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Radical-Mediated Formation of Functionalized Allylic Synthons

Qian Zeng

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Radical-Mediated Formation of Functionalized Allylic Synthons

Qian Zeng (曾倩)

DOCTORAL THESIS
2024

Qian Zeng (曾倩)

Radical-Mediated Formation of Functionalized Allylic Synthons

Doctoral Thesis

Supervised by Prof. Dr. Arjan W. Kleij

ICIQ – Institut Català d'Investigació Química

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Prof. Dr. Arjan W. Kleij, Group Leader at the Institute of Chemical Research of Catalonia (ICIQ) and Research Professor at the Catalan Institution for Research and Advanced Studies (ICREA).

I STATE that the present Doctoral Thesis, entitled "**Radical-Mediated Formation of Functionalized Allylic Synthons**" presented by Qian Zeng to receive the degree of Doctor, has been carried out under my supervision at the Institute of Chemical Research of Catalonia (ICIQ).

Tarragona, December 2024

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Curriculum Vitae

Qian Zeng was born on December 21, 1995 in Suzhou, China. She obtained her BSc degree in July 2017 at Zhengzhou Normal University, majoring in chemistry. Then she started her MSc career in the Soochow University under the supervision of Prof. Xinfang Xu, during which she was working on Rh(II) and Cu(II) catalyzed Buchner reactions of diazo compounds. In July 2020, she obtained her MSc degree and then she joined the Institute of Chemical Research of Catalonia (ICIQ), Tarragona, to pursue her doctoral studies under the supervision of Arjan W. Kleij. Her research was financially supported by China Scholarship council and a CSC predoctoral fellowship. Her PhD research focused on radical-mediated formation of functionalized allylic synthons, and these results are presented in this thesis. Part of the result of this PhD have been communicated at several conferences including 1ª REUNIÓ DE QUÍMICA INORGÀNICA I ORGANOMETÀL·LICA de la SCQ (Barcelona, 2023), XXV Conference on Organometallic Chemistry (Madrid, 2023), 14th Spanish-Italian Symposium on Organic Chemistry (Torino, Italy, 2024) and online at the 2024 ACS Fall Meeting at one of the Global Virtual Symposia focusing on organometallic chemistry.

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I am writing this section at this moment to give my sincere gratitude to those who have been in my life and those who have supported me along the way.

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Qian, 2024

List of Publications

The results described in this doctoral thesis are based on the following publications:

- Q. Zeng, F. Gao, J. Benet-Buchholz, A. W. Kleij, *ACS Catal*. **2023**, *13*, 7514−7522.
- Q. Zeng, N. Yamini, J. Benet-Buchholz, A. W. Kleij, *Angew. Chem. Int. Ed.* **2024**, *63*, e202403651.

Other contributions:

- K. Guo, Q. Zeng, A. Villar-Yanez, C. Bo, A. W. Kleij, *Org. Lett.* **2022**, *24*, 637−641.
- S. Xue, À. Cristofol, B. Limburg, Q. Zeng, A. W. Kleij, *ACS Catal.* **2022**, *12*, 3651−3659.

List of Abbreviations

In this doctoral thesis, the abbreviations and acronyms most commonly used in organic chemistry are based on the recommendations of the ACS "Guidelines for authors" which can be found and consulted at *https://www.cas.org/support/documentation/references/cas-standard-abbreviations#listinga*.

Table of Contents

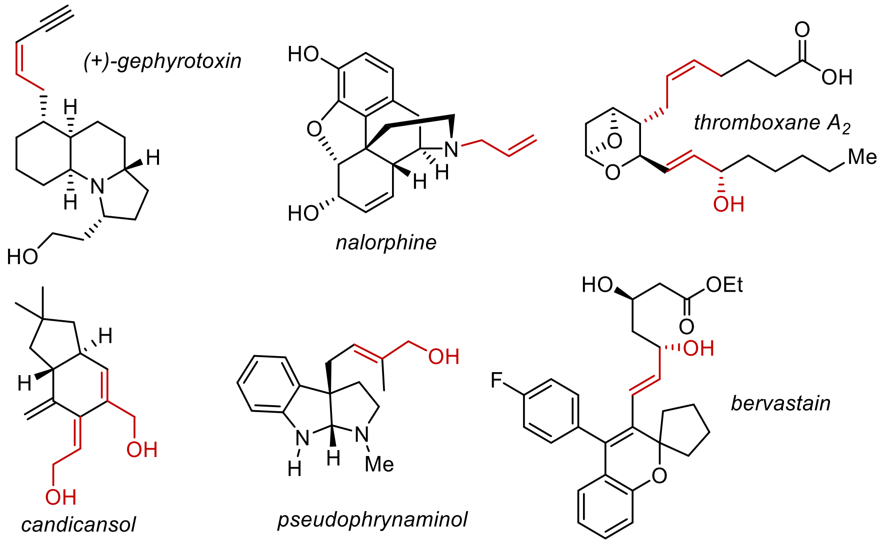
Chapter 1.

Introduction

1.1. Transition-metal/photoredox catalyzed allylic substitution

1.1.1. Allyl groups in organic chemistry

Allylic groups ubiquitous in organic chemistry representing diverse and functionalized subunits present in a wide range of natural products and pharmaceuticals (Scheme 1.1).[1] The presence of suitable leaving groups flanking the C=C double bond is often crucial to promote new types of C–C or C–X bond formation. Compared with traditional organometallic reagents, metal-allyl compounds have proven to be a versatile and effective alternative in organic transformations. In addition, allylic intermediates generated in situ can be stabilized and their reactivity fine-tuned, especially in the presence of suitable metals and during radical-mediated reactions. However, the activation of the allylic position may result in chemo-, stereo- and regio-selectivity challenges upon formation of the substituted allylic product.[2]



Scheme 1.1. Selected natural products and drug molecules containing allyl groups.

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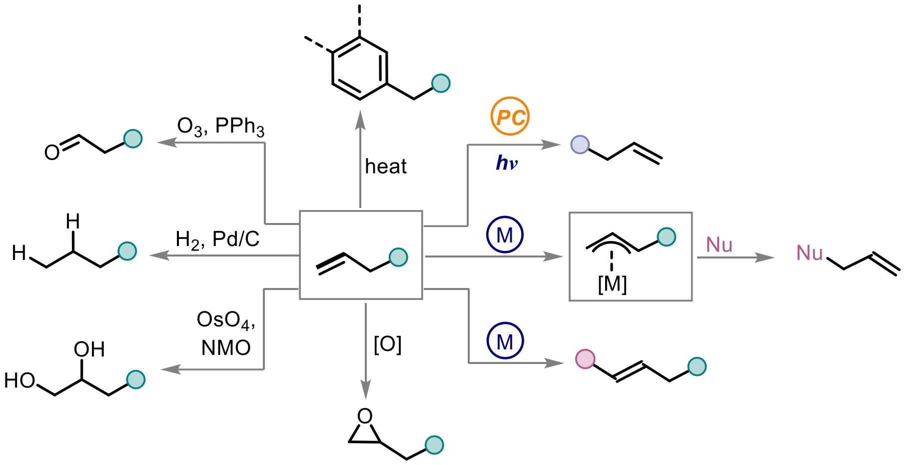
(1) a) J. E. Hochlowski, M. M. Mullally, S. G. Spanton, D. N. Whittern, P. Hill, J. B. McAlpine, *J. Antibiot.* **1993**, *46*, 380-386; b) R. M. Williams, E. M. Stocking, J. F. Sanz-Cervera, *Top. Curr. Chem.* **2000**, *209*, 97-173; c) J. S. Carle, C. Christophersen, *J. Am. Chem. Soc.* **1979**, *101*, 4012-4013; d) A. Arnonr, R. Cardillo, V. D. Modugno, G. Nasini, *J. Chem. Soc., Perkin Trans*. **1989**, *1*, 1995-2000; e) M. J. Kima, J. Dawesb, W. Jessup, *Atherosclerosis* **1994**, *108*, 5-17.

(2) a) K. A. Margrey, D. A. Nicewicz, *Acc. Chem. Res.* **2016**, *49*, 1997−200; b) B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921−2943; c) J. W. J. Kennedy, D. G. Hall, *Angew. Chem. Int. Ed.* **2003**, *42*, 4732–4739.

During the last two decades, there has been remarkable progress in the development of well-established synthetic transformations that have evolved around allylic compounds thereby providing structurally complex and functionally diverse molecules (Scheme 1.2). For instance, olefin metathesis of allylic compounds in the presence of (another) alkene allows to access multi-substituted alkenes. Other classic methods to derivatize allylic compounds involve radical addition, [3] epoxidation, hydrogen-based reduction, dihydroxylation-oxidative of olefins and transition metal catalysis using a variety of (pro)nucleophiles (Nu), which offer pathways to multifunctional synthons of high utility in organic synthesis.[4]



Scheme 1.2. Selected examples of the functionalization of the C=C bonds in allylic compounds. PC stands for photocatalyst, M is a metal catalyst.

1.1.2. Classic transition metal-catalyzed allylic alkylations

Allylic substitution is a powerful tool in the catalytic diversification of various feedstock, and as such represents a valuable reactivity paradigm. The latter is particularly useful to access multifunctional and complex molecules with potential in fine-chemical and pharmaceutical discovery programs.[5] Transition-metal catalysis is a classic method to upgrade allylic precursors and methodologies have often relied on metal systems derived

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(3) L. Debien, B. Quiclet-Sire, S. Z. Zard, *Acc. Chem. Res.* **2015**, *48*, 1237–1253.

(4) a) A. B. Flynn, W. W. Ogilvie, *Chem. Rev*. **2007**, *107*, 4698–4745; b) Q.-H. Xia, H.-Q. Ge, C.-P. Ye, Z.-M. Liu, K. X. Su, *Chem. Rev*. **2005**, *105*, 1603–1662.

(5) a) Trost, B. M. *Acc. Chem. Res*. **1996**, *29*, 355–364; b) L. Süsse, B. M. Stoltz, *Chem. Rev*. **2021**, *121*, 4084–4099; c) C. Du, L. Li, Y. Li, Z. Xie, *Angew. Chem. Int. Ed*. **2009**, *48*, 7853–7856.

from Pd,[6] Cu,[7] Ni,[8] Ir,[9] Mo,[10] Rh[11] among others.[12] Various new chemical bonds such as C–C, C–N and C–O connections can be forged by suitable allylic substitution processes, and these illustrate among the most developed approaches in the area.

The widely accepted mechanistic paradigm that classifies the type of attack of carbon-based nucleophiles onto activated allyl species is its pK_a. Stabilized or "soft" nucleophiles typically have a pK_a lower than 25 and, conversely, unstabilized or "hard" nucleophiles have a pK_a higher than 25.[13] A general pathway for both types of attack is shown in Scheme 1.3. The main distinguishing factor between these two pathways is that the soft nucleophiles are involved in outer-sphere attack on a π-allyl-metal species (**2**) giving product **4** with retention of stereochemistry. Contrary, hard nucleophiles usually induce an inner-sphere attack on **2** first initiated by a transmetalation step between the hard nucleophile and the π-allyl-metal species. The latter subsequently undergoes reductive elimination with formal inversion of the stereocenter to produce products of type **3**. Many of the conventional approaches require the use of pre-activated 'soft' nucleophiles such as for enolates, acyl anions and diethyl malonate derivatives under demanding conditions, while 'hard' nucleophiles often involve moisture-sensitive organometallic reagents which may limit the functional group tolerance of the transformation.

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(6) a) B. M. Trost, J. E. Schultz, *Synthesis* **2019**, *51*, 1–30; b) O. Pàmies, J. Margalef, S. Cañellas, J. James, E. Judge, P. J. Guiry, C. Moberg, J.-E. Bäckvall, A. Pfaltz, M. A. Pericàs, M. Diéguez, *Chem. Rev*. **2021**, *121*, 4373–4505.

(7) a) Y. Lee, K. Akiyama, D. G. Gillingham, M. K. Brown, A. H. Hoveyda, *J. Am. Chem. Soc.* **2008**, *130*, 446–447; b) Y. Makida, H. Ohmiya, M. Sawamura, *Angew. Chem. Int. Ed.* **2012**, *51*, 4122–4127.

(8) a) Y. Kita, R. D. Kavthe, H. Oda, K. Mashima, *Angew. Chem. Int. Ed*. **2016**, *55*, 1098–1101; b) D. Ghorai, À. Cristòfol, A. W. Kleij, *Eur. J. Inorg. Chem*. **2022**, e202100820.

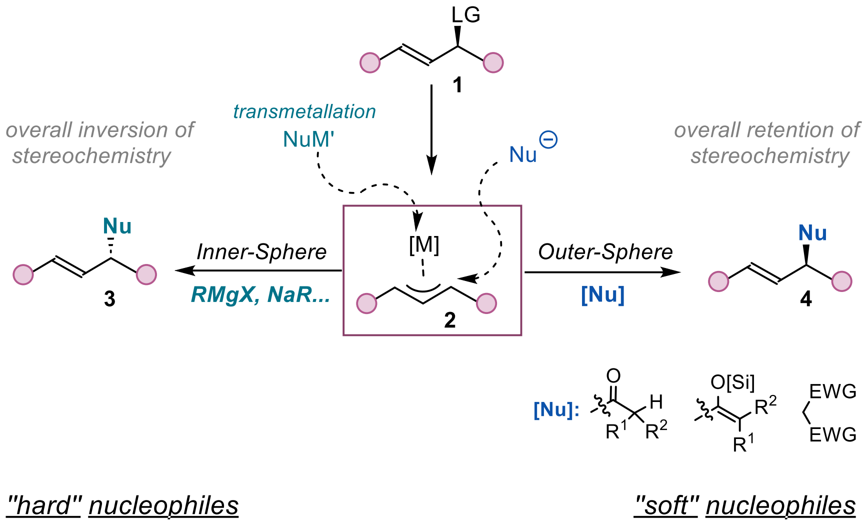
(9) a) J. C. Hethcox, S. E. Shockley, B. M. Stoltz, *ACS Catal*. **2016**, *6*, 6207–6213; b) A. Alexakis, D. Polet, *Org. Lett*. **2004**, *6*, 3529–3532.

(10) a) B. M. Trost, Y. Zhang, *J. Am. Chem. Soc*. **2007**, *129*, 14548–14549; b) B. M. Trost, J. R. Miller, C.M. Hoffman Jr, *J. Am. Chem. Soc*. **2011**, *133*, 8165–8167; c) M. Salman, Y. Xu, S. Khan, J. Zhang, A. Khan, *Chem. Sci*. **2020**, *11*, 5481–5486.

(11) a) P. A. Evans, J. E. Robinson, *J. Am. Chem. Soc*. **2001**, *123*, 4609–4610; b) B. Lu, X. Liang, J. Zhang, Z. Wang, Q. Peng, X. Wang, *J. Am. Chem. Soc.* **2021**, *143*, 11799–11810.

(12) a) W. Rao, P. W. H. Chan, *Org. Biomol. Chem*. **2008**, *6*, 2426–2433; b) M. Bandini, A. Eichholzer, *Angew. Chem. Int. Ed*. **2009**, *48*, 9533–9537; c) S. Oliver, P. A. Evans, *Synthesis* **2013**, *45*, 3179–3198.

(13) a) B. M. Trost, G. M. Schroeder, *J. Am. Chem. Soc*. **1999**, *121*, 6759-6760; b) M. Braun, F. Laicher, T. Meier, *Angew. Chem. Int. Ed.* **2000**, *39*, 3494-3497; c) D. Grassia, A. Alexakis, *Adv. Synth. Catal.* **2015**, *357*, 3171–3186.



Scheme 1.3. General allylic substitution pathways with “soft” and “hard” nucleophiles.

The in situ formation of electrophilic metal-allyl species **7** and their engagement with nucleophilic reaction partners provides one of the most practical tools with synthetic allylic chemistry (Scheme 1.4, catalytic cycle at the right).[5] However, strategies that are based on nucleophilic allyl-metal complexes **8** (often via Umpolung) have also been developed using electrophilic reaction partners such as aldehydes, imines and ketones (Scheme 1.4, catalytic cycle at the left). One prevalent approach towards Umpolung of the metal-allyl species is the addition of reducing agents including $ZnEt_2$, BEt_3 and InI that facilitate the reduction of the metal species. Thus, the metal ion in the π-allyl-metal complex **7** become more electron-rich and the allyl unit in **8** have increased nucleophilic character.[14]

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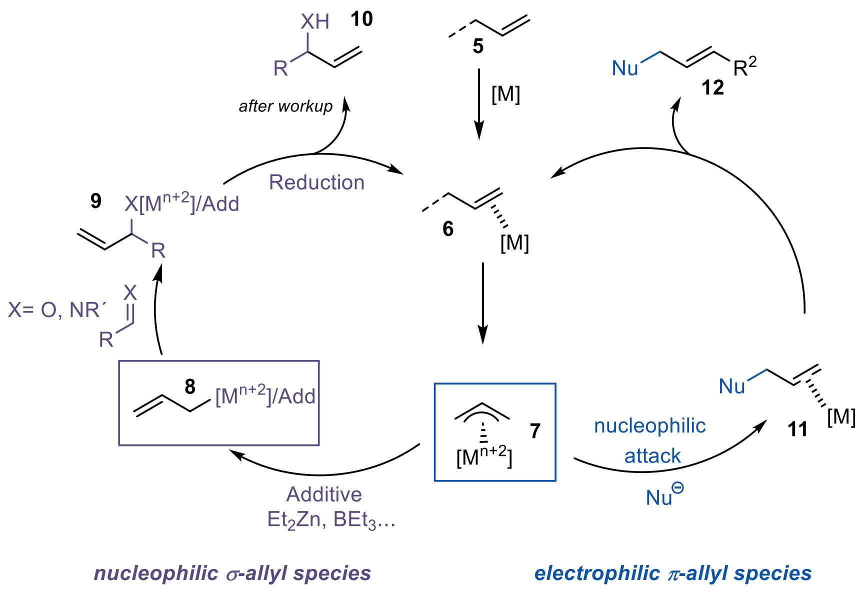
(14) a) K. Spielmann, G. Niel, R. M. de Figueiredo, J.-M. Campagne, *Chem. Soc. Rev.* **2018**, *47*, 1159-1173; b) J. W. J. Kennedy, D. G. Hall, *Angew. Chem. Int. Ed.* **2003**, *42*, 4732 –4739.



Scheme 1.4. General pathways featuring nucleophilic (left) and electrophilic metal-allyl species (right). Add stands for additive.

Since the first Ni-based catalytic allylation process using hard nucleophiles was reported by Felkin and coworkers in 1968,[15] significant efforts have been devoted to transition-metal promoted allylic transformations. For instance, Tamaru proposed a one-pot sequential Tsuji-Trost/Umpolung allylation reaction of vinyl epoxides in the presence of the $Pd(acac)_2$ and BEt_3 as a reducing agent (Scheme 1.5).[16] The α-aldehyde position in compounds **13** undergoes first electrophilic attack by the metal-allyl species derived from vinyl epoxide **14**. Hereafter, the intermediate allylic alcohol serves as a precursor to mediate in situ borylation affording the nucleophilic allyl species **18** (i.e., its α-carbon) that is converted in the presence of the Pd catalyst delivering the 2-vinylcyclobutanol product **15**.

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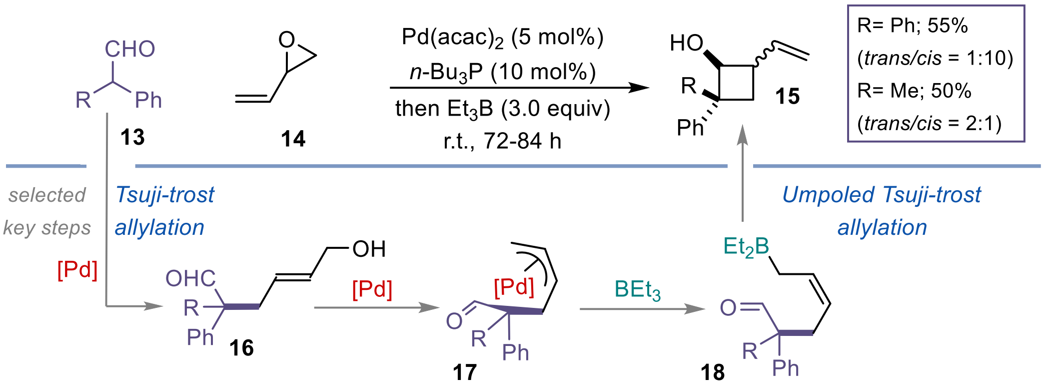
(15) a) C. Chuit, H. Felkin, C. Frajerman, G. Roussi, G. Swierczewski, *Chem. Commun.* **1968**, 1604–1605; b) H. Felkin, G. Swierczewski, *Tetrahedron Lett.* **1972**, *13*, 1433–1436; c) H. Felkin, M. Joly-Goudket, S. G. Davies, *Tetrahedron Lett.* **1981**, *22*, 1157–1160.

(16) M. Kimura, R. Mukai, T. Tamaki, Y. Horino, Y. Tamaru, *J. Am. Chem. Soc.* **2007**, *129*, 4122–4123.



Scheme 1.5. Pd-catalyzed sequential Tsuji-Trost/Umpolung allylation reaction of vinyl epoxides and α-aldehydes.

As an example, in 2020 an interesting protocol for the Ni-catalyzed, chemoselective allylic substitution of allylic alcohols by alkyl Grignard reagents under catalyst control was reported by Wang and coworkers (Scheme 1.6).[17] They disclosed a divergent allylic alkylation process promoted by Ni(dppe)Cl$_2$, though with the formation of reduction product **21** taking primarily place when a mixture of Ni(PCy$_3$)$_2$Cl$_2$ and diphosphine dcype was present. The process starts with the reduction of the Ni(II) by the Grignard reagent followed by oxidative addition of allyloxo-magnesium **22** to deliver the η^3 and η^1-allyl nickel species **23a** and **23b**. Subsequent transmetalation with alkyl Grignard reagents results into the formation of allyl nickel intermediates **24a** and **24b**. The presence of the less bulky ligand dppe favors the generation of alkylated product **20** after reductive elimination through intermediate **23a** and **24a**, whereas the presence of the more bulky and electron-donating dcype ligand favors the stabilization of intermediates **23b** and **24b** and thus leads to the β-hydride elimination product **21**.

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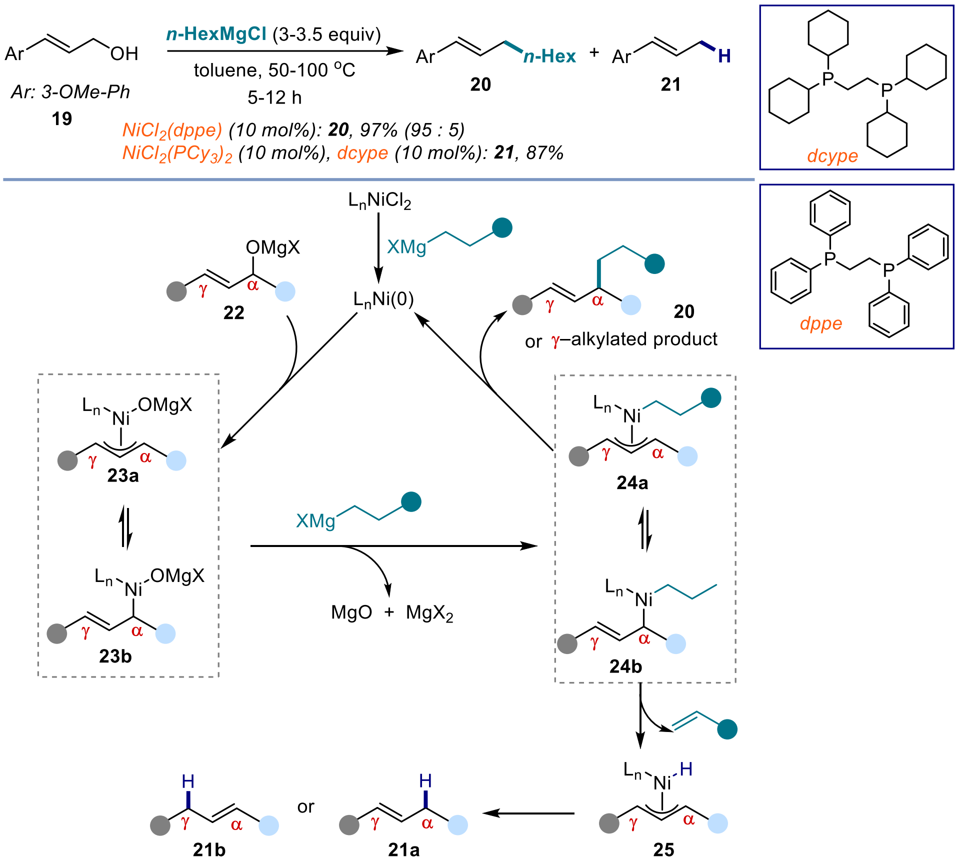
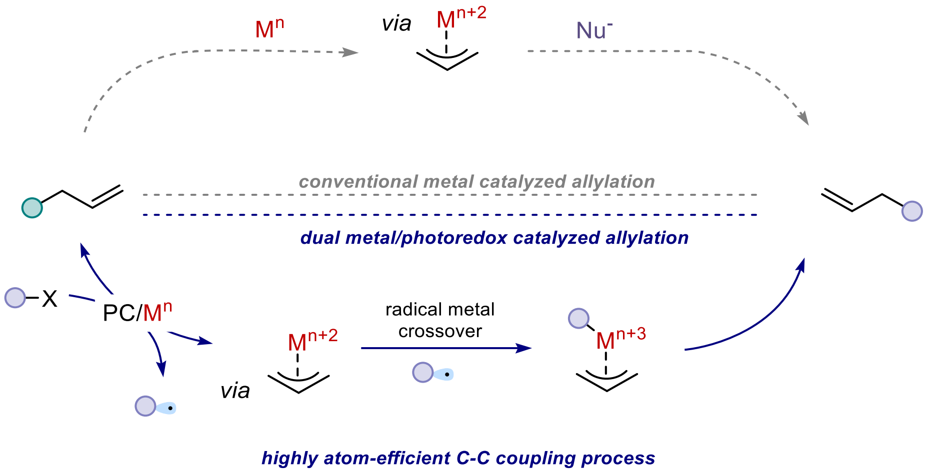
(17) B. Yang, Z. X. Wang, *J. Org. Chem.* **2020**, *85*, 4772–4784.



