalytically active palladium(0) species.[18] A kinetic isotope effect of $k_H/k_D = 2.8$ was observed, thus supporting the notion that carbon–hydrogen bond cleavage was the rate-determining step of the reaction.



Scheme 12 Mechanistic rationale for the synthesis of benzocyclobutenones via palladium-catalyzed intramolecular carbon–hydrogen bond acylation of α-aryl aldehydes

Interestingly, a change on the ligand backbone had remarkable impact on the selectivity; for example, the use of bis(dicyclohexylphosphino)propane bis(tetrafluoroborate) under otherwise identical reaction conditions afforded exclusively the styrene derivatives **47** (Scheme 13).[23] While the mechanism of this transformation had similarities with that for the preparation of benzocyclobutenones (Scheme 12),[18] it was anticipated that **44** could undergo a proton transfer or 1,4-palladium migration in a Larock-type mechanism[24] followed by carbon monoxide extrusion and β-hydride elimination to give rise to the corresponding styrene **47**. Although other mechanisms are also conceivable, isotopic-labelling studies confirmed the proton transfer mechanism from **48** to **49**. Additionally, the intermediacy of acylpalladium species **45** was confirmed by trapping experiments in the presence of alcohols: neither styrene **47** nor benzocyclobutenone **40**, but rather an α-aryl ester, was detected in the crude reaction mixture.

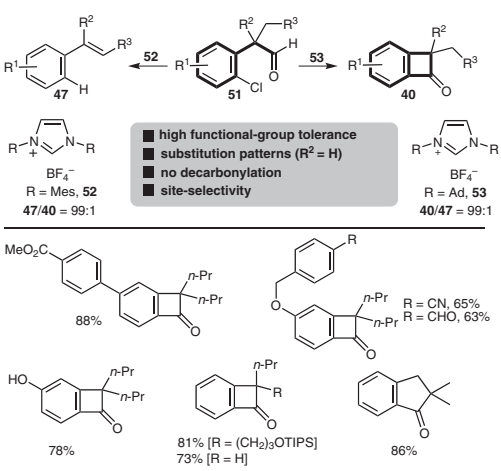


Scheme 13 Synthesis of α-aryl styrenes via a change in the ligand backbone

Unfortunately, however, the synthesis of benzocyclobutenones via palladium-catalyzed intramolecular carbon–hydrogen bond acylation of aryl bromides[18] was not yet satisfactory, since (a) the less reactive and more accessible aryl chlorides were totally inert; (b) the method showed low selectivity with multiple reaction sites; and (c) the reaction was restricted to α,α-disubstituted benzocyclobutenones, a common observation in other related α-arylation processes in which self-condensation via aldol-type reactions is observed as a consequence of the high acidity of the α-hydrogens.[25]

The last decade has been witness to tremendous progress in catalyst design by the fine-tuning of the supporting ligand used in many catalytic transformations.[16] As expected, the nature of the supporting ligand played a critical role in the coupling of the more readily available aryl chlorides (Scheme 14).[26] It was found that the use of the

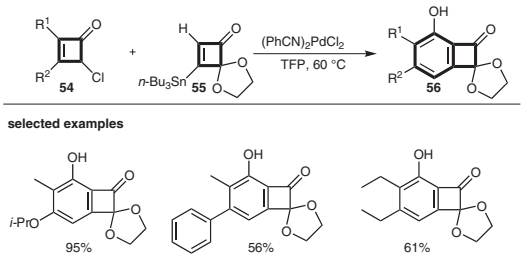
Arduengo N-heterocyclic carbene (IAd; **53**) in combination with palladium precatalysts afforded benzocyclobutenones in excellent yield.[27] This new protocol for the preparation of benzocyclobutenones gave comparable, if not better, results than BINAP in the palladium-catalyzed intramolecular carbon–hydrogen bond acylation of aryl bromides (Scheme 12).[18] Thus, the electronic nature of the aryl chloride had little effect on the success of the cross-coupling reaction.[26] Unlike the protocol based on the coupling of aryl bromides (Scheme 12),[18] however, this new method allowed for the synthesis of α-monosubstituted benzocyclobutenones, and was amenable to the preparation of larger rings and showed an exquisite site-selectivity with multiple reaction sites. Interestingly, the use of additives such as allyl ether in catalytic amounts had a beneficial effect. It was speculated that allyl ether could stabilize the resting state of the catalyst consisting of a monoligated IAd–Pd(0) species.[28] As for the coupling of aryl bromides,[23] a subtle ligand change had a detrimental impact on the reaction outcome, affording exclusively styrene derivatives **47** when operating with IMes (**52**) as the supporting ligand (Scheme 14).



Scheme 14 Catalytic intramolecular carbon–hydrogen bond acylation of α-aryl aldehydes for the synthesis of benzocyclobutenones in which the ligand dictates the selectivity pattern

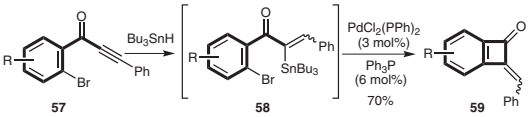
2.3.2 Stille Cross-Coupling Reactions

Prompted by the regioselectivity issues in the cycloaddition approaches employing benzyne derivatives, Liebeskind and co-workers described, in 1993, a Stille cross-coupling reaction of 4-chlorocyclobutenones **54** with 3-(tri-*n*-butylstannyl)cyclobutene derivatives **55** (Scheme 15).[29] Interestingly, this reaction set the stage for a rather exclusive ring-expansion event that took place in the same pot, thus providing access to trisubstituted benzocyclobutenone monoacetals in good yields. For the catalytic system, Liebeskind used (NCPh)$PdCl_2$ (0.4 to 1 mol%) and tris(2-furyl)phosphine (TFP; 2 mol%) as ligand.



Scheme 15 Preparation of benzocyclobutenone acetals via Stille cross-coupling reaction followed by ring-strain-promoted ring expansion

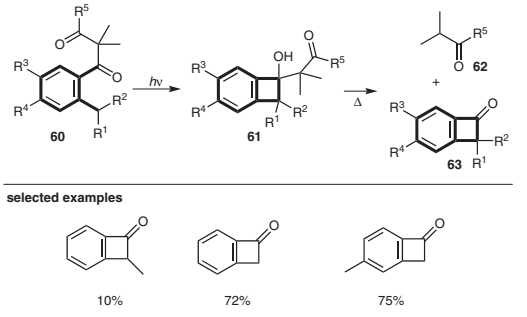
In 1991, Durst and Bradley developed a synthesis of 2-benzylidenebenzocyclobutenones **59** via an intramolecular palladium-catalyzed Stille cross-coupling reaction.[30] The methodology involved an initial regioselective hydrostannylation event promoted by tributyltin hydride, followed by an intramolecular cyclization (Scheme 16).