Scheme 1.6. Divergent Ni-catalyzed allylation using allylic alcohols and Grignard reagents under catalyst control.

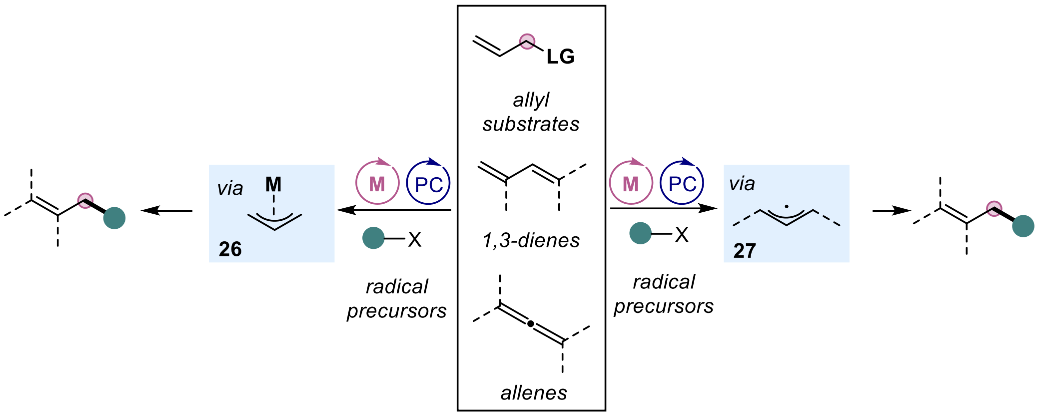
1.1.3. Dual photo/metal catalyzed allylic alkylation

Apart from traditional metal-mediated allylations, radical-mediated and metal/photoredox assisted reactions are synthetically attractive as radicals can facilitate the formation of allylic intermediates from the sp^2-hydridized substrates and provide mild strategies for the generation of hard (C-based) nucleophiles (Scheme 1.7). This comparatively mild, dual catalysis approach combines photo- with transition metal catalysis and usually exhibits significantly amplified functional group tolerance, allowing for the rapid synthesis of large(r) series of products from diverse radical and allylic starting materials. Moreover, the stabilization of radical species via a radical metal crossover step enables to control radical reactivity towards the reductive elimination product enhancing thereby the atom-economy of the process.



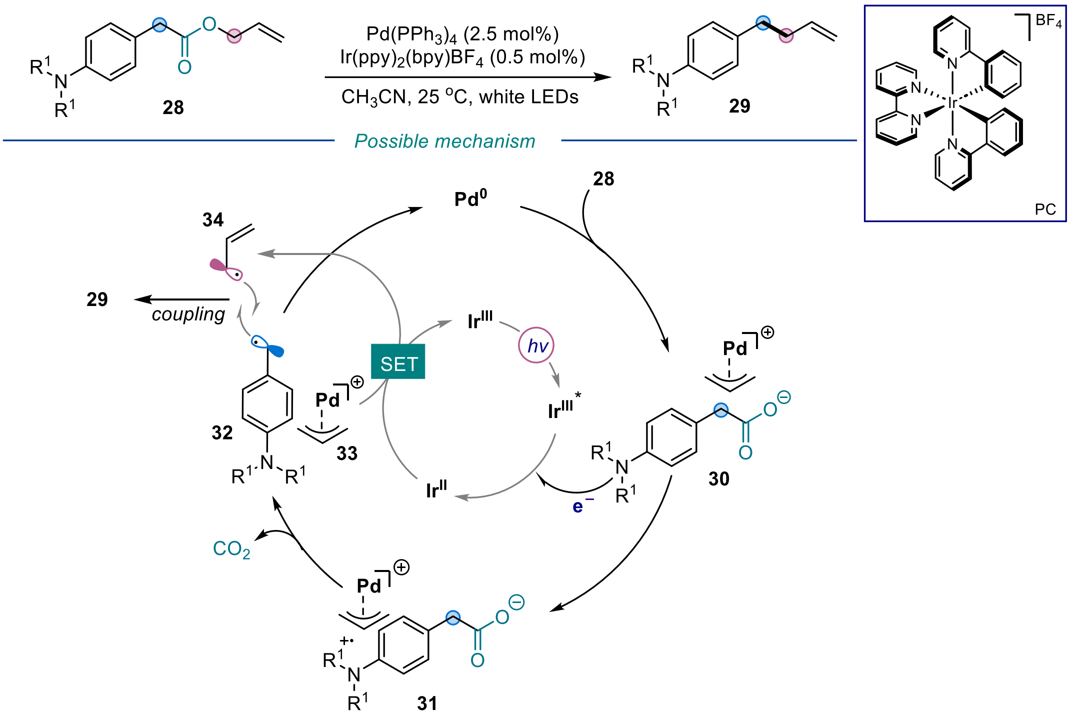
Scheme 1.7. Metal π-allyl based allylation: conventional metal catalyzed (top) and dual metal/photoredox catalyzed allylation (below).

Here we further discuss two radical-based pathways, i.e. involving the formation of a π-allyl-metal species **26** and the generation of an allylic radical species **27** (Scheme 1.8). The current section is dedicated to examples affording products containing allyl moieties originating from various precursors such as allylic compounds, 1,3-dienes and allenes, and enabled by allylic alkylation or formal C–H activation/allylation reaction while promoted by dual metal/photoredox catalysis.



Scheme 1.8. Mechanistic scenarios in dual catalytic allylations involving radicals.

Benzylic nucleophiles, having a pK_a values above 40, are preferentially employed in dual metal/photo-catalyzed allylic benzylations. For instance, Tunge's group reported on photoredox/Pd cocatalyzed decarboxylative allylic benzylation (Scheme 1.9).[18] They proposed radical cross-coupling from benzylic radical **32** and allylic radical **34** with the latter being generated from a single-electron reduction (SET step) of π-allyl-Pd intermediate **33**. As an alternative, radical metal crossover leading to a Pd(III) complex followed by reductive elimination to give the final product can also be a plausible pathway.



Scheme 1.9. Radical cross-coupling of allylic and benzyl radicals via dual Pd/photocatalytic decarboxylation.

Additionally, Yu and coworkers developed Pd/photoredox catalyzed asymmetric allylic alkylation *via* a radical metal crossover pathway with alkyl radicals formed from DHPs (4-alkyl-1,4-dihydropyridines) acting as hard nucleophiles, which then participate in decarboxylative allylic benzylation using carboxylic acids with high regio- and enantioselectivity.[19]

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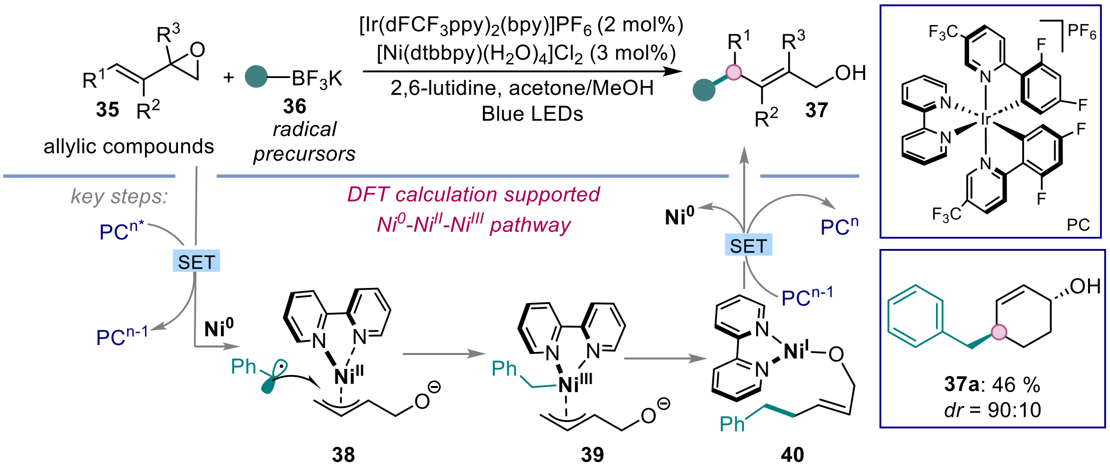
(18) a) S. B. Lang, K. M. O'Nele, J. A. Tunge, *J. Am. Chem. Soc.* **2014**, *136*, 13606−13609; b) K. C. Cartwright, J. A. Tunge, *Chem. Sci.* **2020**, *11*, 8167–8175.

(19) a) H.-H. Zhang, J.-J. Zhao, S. Yu, *J. Am. Chem. Soc.* **2018**, *140*, 16914−16919; b) C. Song, H.-H. Zhang, S. Yu, *ACS Catal.* **2022**, *12*, 1428−1432.

A series of examples of dual Ni/photoredox catalysis protocols have been reported by Molander,[20] Gong[21] and Breit.[22] The Molander group disclosed a dual catalytic allylation of secondary, benzyl, and α-alkoxy radical precursors (Scheme 1.10). From computational studies, the authors concluded that the oxidative addition step (to form Ni(II) complex **38**) first occurs before inner-sphere radical addition takes place via **39**. The proposed Ni(0)-Ni(II)-Ni(III) pathway favors the formation of the Ni(III) complex **39**, with subsequent reductive elimination releasing product **40**. The SET reduction of **40** leads to linear products **37** along with regenerated Ni(0). A similar manifold that involved 1,2-epoxy-3,4-cyclohexene as substrate results in formation of the *anti*-isomer **37a** as the major product, with overall net inversion of stereochemistry observed for this dual catalyst system.



Scheme 1.10. Dual Ni/photoredox promoted allylation of vinyl epoxides.

In the case of allylic radical formation, extensive efforts have been devoted to forge functionalized allylic scaffolds. The Glorius and Kanai group, respectively, reported on similar single-electron oxidation strategies of allylic substrates **42** that requires a Cr(II) catalyst to mediate diastereo- and enantio-selective formation of products **43** by the combination of a Cr-allyl species stemming from an allylic radical (**44**), and aldehydes

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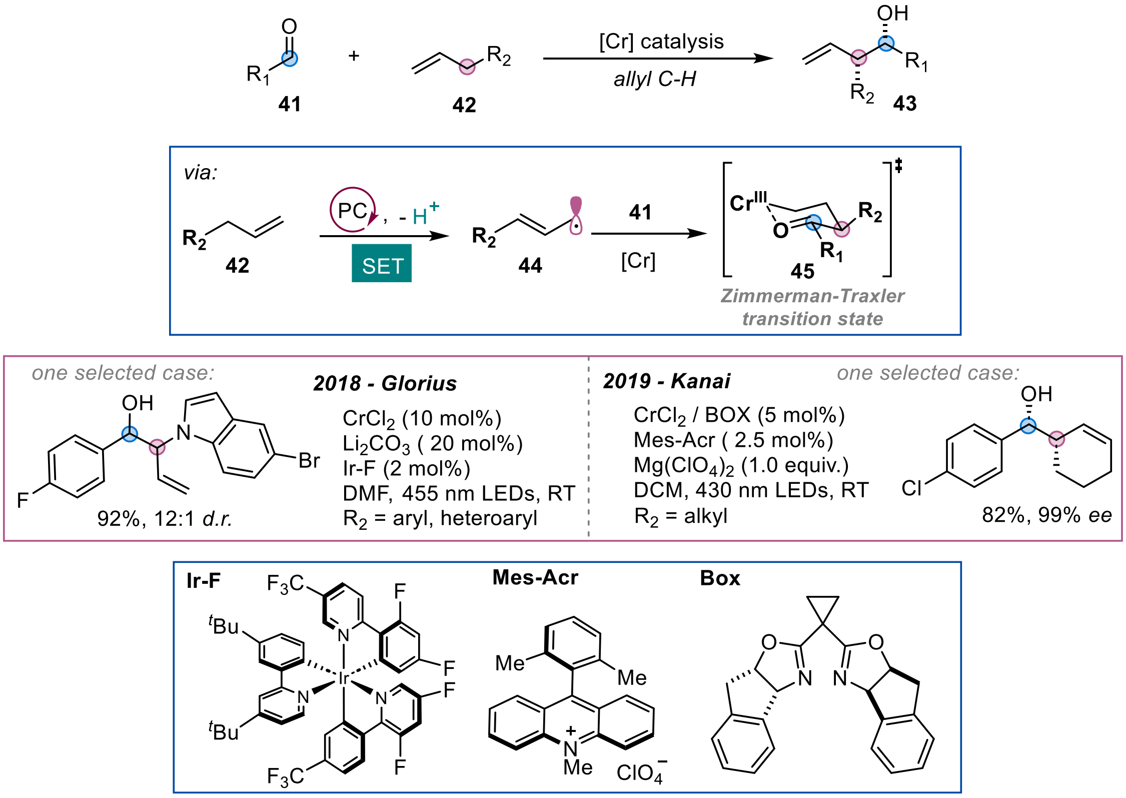
(20) a) J. K. Matsui, l. Gutiérrez-Bonet, M. Rotella, R. Alam, O. Gutierrez, G. A. Molander, *Angew. Chem. Int. Ed*. **2018**, *57*, 15847–15851; b) Z.-J. Wang, S. Zheng, E. Romero, J. K. Matsui, G. A. Molander, *Org. Lett*. **2019**, *21*, 6543−6547.

(21) Y. Jin, E. W. H. Ng, T. Fan, H. Hirao, L.-Z. Gong, *ACS Catal*. **2022**, *12*, 10039−10046.

(22) J. Zheng, C. Nopper, R. Bibi, A. Nikbakht, F. Bauer, B. Breit, *ACS Catal*. **2022**, *12*, 5949−5960.

15 via a Zimmerman–Traxler type cyclic transition state **45** (Scheme 1.11).[23] The group of Kanai developed a catalytic asymmetric allylation protocol providing highly enantioenriched homoallylic alcohols starting from a wide combination of aldehydes and simple alkenes. This is in contrast to the process reported by Glorius, which is restricted to heteroaryl-based allylic compounds.



Scheme 1.11. Dual Cr/photoredox catalyzed allylic substitution *via* allylic radical formation and a Zimmerman–Traxler transition state.

1,3-Dienes are of great value in photoredox metal catalysis serving as radical acceptors thereby forming allyl radicals, which subsequently can be captured by suitable Cr, Ti, Ni (among others) catalysts offering a productive way to prepare allylic products.[24] In 2020, the Glorius group found that dialkylation of 1,3-dienes in the presence of aldehydes and

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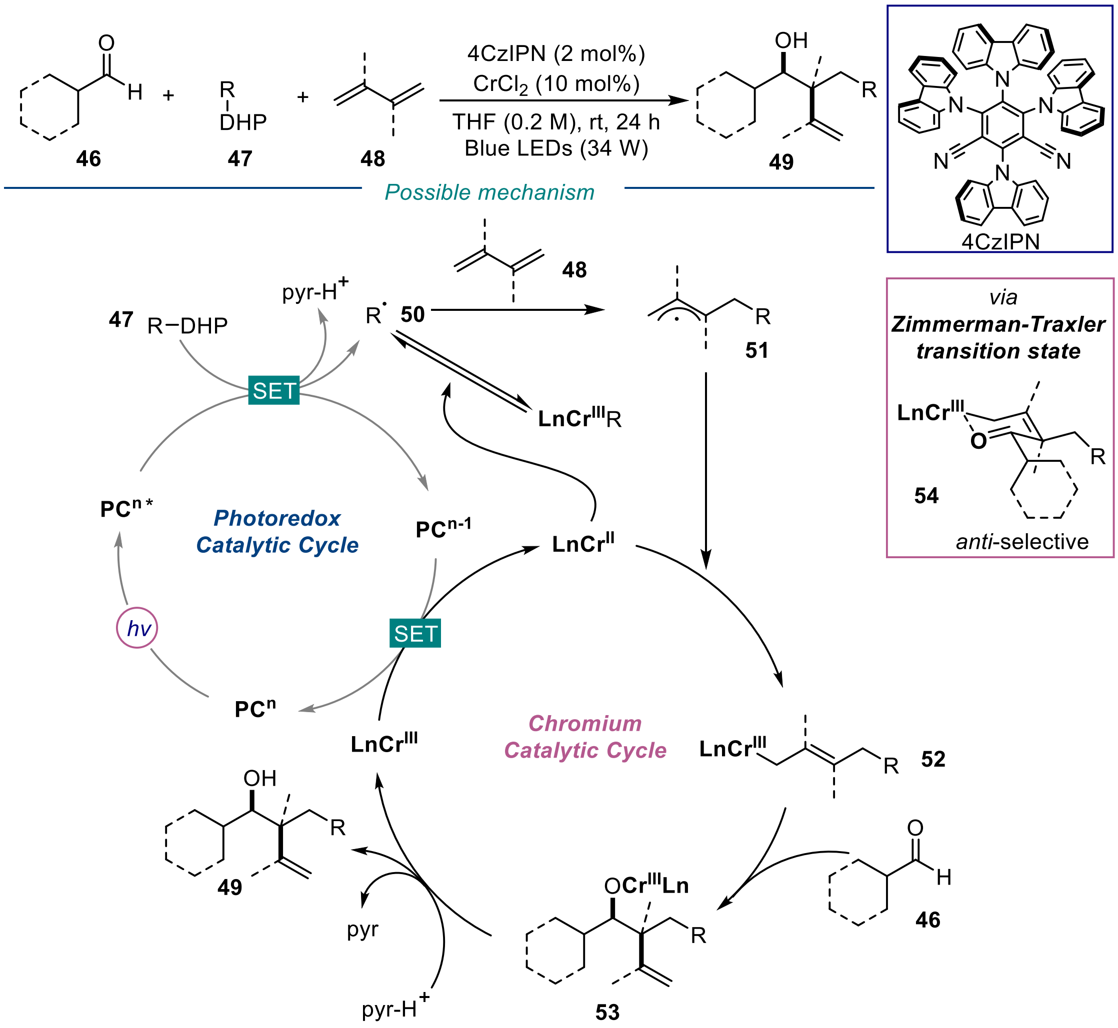
(23) a) J. L. Schwarz, F. Schäfers, A. Tlahuext-Aca, L. Lückemeier, F. Glorius, *J. Am. Chem. Soc.* **2018**, *140*, 12705–12709; b) H. Mitsunuma, S. Tanabe, H. Fuse, K. Ohkubo, M. Kanai, *Chem. Sci.* **2019**, *10*, 3459–3465.

(24) a) F.-D. Lu, G.-F. He, L.-Q. Lu, W.-J. Xiao, *Green Chem.* **2021**, *23*, 5379–5393; b) Y. L. Li, W. D. Li, Z. Y. Gu, J. Chen, J. B. Xia, *ACS Catal.* **2020**, *10*, 1528–1534; c) A. Gualandi, F. Calogero, M. Mazzarini, S. Guazzi, A. Fermi, G. Bergamini, P. G. Cozzi, *ACS Catal.* **2020**, *10*, 3857–3863.

Hantzsch esters takes place enabled by dual Cr/photoredox catalysis furnishing 1,2-dialkylated products with excellent diastereoselectivity (Scheme 1.12).[25] A plausible mechanism was proposed involving a photoredox catalytic cycle and Cr-based catalytic cycle. The Hantzsch ester **47** is first quenched by the excited-state photocatalyst to release reduced PC^{n-1} and radical **50** after homolysis step. The alkyl radical **50** can be reversibly trapped by the Cr^{II} species form alkyl-Cr^{III} species or add onto the 1,3-diene **48** to generate allylic radical intermediate **51**. Then, the chromium alkoxide **53** is formed via a six-membered Zimmerman-Traxler transition state **54** involving the allylic radical **51** and an aldehyde, followed by protodemetalation by the pyr-H^+ to give product **49** and a Cr^{III} complex that undergoes reduction by PC^{n-1} to regenerate the starting Cr^{II} species.



Scheme 1.12. Dual Cr/photoredox catalyzed allylation of 1,3-dienes.

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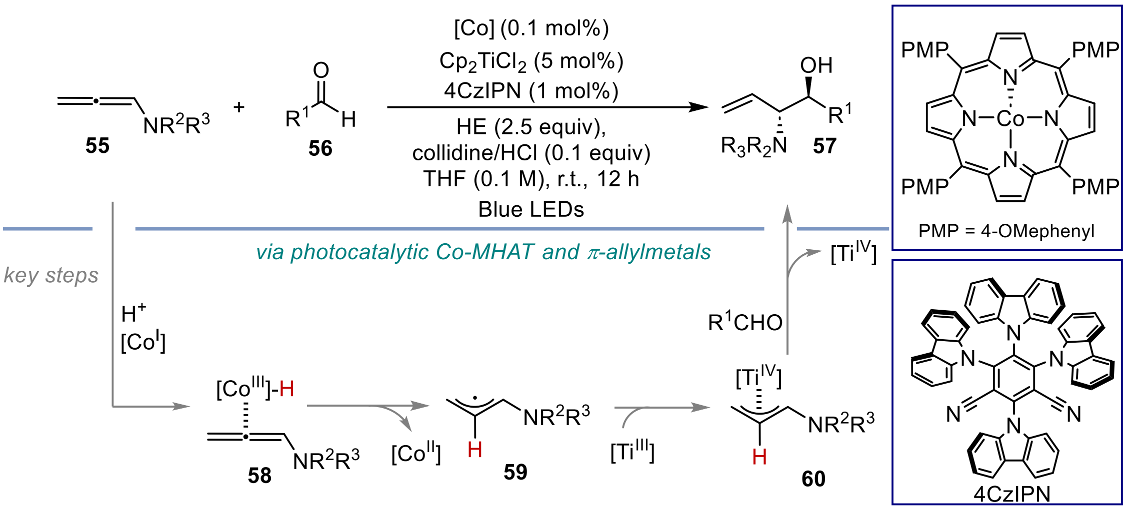
(25) J. L. Schwarz, H.-M. Huang, T. O. Paulisch, F. Glorius, *ACS Catal.* **2020**, *10*, 1621–1627.

In general, radical addition onto the central carbon of substituted allenes allows for the generation of transient allylic radicals.[26] In 2023, Shi and coworkers developed a photocatalytic approach by combining a metal hydride hydrogen atom transfer (MHAT) and Ti catalyst that induce formation of allylic radical **59** from allene **55** (Scheme 1.13).[27] This process is believed to start with the formation of a Co^{III}-H from Co^{I} and H^+, which then transfers an hydrogen atom to the allene substrate releasing a Co^{II} complex and an allyl radical (**59**), with the latter being subsequently captured by Ti^{III} to yield the nucleophilic π-allyl-Ti(IV) species **60**. The coupling between allyl-Ti species **60** and an aldehyde **56** provides the allyl-free complex [Ti^{IV}] and a protonated, homoallylic alcohol **57**. The excited photocatalyst $4CzIPN^{\bullet-}$ [$E_{1/2}$ 4CzIPN/$4CzIPN^{\bullet-}$ = -1.24 V vs SCE] should be an effective reductant for both Co^{II} [$E_{1/2}$ (Co^{II}/Co^{I}) = -0.70 V vs SCE] and Ti^{IV} [$E_{1/2}$(Ti^{IV}/Ti^{III}) = -0.57 V vs SCE]. Both the cycle based on the redox ensembles Co^{II}-Co^{I}-Co^{III} and Ti^{III}-Ti^{IV} are intertwined with the photoredox catalysis cycle as to maintain an efficient C–C bond formation event.



Scheme 1.13. Metal/photoredox mediated allylation of allenes via a Co-MHAT process.

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(26) J. Singh, A. Sharma, A. Sharma, *Org. Chem. Front.* **2021**, *8*, 5651-5667.
(27) H. Yan, Q. Liao, Y. Chen, G. G. Gurzadyan, B. Lu, C. Wu, L. Shi, *Angew. Chem. Int. Ed.* **2023**, *62*, e202302483.

1.2. Cascade reactions initiated by radical additions

1.2.1. Radical addition-induced allylations

Radical addition is one of the most versatile approaches to furnish or functionalize a molecular skeleton in organic synthesis. This strategy allows flexible structural modifications of organic compounds, including elaborated examples of alkene/alkanes and other, even more sophisticated structures obtained from the simple and readily available feedstock. Substrate polarity typically affect the overall process kinetics of radical addition reactions, and rely on the polarity matching of the reaction partners. In radical additions to alkenes, the level of polarity matching between the other reaction components and the olefins is crucial to control the reaction rate. For example, Barriault and McCallum demonstrated a highly selective Minisci-type[28] three component reaction (3CR) via proper polarity matching between an α-bromoester, heterocycles and an alkene (Scheme 1.14a).[29] The addition of electrophilic α-ester radical **65** to electron-rich alkene **62** is straightforward, with the polar character of the resulting radical adduct **66** being reversed. The latter then can attack the electrophilic, protonated heteroaromatic base **63a**, affording selectively the substituted heterocyclic ring product **64**.

Another case of polarity matching in radical addition chemistry is based on the addition of azide radical **70** to electron-rich olefins **62**, and subsequent addition of the in situ generated nucleophilic radical adduct **71** onto heteroarenes. Through this sequence, selective azido-heteroarylation of olefins was achieved (Scheme 1.14b).[30] Liu and co-workers proposed that azide radicals are generated via species **69** prepared from $TMSN_3$ and PIDA (PIDA = diacetoxyiodo-benzene) that triggers the radical addition and subsequent Minisci-type reaction in a relatively short time frame allowing to prepare a library of azido-alkylated heteroaromatics of type **68**.

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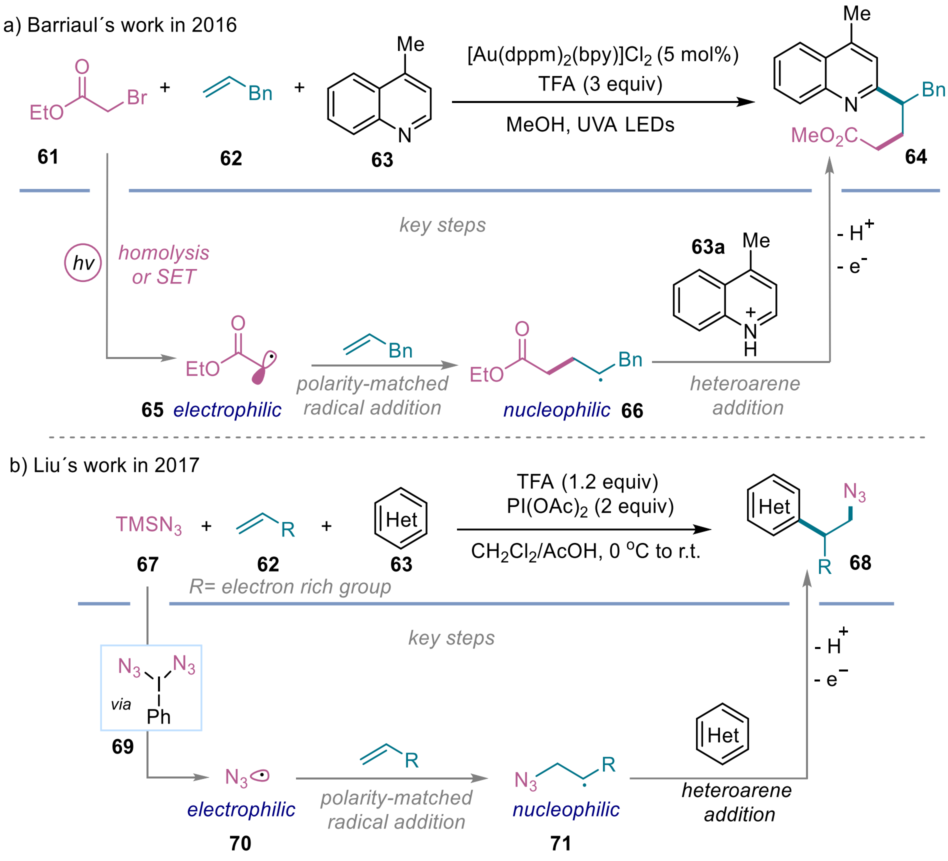
(28) a) M, R. Galli, M. Cecere, V. Malatesta, T. Caronna, *Tetrahedron Lett.* **1968**, *9*, 5609–5612; b) F. Antonietti, A. Mele, F. Minisci, C. Punta, F. Recupero, F. Fontana, *J. Fluorine Chem.* **2004**, *125*, 205–211.

(29) T. McCallum, L. Barriault, *Chem. Sci.* **2016**, *7*, 4754–4758.

(30) Z. Liu, Z.-Q. Liu, *Org. Lett.* **2017**, *19*, 5649–5652.



Scheme 1.14. Metal/photoredox catalyzed 3CR approaches using polarity-matched substrates.

Additionally, allyl leaving groups can also be of importance to facilitate the formation of new chemical bonds formations in radical-mediated allylations. In this regard, the emergence of allylic sulfones as efficient allylating reagents in various transformations has demonstrated these precursors are powerful in the synthesis of valuable compounds.[31] Since the radical-induced desulfonylative allylation process developed by Zard et al.,[32] significant efforts have been paid to analogous cascade reactions.[26] In 2016, Chen reported that visible light induced polarity-reversed allylation of alkyl imines, aldehydes or ketones in the presence of allylic sulfones offers a viable route to homoallylic amines and alcohols (Scheme 1.15).[33] This radical Umpolung protocol transforms an

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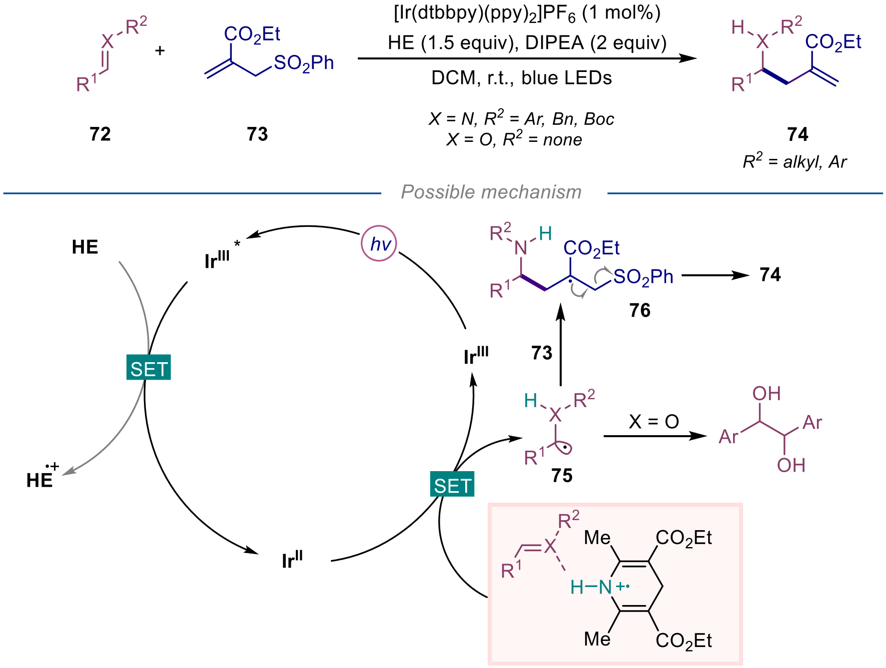
(31) X.-Q. Chu, D. Ge, Y.-Y. Cui, Z.-L. Shen, C.-J. Li, *Chem. Rev.* **2021**, *121*, 12548−12680.

(32) a) B. Quiclet-Sire, S. Z. Zard, *J. Am. Chem. Soc.* **1996**, *118*, 1209−1210; b) F. Le Guyader, B. Quiclet-Sire, S. Seguin, S. Z. Zard, *J. Am. Chem. Soc.* **1997**, *119*, 7410−7411; c) B. Quiclet-Sire, S. Seguin, S. Z. Zard, *Angew. Chem. Int. Ed.* **1998**, *37*, 2864−2866; d) N. Charrier, S. Z. Zard, *Angew. Chem. Int. Ed.* **2008**, *47*, 9443−9446.

(33) L. Qi, Y. Chen, *Angew. Chem. Int. Ed.* **2016**, *55*, 13312−13315.

electrophilic imine or carbonyl group into a nucleophilic *α*-amino and *α*-hydroxymethyl radical using an activated Hantzsch ester radical cation, and represent a distinct and useful paradigm for retrosynthesis.

The authors proposed that the partially oxidized Hantzsch ester acts as a hydrogen donor, and might interact with the imine or aldehyde (**72**) to promote a single electron transfer (SET) by the Ir(II) species undergoing a proton-coupled-electron-transfer (PCET).[34] The in situ generated nucleophilic radical **75** adds onto the electron-deficient double bond of allylic compound **73** following polarity match principles to give the desulfonylated, allylic product **74**.



Scheme 1.15. Radical-induced desulfonylative allylation via a PCET pathway.

In view of the fact that various radical precursors are accessible for organic synthesis, considerable efforts have been devoted to explore such substrates in radical allylation. For example, the Ollivier and Zhu groups, respectively, both reported a highly diastereoselective ring-opening/allylation sequence based on *α*-keto-epoxides/aziridines **77.1** (*Ollivier*) and decarboxylative allylation of *N*-aryl-glycine derivatives **77.2** (*Zhu*)

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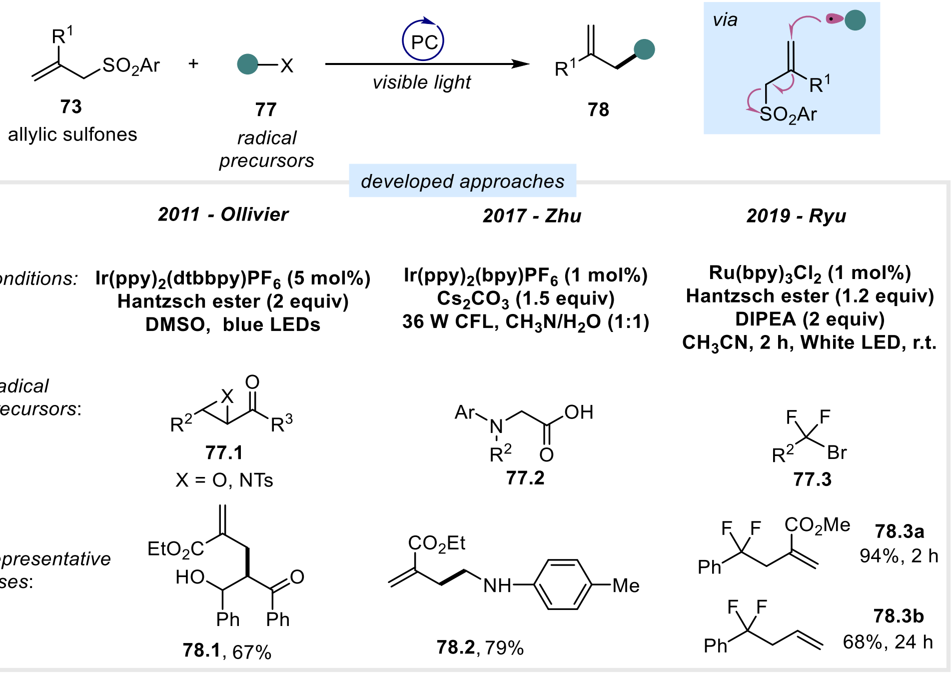
(34) K. T. Tarantino, P. Liu, R. R. Knowles, *J. Am. Chem. Soc.* **2013**, *135*, 10022−10025.

using allyl sulfones **73**.[35] In these two cases, electron-deficient allylic sulfones are combined with nucleophilic radicals following the polarity matching principle to generate the allylation products **78.1** and homoallylic amines **78.2**, respectively, in moderate to good yields. Ryu and coworkers reported on a reductive allylation by combining difluoromethylene-containing alkyl halides **77.3** and allyl sulfones **73** to give 4,4-difluoroalkenes **78.3**.[36] A comparison between products **78.3a** and **78.3b** shows that difluorobenzyl radical addition favors electron deficient alkene partners over relatively electron-rich ones, and thus in the latter case a longer reaction time was needed (Scheme 1.16).



Scheme 1.16. Representative examples of radical-mediated allylation based on the use of allylic sulfones and various radical species.

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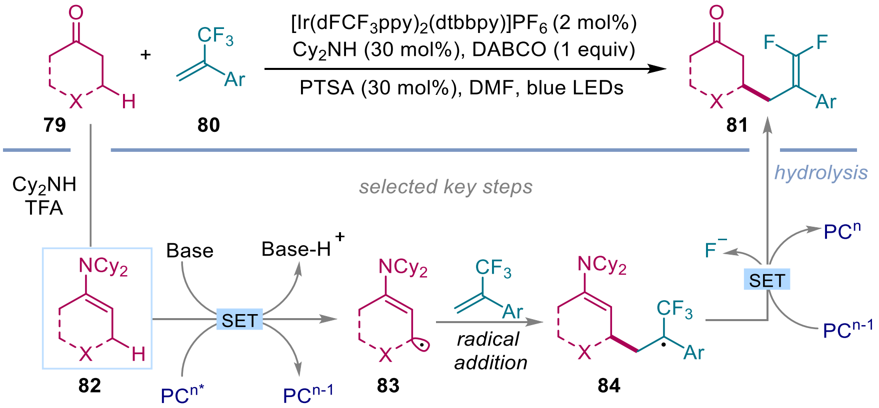
[35] a) M.-H. Larraufie, R. Pellet, L. Fensterbank, J.-P. Goddard, E. Lacôte, M. Malacria, C. Ollivier, *Angew. Chem. Int. Ed.* **2011**, *50*, 4463−4466; b) Y. Duan, M. Zhang, R. Ruzi, Z. Wu, C. Zhu, *Org. Chem. Front.* **2017**, *4*, 525−528.

[36] M. Uno, S. Sumino, T. Fukuyama, M. Matsuura, Y. Kuroki, Y. Kishikawa, I. Ryu, *J. Org. Chem.* **2019**, *84*, 9330−9338.

Apart from allylic sulfones employed in radical-based allylations towards elaborate skeletons, it was demonstrated that allyl halides,[37] allyl silanes[38] and allyl alcohols[39] can also be suitable allylating agents through a homolytic fragmentation of the carbon-halide, carbon-silicon, and carbon-oxygen bond. In 2020, a productive and mild protocol for visible-light promoted *gem*-difluoroallylation of aliphatic aldehydes and cyclic ketones was achieved by the Zhou group (Scheme 1.17).[40] The enamine **82** is generated via the condensation of aldehyde **79** and Cy_2NH in the presence of a catalytic amount of a Brønsted acid, followed by a single electron-transfer (SET) with the excited Ir(III) based PC to deliver a radical cation and a reduced Ir(II) PC. Deprotonated, nucleophilic radical species **83** is able to couple with electron-deficient olefins **80** aligning with a radical polarity match, which results in the formation of α-CF_3 radical species **84**. The single-electron reduction of radical **84** by Ir(II) generates an anionic intermediate that undergoes β-F elimination and hydrolysis, providing the desired carbonyl-functionalized *gem*-difluoroalkenyl product **81**.



Scheme 1.17. Photocatalytic β-CH *gem*-difluoroallylation of carbonyl compounds with α-CF_3 substituted olefins.

Alternatively, a polarity mismatched reaction in the presence of an effective catalyst can be replaced by a set of two polar-matched hydrogen-atom transfer reactions (Scheme 1.18a).[41] In this scenario, a two-step reaction with a low activation energy accelerates the

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(37) a) G. A. Russell, *Acc. Chem. Res.* **1989**, *22*, 1−8; b) C. C. Huval, D. A. Singleton, *Tetrahedron Lett.* **1993**, *34*, 3041−3042.

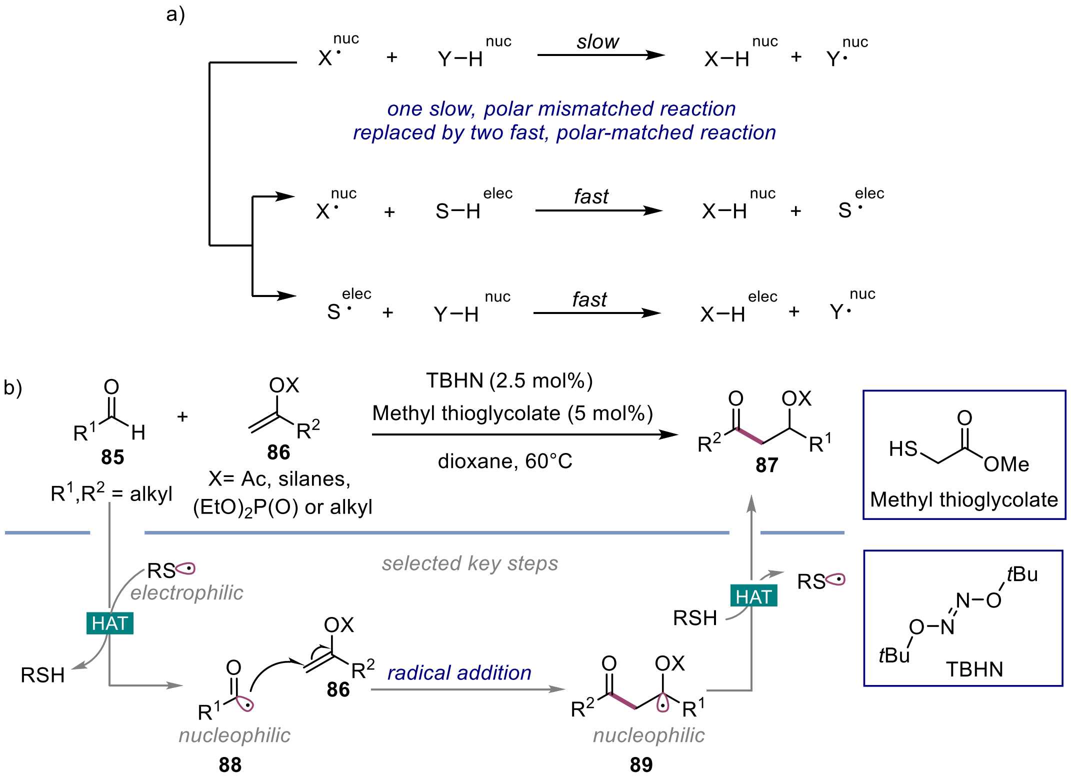
(38) a) C. Chatgilialoglu, C. Ferreri, M. Ballestri, D. P. Curran, *Tetrahedron Lett.* **1996**, *37*, 6383−6386; b) B. Cardinal-David, B. Guerin, Y. Guindon, *J. Org. Chem.* **2005**, *70*, 776−784.

(39) a) N. Charrier, B. Quiclet-Sire, S. Z. Zard, *J. Am. Chem. Soc.* **2008**, *130*, 8898−8899; b) P. Salomon, S. Z. Zard, *Org. Lett.* **2014**, *16*, 2926−2929.

(40) D. Anand, Z. Sun, L. Zhou, *Org. Lett.* **2020**, *22*, 2371–2375.

(41) B. P. Roberts, *Chem. Soc. Rev.* **1999**, *28*, 25−35.

overall reaction rate in comparison to a single-step reaction bearing a higher activation energy. Roberts and coworker reported a radical-induced hydrosilylation reaction occurring via a polarity-reversal approach using a chiral thiol catalyst (Scheme 1.18b).[42] Di-*tert*-butylhyponitrite (TBHN) was used as an initiator of this reaction and delivers *tert*-butoxy radicals. The hydrogen-atom transfer (HAT) reaction occurs between the *tert*-butoxy radicals and RSH or aldehyde **85**. Starting from the electrophilic thiyl radical that undergoes a polarity-matched HAT reaction with aldehyde **85** to afford the nucleophilic acyl radical **88**, subsequent addition takes place to alkenes **86**. The generated nucleophilic radical **89** abstracts a hydrogen from RSH (while abstraction from aldehyde **85** is unlikely as a result of the adverse polar effect) thereby regenerating thiyl radical and giving the product **87**. Notably, the thiol catalysts are effective towards the radical-chain addition of aldehydes to various alkenes, in particular to electron-rich and -neutral ones.



Scheme 1.18. a) Polarity-reversal reaction via hydrogen-atom transfer using thiols as a catalyst; b) Radical-induced hydroacylation of electron-rich alkenes via thiol catalysis through polarity-reversal addition and hydrogen-atom transfer.

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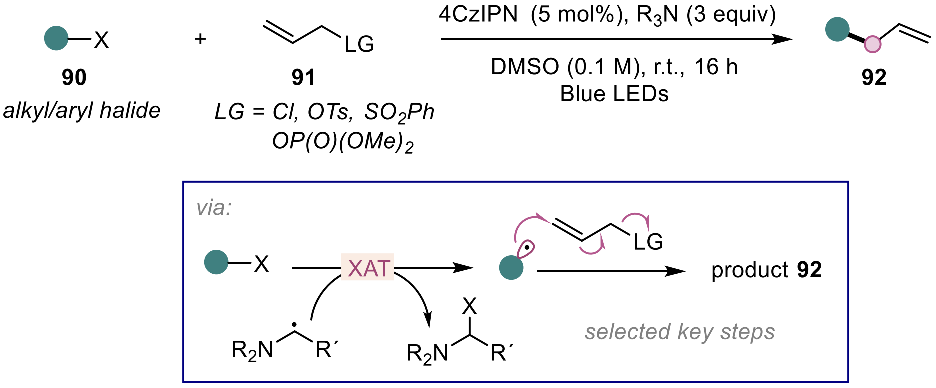
(42) H.-S. Dang, B. P. Roberts, *J. Chem. Soc., Perkin Trans. 1*, **1998**, 67−76.

Although the thiol can be a reliable starting point for the polarity-reversal catalysis via hydrogen-atom transfer, polarity-mismatched catalysis remains rare and the likelihood of this kind of transformation to occur may depend on whether the alkene reagents incorporate suitable leaving groups, if ring-opening can be used as a driving force or if harsh(er) conditions can be applied without affecting the process outcome.[43] Leonori and Juliá reported halogen-atom transfer (XAT) mediated alkylation of allylic precursors such as allyl halides, allyl sulfonates and allyl phosphates acting as radical acceptors (Scheme 1.19, **91**).[44] This last contribution demonstrates that the nucleophilic alkyl radical addition is not limited to electron-deficient alkenes, overcoming thus a radical polar mismatch and enabling a highly efficient coupling of the alkyl halide reagents **90** and allylic precursors **91**.



Scheme 1.19. Halogen-atom transfer (XAT) mediated allylation via polarity-reversal radical addition.