Scheme 16 Synthesis of 2-benzylidenebenzocyclobutenones via a regioselective hydrostannylation and Stille cross-coupling reaction

2.4 Other Synthetic Methods for Preparing Benzocyclobutenones

The photochemical reaction of *o*-alkylphenyl 1,3-diketone compounds **60** was introduced by Hasegawa and coworkers in the early 1990s (Scheme 16).[31] The procedure used a high-pressure mercury lamp (100 W) to induce a Norrish-type photochemical reaction to afford the corresponding benzocyclobutenol **61** under thermal conditions (150–180 °C). Subsequently, **61** undergoes a retro-aldol cleavage to form benzocyclobutenones **63** in low to good yields (Scheme 17).



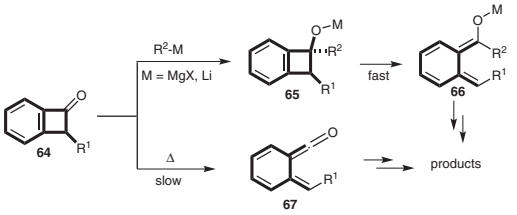
Scheme 17 Photochemical reaction of *o*-alkylphenyl 1,3-diketones en route to benzocyclobutenone backbones

3 Synthetic Application of Benzocyclobutenones and Related Compounds

Similar to their corresponding acyclic analogues,[2] benzocyclobutenones are particularly versatile building blocks. Their versatility is primarily attributed to the exceptional electrophilicity of the carbonyl unit as compared to that in other carbonyl compounds and the strain-relief associated with expansion of the four-membered ring. Undoubtedly, the innate proclivity of benzocyclobutenones to generate highly reactive *o*-quinone dimethide type intermediates makes them ideally suited for promoting ring-expansion and cycloaddition reactions. In this section, we summarize a selected number of new synthetic methods that employ benzocyclobutenones as the starting material.

3.1 Synthesis of Polycyclic Compounds via *o*-Quinone Dimethides

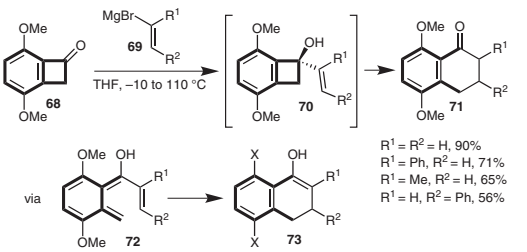
As for other cyclobutanones,[2] benzocyclobutenones undergo thermal conrotatory retro-4π cyclization, thus producing vinyl ketene intermediates that can participate in cycloaddition approaches (Scheme 18, bottom pathway). Unfortunately, the high temperatures required for such transformations with benzocyclobutenones are oftentimes not practical in the presence of more functionalized and sensitive backbones.[2] Interestingly, derivatives bearing electron-rich substituents on the cyclobutane ring undergo much easier outward ring opening. Among these, those with oxyanions, derived from benzocyclobutenols, are typically preferred as the corresponding retro-4π cyclization takes place at temperatures below 0 °C (Scheme 18, top pathway).[2]



Scheme 18 Thermal retro-4π cyclization of benzocyclobutenones and oxyanion ring-opening events on benzocyclobutenol derivatives

3.1.1 Synthesis of α-Tetralones

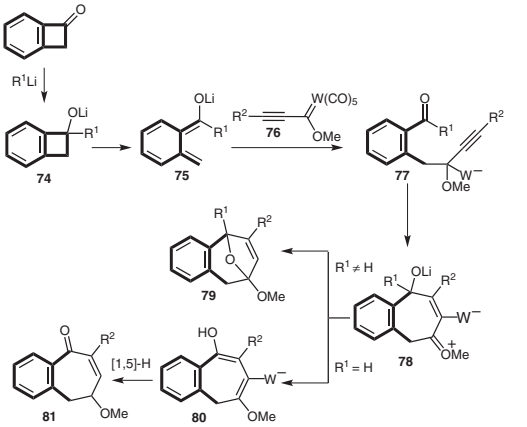
Wardleworth and co-workers described the thermal conversion of in situ generated alkenylbenzocyclobutenols **70** into α-tetralone derivatives (Scheme 19).[32] The key electrocyclic ring-opening reaction was accomplished via the intermediacy of an *o*-quinone dimethide followed by a disrotatory 6π-electrocyclization event, giving rise to the enol derivative **72**.



Scheme 19 Synthesis of α-tetralones via *o*-quinone dimethide intermediates

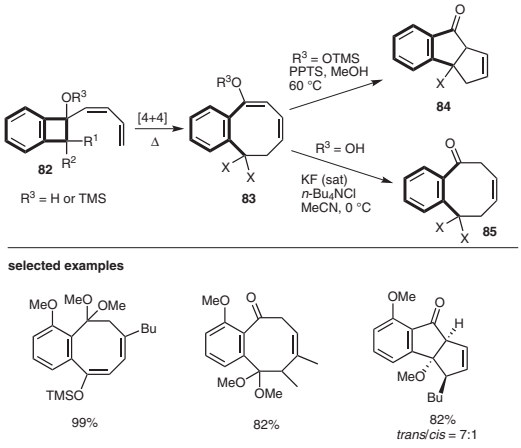
3.1.2 Synthesis of Benzo[n]annulenes

Benzo[n]annulenes are key structural constituents of many compounds with important biological properties, including (–)-presphaerene,[33] dragmacidin E,[34] (–)-colchicine[35] and hamigeran C.[36] Recently, Aguilar and coworkers reported a methodology that directly converted benzocyclobutenones into benzo[7]annulenes via an unprecedented [4+3] cycloaddition in which the initially generated *o*-quinone dimethides **75** act as four-carbon synthons (Scheme 20).[37] Interestingly, the solvent and the nature of the substituents dictated the selectivity pattern for preparing either benzocycloheptenones **81** or benzocycloheptene ketals **79**, respectively (Scheme 20). The mechanism of this transformation formally consists of the formation of *o*-quinone dimethide **75** at low temperature; rather than acting as a 1,3-diene that participates in a 6π-electrocyclization, this intermediate behaves as a vinylogous enolate. Subsequent nucleophilic attack on the carbene carbon of Fischer carbene complex **76** followed by 1,2-metal migration affords the key intermediate **78**. Then, two different pathways are conceivable: intramolecular nucleophilic attack to deliver the benzocycloheptene ketal **79**, or intramolecular acid–base exchange and 1,5-hydrogen shift, leading to benzocycloheptenone **81**.



Scheme 20 Synthesis of substituted benzo[7]annulenes using Fischer-type carbenes

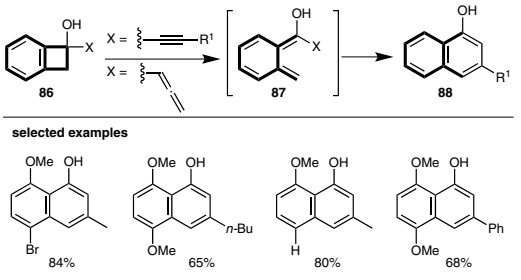
The use of stoichiometric amounts of Fischer carbene complexes might be seen as a drawback, particularly at large scale; however, related annulenes can be obtained by other means. For instance, addition of dienyllithium to a protected benzocyclobutenone affords a dienyl oxyanion intermediate that sets the stage for an 8π-electrocyclization (Scheme 21).[38] As in the previous synthesis of benzo[7]annulenes,[37] the nature of the substituents played a critical role in obtaining either benzo[8]annulenes **85** or indanone-fused compounds **84** via a transannular bond-forming reaction.



Scheme 21 Synthesis of benzo[8]annulenes via dienyl oxyanion benzocyclobutenol intermediates

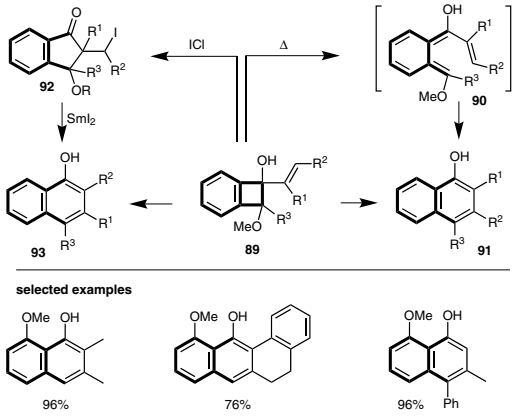
3.1.3 Synthesis of Naphthalene Derivatives

The preparation of fused π-aromatic systems illustrates the potential of benzocyclobutenone derivatives as synthetic intermediates. In close analogy to the preparation of α-tetralones,[32] the addition of an organometallic reagent facilitates the formation of *o*-quinone dimethide **87** that subsequently triggers a disrotatory 6π-electrocyclization, affording 1-naphthol derivatives **88** (Scheme 22). The required use of allenyl or propargyl organometallic species, however, limits the scope of this reaction to 1,3-substituted naphthols.[39]



Scheme 22 Synthesis of 1,3-substituted naphthols via retro-4π-cyclization followed by 6π-electrocyclization

A remarkable alternative is the elegant conversion of alkenyl benzocyclobutenol derivatives into 1-naphthol derivatives, depicted in Scheme 23. Interestingly, while thermal electrocyclic reaction followed by rearomatization gave access exclusively to regioisomer **91**, cyclization triggered by a halonium ion and subsequent treatment with samarium(II) iodide resulted in a different regioisomer, namely **93**.[40] The latter transformation can be formally visualized as an intramolecular Barbier-type reaction followed by an in situ Grob fragmentation. In any case, these reported protocols clearly demonstrate the considerable potential of benzocyclobutenones for accessing molecular diversity from common synthetic precursors.



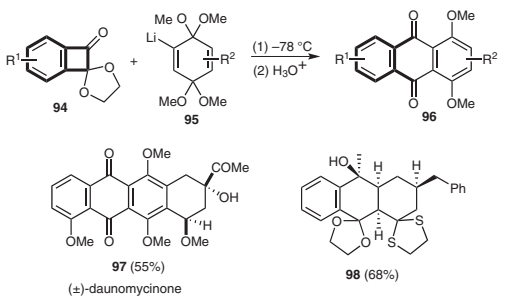
Scheme 23 Synthesis of highly substituted naphthols via retro-4π-cyclization or iodonium-triggered cyclization

The anion-accelerated ring-opening reaction of benzocyclobutenols could also be applied to the synthesis of other extended π-systems such as isoquinolines. For instance, the *o*-quinone dimethide that is generated from **89** reacted with benzonitrile to afford an easily aromatized intermediate.[41] Interestingly, the obtained isoquinoline cannot be accessed through standard Bischler–Napieralski synthesis.

3.1.4 Synthesis of Anthraquinones

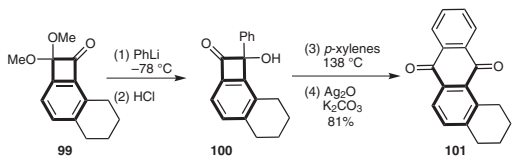
The anthraquinone core is present in a myriad of natural products with important biological activities. As a result, chemists have been challenged to devise new processes aimed at shortening the routes toward these compounds. Benzocyclobutenones are excellent intermediates for the preparation of the anthraquinone core. An illustrative example is shown in Scheme 24: the reaction of a lithiated quinone bis-ketal **95** with an appropriately protected benzocyclobutenone **94** provided, after hydrolytic workup, the expected anthraquinone structure **96**.[42] A similar approach for different organolithium compounds gave comparable overall yields. Importantly, this rather simple

sequence was applied in the rapid assembly of anthracycline aglycon-type molecules **97** and **98**.[43]



Scheme 24 Synthesis of anthraquinones and derivatives via addition of vinyllithiums and subsequent 6π-electrocyclization and rearomatization

A related annulation approach was employed for accessing angularly fused anthraquinones **101** (Scheme 25). In this particular case, the route commenced with the addition of an aryllithium, hydrolysis of the acetal, thermal retro-4π-cyclization, 6π-electrocyclization and, finally, oxidation of the resulting hydroquinone to afford the expected anthraquinone.[44]