1.2.2. Radical addition induced ring-opening process by strain release

Among radical addition approaches, the radical promoted ring-opening of strained molecules has been utilized in combination with substrates featuring either double or triple bonds to foster new bond formation reactions, in particular for the construction of elaborated double bonds. An early case of a radical-mediated ring-opening process triggered by radical addition to terminal alkenes and alkynes was reported by Brown, Suzuki and coworkers in the 1970s.[45] They used an organoboron compound,[46] an

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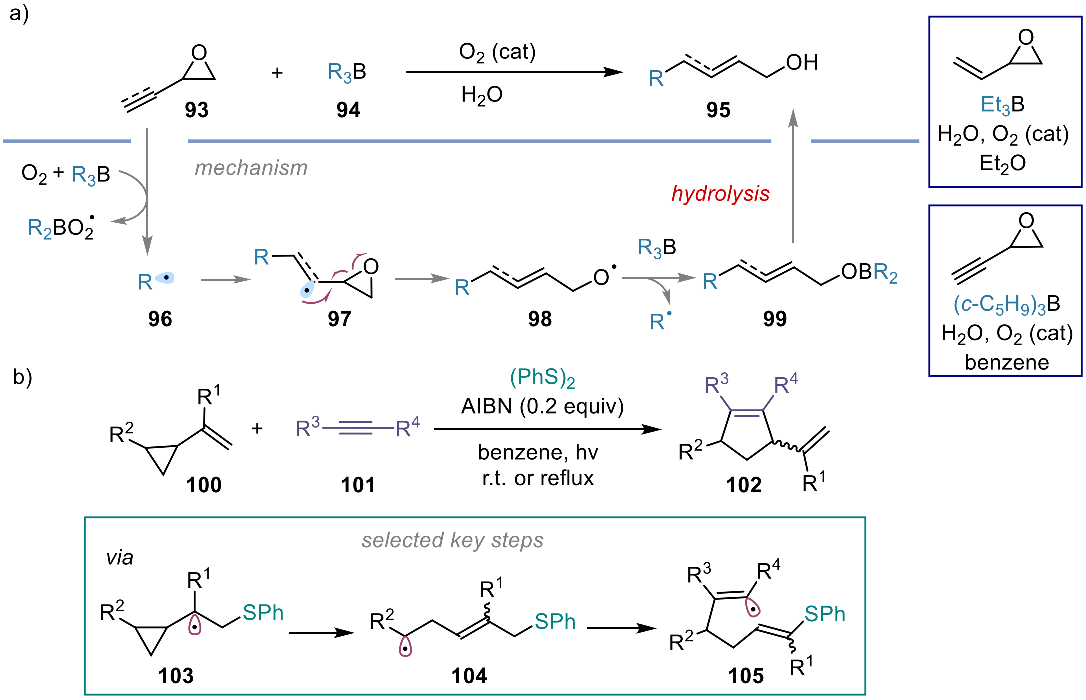
(43) E. Montaudon, F. Rakotomanana, B. Maillard, *Tetrahedron* **1985**, *41*, 2727-2735.
(44) T. Constantin, M. Zanini, A. Regni, N. S. Sheikh, F. Juliá, D. Leonori, *Science* **2020**, *367*, 1021–1026.
(45) a) A. Suzuki, N. Miyaura, M. Itoh, H. C. Brown, G. W. Holland, E. Negishi, *J. Am. Chem. Soc.* **1971**, *93*, 2792; b) A. Suzuki, N. Miyaura, M. Itoh, H. C. Brown, P. Jacob, III. *Synthesis* **1973**, 305; c) N. Miyaura, M. Itoh, N. Sasaki, A. Suzuki, *Synthesis* **1975**, 317; d) C. Ollivier, P. Renaud, *Chem. Rev.* **2001**, *101*, 3415−3434.
(46) C. Ollivier, P. Renaud, *Chem. Rev.* **2001**, *101*, 3415−3434.

attractive alternative to hazardous tin reagents, in the presence of a catalytic amount of O_2 to produce nucleophilic radical **96** which induce a radical cascade reaction. In this radical chain process (Scheme 1.20a), the initially formed alkyl or vinyl radical **97** induces epoxide strain release to generate an allylic/allenic type alkoxy radical intermediate **98**. The latter is conveniently captured by the boron reagent in a chain-propagating step to produce alkyl radical **96** and afford an allylic alcohol or allenic alcohol **95** after hydrolysis.

In 1989, Romanelli et al. disclosed another example of a radical-mediated cascade reaction using vinyl cyclopropanes to synthesize substituted cyclopentenes (Scheme 1.20b).[47] In this manifold, a phenylthiyl radical PhS· was generated from a disulfide via homolysis under visible light, and promotes radical addition to the double bond of vinyl cyclopropanes **100** to deliver the *α*-cyclopropyl radical species **103**. Next, radical-initiated ring-opening of the cyclopropane occurs followed by addition to the alkyne reagent, which ultimately leads to the cyclization products **102**.



Scheme 1.20. a) Radical-induced ring-opening of substituted epoxides with organoborane reagents; b) Radical-mediated ring-opening/cyclization of vinyl cyclopropanes and alkynes.

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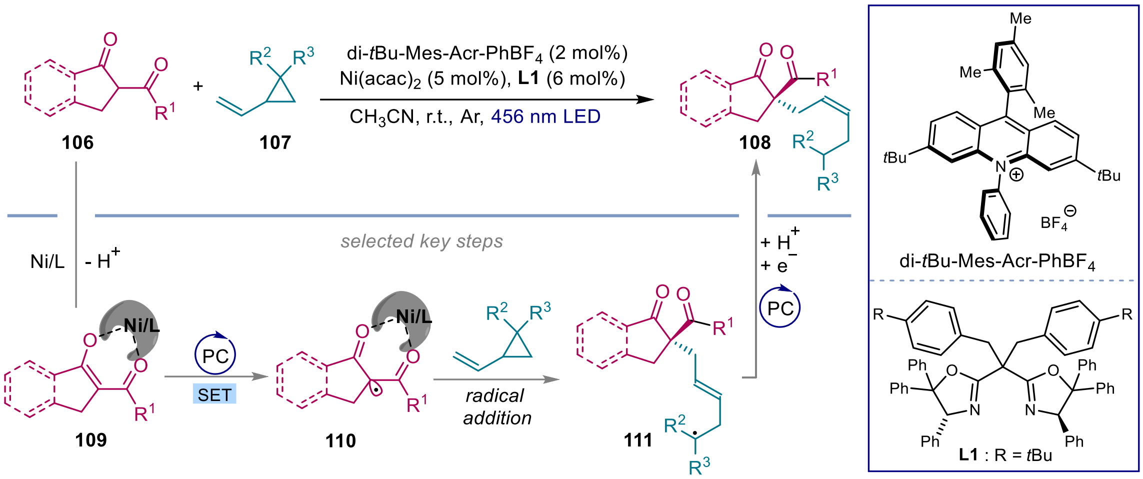
(47) K. S. Feldman, R. E. Ruckle Jr, A. L. Romanelli, *Tetrahedron Lett.* **1989**, *30*, 5845-5848.

Recently, Chen and coworkers reported a radical-induced ring-opening/allylation reaction involving various vinyl cyclopropanes enabled by a dual Ni/photoredox catalyst (Scheme 1.21).[48] They proposed that *β*-keto esters **106** can be activated by a chiral nickel complex and forming a more redox-active chiral species **109** which undergoes single electron transfer to deliver radical intermediate **110**. The enantioselective radical addition of various alkenes via ring-opening allylation affords substituted *β*-keto esters **108**.



Scheme 1.21. *β*-keto radical-induced ring opening/allylation of vinyl cyclopropanes enabled by dual Ni/photoredox catalysis.

A similar reactivity pattern involving a C–C bond activation/radical ring-opening sequence was projected for cyclobutanol and reported by both Ackermann and Huang (Scheme 1.22; Ackermann´s work).[49] Ackermann and coworkers proposed that generation of γ,δ-unsaturated aldehydes **114** can be realized via a radical cascade pathway with a sulfonyl radical as the initiator releasing the ring strain of **112** to provide the ketyl radical **116**. The ketyl radical **116** is then oxidized by *fac*-[Ir^{IV}(ppy)$_3$] via SET to afford the cationic intermediate **117**, followed by deprotonation culminating into product (*E*)-**114**, which photo-isomerizes into a mixture of stereoisomers under visible light. This synthetic protocol was extended to product with versatile functional groups based on a

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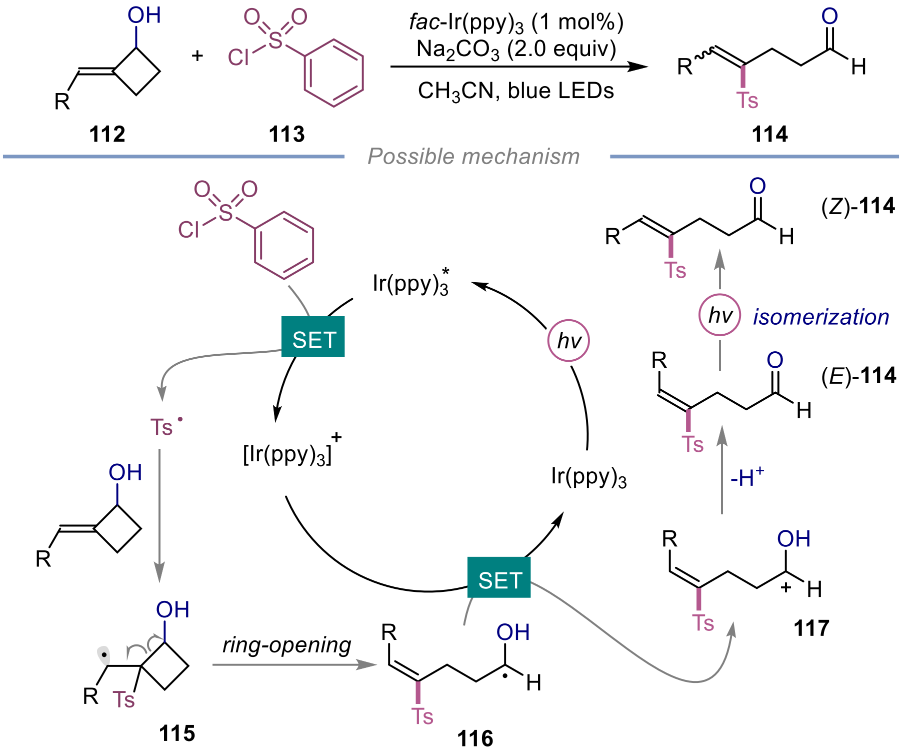
[48] W.-Y. Qu, X.-S. Zhou, W.-J. Xiao, J.-R. Chen, *Sci. China Chem.* **2024**, *67*, https://doi.org/10.1007/s11426-024-2249-x.

[49] a) Y. Zhang, C. Zhao, C. Ma, Z. Cai, S. Trienes, L. Ackermann, *Angew. Chem. Int. Ed.* **2023**, *62*, e202300166; b) T. He, C. Liang, P. Jiang, H. Liang, S. Liao, S. Huang, *Org. Lett.* **2024**, *26*, 5577–5581.

wider assortment of substrates, though a lack of overall stereocontrol remains an open challenge.



Scheme 1.22. Photocatalyzed C–C cleavage of cyclobutanol toward the synthesis of γ,δ-unsaturated aldehydes.

1.3. Cascade 3CR reactions using [1,1,1]-propellane

1.3.1. [1,1,1]-Propellane to substituted bicyclo[1.1.1]pentanes

During drug discovery, a target drug molecule should retain typical favorable pharmaceutical properties including metabolic stability, lipid solubility and membrane permeability.[50] In this regard, *sp*^{3}-rich bicyclo[1,1,1]pentanes (BCPs) motifs have shown to be bioisosteric replacements for internal alkynes and monosubstituted/*para*-substituted arenes, and well-known to improve relevant medicinal properties (Scheme 1.23).[51]

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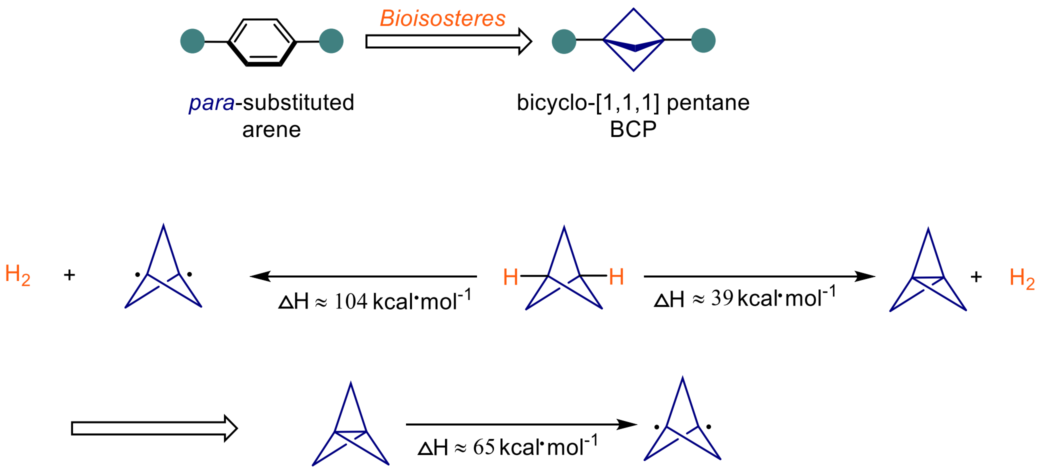
(50) H. van de Waterbeemd, E. Giford, *Nat. Rev. Drug Discov.* **2003**, *2*, 192–204.

(51) a) M. V. Westphal, B. T. Wolfstadter, J.-M. Plancher, J. Gatfield, E. M. Carreira, *ChemMedChem* **2015**, *10*, 461−469; b) N. D. Measom, K. D. Down, D. J. Hirst, C. Jamieson, E. S. Manas, V. K. Patel, D. O. Somers, *ACS Med. Chem. Lett.* **2017**, *8*, 43−48; c) Y. P. Auberson, C. Brocklehurst, M. Furegati, T. C. Fessard, G. Koch, A. Decker, L. La Vecchia, E. Briard, *ChemMedChem* **2017**, *12*, 590−598.

[1.1.1]-Propellane, as a precursor to BCPs, was first synthesized in 1982 by Wiberg and coworkers, and is particularly useful in the library synthesis of bicyclo[1.1.1]pentane derivatives within development studies.[52] This tricyclic compound features a unique bridgehead carbon, whose geometry significantly deviates from a tetrahedral coordination typically present in sp^3 hybridized systems. From calculations (Scheme 1.23), Wiberg proposed that the bond dissociation energy (BDE) of the central carbon bond is approximately 65 kcal·mol^{-1} according to the enthalpy change during the conversion of bicyclo[1.1.1]pentane into [1.1.1]-propellane having two hydrogen atoms added, and an estimated C-H bond dissociation energy of 104 kcal·mol^{-1} for bicyclo[1.1.1]pentane into its diradical species. Their calculations also showed that [1.1.1]-propellane is relatively stable when comparing to other tricyclic compounds such as [3.1.1]- and [2.2.1]-propellane,[53] with the latter undergoing rapid radical polymerization. The distinctive bond situation in [1.1.1]-propellane contributes to a “universal” reactivity in polar reactions and radical-mediated methods.



Scheme 1.23. Calculation summary of the BDE of the central bond in [1.1.1]-propellane performed by the Wiberg´s group.

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(52) K. B. Wiberg, F. H. Walker, *J. Am. Chem. Soc.* **1982**, *104*, 5239−5240.

(53) a) P.G. Gassman, G.S. Proehl, *J. Am. Chem. Soc.* **1980**, *102*, 6862−6863; b) K. Mlinaric-Majerski, Z. Majerski, *J. Am. Chem. Soc.* **1980**, *102*, 1418−1419; c) K. B. Wiberg, F. H. Walker, J. Michl, *J. Am. Chem. Soc.* **1982**, 104, 2056-2057.

1.3.2. Difunctionalization of [1.1.1]-propellane

A wide library of approaches for converting [1.1.1]-propellane into functionalized BCPs have been developed, such as anionic strain-release amination by Baran[54] and Gleason[55] as well as radical-empowered methods reported by MacMillan,[56] Molander,[57] Anderson,[58] Leonori,[59] Uchiyama,[60] and Dell'Amico[61] among others. The utilization of organometallic reagents promoting the formation of Grignard-activated BCPs **119** allow for additional types of transformations leading to functionalized BCP scaffolds (Scheme 1.24).[62] For instance, Knochel reported an effective three component reaction (3CR) approach for the synthesis of arylated BCP esters **121b** by combining the BCP magnesium intermediate **119** and ethyl chloroformate **120b**. Along these lines, Aggarwal communicated a multicomponent, 1,3-difunctionalizations of [1.1.1]-propellane **118** with organometallic reagents and organoboronic esters via a 1,2-metallate rearrangement of a boronated intermediate. A variety of methods relying on [Cu], [Pd] and [Ni] catalysis enabled the cross-coupling between Grignard-BCPs and halogenated reagents (**120a** and

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(54) a) R. Gianatassio, J. M. Lopchuk, J. Wang, C.-M. Pan, L. R. Malins, L. Prieto, T. A. Brandt, M. R. Collins, G. M. Gallego, N. W. Sach, J. E. Spangler, H. Zhu, J. Zhu, P. S. Barran, *Science* **2016**, *351*, 241– 246; b) J. M. Lopchuk, K. Fjelbye, Y. Kawamata, L. R. Malins, C.-M. Pan, R. Gianatassio, J. Wang, L. Prieto, J. Bradow, T. A. Brandt, M. R. Collins, J. Elleraas, J. Ewanicki, W. Farrell, O. O. Fadeyi, G. M. Gallego, J. J. Mousseau, R. oliver, N. W. Sach, J. K. Smith, J. E. Spangler, H. Zhu, J. Zhu, P. S. Barran, *J. Am. Chem. Soc.* **2017**, *139*, 3209– 3226.

(55) J. M. E. Hughes, D. A. Scarlata, A. C.-Y. Chen, J. D. Burch, J. L. Gleason, *Org. Lett.* **2019**, *21*, 6800–6804.

(56) Y. Liang, X. Zhang, D. W. MacMillan, *Nature* **2018**, *559*, 83–88.

(57) a) S. Kim, H. Oh, W. Dong, J. Majhi, M. Sharique, B. Matsuo, S. Keess, G. A. Molander, *ACS Catal.* **2023**, *13*, 9542–9549; b) W. Huang, S. Keess, G. A. Molander, *Angew. Chem. Int. Ed.* **2023**, *62*, e202302223; c) W. Huang, Y. Zheng, S. Keess, G. A. Molander, *J. Am. Chem. Soc.* **2023**, *145*, 5363–5369.

(58) a) D. F. J. Caputo, C. Arroniz, A. B. Dgrr, J. J. Mousseau, A. F. Stepan, S. J. Mansfield, E. A. Anderson, *Chem. Sci.* **2018**, *9*, 5295–5300; b) J. Nugent, C. Arroniz, B. R. Shire, A. J. Sterling, H. D. Pickford, M. L. J. Wong, S. J. Mansfield, D. F. J. Caputo, B. Owen, J. J. Mousseau, F. Duarte, E. A. Anderson, *ACS Catal.* **2019**, *9*, 9568–9574; c) J. Nugent, B. R. Shire, D. F. J. Caputo, H. D. Pickford, F. Night-ingale, I. T. T. Houlsby, J. J. Mousseau, E. A. Anderson, *Angew. Chem. Int. Ed.* **2020**, *59*, 11866–11870; d) J. Nugent, A. J. Sterling, N. Frank, J. J. Mousseau, E. A. Anderson, *Org. Lett.* **2021**, *23*, 8628–8633.

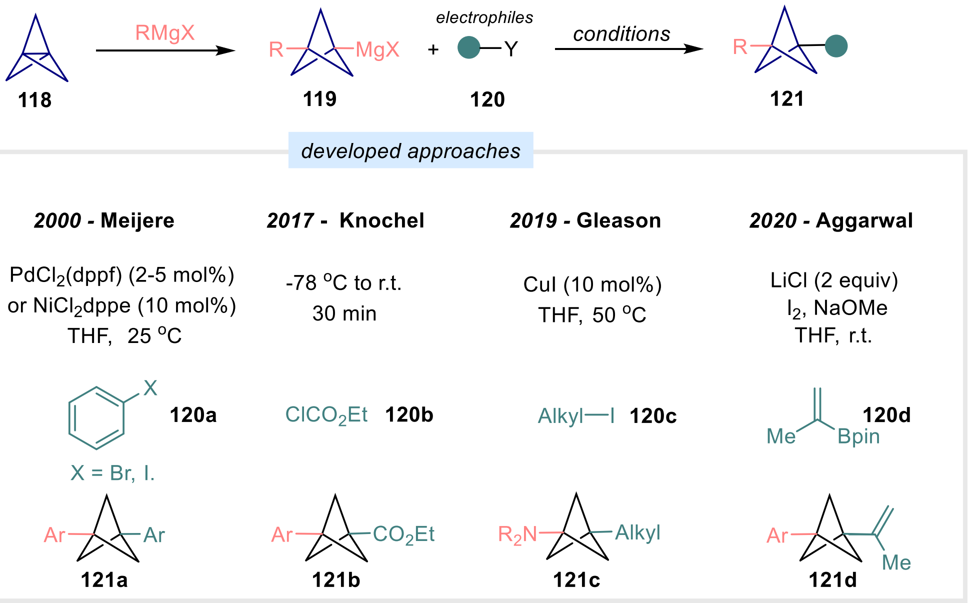
(59) J. H. Kim, A. Ruffoni, Y. S. S. Al-Faiyz, N. S. Sheikh, D. Leonori, *Angew. Chem. Int. Ed.* **2020**, *59*, 8225–8231.

(60) J. Kanazawa, K. Maeda, M. Uchiyama, *J. Am. Chem. Soc.* **2017**, *139*, 17791–17794.

(61) S. Cuadros, G. Goti, G. Barison, A. Raulli, T. Bortolato, G. Pelosi, P. Costa, L. Dell'Amico, *Angew. Chem. Int. Ed.* **2023**, *62*, e202303585.

(62) a) K. B. Wiberg, N. McMurdie, *J. Am. Chem. Soc.* **1994**, *116*, 11990–11998; b) I. S. Makarov, C. E. Brocklehurst, K. Karaghiosoff, G. Koch, P. Knochel, *Angew. Chem., Int. Ed.* **2017**, *56*, 12774–12777; c) S. Yu, C. Jing, A. Noble, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2020**, *59*, 3917–3921; d) C. Andersen, V. Ferey, M. Daumas, P. Bernardelli, A. Guérinot, J. Cossy, *Org. Lett.* **2020**, *22*, 6021–6025.

120c), which is considered a practical alternative to achieve complex and diverse BCP compounds.[63]



Scheme 1.24 Synthesis of difunctionalized BCPs via polar reactions.

Apart from polar reactions discussed above, both Anderson and Molander separately developed a series of radical-mediated transformations for preparation of 1,3-difunctionalized BCPs using photocatalytic 3CR approaches. For instance, Molander et al. demonstrated an effective alkylborylation of [1.1.1]-propellane under visible light to yield synthetically versatile BCP boronates (Scheme 1.25).[64] The authors proposed that the in situ generated BCP species behaves as a sp^2-like radical with a relative electrophilic character. As such, the borylation could be performed with YBpin as acceptor (**123**) having a lower kinetic barrier of 11-13 kcal·mol^{-1} compared to conventional nucleophilic alkyl radical borylation. The alkyl radical chemoselectively induces strain release of [1.1.1]-propellane to afford a BCP-based radical which undergoes a polarity-matched reaction with YBpin **123**, allowing to prepare a wide range of BCP-Bpin type building blocks (**124**) that could be post-modified in various ways.