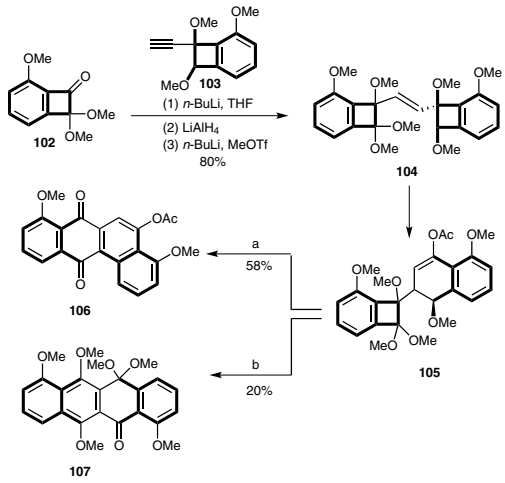


Scheme 25 Synthesis of angularly fused anthraquinones via 6π-electrocyclization and oxidation events

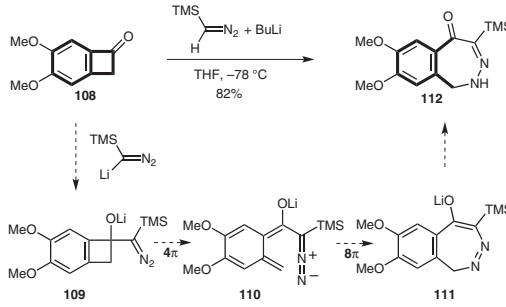
Suzuki and co-workers reported a straightforward and elegant synthesis of both linear and angular tetracycles with an anthraquinone core.[45] The approach involved sequential ring-opening reactions of two benzocyclobutenone rings joined by an ethynyl linker (Scheme 26). Notably, the reaction conditions determined whether angular or linear anthraquinones were obtained. Angular tetracycles **106** could be prepared exclusively by an initial aromatization followed by 6π-electrocyclization; in sharp contrast, a 1,2-double-bond shift could trigger the subsequent 6π-electrocyclization, thus giving access to linear tetracycles **107**.

3.1.5 Synthesis of Benzodiazepines

The reactivity of in situ generated *o*-quinone dimethides is certainly not limited to the construction of carbocycles.[2] Indeed, Nemoto and co-workers demonstrated that these highly reactive intermediates can also participate in electrocyclization reactions for the synthesis of benzodiazepines (Scheme 27).[46] As in related approaches,[2] the addition of a diazomethylene anion to the benzocyclobutenone backbone precedes a fast retro-4π-cyclization via an oxyanion intermediate at low temperatures. Unlike the corresponding formation of six-membered rings from *o*-quinone dimethides, an 8π-electrocyclization takes place in the presence of the diazo moiety in **110**, ultimately affording the benzodiazepine backbone **112** in high yield and by way of a one-pot procedure from the corresponding benzocyclobutenone.



Scheme 26 Suzuki's approach to the synthesis of linear and angular tetracycles. *Reagents and conditions:* (a) (i) PPTS, MeOH; (ii) $TsOH \cdot H_2O$, acetone; (iii) mesitylene, reflux; (b) (i) MeLi, *N*-*tert*-butylbenzenesulfinimidoyl chloride; (ii) $HF \cdot H_2O$, MeCN; (iii) $PhI(OAc)_2$, MeOH; (iv) *p*-xylenes, reflux.

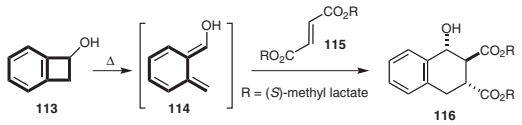


Scheme 27 Synthesis of a benzodiazepine derivative via two consecutive electrocyclization events

3.1.6 Synthesis of Tetrahydronaphthalenes

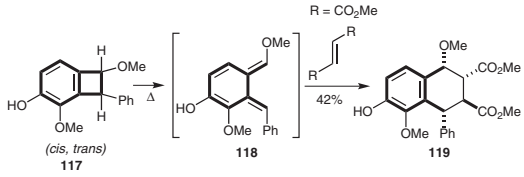
The ability of *o*-quinone dimethides to participate in cycloaddition reactions is not restricted to intramolecular processes. In a series of papers, Charlton et al. described the asymmetric Diels–Alder reactions of *o*-quinone dimethides with chiral acrylates, thus yielding tetrahydronaphthalene derivatives such as **116**.[47] As shown in Scheme 28, the reaction with chiral fumarate **115** afforded a single 1,2-*trans*-configured cycloadduct **116** with very

high diastereoselectivity (95% de). It is worth noting that the observed stereoselectivity does not match with the expected Diels–Alder *endo* rule for activated dienophiles.



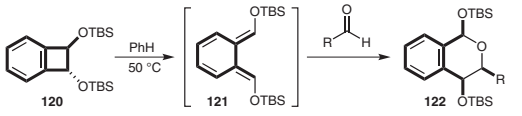
Scheme 28 Diastereoselective synthesis of tetrahydronaphthalene derivatives via *o*-quinone dimethides and intermolecular Diels–Alder reaction

Saá and co-workers described a related cycloaddition procedure with dimethyl fumarate and a mixture of *cis*- and *trans*-benzocyclobutenols **117**, delivering highly substituted tetrahydronaphthalene **119** in 42% yield (Scheme 29).[48] Strikingly, an isomerization of the *cis*- to the *trans*-isomer, most likely via a radical process, preceded the retro-4π-cyclization. Although this method provided low yields, the rapid preparation of stereodefined tetrahydronaphthalene derivatives is certainly noteworthy.



Scheme 29 Synthesis of a highly substituted tetrahydronaphthalene in a diastereoselective fashion via *o*-quinone dimethides and subsequent [4+2] cycloaddition

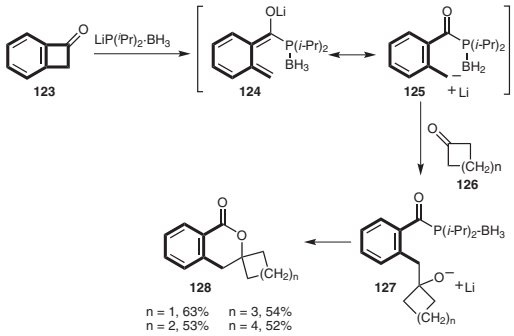
Danishefsky and co-workers described that *o*-quinone dimethides could also react with heterodienophiles in an intermolecular fashion.[49] Notably, a single isomer was obtained when the *tert*-butyldimethylsilyl-protected benzocyclobutenol **120** reacted with either aliphatic or aromatic aldehydes under mild conditions (Scheme 30). These results clearly show that hetero-Diels–Alder reactions are no longer restricted to the use of transition metals as catalysts and demonstrate the particular and unique reactivity of *trans*-1,2-bis(siloxy) derivatives in cycloaddition reactions.