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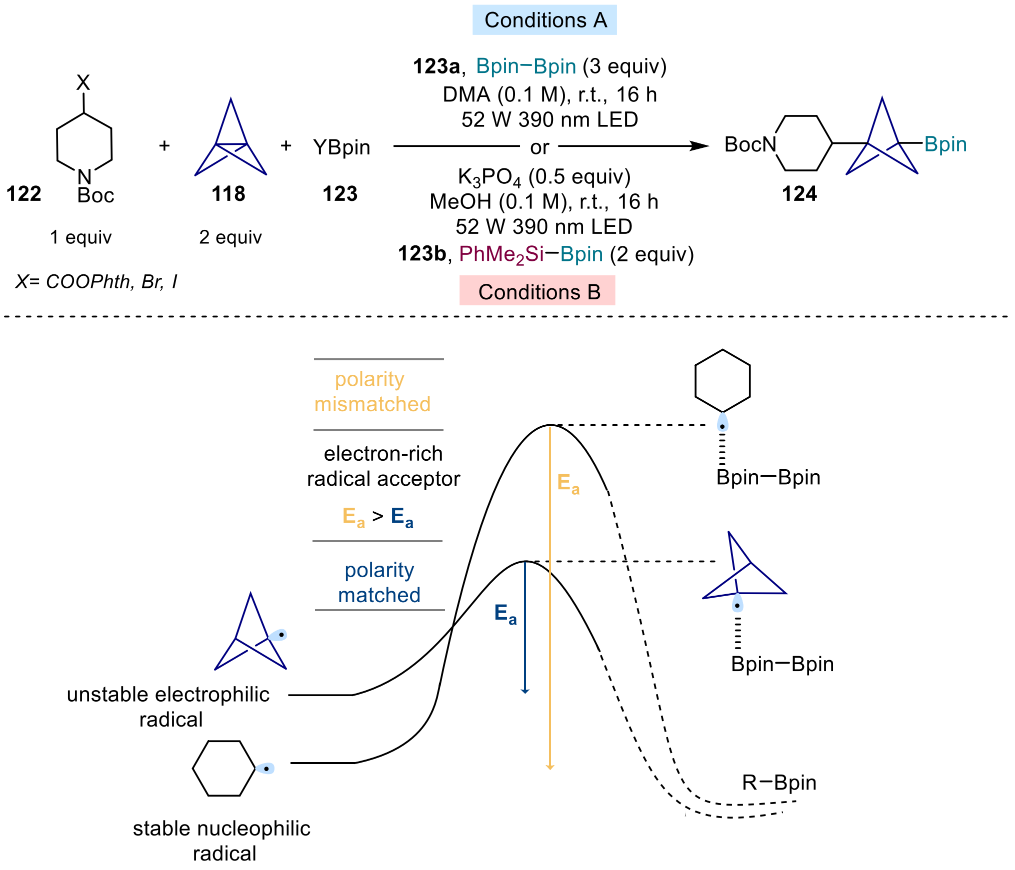
(63) a) M. Messner, S. I. Kozhushkov, A. Meijere, *Eur. J. Org. Chem.* **2000**, 1137−1155; b) I. S. Makarov, C. E. Brocklehurst, K. Karaghiosoff, G. Koch, P. Knochel, *Angew. Chem. Int. Ed.* **2017**, *56*, 12774–12777; c) J. M. E. Hughes, D. A. Scarlata, A. C.-Y. Chen, J. D. Burch, J. L. Gleason, *Org. Lett.* **2019**, *21*, 6800−6804; d) S. Yu, C. Jing, A. Noble, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2020**, *59*, 3917–3921.

(64) W. Dong, E. Yen-Pon, L. Li, A. Bhattacharjee, A. Jolit, G. A. Molander, *Nat. Chem.* **2022**, *14*, 1068–1077.



Scheme 1.25. Visible light-promoted alkylborylation of [1.1.1]-propellane for the synthesis of versatile BCP boronates.

Enantioselective construction of α-chiral BCP synthons has also been developed. For instance, Rh-catalyzed C-H insertion of monosubstituted BCP into α-diazoesters or dual organophotoredox/HAT catalysis while combining aldehydes and [1.1.1]-propellane have illustrated their usefulness to achieve chiral BCP synthons.[65] Strategies towards 3CR allylation of [1.1.1]-propellane have further demonstrated that the complexity and variety of disubstituted BCPs scaffolds can be amplified (Scheme 1.26). Both Aggarwal and Fañanás-Mastral separately reported on asymmetric allylation of in situ prepared Grignard-BCP intermediates to produce allyl-BCP derivatives using Ir- and *N*-heterocyclic carbene (NHC) catalysis, respectively.[66] In a related study, allylated BCPs

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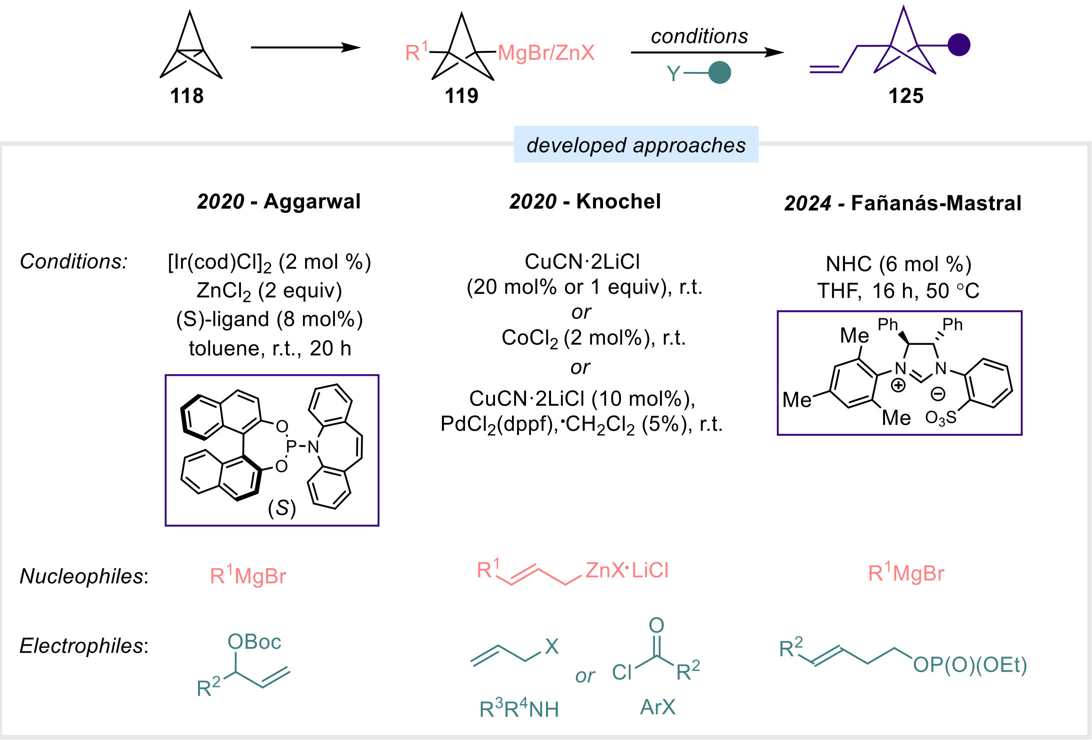
(65) a) Z. J. Garlets, J. N. Sanders, H. Malik, C. Gampe, K. N. Houk, H. M. L. Davies, *Nat. Catal.* **2020**, *3*, 351–357; b) M. L. Wong, A. J. Sterling, J. J. Mousseau, F. Duarte, E. A. Anderson, *Nat. Commun.* **2021**, *12*, 1644.

(66) a) S. Yu, C. Jing, A. Noble, V. K. Aggarwal, *Org. Lett.* **2020**, *22*, 5650−5655; b) S. Barbeira-Arán, I. Sánchez-Sordo, M. Fañanás-Mastral, *Org. Lett.* **2024**, *26*, 3784–3789.

were forged by combining in situ formed zincated BCP species and suitable acyl, aryl and allyl halide electrophiles thereby furnishing allyl-BCP synthons **125**.[67]



Scheme 1.26. Synthesis of the allyl-functionalized BCPs from Grignard-derived and zincated BCP intermediates using various electrophiles

The Anderson group further developed a twofold radical functionalization protocol for the synthetic allylation of aminated BCPs (Scheme 1.27).[68] This stepwise method included the use of *N*-centered radicals generated from the fragmentation of *α*-iodoaziridines induced by an organoboronic reagent under air. Radical addition to [1.1.1]-propellane through strain release provided stable iodo-BCPAs and transformation of these products in photoredox-assisted allylation gave access to allyl substituted-BCPAs. Mechanistically, a silanolate anion generated from the deprotonation of $(TMS)_3SiOH$ is first oxidized by the excited Ir(III) photocatalyst, and subsequently radical-based Brook rearrangement occurs to release the silyl radical species. Next, the iodo-BCPAs undergo a halogen-atom transfer (XAT) with the silyl radical to afford BCPAs as radical intermediate, which then add to an allyl sulfone reagent. The product, an

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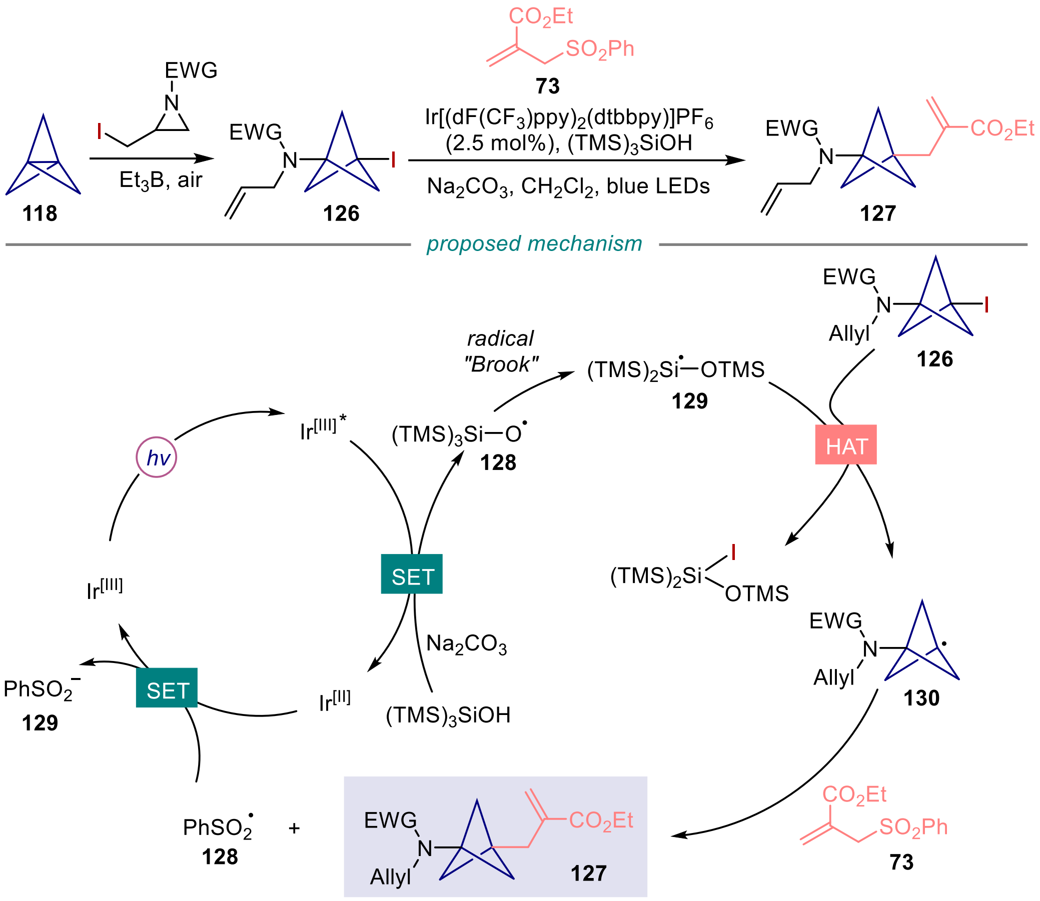
(67) K. Schw-rzer, H. Zipse, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2020**, *59*, 20235–20241.
(68) H. D. Pickford, J. Nugent, B. Owen, J. J. Mousseau, R. C. Smith, E. A. Anderson, *J. Am. Chem. Soc.* **2021**, *143*, 9729–9736.

aminated/allylated BCP and a sulfinate radical are concomitantly generated by desulfonylation. The latter is finally reduced via SET to a sulfonate anion by the Ir(II) to allow for additional turnover.



Scheme 1.27. Radical functionalization of [1.1.1] propellane offers versatile 1,3-*N*,*C*-disubstituted BCPs via a photocatalytic and halogen atom transfer (XAT) process.

1.4. Aims of this thesis

Functionalized allylic fragments are ubiquitous elements present in natural products, and contribute beneficially to synthetic diversity of pharmaceutical molecules in medicinal discovery and development through follow-up transformations. In this thesis, dual metal/photoredox strategies are shown to offer useful alternatives to conventional metal catalysis approaches while combining multiple components. In particular, radical-induced cascade allylation allows for a versatile and promising coupling approach to construct multifunctionalized allylic building blocks. Despite the remarkably advances achieved in the field of allylation, the scope of structural diversity and functionality in these allyl groups remains relatively scarce. Additionally, in the synthesis of allylic skeletons, there remain important challenges in terms of regio-, chemo- and stereocontrol as well as in structural flexibility. Therefore, the **Main Aim** of the research work in this doctoral thesis is to design and develop new radical-mediated, stereoselective catalytic processes based on modular substrates to access amplified chemical space for allylic products with high structural complexity and post-synthetic potential. The thesis is outlined as follows:

In **Chapter 2**, a dual Ni/photoredox catalyzed three-component reaction (3CR) is described for the stereoselective formation of elaborate allylic alcohols featuring sterically congested and functionalized allylic scaffolds. This catalytic protocol expands the potential of radical-based allylic alkylation to multi-component strategies under high regio- and stereocontrol with diverse and highly modular reagents.

In **Chapter 3**, a user-friendly approach is described for the decarboxylative formation of allylic derivatives featuring stereodefined and complex tri- and tetra-substituted double bonds with vinyl cyclic carbonates and amines serving as modular substrates and radical precursors, respectively. This protocol is efficient for both polarity-mismatched and –matched substrate combinations, and allows to forge a wide library of elaborate, stereodefined olefins including drug-functionalized derivatives and other advanced structures.

In **Chapter 4**, a radical induced difunctionalization of [1.1.1]-propellane is discussed that propels a highly selective three-component reaction using various radical precursors and heterocyclic substrates. This practical cascade process combines mild operating conditions as well as an exquisite scope of precursors and allylic partners to access diverse

1,3-difunctionalized bicyclo[1.1.1]pentanes (BCPs). BCP synthons with pharma-relevant CF_3, N_3 and sulfone groups can be developed that are flanked by a stereodefined allyl unit that can be transformed into other functional groups, and also conjugated with secondary drug-relevant fragments.

Finally, the thesis is concluded in the section Summary and General Conclusions to highlight the main achievements, the limitations and the open challenges, and to indicate the opportunities that exist for future work in the area.

Chapter 2.

Stereoselective Three-Component Allylic Alkylation enabled by Dual Photoredox/Ni Catalysis

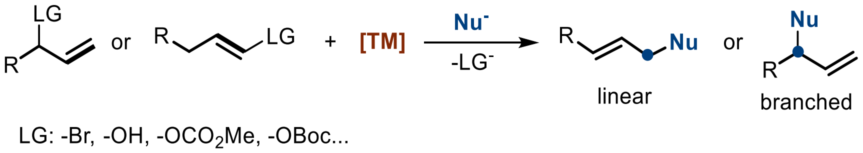
The results described in this chapter have been published in:

Q. Zeng, F. Gao, J. Benet-Buchholz, A. W. Kleij, *ACS Catal*. **2023**, *13*, 7514−7522.

2.1. Introduction

2.1.1. Nickel-catalyzed allylic substitution with nucleophiles

Advances in reaction methodology are evergrowing, showing benefits of organic synthesis and pharmaceutical research.[1] In particular, the Ni-catalyzed allylic substitution has been an attractive approach towards the development of relevant small and complex molecules.[2] A considerable amount of effort has focused on Ni-catalyzed allylic substitutions with divergent allylic substrates, resulting in regioselective outcomes (Scheme 2.1) delivering either linear or branched products.



Scheme 2.1. Ni-catalyzed regioselective construction of allylic skeletons.

After the first known case of a catalytic conversion reported by Felkin[3] in 1968, the Consiglio,[4] Hiyama[5] and Hoveyda[6] groups, respectively, communicated Ni-catalyzed allylic substitution for enantioselective transformations. In most cases, Ni-catalyzed allylation is distinct from both Pd and Co catalysis, allows the selective coupling of nucleophiles and allyl electrophiles in a linear fashion. In 2011, the Kobayashi group discovered that Ni-catalyzed coupling of allylic alcohols and allylboronic esters provides the 1,5-diene product **5** (Scheme 2.2) with excellent linear selectivity.[7] Later, related

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(1) A. Biffis, P. Centomo, A. Del Zotto, M. Zecca, *Chem. Rev.* **2018**, *118*, 2249–2295; b) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2009**, *48*, 5094–5115; c) C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215–1292; d) Y. Liu, S.-J. Han, W.-B. Liu, B. M. Stoltz, *Acc. Chem. Res.* **2015**, *48*, 740–751; e) T. Ling, F. Rivas, *Tetrahedron* **2016**, *72*, 6729−6777; f) B. W. H. Turnbull, P. A. Evans, *J. Am. Chem. Soc.* **2015**, *137*, 6156−6159.

(2) B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921–2944.

(3) a) C. Chuit, H. Felkin, C. Frajerman, G. Roussi, G. Swierczewski, *Chem.Commun.* **1968**, 1604–1605; b) H. Felkin, G. Swierczewski, *Tetrahedron Lett.* **1972**, *13*, 1433–1436; c) H. Felkin, M. Joly-Goudket, S. G. Davies, *Tetrahedron Lett.* **1981**, *22*, 1157–1160.

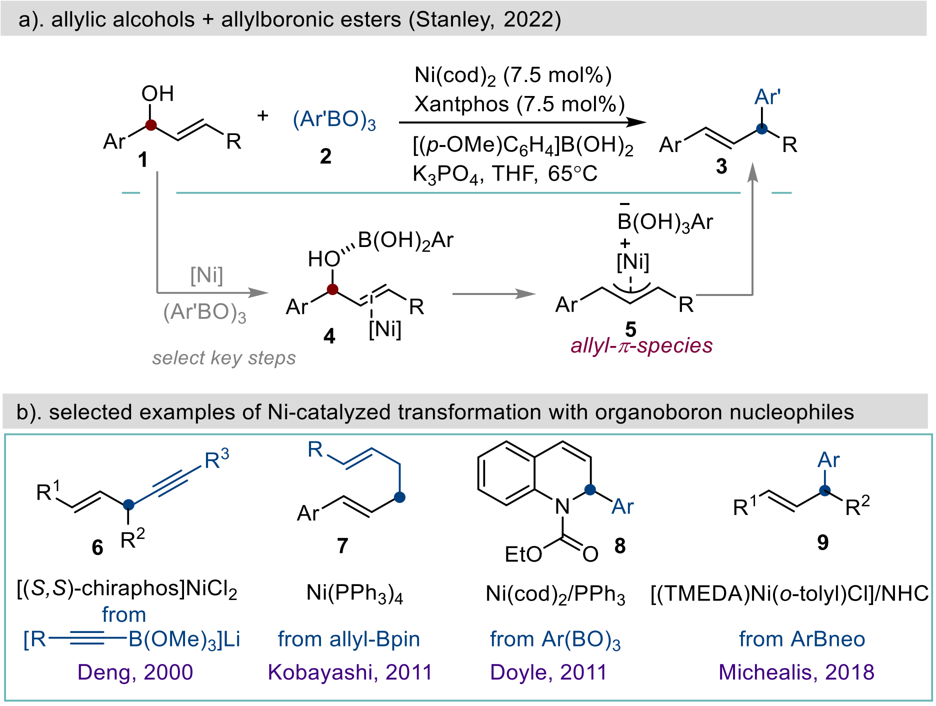
(4) a) G. Consiglio, F. Morandini, O. Piccolo, *J. Am. Chem. Soc.* **1981**, *103*, 1846–1847; b) G. Consiglio, F. Morandini, O. Piccolo, *J. Chem. Soc. Chem. Commun.* **1983**, 112–114; c) G. Consiglio, O. Piccolo, L. Roncetti, F. Morandini, *Tetrahedron* **1986**, *42*, 2043–2053.

(5) T. Hiyama, N. Wakasa, *Tetrahedron Lett.* **1985**, *26*, 3259–3262.

(6) E. Gomez-Bengoa, N. M. Heron, M. T. Didiuk, C. A. Luchaco, A. H. Hoveyda, *J. Am. Chem. Soc.* **1998**, *120*, 7649–7650.

(7) A. Jiménez-Aquino, E. Ferrer Flegeau, U. Schneider, S. Kobayashi, *Chem. Commun.* **2011**, *47*, 9456−9458.

allylic alkynylation and arylations[8] promoted by the Ni/(*S*,*S*)-Chiralphos and Ni/NHC based catalytic systems, respectively, resulted in the formation of conjugated alkene scaffold **6** and **9** as illustrated by the Deng and Michaelis laboratories. In addition, Stanley and co-workers disclosed that *para*-methoxyphenylboronic acid **2** could activate alcohol compound **1**, and that in situ alkene migration generates a linear allylic alcohol, followed formation of ionic π-allyl-Ni species **5** with subsequent reductive elimination to furnish the allylic product **3** with high regioselectivity.[9]



Scheme 2.2. Ni-catalyzed allylic substitution using organoboron reagent as nucleophiles.

Although Grignard reagents, organoboron substrates and other organometallic reagents can be effective carbon-based nucleophiles enabling the preparation of functionalized allyl derivatives, the diversity and compatibility of such nucleophiles can still be improved. ‘Soft’ nucleophiles[10] have been alternative reagents for these metal-based catalytic transformations towards the formation of functionalized allylic products.

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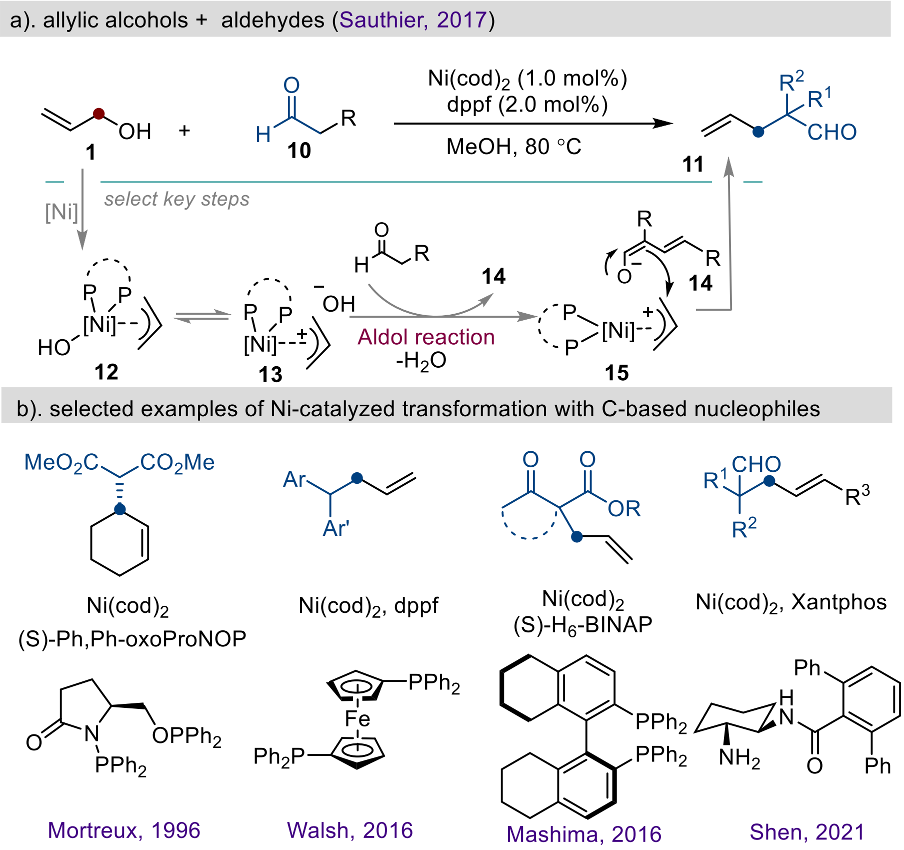
(8) a) G. Wang, Y. Gan, Y. Liu, *Chin. J. Chem.* **2018**, *36*, 916-920; b) Y.-B. Wang, B.-Y. Liu, Q. Bu, B. Dai, N. Liu, *Adv. Synth. Catal.* **2020**, *362*, 2930–2940; c) D. Zhao, B. Xu, C. Zhu, *Nature Communications* **2023**, *14*, 3308; d) T. J. A. Graham, J. D. Shields, A. G. Doyle, *Chem. Sci.* **2011**, *2*, 980; e) H. Chen, M.-Z. Deng, *J. Organomet. Chem.* **2000**, *603*, 189; f) S. H. Nazari, J. E. Bourdeau, M. R. Talley, G. A. Valdivia-Berroeta, S. J Smith, D. J. Michaelis, *ACS Catal.* **2018**, *8*, 86−89.

(9) H. N. Tran, C. M. Nguyen, M. T. Koeritz, D. D. Youmans, L. M. Stanley, *Chem. Sci.* **2022**, *13*, 11607−11613.

(10) H. Bricout, J.-F. Carpentier, A. Mortreux, *Tetrahedron Lett.* **1996**, *37*, 6105.

For example, Sauthier and co-workers (Scheme 2.3a) reported that *α*-allylation of aldehydes **10** and tandem aldol condensation/allylation in the presence of a suitable Ni precursor and dppf as a ligand offers a direct route to products **11**.[11] They proposed that cationic allylic Ni complexes **13** are the key intermediates for the aldol condensation to release **14** which then undergoes allylation. Moreover, the Ni-catalyzed allylation involving either a *β*-unsaturated aldehyde, diarylmethane pronucleophiles, enolates and other carbon-based nucleophiles have also been utilized in the formation of multifunctional allylic compounds (Scheme 2.3b).[12]



Scheme 2.3. Ni-catalyzed allylic substitution reactions using carbon-based nucleophiles.

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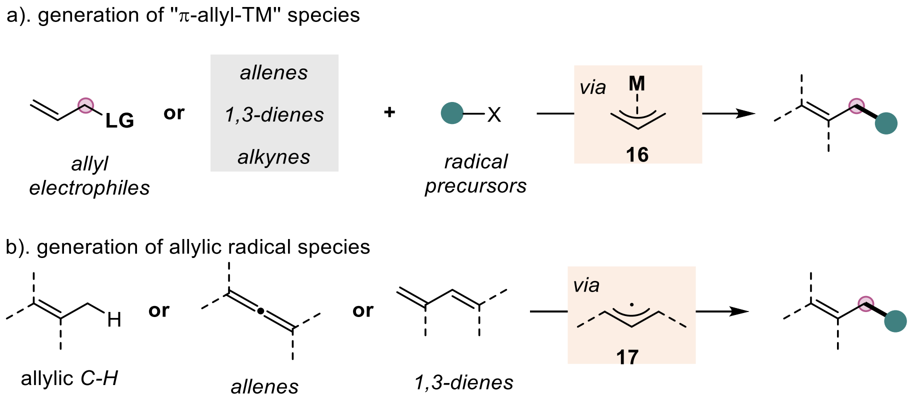
[11] Y. Kita, R. D. Kavthe, H. Oda, K. Mashima, *Angew. Chem. Int. Ed.* **2016**, *55*, 1098−1101.

[12] a) H. Bricout, J.-F. Carpentier, A. Mortreux, *Tetrahedron Lett.* **1996**, *37*, 6105-6108; b) S.-C. Sha, H. Jiang, J. Mao, A. Bellomo, S. A. Jeong, P. J. Walsh, *Angew. Chem. Int. Ed.* **2016**, *55*, 1070-1074; c) Y. Bernhard, B. Thomson, V. Ferey, M. Sauthier, *Angew. Chem. Int. Ed.* **2017**, *56*, 7460-7464; d) W.-Q. Zhang, H.-C. Shen, *ACS Catal.* **2021**, *11*, 11849-11854.

2.1.2. Photo/metal-catalyzed allylic substitution with radical intermediates

During the last decade, the development of metal/photoredox catalyzed allylic alkylation processes have been shown to promote single-electron pathways, harnessing radical with metal-allyl reactivity (**16**) or enabling the coupling of allylic radical intermediates (**17**) with various reaction partners allowing the rapid increase of alternative pathways towards functionalized allylic synthons (Scheme 2.4).[13,15]



Scheme 2.4. Two mechanistic pathways in photoredox/metal catalyzed allylic substitutions involving radical generation.

Successful dual strategies based on Pd[14] and Ni[15] have significantly extended conventional manifolds to radical pathways in which high regiocontrol is retained under mild operating conditions (Scheme 2.5a). Molander reported the use of vinyl epoxides as allylic surrogates and their functionalization with organotrifluoroborate salts acting as radical precursors under Ni/photoredox catalysis (Scheme 2.5b). Later on, they extended this approach to the use of allylic carbonates and 1,4-dihydropyridines (DHPs) as reaction

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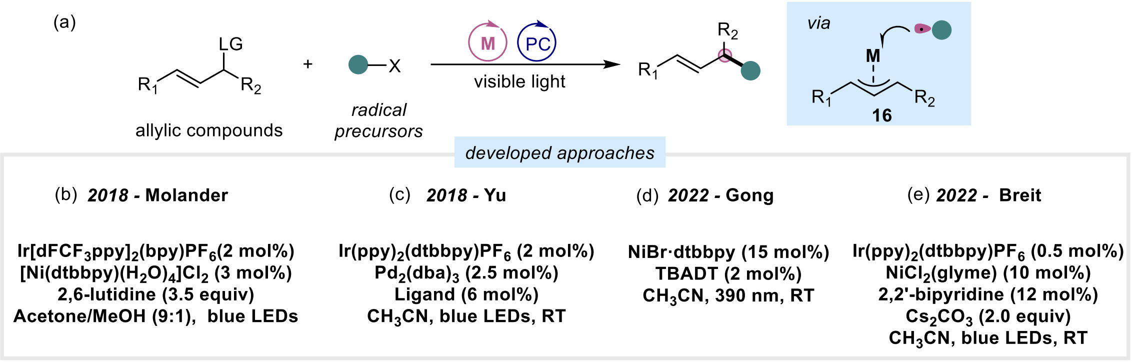
(13) a) L. Huang, M. Szewczyk, R. Kancherla, B. Maity, C. Zhu, L. Cavallo, M. Rueping, *Nat. Commun.* **2023**, *14*, 548; b) Y. Ueda, Y. Masuda, T. Iwai, K. Imaeda, H. Takeuchi, K. Ueno, M. Gao, J. Hasegawa, M. Sawamura, *J. Am. Chem. Soc.* **2022**, *144*, 2218-2224; c) R. Wang, P. Fan, C. Wang, *ACS Catal.* **2023**, *13*, 141-146; d) R.-X. Wang, P. Yang, Y.-Z. Cheng, S.-L. You. *ACS Catal.* **2024**, *14*, 12403−12409.

(14) a) C. Song, H.-H. Zhang, S. Yu, *ACS Catal*. **2022**, *12*, 1428−1432; b) H.-H. Zhang, M. Tang, J.-J. Zhao, C. Song, S. Yu, *J. Am. Chem. Soc.* **2021**, *143*, 12836−12846; c) X. Shen, L. Qian, S. Yu, *Sci. China Chem.* **2020**, *63*, 687–691.

(15) H.-M. Huang, P. Bellotti, F. Glorius, *Chem. Soc. Rev*. **2020**, *49*, 6186-6197.

partners.[16] A radical-centered, asymmetric protocol for allylic Csp^3-Csp^3 bond formation was developed by Yu and co-workers combining allylic acetates and DHPs as radical precursors (Scheme 2.5c).[14a] Further to this, Hirao and Gong reported an intriguing Ni/photo-HAT (HAT = hydrogen atom transfer) promoted allylation of alkanes (Scheme 2.5d).[17] In the same year, the Breit group disclosed an approach for the synthesis of homoallylic amines via photoredox/Ni catalysis inducing the addition of allyl-metal species to imines (Scheme 2.5e).[18]



Scheme 2.5. Metal/photo-catalyzed allylic substitution using "π-allyl-TM" species.

Moreover, generation of allyl radical intermediates from allylic C–H bonds, 1,3-dienes and allenes via metal/photoredox catalysis can empower radical addition and incorporating other reaction components, which improves the diversity and structural complexity of allylic synthons in organic synthesis.[15,19] Two main mechanistic scenarios have been developed to achieve the formation of allylic radical species involving either single electron transfer (SET) or hydrogen atom transfer (HAT), see Scheme 2.6. Macmillan proposed a HAT strategy by employing a thiol as the hydrogen-atom abstracting agent to activate the allylic C–H bond in compound **19** and releasing radical species **17a**. This is then followed by a radical cross-coupling process involving long-lived (persistent) radical anions and forming the re-aromatized product **20** within a

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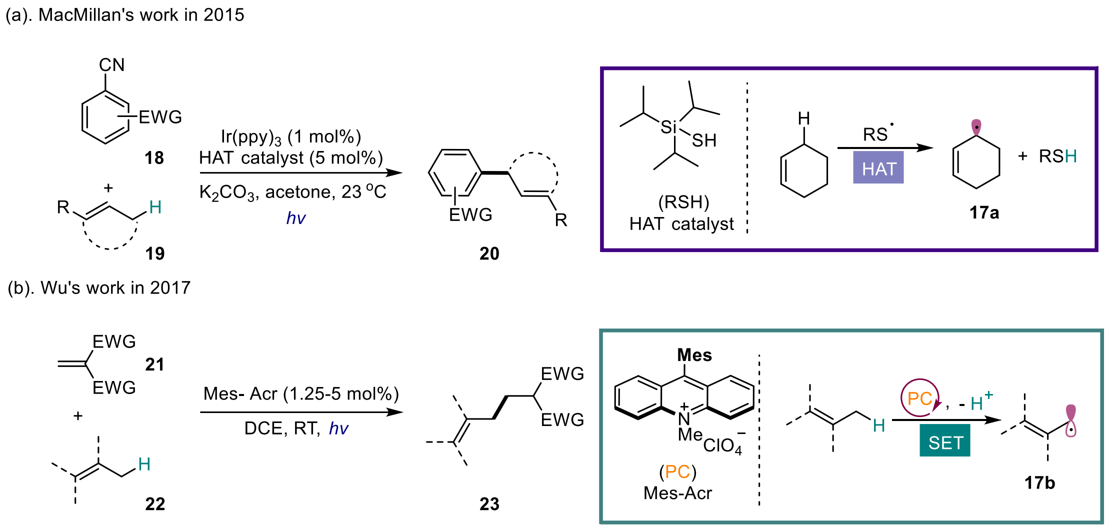
(16) a) J. K. Matsui, l. Gutiérrez-Bonet, M. Rotella, R. Alam, O. Gutierrez, G. A. Molander, *Angew. Chem. Int. Ed.* **2018**, *57*, 15847–15851; b) Z.-J. Wang, S. Zheng, E. Romero, J. K. Matsui, G. A. Molander, *Org. Lett*. **2019**, *21*, 6543−6547.

(17) Y. Jin, E. W. H. Ng, T. Fan, H. Hirao, L.-Z. Gong, *ACS Catal.* **2022**, *12*, 10039−10046.

(18) J. Zheng, C. Nopper, R. Bibi, A. Nikbakht, F. Bauer, B. Breit, *ACS Catal*. **2022**, *12*, 5949−5960.

(19) a) J. L. Schwarz, H.-M. Huang, T. O. Paulisch, F. Glorius, *ACS Catal.* **2020**, *10*, 1621–1627; b) P.-Z. Wang, X. Wu, Y. Cheng, M. Jiang, W.-J. Xiao, J.-R. Chen, *Angew. Chem. Int. Ed.* **2021**, *60*, 22956–22962; c) H. Yan, Q. Liao, Y. Chen, G. G. Gurzadyan, B. Lu, C. Wu, L. Shi, *Angew. Chem. Int. Ed.* **2023**, *62*, e202302483; d) X. Dai, R. Mao, B. Guan, X. Xu, X. Li, *RSC Adv*. **2015**, *5*, 55290–55294.

photocatalytic regime (Scheme 2.6a).[20] Alternatively, the coupling between electronically biased alkenes of type **21** and allylic compounds **22** promoted by single-electron oxidation was demonstrated by Wu et al. generating a highly substituted allylic coupling product **23**.[21] Notably, the acridinium photocatalyst (Mes-Acr in Scheme 2.6b) has a strong oxidation ability allowing to convert the allylic substrate into an allylic radical cation species, followed by deprotonation generating radical species **17b**. The latter can then be intercepted by highly electron-deficient olefins **21** resulting thus in the desired product after a series of reduction and deprotonation steps.



Scheme 2.6. Two different pathways generating allylic radical intermediates.

2.1.3. Aims of the work in this chapter

As far as we are aware, photo-assisted allylic substitutions of allylic radical species generated from a metal-allyl intermediate and based on radical cross-coupling mediated by either Pd or Ni catalysis remain extremely rare.[22] Xiao et al. reported a Pd/photoredox catalyzed reaction of allylic esters **24** with amines **26** based on a radical cross-coupling pathway with the generation of allylic radical species **29** from the π-allyl-Pd complex **30** (Scheme 2.7). Tunge et al. reported the formal decarboxylative allylation of amino

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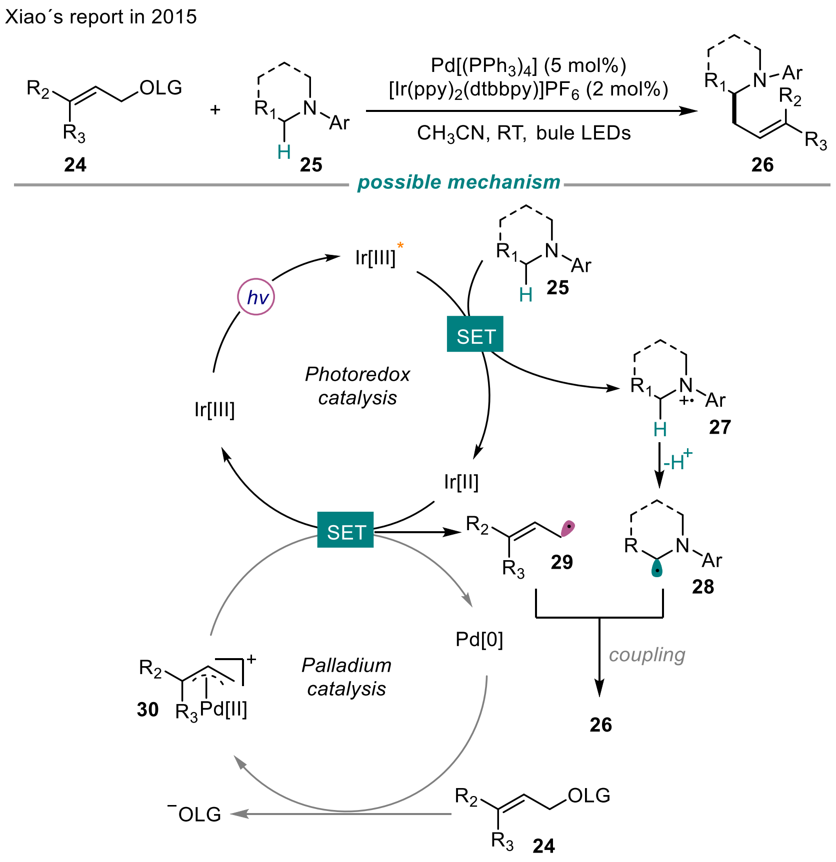
(20) J. D. Cuthbertson, D. W. C. MacMillan, *Nature* **2015**, *519*, 74–77.
(21) R. Zhou, H. Liu, H. Tao, X. Yu, J. Wu, *Chem. Sci.* **2017**, *8*, 4654–4659.
(22) a) S.-I. Sasaoka, T. Yamamoto, H. Kinoshita, K. Inomata, H. Kotake, *Chem. Lett.* **1985**, 315–318; b) A. G. Campa, B. Bazdi, N. Fuentes, R. Robles, J. M. Cuerva, J. E. Oltra, S. Porcel, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2008**, *47*, 7515–7519; c) K. C. Cartwright, J. A. Tunge, *Chem. Sci.* **2020**, *11*, 8167-8175.

alkanoic acids and esters through a similar dual catalytic system.[23] These two examples clearly demonstrate the potential of simple allyl groups as radical coupling partners. However, the use of more complex allylic precursors would require the control of both the regio- and stereo-chemistry of the process while expanding substrate modularity to deliver more generic protocols. Undoubtedly, there has been significant progress enabled by dual metal/photoredox catalysis amplifying the role of allylic alkylation as a versatile approach in new carbon-carbon bond formation reactions. Despite these advances, the scope of structurally diverse and functional allyl groups (especially sterically congested ones) as cross-coupling partners remains underdeveloped, especially when the process is targeting multi-component couplings.



Scheme 2.7 Simplified manifold for the formation of allylic products based on a Pd/photoredox catalyzed generation of an allylic radical and its cross-coupling.

In this chapter, we report on a 3CR approach that allows for productive coupling between three species, *viz*. an allyl intermediate generated from a vinyl cyclic carbonate,

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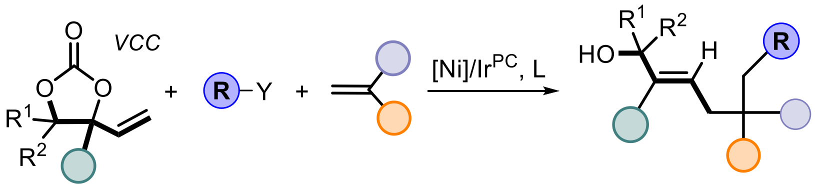
(23) a) J. Xuan, T.-T. Zeng, Z.-J. Feng, Q.-H. Deng, J.-R. Chen, L.-Q. Lu, W.-J. Xiao, H. Alper, *Angew. Chem. Int. Ed.* **2015**, *54*, 1625–1628; b) S. B. Lang, K. M. O'Nele, J. A. Tunge, *J. Am. Chem. Soc.* **2014**, *136*, 13606−13609.

an alkene and suitable radical precursor (Scheme 2.8) promoted by Ni/photoredox catalysis. The method combines a wide range of structurally diverse substrates and includes the productive generation and use of primary, secondary and tertiary alkyl radicals affording allylic alcohols with up to two sterically congested quaternary/tertiary carbon centers. The dual photo/Ni catalytic system also shows value generating these allylic scaffolds with excellent regio- and stereo-selectivity.



Excellent regio- and stereocontrol
41 examples, E/Z typically >95:5
Elaborate quaternary carbon centers
Use of 1º, 2º and 3º radicals
Extendable to other allylic substrates

Scheme 2.8 Focus of the work in this chapter: photoredox/Ni catalyzed stereoselective 3CR using VCCs as allylic precursors. R-Y stands for a radical precursor.

2.2. Results and discussion

2.2.1. Optimization studies

We commenced our investigation by combining vinyl cyclic carbonate **2.1a**, potassium *tert*-butyl trifluoroborate **2.2a** and 1,1-diphenylethylene **2.3a** (Table 2.1) under various conditions including different [Ni] precursors, ligands **L** and photocatalysts in a basic regime following previous work in photoredox/Ni dual catalysis.[24] During a pre-optimization, we found that the presence of K_2HPO_4 as base and CH_3CN as solvent was most productive under blue LED irradiation, with the **2.1a**:**2.2a**:**2.3a** ratio being 1:2:1.2. The photocatalyst optimization data is provided in **Table 2.1**. The first entry is based on the aforementioned reaction conditions in a volume of 1 mL of solvent at 35 ºC while using 5 mol% of $Ni(bpy)Br_2$ and 1 mol% of $[Ir(dFCF_3ppy)_2(bpy)]PF_6$. After 22 h, product **2.4a** had been formed in 33% NMR yield and, importantly, under high regio- and stereocontrol (*E*/*Z* >95:5). Other Ir-based PCs were then tested (entries 2-4), with $[Ir(dFCF_3ppy)_2(dtbppy)]PF_6$ and $[Ir(dF(Me)ppy)_2(dtbppy)]PF_6$ providing inferior yields

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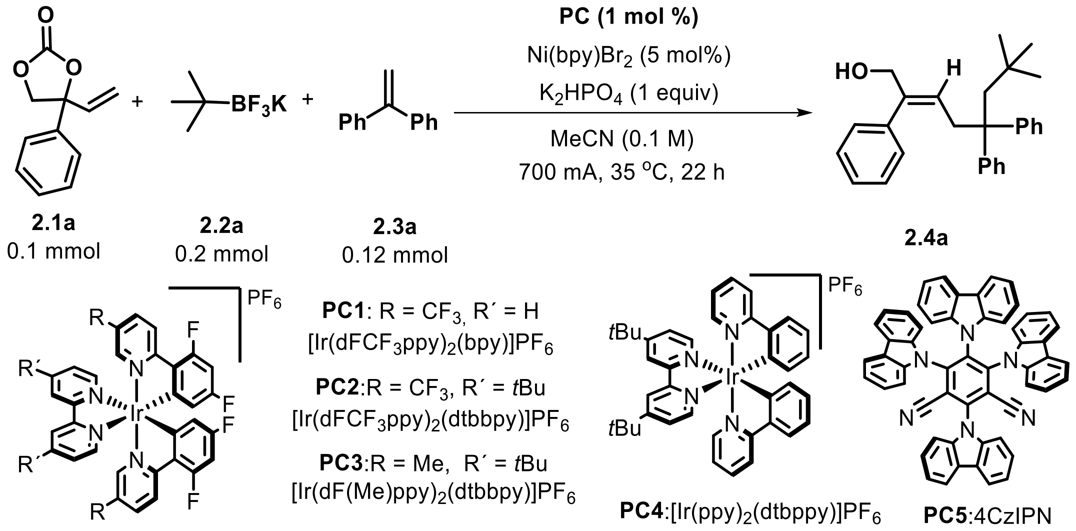
(24) a) M. W. Campbell, J. S. Compton, C. B. Kelly, G. A. Molander, *J. Am. Chem. Soc.* **2019**, *141*, 20069−20078; b) L. Guo, H.-Y. Tu, S. Zhu, L. Chu, *Org. Lett.* **2019**, *21*, 4771−4776.

while the use of [Ir(ppy)$_2$(dtbppy)]PF$_6$ provided even lower yield. The use of organophotocatalyst 4CzIPN resulted in a 35:65 *E/Z* mixture of stereoisomers (entry 5).

Table 2.1. Screening of photocatalysts.[a]

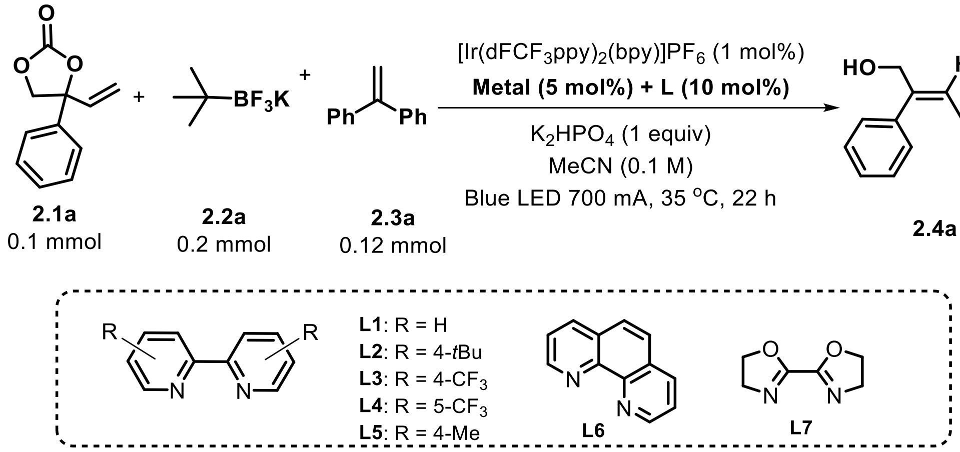


Entry	PC	Conv. (%)	Yield of **2.4a** (%)[b]
1	**[Ir(dFCF$_3$ppy)$_2$(bpy)]PF$_6$**	**38**	**33**
2	[Ir(dFCF$_3$ppy)$_2$(dtbppy)]PF$_6$	22	19
3	[Ir(dF(Me)ppy)$_2$(dtbppy)]PF$_6$	21	18
4	[Ir(ppy)$_2$(dtbppy)]PF$_6$	13	7
5	4CzIPN	>99	22[c]

[a] General procedure A (Experimental section 2.4.3): **2.1a** (0.1 mmol), **2.2a** (0.2 mmol), **2.3a** (0.12 mmol), Ni(bpy)Br$_2$ (5 mol%), PC (1 mol%), K$_2$HPO$_4$ (1 equiv), MeCN (1 mL), 700 mA blue LED, 35 ºC for 22 h. [b] Yields were determined by ^{1}H NMR using mesitylene as internal standard. [c] The NMR yield (fraction) of the *Z* isomeric product was 40%.

We then tried various combinations of Ni-precursors and ligands **L** (**L1-L7**) to examine their potential in the stereoselective formation of **2.4a** (**Table 2.2**). While Ni(glyme)Br$_2$ as the Ni-precatalyst combined with **L1** only shows a slightly better result compared to Ni(glyme)Cl$_2$ (**Table 2.2**, entries 1 and 2), the choice of ligand was found to be a more crucial factor in this reaction (**Table 2.2** entry 3-7). A Ni-precatalyst derived from **L3** promoted the formation of **2.4a** in 71% yield. Screening of other commercially available pyridine ligands **L2**, **L4**, **L5**, **L6** and **L7** do not improve the yield of the product (**Table 2.2**, entries 2-8). By switching to Ni(COD)$_2$ as the Ni source (entry 9), the product yield could also not be improved. Therefore, we selected **L3** and Ni(glyme)Br$_2$ to further continue the optimization studies.