Scheme 30 Reaction of *o*-quinone dimethides with heterodienophiles for the preparation of highly diastereoselective isochroman derivatives

3.1.7 Synthesis of Isochromanones

Isochromanone and spiro-annelated isochromanone derivatives can easily be prepared from the treatment of benzocyclobutenones with lithium tetramethylpiperidine (LiTMP) or lithium diisopropylphosphide–borane adduct (LDP·BH_3) (Scheme 31).[50] For spiro-annelated isochromanone derivatives, attack by LDP·BH_3 to the carbonyl unit triggers the subsequent retro-4π-cyclization. The resulting *o*-quinone dimethide type structure **124** is likely in equilibrium with **125**, which undergoes 1,2-addition across the carbon–oxygen double bond of cyclic ketone **126**. The resulting alkoxide attacks the diisopropylphosphino carbonyl core in an intramolecular fashion, finally producing the targeted compound **128**. A similar rationale could also be applied to the reaction with aldehydes, leading to isochromanone derivatives.



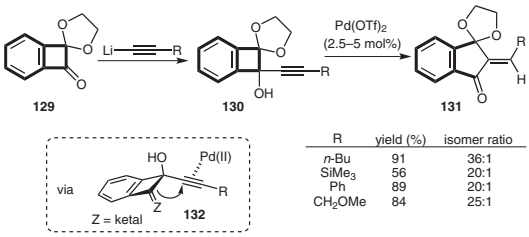
Scheme 31 Synthesis of spiro-annelated isochromanones

3.2 Synthesis of Fused Rings via Non-Electrocyclization Techniques

3.2.1 Ring Expansions from Four- to Five-Membered Rings

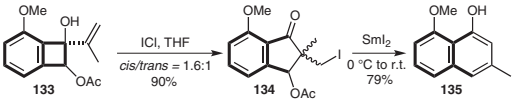
3.2.1.1 Synthesis of Indanones

Benzocyclobutenones can also be employed as manifolds for ring-expansion reactions from four- to five-membered rings without the need for *o*-quinone dimethide intermediates. In 1987, Liebeskind et al. described a synthesis of indanones via ring expansion of ketal-protected benzocyclobutenone derivatives **129** with excellent yields and stereoselectivities in the presence of catalytic amounts of palladium(II) triflate at room temperature (Scheme 32).[51] The sequence was initiated by electrophilic activation of alkyne derivative **130** with palladium(II) triflate followed by ring expansion via carbon–carbon bond cleavage. Interestingly, the $C(sp^3)$–$C(sp^3)$ bond migrated selectively, likely owing to the stabilization of the positive charge of the migrating group. The reaction was stereospecific and the authors observed only the final product that originated from a *trans*-addition across the alkyne moiety.



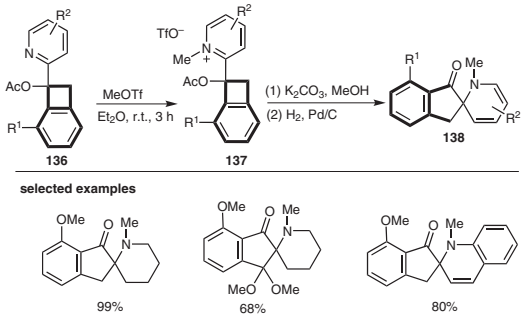
Scheme 32 Palladium-catalyzed synthesis of indanones via ring expansion of alkynyl benzocyclobutenol derivatives

Suzuki and co-workers reported an elegant ring expansion of vinyl-substituted benzocyclobutenol **133**, promoted by iodine monochloride, that resulted in the preparation of indanones **134** with well-defined quaternary centers (Scheme 33).[40] The reaction was believed to proceed in analogy with other related cyclizations;[52] however, iodine monochloride was utilized to activate the π-system, thus inducing a ring expansion via carbon–carbon bond cleavage without the intermediacy of an *o*-quinone dimethide. Interestingly, this methodology allowed for the preparation of halogen-substituted indanones that could be further functionalized via conventional organic synthesis methodologies. Indeed, these compounds were shown to react efficiently with samarium(II) iodide in a preparation of naphthol derivatives **135** (Scheme 33).



Scheme 33 Synthesis of an indanone, promoted by iodine monochloride, without the intermediacy of an *o*-quinone dimethide

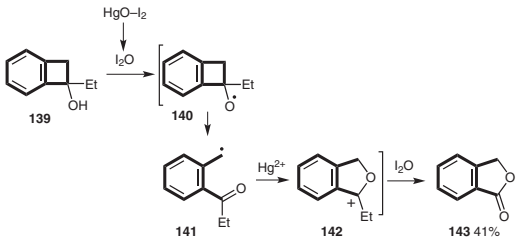
Similarly to their previous procedures for the synthesis of indanones,[40] Suzuki and co-workers envisioned that the preparation of spiro-fused indanones **138** substituted with a pyridyl ring could take place via electrophilic activation of the heterocyclic core, thus setting the stage for a ring-expansion event (Scheme 34).[53] As expected, N-methylation of the heterocyclic ring triggered the desired ring expansion, yielding the targeted compounds in good yields after hydrogenolysis in order to prevent decomposition of the enamine-type intermediates. Importantly, the reaction was not limited to pyridyl-fused compounds, as quinolinium and isoquinolinium heterocycles were also within reach. It is worth mentioning that, as shown for the above-mentioned ring expansions to indanones, the $C(sp^3)$–$C(sp^3)$ is preferentially cleaved, affording exclusively one regioisomer. It is anticipated that this powerful methodology will be applied in the near future for the preparation of natural products with spiro-fused indanone heterocycles such as parfumine or fumarofine, among others.[54]



Scheme 34 Synthesis of spiro-fused indanones via ring expansion of benzocyclobutenol derivatives

3.2.1.2 Synthesis of Phthalides

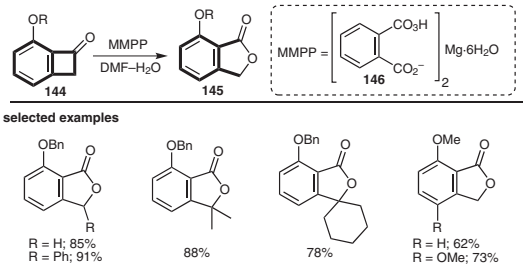
The phthalide unit is a prominent structural motif in many bioactive natural products and pharmaceutically important compounds.[55] An example of this family of compounds is mycophenolic acid, a compound with significant antiviral and antitumor activities.[56] Classical methods for the synthesis of phthalides include the cyclization of hydroxy acids or halolactonization processes, among others.[57] Kobayashi et al. reported a procedure for the preparation of phthalides in which β-scission of an alkoxy radical occurs upon photolysis of the hypoiodite that is formed by addition of the mercury(II) oxide–molecular iodine couple to benzocyclobutenol intermediate **139** (Scheme 35).[58] However, the yields were moderate, thus reinforcing the notion that a new methodology for preparing phthalides would be needed.



Scheme 35 Synthesis of phthalides from benzocyclobutenols by photochemical reaction in the presence of mercury(II) oxide and molecular iodine

Suzuki and co-workers reported a much more general approach for the preparation of phthalides without the use of a transition metal.[59] Formally, the sequence is based upon a regioselective Baeyer–Villiger oxidation of readily available *ortho*-substituted benzocyclobutenones **144** (Scheme 36). Although other oxidants could be used, magnesium monoperoxyphthalate hexahydrate (MMPP; **146**) provided the best results and a wide variety of compounds with a diverse set of substitution patterns could be used as substrates. Priority rules were established for controlling the regioselectivity with unsymmetrically substi-

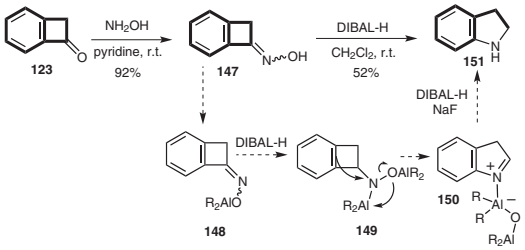
tuted derivatives: tertiary > secondary > primary > methyl.



Scheme 36 Synthesis of phthalides via regioselective Baeyer–Villiger oxidation promoted by MMPP (**146**)

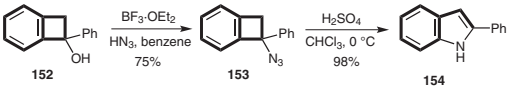
3.2.1.3 Synthesis of Indolines and Indoles

In 2010, Cho, Tokuyama and co-workers described a reductive ring-expansion reaction of ketoximes **147** with diisobutylaluminum hydride (Scheme 37).[60] The reaction cleanly afforded a wide variety of bicyclic heterocycles with the nitrogen adjacent to the aromatic ring. The reaction mechanism could formally be understood as a Beckmann-type rearrangement; however, in this case, the reaction is initiated by reduction of the carbon–nitrogen double bond followed by rearrangement involving nitrogen–oxygen bond cleavage (**149** to **150**) and, finally, re-aromatization to deliver indoline.



Scheme 37 Synthesis of indolines via a reductive ring-expansion reaction of initially generated ketoximes

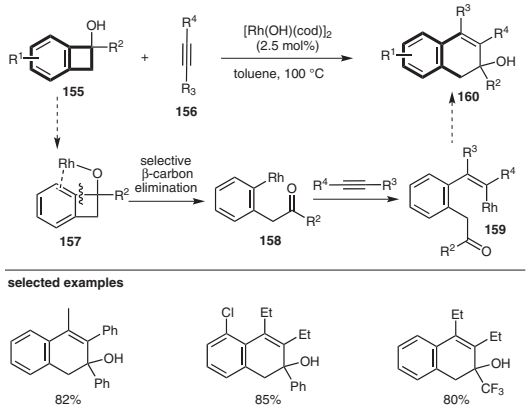
In a related procedure, Adam and co-workers reported a variant of the Schmidt reaction for converting benzocyclobutenol derivatives **152** into 2-substituted indoles **154**.[61] The sequence of events started with the exposure of benzocyclobutenol to hydrazoic acid in boron trifluoride–diethyl ether complex and subsequent treatment with sulfuric acid in chloroform at 0 °C (Scheme 38).



Scheme 38 Synthesis of 2-substituted indoles via ring expansion of azido-benzocyclobutene derivatives promoted by acidic media

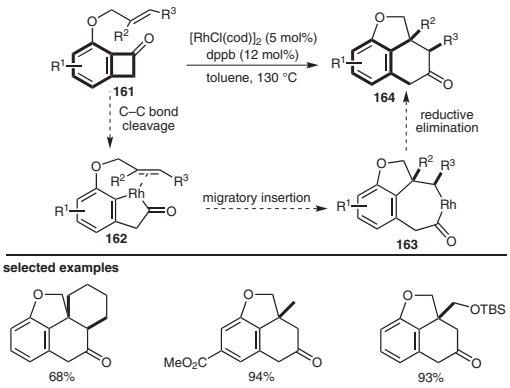
3.2.2 Ring Expansions from Four- to Six-Membered Rings

While the reactivity of benzocyclobutenones and their derivatives is often exploited for the formation of six-membered rings via 6π-electrocyclization of in situ generated *o*-quinone dimethides, Murakami and co-workers recently demonstrated a similar reactivity without the generation of these highly reactive intermediates, thus delivering dehydronaphthalene derivatives **160** (Scheme 39).[62] The reaction was believed to proceed via the initial formation of alkoxyrhodium species **157** that would then undergo regioselective β-carbon elimination,[63] alkyne insertion and intramolecular 1,2-addition across the carbon–oxygen double bond. Given the known precedents for promoting enantioselective β-carbon elimination processes,[63] it is expected that the authors will further extend the scope of this reaction for the intermolecular coupling of alkenes, thus accessing polycyclic fused compounds with great synthetic potential.