Table 2.2. Screening of various metal precursors and ligands.[a]

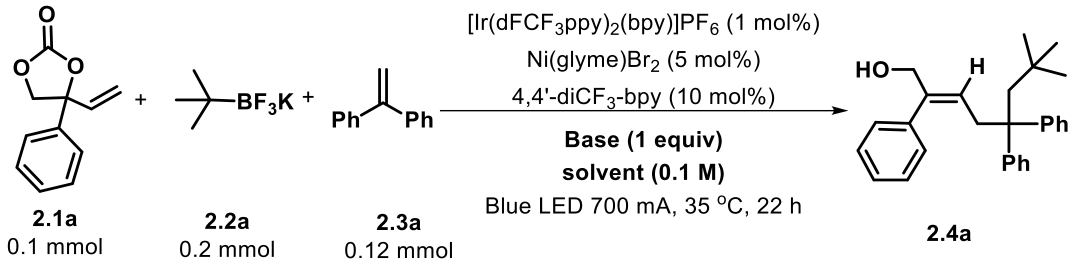


Entry	[M] + Ligand	Conv. (%)	Yield of **2.4a** (%)[b]
1	Ni(glyme)Br$_2$ + **L1**	42	34
2	Ni(glyme)Cl$_2$ + **L1**	60	27
3	Ni(glyme)Br$_2$ + **L2**	76	34
4	**Ni(glyme)Br$_2$ + L3**	**>99**	**71**
5	Ni(glyme)Br$_2$ + **L4**	59	46
6	Ni(glyme)Br$_2$ + **L5**	50	16
7	Ni(glyme)Br$_2$ + **L6**	23	10
8	Ni(glyme)Br$_2$ + **L7**	54	25
9	Ni(COD)$_2$ + **L3**	>99	55

[a] General procedure A (Experimental section 2.4.3): **2.1a** (0.1 mmol), **2.2a** (0.2 mmol), **2.3a** (0.12 mmol), metal precursor [M] (5 mol%), ligand **L** (10 mol%), [Ir(dFCF$_3$ppy)$_2$(bpy)]PF$_6$ (1 mol%), K$_2$HPO$_4$ (1 equiv), MeCN (1 mL), 700 mA blue LED, 35 °C for 22 h. [b] Yields were determined by ^{1}H NMR using mesitylene as internal standard.

The screening of the other solvents and bases was next performed, but variation of the solvent did not provoke any improvement. The choice for DMA and DME led to 34-52% yield of product **2.4a** (**Table 2.3**, entries 2 and 3), while the use of other solvents resulted in lower effiencies (**Table 2.3**, entries 1 and 4). Contrary, the base was also found to be important, and using K$_2$HPO$_4$ or DMAP provided totally different results (**Table 2.3**, entries 6 and 11). Utilizing other bases was not productive as to increase the yield of **2.4a** (**Table 2.3**, entries 7-10). In the absence of any base, product **2.4a** could only be generated in a moderate yield of 55% (**Table 2.3**, entry 5).

Table 2.3. Screening of various types of bases and solvents.[a]

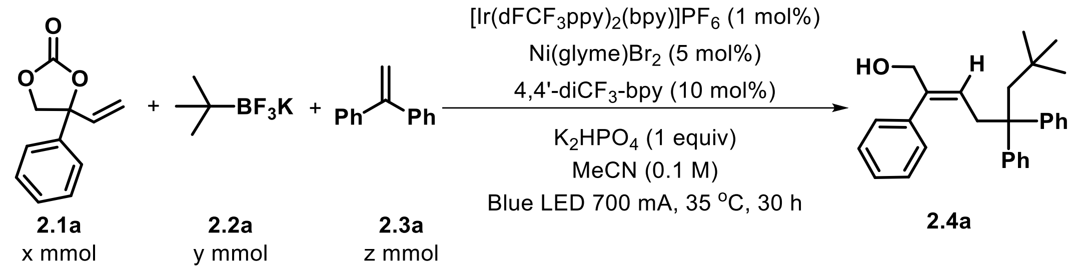


Entry	Base	Solvent	Conv. (%)[b]	Yield of **2.4a** (%)[b]
1	K_2HPO_4	THF	23	8
2	K_2HPO_4	DMA	>99	52
3	K_2HPO_4	DME	>99	34
4	K_2HPO_4	EtOAc	40	18
5	–	MeCN	81	55
6	**K_2HPO_4**	**MeCN**	**>99**	**71**
7	$NaHCO_3$	MeCN	>99	66
8	Cs_2CO_3	MeCN	57	38
9	K_3PO_4	MeCN	31	16
10	K_2CO_3	MeCN	69	53
11	DMAP	MeCN	–	–

[a] General procedure A (Experimental section 2.4.3): **2.1a** (0.1 mmol), **2.2a** (0.2 mmol), **2.3a** (0.12 mmol), Ni(glyme)Br_2 (5 mol%), 4,4'-diCF_3-bpy (10 mol%), [Ir(dFCF_3ppy)$_2$(bpy)]PF_6 (1 mol%), Base (1 equiv), solvent (1 mL), 700 mA blue LED, 35 °C for 22 h. [b] Conversions and yields were determined by ^1H NMR using mesitylene as internal standard.

Next, we evaluated the influence of the reaction stoichiometry on this allylic substitution. By increasing the relative amount of *tert*-butyl salts **2.2a** and extending the reaction time to 30 h, a slightly improved yield of 75% of **2.4a** was noted (**Table 2.4**, entry 3). We additionally found that a higher relative excess of the vinyl cyclic carbonate resulted in decreased process efficiency, so we decided to use the conditions of entry 3 as the optimized conditions.

Table 2.4. Variation of the reaction stoichiometry in the allylic substitution process.[a]

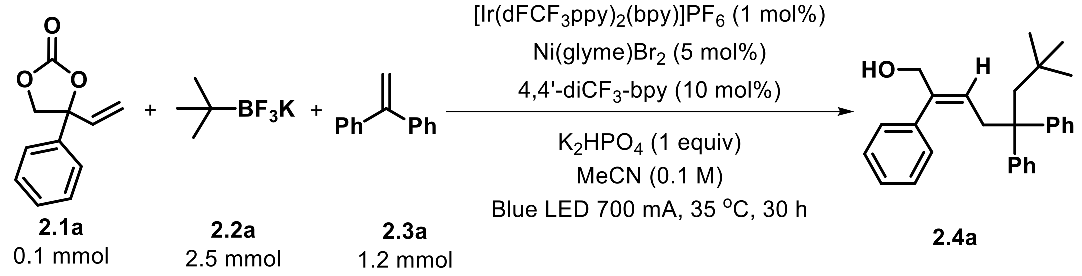


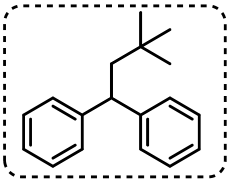
Entry	x (equiv)	y (equiv)	z (equiv)	Conv. (%)	Yield of **2.4a** (%)[b]
1	1.0	2.0	1.2	>99	71
2	1.0	1.5	1.2	81	57
3	**1.0**	**2.5**	**1.2**	**>99**	**75 (74)[c]**
4	1.0	3.0	1.2	>99	71
5	1.2	2.0	1.0	81	67
6	1.2	2.5	1.0	68	68

[a] General procedure A (Experimental section 2.4.3): **2.1a** (x mmol), **2.2a** (y mmol), **2.3a** (z mmol), Ni(glyme)Br$_2$ (5 mol%), 4,4'-diCF$_3$-bpy (10 mol%), [Ir(dFCF$_3$ppy)$_2$(bpy)]PF$_6$ (1 mol%), base (1 equiv), MeCN (1 mL), 700 mA blue LED, 35 °C for 30 h. [b] Yields were determined by ^{1}H NMR using mesitylene as internal standard. [c] Yield of the isolated product.

Before expanding the scope of this transformation, additional control experiments were carried out for this process. As mentioned above, this reaction also proceeds in absence of base though with a slightly decreased yield of product compared with the standard condition. The presence of a suitable light source, photocatalyst and ligand are crucial towards the formation of **2.4a** in this formal three-component coupling process. As expected, no desired product was formed in the absence of the Ni-complex, but instead the radical addition byproduct **2.5a** (**Table 2.5**) was generated.

Table 2.5. Control reactions based on the use of substrate **2.1a**.[a]





2.5a
coupling byproduct

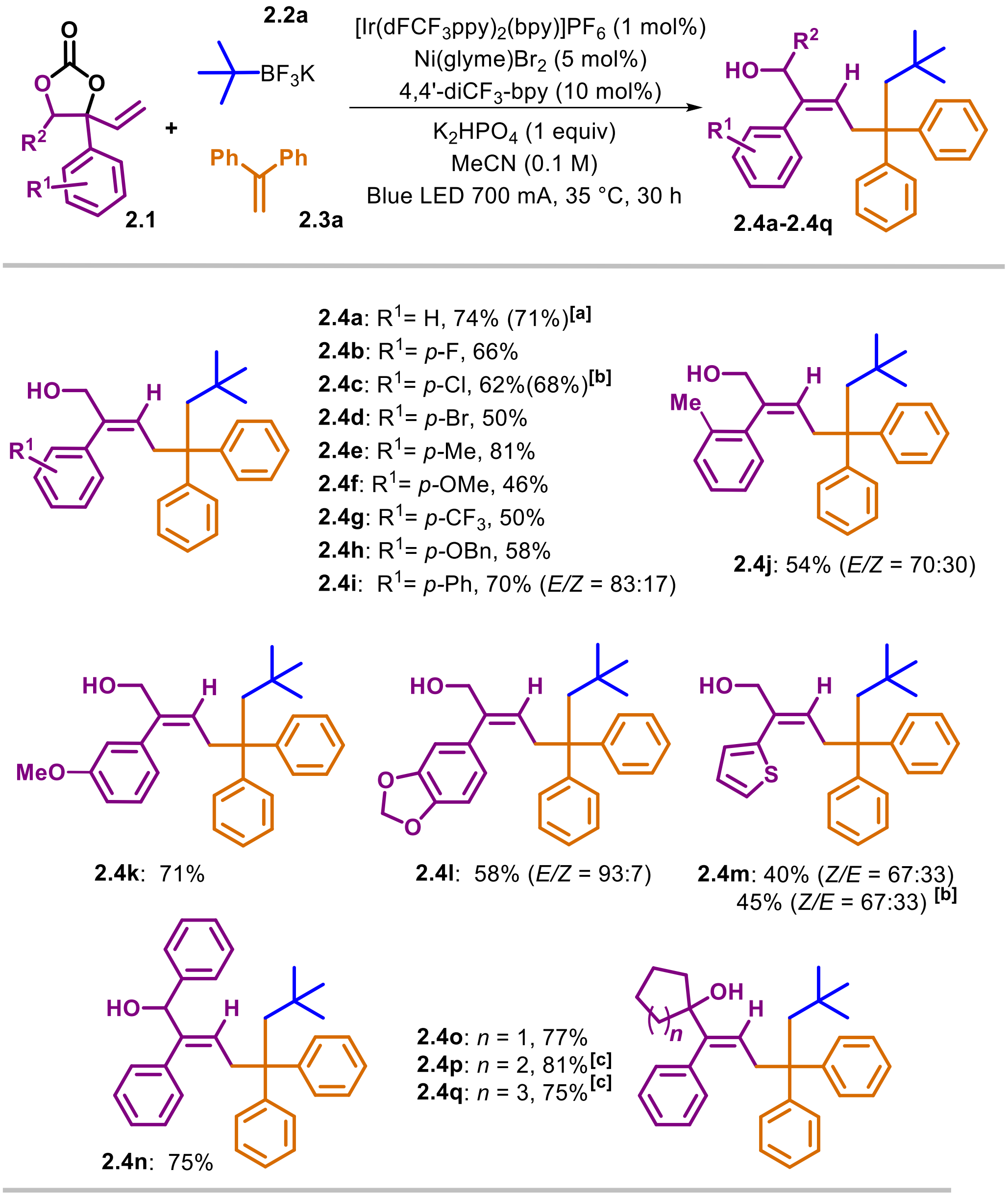
Entry	Change with standard	Yield of **2.4a** (%)[b]
1	Without light	–
2	Without [Ir]^{PC}	–
3	Without Ni(glyme)Br$_2$	(78)[c]
4	Without 4,4'-diCF$_3$bpy	12
5	Without base	63

[a] General procedure A (Experimental section 2.4.3): **2.1a** (0.1 mmol), **2.2a** (0.25 mmol), **2.3a** (0.12 mmol), Ni(glyme)Br$_2$ (5 mol%), 4,4'-diCF$_3$-bpy (10 mol%), [Ir(dFCF$_3$ppy)$_2$(bpy)]PF$_6$ (1 mol%), base (1 equiv), MeCN (1 mL), 700 mA blue LED, 35 °C for 30 h. [b] Yields were determined by ^{1}H NMR using mesitylene as internal standard. [c] The direct coupling byproduct **2.5a** was formed in 78%.

2.2.2. Product scope of Ni/photoredox catalyzed 3CR process

With the optimized conditions established, we first scrutinized the scope of VCCs **2.1** using potassium *tert*-butyl trifluoroborate **2.2a** and 1,1-diphenylethylene **2.3a** as reaction partners (Scheme 2.9). A variety of VCCs **1** bearing electron-rich and electron-poor aryl groups were all productive substrates in the 3CR providing modest to good isolated yields for **2.4a**-**2.4i** (46-81%), and the scale up of **2.4a** was also straightforward (see the Experimental section). VCCs equipped with *ortho*- or *meta*-substituted aryl groups (i.e., the preparation of **2.4j** and **2.4k**) were also suitable precursors leading to 54% and 71% product yield, respectively. Compounds **2.4i** (70%), **2.4j** (54%) and **2.4l** (58%) were formed with somewhat lower (*E/Z*) stereocontrol which may be the result of some degree of electronic/steric modulation in this 3CR.

When a thiophene-based VCC was utilized, a stronger decrease of stereocontrol was noted (**2.4m**: *Z/E* = 67:33). Although the exact reason for this is unknown, we observed that certain (*Z*)-configured products can photo-isomerize under the experimental conditions. Pleasingly, we found that VCCs that have both C-atoms of the carbonate ring substituted by various groups offer access to products with a combination of more complex tri- and tetrasubstituted carbon centers (**2.4n-2.4q**) including *spiro*-derivatives with excellent regio- and stereoselectivity, and in good yields (75-81%).



Scheme 2.9. Scope of vinyl cyclic carbonates to afford products **2.4a–2.4q**. Reaction conditions: **2.1a** (0.1 mmol), **2.2a** (0.25 mmol), **2.3a** (0.12 mmol), Ni(glyme)Br_2 (5 mol%), 4,4’-diCF$_3$-bpy (10 mol%), [Ir(dFCF$_3$ppy)$_2$(bpy)]PF_6 (1 mol%), base (1 equiv), MeCN (1 mL), 700 mA blue LED, 35 ºC for 30 h. All *E/Z* values are >95:5 unless reported otherwise. [a] The yield of the scale up reaction (10-fold, 272 mg) is provided in brackets. [b] The ligand 2,2-bipyridine was used. [c] The reaction time was extended to 48 h.

Next, we examined the scope of alkyl radical precursors **2.2** in this dual catalytic multicomponent approach (Scheme 2.10). As may be expected, the utilization of tertiary alkyl potassium trifluoroborates was productive under photoredox/Ni catalysis providing access to products **2.6a**-**2.6f** featuring two quaternary carbon centers in up to 70% yield and with excellent stereocontrol (*E/Z*>95:5). The generation of primary and secondary alkyl radicals (Scheme 2.10a) under slightly modified reaction conditions and their utilization in the multi-component coupling procedure was also feasible (cf., synthesis of **2.6g-2.6k**) allowing the introduction of linear and cyclic alkyl groups. Further elaboration of the protocol was done through the use of 1,4-dihydropyridines (DHPs) as alternative radical precursors (Scheme 2.10b)[25] under similar reaction conditions. Products **2.4a** (67 *vs*. 74%), **2.6g** (51 *vs*. 66%) and **2.6i** (34 *vs*. 41%) were produced with slightly lower yields, while **2.6l** (40%) and **2.6m** (56%) expanded the scope of the process to secondary alkyl radicals. These results demonstrate the versatility of this multicomponent approach upon changing the radical precursor without changing significantly the process outcome.

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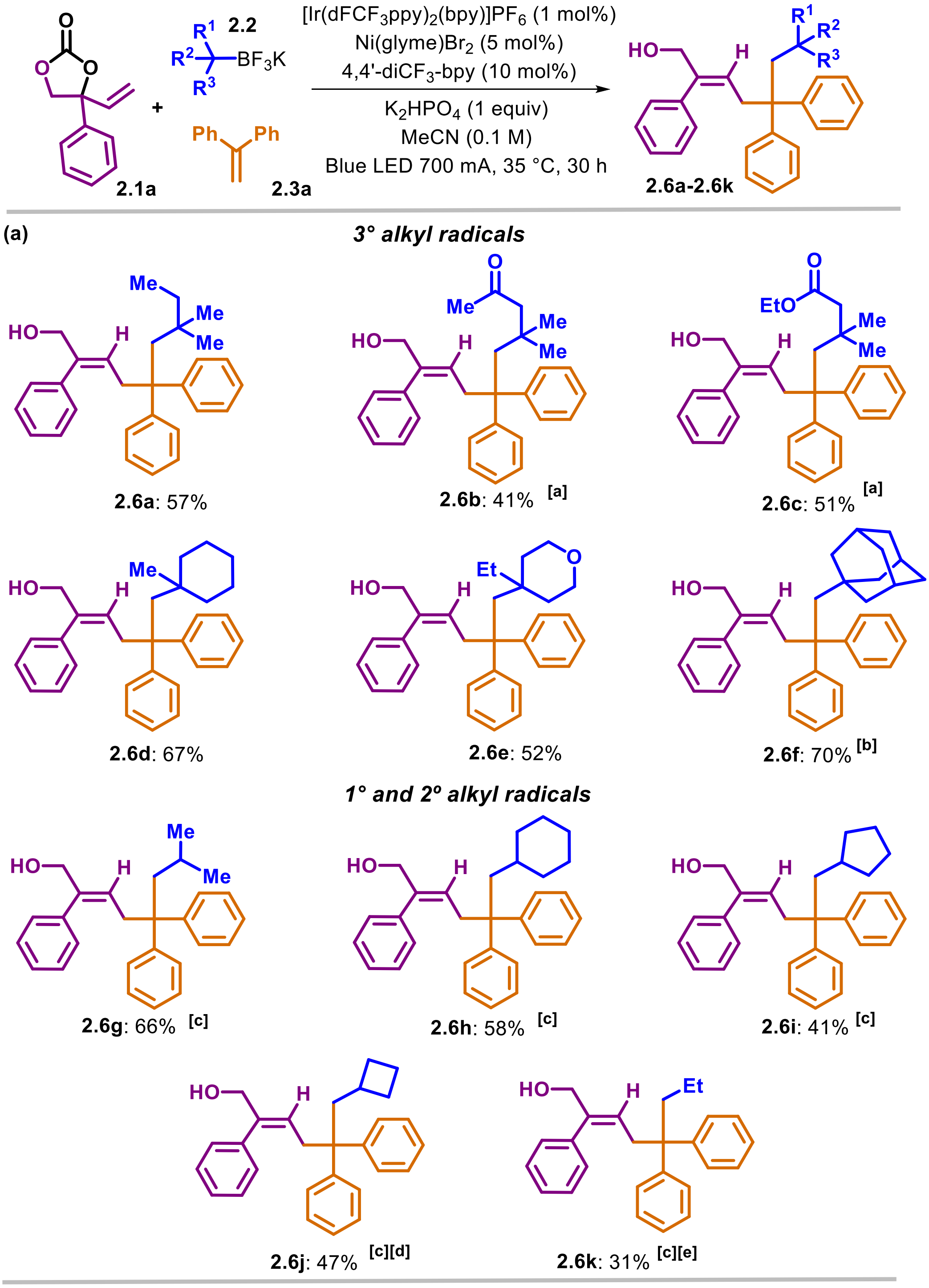
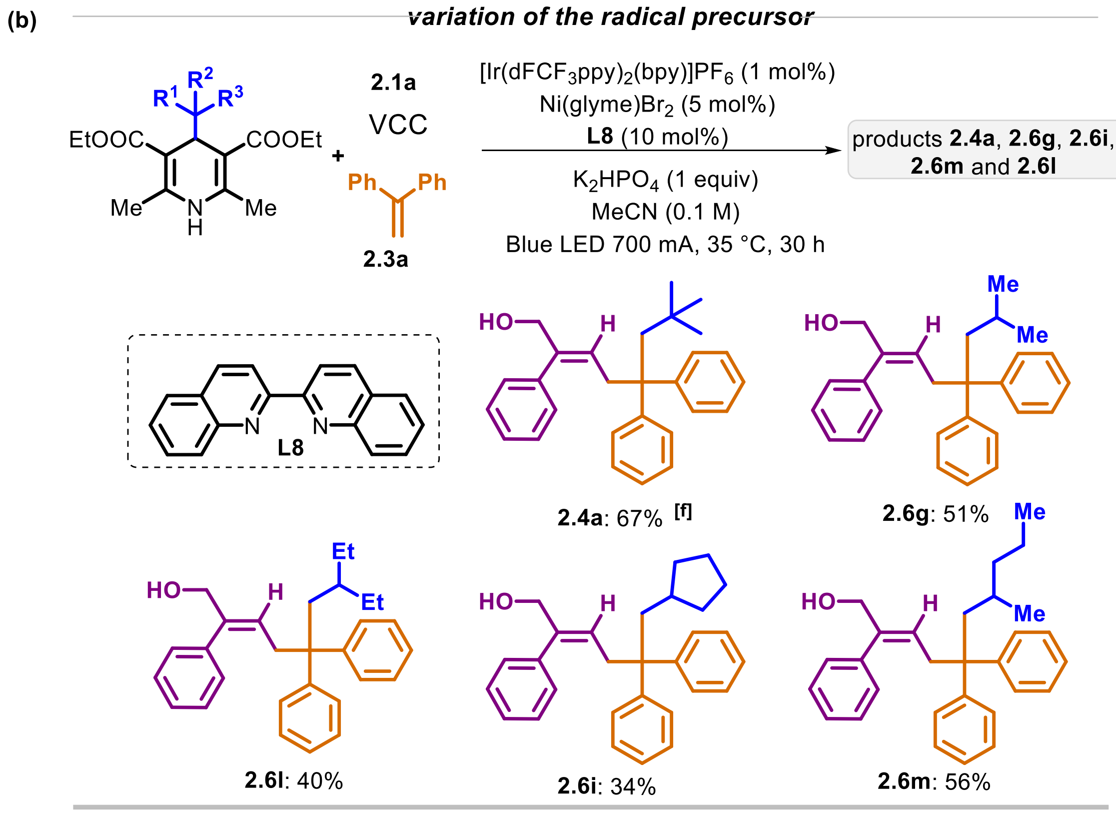
(25) V. Corcé, C. Ollivier, L. Fensterbank, *Chem. Soc. Rev*. **2022**, *51*, 1470–1510.


2.1a
2.2
R^1 R^2 R^3 BF_3K
Ph Ph
2.3a
$[Ir(dFCF_3ppy)_2(bpy)]PF_6$ (1 mol%)
$Ni(glyme)Br_2$ (5 mol%)
4,4'-diCF_3-bpy (10 mol%)
K_2HPO_4 (1 equiv)
MeCN (0.1 M)
Blue LED 700 mA, 35 °C, 30 h
2.6a-2.6k
(a)
3° alkyl radicals
2.6a: 57%
2.6b: 41% [a]
2.6c: 51% [a]
2.6d: 67%
2.6e: 52%
2.6f: 70% [b]
1° and 2° alkyl radicals
2.6g: 66% [c]
2.6h: 58% [c]
2.6i: 41% [c]
2.6j: 47% [c][d]
2.6k: 31% [c][e]



Scheme 2.10. (a) Scope of alkyl trifluoroborate salts **2.2** to yield **2.6a–2.6k**. (b) Scope of DHPs as radical precursors to give access to **2.6g–2.6m**. Reaction conditions: **2.1a** (0.1 mmol), radical precursor (0.25 mmol), **2.3a** (0.12 mmol), Ni(glyme)Br_2 (5 mol%), ligand **L3** (10 mol%), [Ir(dFCF$_3$ppy)$_2$(bpy)]PF$_6$ (1 mol%), base (1 equiv), MeCN (1 mL), 700 mA blue LED, 35 ºC for 30 h. All *E/Z* values are >95:5. [a] Dimethylacetamide was used as solvent. [b] The ligand 1,10-phenanthroline (1.8 mg, 10 mol%) was used together with a mixture of 1.5 mL CH_3CN/DMF (2:1 v/v). [c] The reactions with secondary radical precursors were carried out with 4,4'-di-*t*Bu-bpy **L2** (10 mol%) and Cs_2CO_3 as base (0.10 mmol) combined in 1,4-dioxane (1.0 mL). [d] CH_3CN/1,4-dioxane (1.5 mL, 2:1 v/v) was used. [e] 2,6-Lutidine (0.10 mmol) in DMF (1.0 mL) were used. For Scheme 2.10b: similar to Scheme 2.10a, though **2.2** was replaced by a DHP and using **L8** in the absence of base. [f] The ligand 4,4'-di-CF$_3$-bpy **L3** (10 mol %) was used.