Scheme 39 Rhodium-catalyzed ring-expansion reaction en route to dehydronaphthalene derivatives via regioselective carbon–carbon bond cleavage

In a related procedure, Dong and Xu recently described an intramolecular rhodium-catalyzed carboacylation of benzocyclobutenones in order to rapidly prepare polyfused ring systems (Scheme 40).[64a] As in Murakami's approach,[62] this method involved a regioselective carbon–carbon bond cleavage in order to generate the rather stable C(sp^2)–Rh intermediate **162** that coordinates with the pending alkene and triggers a migratory insertion and a reductive elimination. Taking into consideration the ubiquity of polyfused rings in compounds with important biological activity, it came as no surprise that very recently an enantioselective version of this reaction has appeared in the literature.[64b]

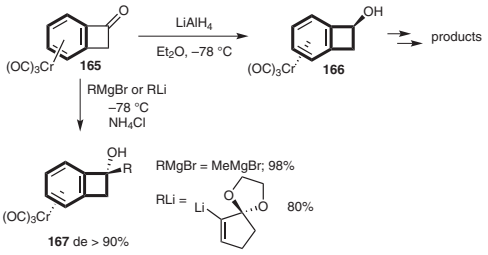


Scheme 40 Rhodium-catalyzed carboacylation of benzocyclobutenones via regioselective carbon–carbon bond cleavage

3.3 Other Synthetic Applications

3.3.1 Tricarbonylchromium Complexes

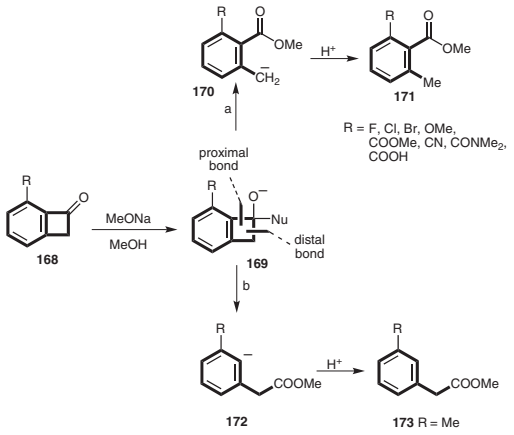
Upon reaction with chromium hexacarbonyl, benzocyclobutenone motifs coordinated to tricarbonylchromium are no longer planar. Such coordination has tremendous synthetic implications as this simple coordination event allows for the development of diastereoselective transformations, for example via nucleophilic attack into the carbonyl motif. For example, Butenschön and co-workers demonstrated the utility of these tricarbonylchromium complexes by preparing benzocyclobutenols with total diastereoselectivity (Scheme 41).[65] For example, the diastereoselective reduction of benzocyclobutenone **165** gave the *syn*-alcohol **166** in 98% yield, and the nucleophilic addition of organometallic reagents afforded *endo*-1-benzocyclobutenolchromium complexes **167**.[52c,66]



Scheme 41 Reactivity of tricarbonylchromium–benzocyclobutenone complexes

3.3.2 Base-Induced Carbon–Carbon Bond Cleavage

In principle, the ring opening of benzocyclobutenones with no *o*-quinone dimethide being generated can afford two different compounds, depending on which bond is cleaved (Scheme 42). Initial based-induced ring-opening reactions revealed that the regioselectivity was indeed poor (1:1).[67] Further studies performed by Schiess and Gokhale showed that the critical carbon–carbon bond cleavage was strongly influenced by the nature of the substituents present in the aromatic backbone.[68] Interestingly, the proximal carbon–carbon bond cleavage to form 2-methylbenzoate derivatives **171** was preferred when R was an electron-withdrawing group. In sharp contrast, the distal carbon–carbon bond cleavage toward 2-phenylacetate compounds **173** was only selective for an *ortho*-methyl substituent (R = Me). Still, however, the ring-opening reaction has selectivity issues for heavily substituted benzocyclobutenone derivatives.[69]

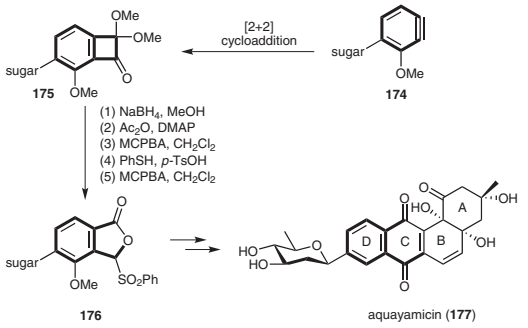


Scheme 42 Base-induced ring opening of benzocyclobutenones for the synthesis of ester derivatives

3.4 Benzocyclobutenones and Their Derivatives in Natural Product Synthesis

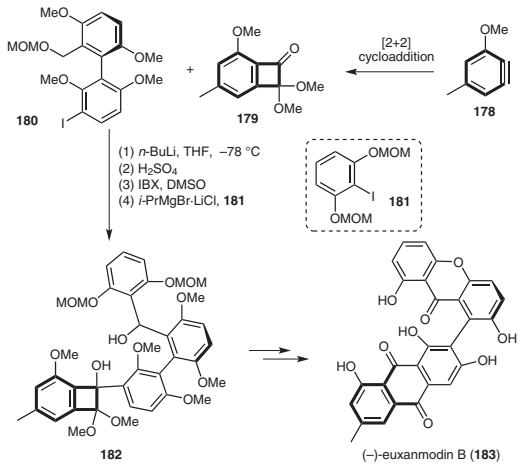
Once the non-negligible potential of benzocyclobutenones as synthetic intermediates was realized, their application to target-oriented and other areas of organic synthesis began to appear in the literature. This section includes illustrative examples for the use of benzocyclobutenones as key building blocks in natural product synthesis.

In 2000, Suzuki and co-workers reported the total synthesis of aquayamycin (**177**), an anthraquinone derivative with a C-glycoside structure that has been shown to inhibit the enzyme tyrosine hydroxylase.[70] The approach relied on the initial preparation of benzocyclobutenone **175** via [2+2] cycloaddition of the in situ generated benzyne derivative with ketene silyl acetal in the presence of a sugar-type backbone (Scheme 43). Subsequently, regioselective Baeyer–Villiger oxidation promoted by *m*-chloroperoxybenzoic acid delivered 3-(phenylsulfonyl)phthalide **176** that engaged in a Hauser-type reaction with an enone derivative, ultimately leading to aquayamycin (**177**).



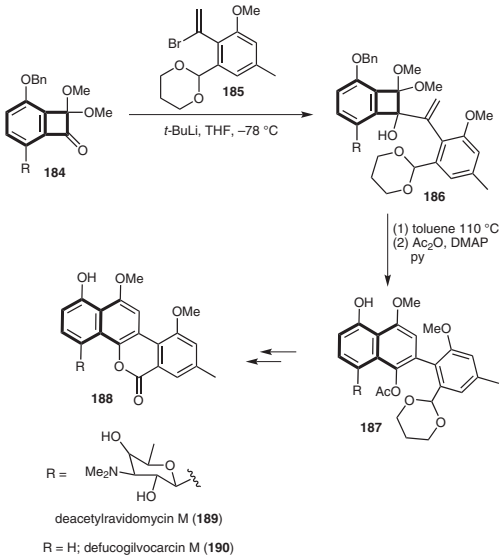
Scheme 43 Total synthesis of aquayamycin (**177**) via regioselective Baeyer–Villiger reaction on a benzocyclobutenone motif

Sterically congested biaryl compounds possessing atropisomerism have been found in many compounds with important biological activities; however, their synthesis still constitutes a great synthetic challenge.[71] Matsumoto, Suzuki and co-workers reported an elegant synthesis of (–)-euxanmodin B (**183**),[72] an axially chiral natural product with an anthraquinone–xanthone composite structure (Scheme 44). Notably, the anthraquinone backbone was efficiently secured by a thermal ring expansion through initially generated *o*-quinone dimethide derivatives.



Scheme 44 Total synthesis of (–)-euxanmodin B

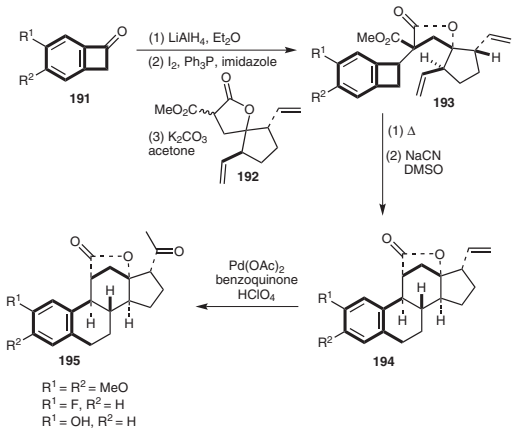
Suzuki and co-workers reported the synthesis of gilvocarcin-class antibiotics such as defucogilvocarcin M (**190**) and deacetylravidomycin M (**189**) involving benzocyclobutenol intermediates (Scheme 45).[73] Interestingly, the authors built up the key naphthalene backbone utilizing a rather efficient pericyclic reaction followed by aromatization via in situ elimination of methanol. A final cyclization event furnished the desired gilvocarcin-type antibiotics.



Scheme 45 Total synthesis of the gilvocarcin-class antibiotics defucogilvocarcin M and deacetylravidomycin M

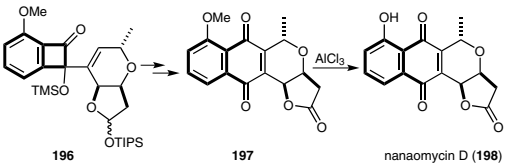
An application of benzocyclobutenones in the synthesis of advanced steroids is illustrated in Scheme 46. The strategy was built around the alkylation of activated spirolactone **192** with an iodobenzocyclobutenone that yielded **193**.[6a,74] Upon heating, this intermediate generated an *o*-xylene that rapidly underwent an intramolecular Diels–Alder-type cycloaddition, delivering the key polycyclic backbone in an essentially one-step operation. Krapcho decarboxylation and subsequent Wacker oxidation finally afforded the steroid derivatives **195**.

The total synthesis of (–)-nanaomycin D (**198**), a compound with potent inhibitory activity against fungi, is another illustrative example of the synthetic utility of in situ



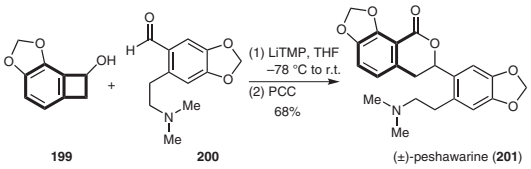
Scheme 46 Synthesis of advanced steroids from benzocyclobutenones

generated *o*-quinone dimethides.[75] In this particular case, exposure of 3-methoxybenzocyclobutenedione to a vinyllithium reagent in tetrahydrofuran, trimethylsilyl quench (to form **196**) and subsequent thermolysis followed by oxidation gave 9-*O*-methylnanaomycin D (**197**). Demethylation in the presence of aluminum trichloride finally delivered the natural product (Scheme 47).



Scheme 47 Total synthesis of (–)-nanaomycin D

Olofson and co-workers reported the total synthesis of (±)-peshawarine (**201**) in an essentially two-step procedure.[76] The sequence was initiated by an oxyanion-accelerated ring opening of benzocyclobutenol **199** followed by cycloaddition with heterodienophile **200** (Scheme 48). It is quite remarkable that this hetero-Diels–Alder reaction occurred under mild reaction conditions and in the absence of a catalyst. Oxidation in the presence of pyridinium chlorochromate then cleanly afforded the natural product in high overall yield.



Scheme 48 Total synthesis of (±)-peshawarine

4 Conclusions

Despite the recent contributions and advancements in the field of benzocyclobutenone chemistry, a large number of investigations, both qualitative and quantitative, remain to be conducted. Among them, the design of new methodologies for preparing benzocyclobutenones would allow for further improvements in terms of the utilization of these unique motifs in organic synthesis. Particularly attractive would be the development of novel synthetic methodologies that occur in an enantioselective fashion. In recent years, there have been only few advances in this topic, suggesting that the development of enantioselective protocols of these processes is not a simple task.

While it is true that the use of benzocyclobutenones is still in its infancy relative to related transformations employing cyclobutenones, one can look at the recent developments reported in the literature to track its potential future progress. Indeed, the use of transition metals to efficiently catalyze both the preparation and transformation of benzocyclobutenones definitely opens up new vistas in organic synthesis. In view of the rich chemistry that these rather unique backbones offer to our synthetic arsenal, a bright future is predicted for these scaffolds.

Acknowledgment

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