Finally, the scope of substituted alkenes (Scheme 2.11) was further extended. Variation of the aryl moieties in **2.3** allowed to prepare compounds **2.7a**-**2.7d** in up to 83% yield without changing the stereofidelity of the 3CR. An X-ray crystallographic analysis of **2.7a** (inset in Scheme 2.11)[26] provided unambiguous proof for the proposed inter-atom connectivity and its stereochemistry. The introduction of other mixed (hetero)aryl groups such as in **2.7e** (65%) is also possible. Products with mixed aryl/ester (**2.7f** + **2.7g**) and aryl/protected alkyne combinations (**2.7h**) further illustrate the synthetic diversity of the developed 3CR. Notably, using an olefin precursor with a lower degree of steric bulk (a vinyl-boronate) produced **2.7i** in 31% yield along with 21% of a homocoupled, bis-allyl product (**2.5b** + **2.5c**, see the Experimental section 2.4.6.3).

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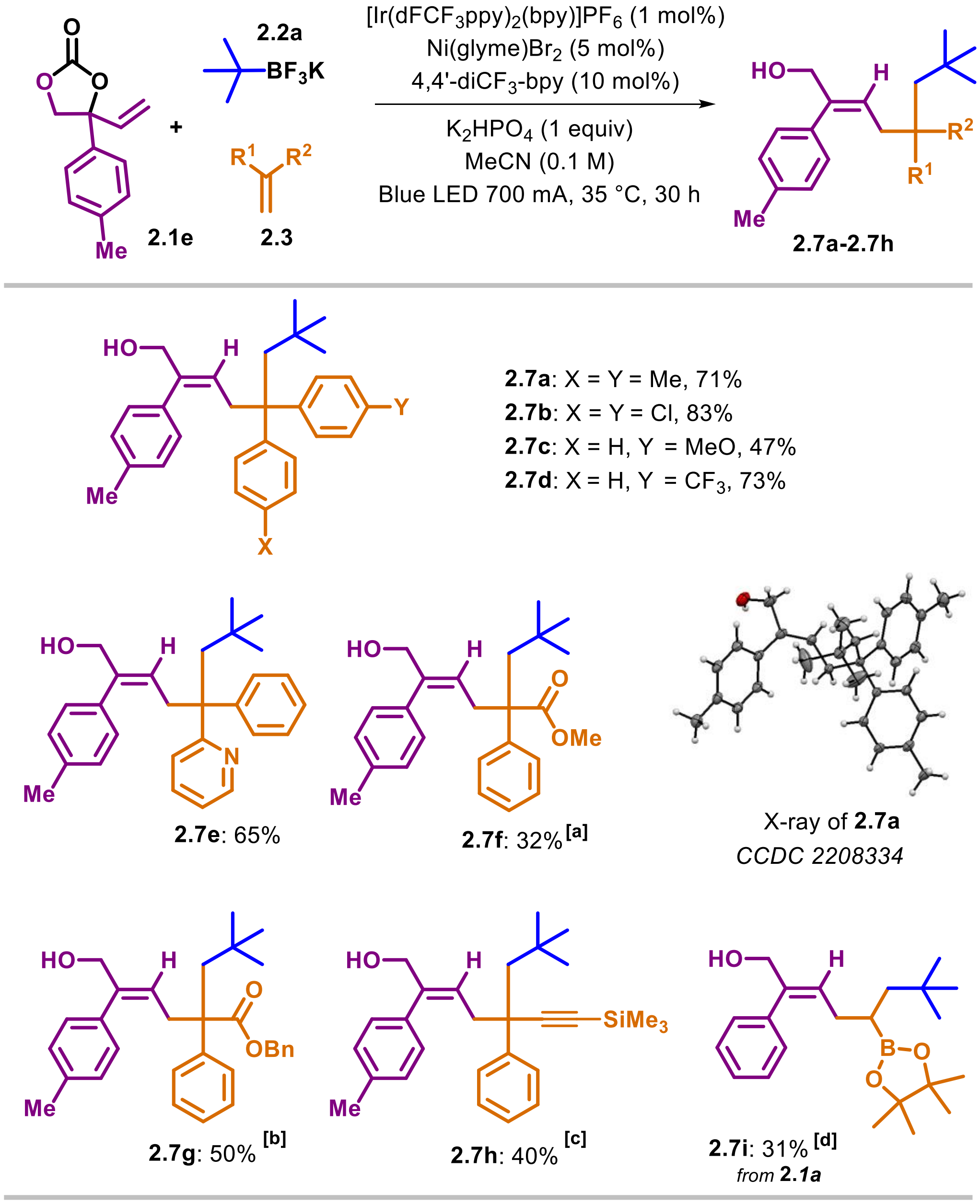
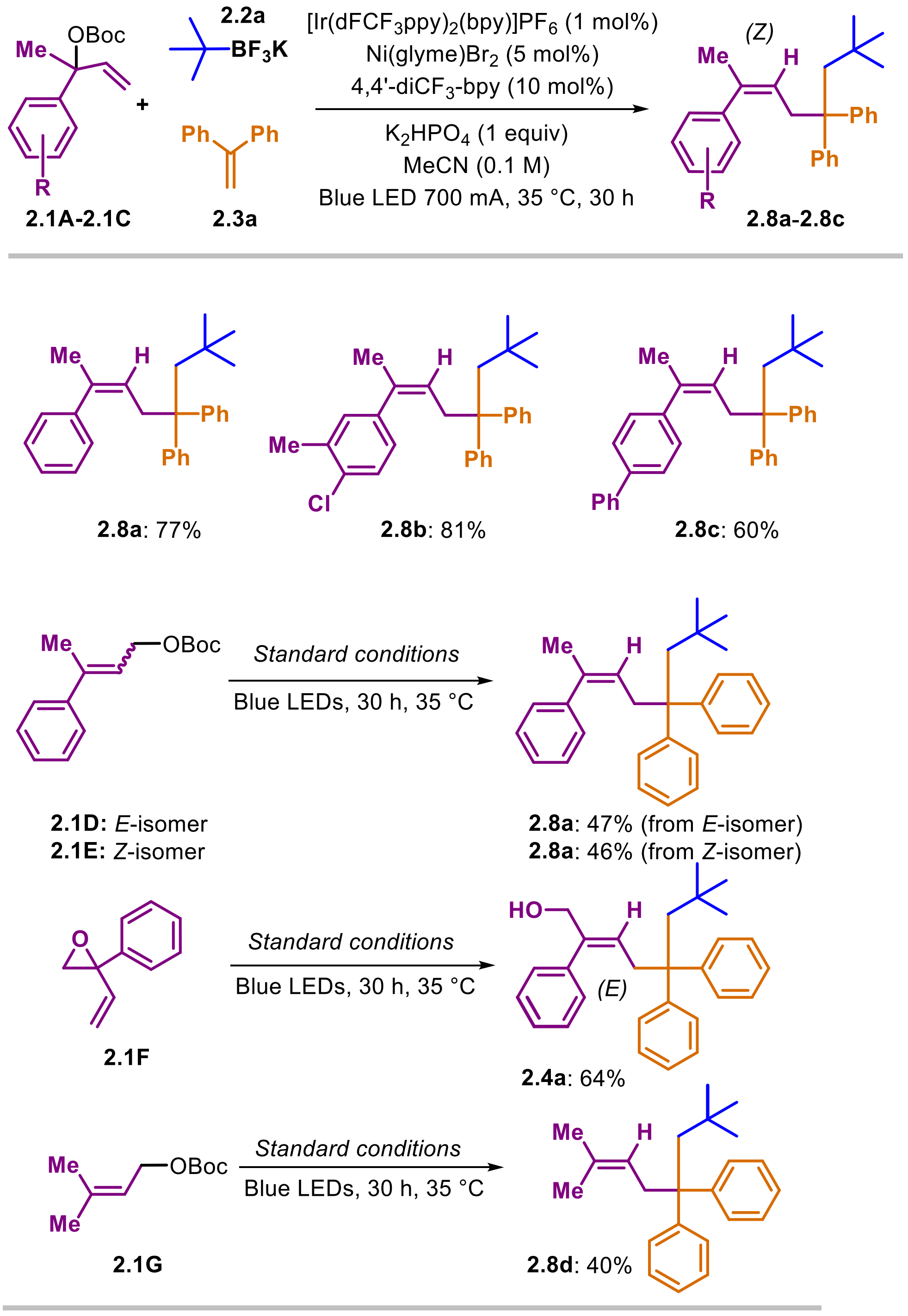
(26) For details, please refer to CCDC-2208334 and the Experimental section 2.4.3.



Scheme 2.11. Widening the scope of alkenes towards products **2.7a–2.7i**. Reaction conditions: **2.1e** (0.1 mmol), **2.2a** (0.25 mmol), **2.3** (0.12 mmol), Ni(glyme)Br_2 (5 mol%), ligand **L3** (10 mol%), [Ir(dFCF_3ppy)$_2$(bpy)]PF_6 (1 mol%), base (1 equiv), MeCN (1 mL), 700 mA blue LED, 35 ºC for 30 h. All *E/Z* values are >95:5. [a] 3 equiv of alkene precursor were used. [b] 3.5 equiv of alkene precursor were used and the reaction time was 48 h. [c] 1.8 equiv of alkene precursor were used. [d] Two isomers of a homocoupled bisallyl byproduct (**2.5b** + **2.5c**) were isolated in a combined 21% yield with the ratio **2.5b**/**2.5c** being 60:40.

Additionally, other allylic precursors (branched type linear carbonates and vinyl epoxides) are also suitable substrates in this 3CR protocol (Scheme 2.12). Carbonate precursors **2.1A**-**2.1C** are converted under the optimized conditions in the presence of **2.2a** and **2.3a** providing access to products **2.8a**-**2.8c** in moderate to good yields of up to 81% and with excellent regio- and stereocontrol (*Z/E*>95:5). Apart from branched carbonate **2.1A**, both linear carbonate substrates (*E*)-**2.1D** and (*Z*)-**2.1E** irrespective from their original stereochemical configuration are converted into **2.8a** although with a significantly lower yield (46-47%), which points at a more reactive nature of the branched carbonate precursors. Vinyl epoxide **2.1F** is transformed into product **2.4a** in 64% yield, which is slightly lower than the 74% when using vinyl cyclic carbonate **2.1a**. Moreover, the engagement of linear carbonate **2.1G** bearing a methyl instead of phenyl group also provides a 3CR product (**2.8d**) in 40%. The combined data presented in Scheme 2.12 clearly validates that the developed dual photoredox/Ni catalyzed 3CR cross-coupling process tolerates a wide range of allylic precursors and co-reactants thus delivering a wide scope of attractive allylic alcohol synthons with sterically congested carbon centers.



Scheme 2.12. Variation of the allylic precursor. Reaction conditions: allylic precursor **2.1A-2.1G** (0.1 mmol), **2.2a** (0.25 mmol), **2.3a** (0.12 mmol), Ni(glyme)Br$_2$ (5 mol%), ligand **L3** (10 mol%), [Ir(dFCF$_3$ppy)$_2$(bpy)]PF$_6$ (1 mol%), base (1 equiv), MeCN (1 mL), 700 mA blue LED, 35 ºC for 30 h. All *E/Z* values are >95:5.

2.2.3. Post-synthetic manipulations of 2.4a and influence of the PC on the stereo-outcome of the 3CR

Allylic alcohol **2.4a** was subjected to various reaction conditions to show the synthetic diversification potential of these scaffolds (Scheme 2.13; further details in the Experimental section). Treatment of **2.4a** with phenyl isocyanate under basic conditions provides simple access to carbamate product **2.9a** in 93%. Epoxidation of **2.4a** under vanadium catalysis using *tert*-butyl hydroperoxide (TBHP) as oxidant delivers **2.9b** in 51% yield. The allylic OH group in **2.4a** can also be easily converted into a linear carbonate (**2.9c**: 70%) in the presence of Boc anhydride (di-*tert*-butyl dicarbonate) and DMAP. As such, it creates a viable starting point for allylic substitution reactions under metal catalysis with the OBoc acting as a powerful leaving group.[27] Dess-Martin oxidation of **2.4a** produces the enal product **2.9d** in 75%. The allylic borane **2.9e** (31%) can be prepared by reacting **2.4a** with B_2Pin_2/*p*-toluene sulfonic acid under Pd-catalysis in dry DMSO/MeOH.[28] The allylic alcohol **2.4a** can be converted into allylic amine **2.9f** (53%) by first activating the OH group through PBr_3 followed by addition of benzyl amine.

During the screening and process optimization phase (Table 2.1, entry 5) we observed that the presence of 4CzIPN provided the product with a significant *Z*-isomer content. Under the optimized conditions of entry 3 in Table 2.4, **2.4a** is produced in 74% yield and virtually as a single stereoisomer (*E/Z* >95:5). We found that the stereoselectivity could be switched in the presence of 4CzIPN giving **2.4a** in 71% yield and with a *Z/E* ratio of 83:17. A rather similar outcome was achieved in the synthesis of **2.6a**, where PC1 induces the formation of the *E*-isomer in 57%, whereas the presence of PC5 yields **2.6a** (48%) with a *Z/E* ratio of 86:14. The mechanistic rationale behind this stereoselectivity switch is not yet well-understood though has gained recent momentum in organic synthesis[29] offering thus leverage to prepare individual product stereoisomers.

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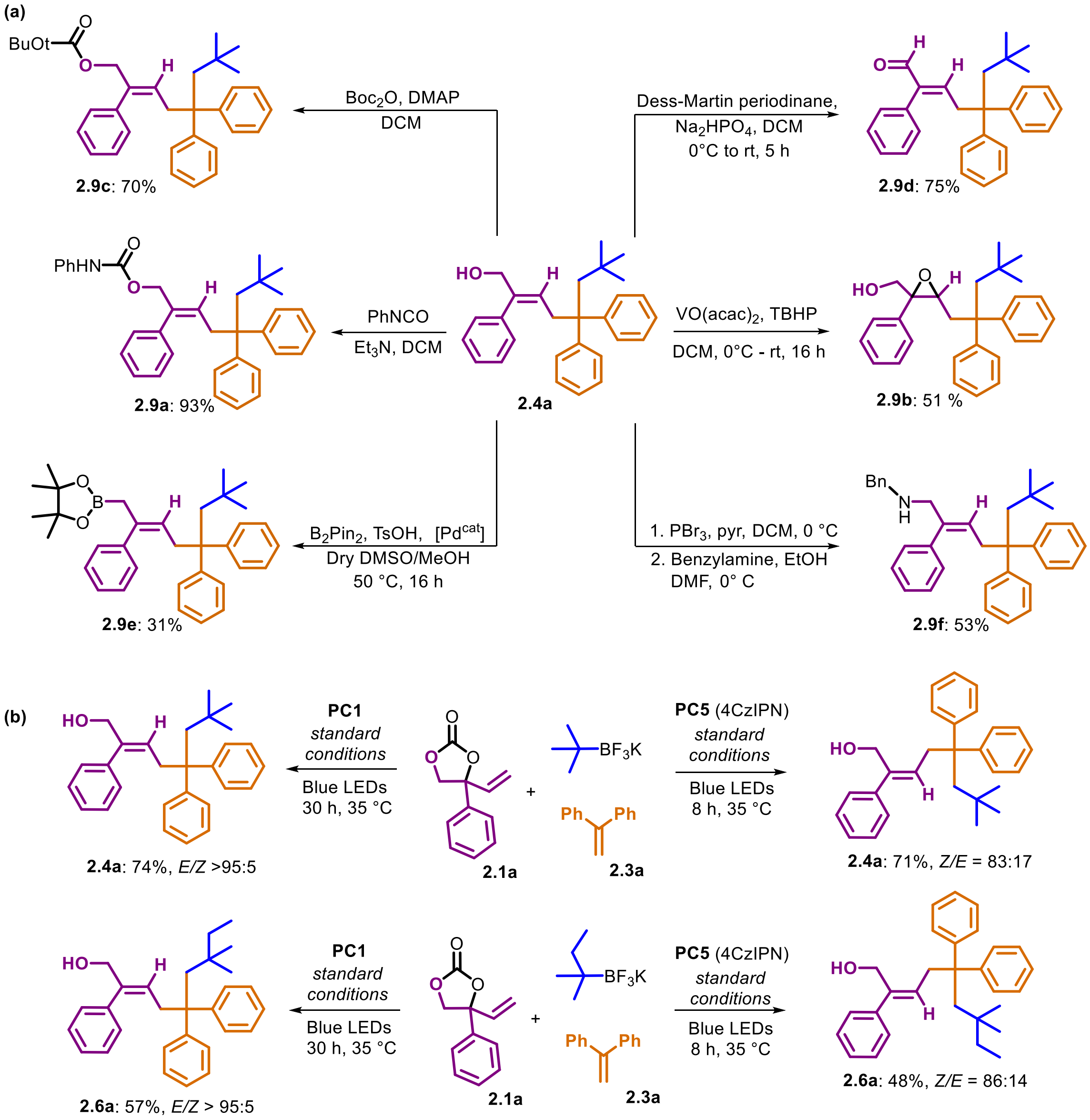
(27) a) J. Tsuji, I. Shimizu, I. Minami, Y. Ohashi, T. Sugiura, K. Takahashi, *J. Org. Chem.* **1985**, *50*, 1523–1529; b) B. N. Thomas, P. J. Moon, S. Yin, A. Brown, R. J. Lundgren, *Chem. Sci*. **2018**, *9*, 238-244.

(28) G. Dutheuila, N. Selanderb, K. J. Szabó, V. K. Aggarwal, *Synthesis* **2008**, *14*, 2293-2297.

(29) a) J. S. DeHovitz, T. K. Hyster, *ACS Catal*. **2022**, *12*, 8911−8924; b) F. Strieth-Kalthoff, F. Glorius, *Chem* **2020**, *6*, 1888–1903; c) T. Nevesely, M. Wienhold, J. J. Molloy, R. Gilmour, *Chem. Rev*. **2022**, *122*, 2650−2694; d) J. Xu, Z. Li, Y. Xu, X. Shu, H. Huo, *ACS Catal.* **2021**, *11*, 13567−13574.

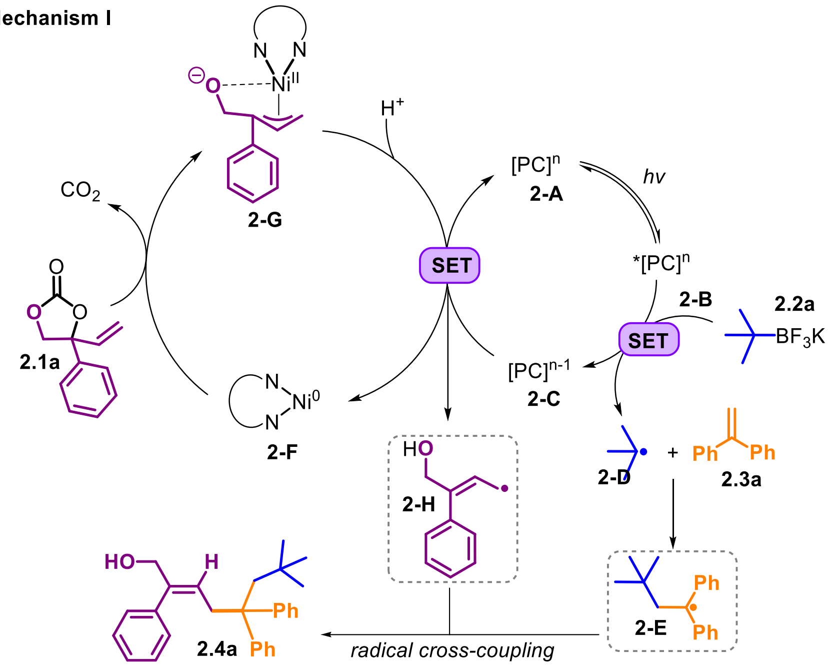


Scheme 2.13. (a) Post-synthetic manipulations of **2.4a**. (b) Influence of the PC on the stereo-outcome of the 3CR involving **2.1a**, **2.3a** and two different alkyl potassium trifluoroborates. Note that only the major stereoisomers are represented in the scheme.

2.2.4. Mechanistic considerations

Our mechanistic proposal (Scheme 2.14) is based on a series of control experiments and previous precedents.[13,14,15,30] It starts off with the oxidative addition of the vinyl cyclic carbonate **2.1a** to Ni(0) following CO_2 extrusion, and concomitant formation of the alkyl radical from the trifluoroborate precursor enabled by the excited PC*. The latter then adds to the disubstituted alkene to afford radical product **2-E** which possesses a persistent character.[31] Next, the Ni(II)allyl species **2-G** is reduced by PC^{n-1} to give the allyl radical **2-H** and regenerates a Ni(0) intermediate along with the ground-state PC^{n}.[32] From here, radical cross-coupling between the allyl radical **2-H** and tertiary radical **2-E** produces the product **2.4a** (see details in Scheme 2.14a below). Alternatively, one can envision a manifold that involves a radical metal crossover step giving rise to a Ni(III) intermediate **2-J**. In this pathway, reductive elimination from the Ni(III) complex provides the final product **2.4a** and a Ni(I) species **2-K** that is reduced via a single-electron transfer (SET) to Ni(0) **2-F** by the PC^{n-1} to allow for additional turnover (see details in Scheme 2.14b, next page).

(a) Mechanism I



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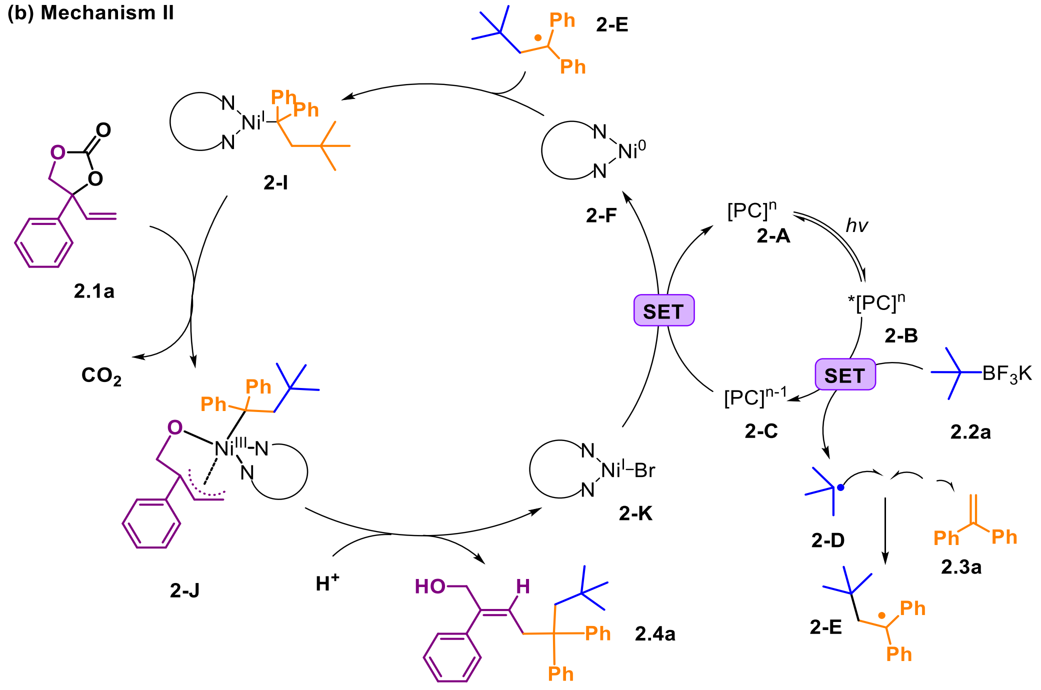
(30) A. Y. Chan, I. B. Perry, N. B. Bissonnette, B. F. Buksh, G. A. Edwards, L. I. Frye, O. L. Garry, M. N. Lavagnino, B. X. Li, Y. Liang, E. Mao, A. Millet, J. V. Oakley, N. L. Reed, H. A. Sakai, C. P. Seath, D. W. C. MacMillan, *Chem. Rev.* **2022**, *122*, 1485−1542.

(31) a) D. Leifert, A. Studer, *Angew. Chem. Int. Ed.* **2020**, *59*, 74–108; b) E. Le. Saux, M. Zanini, P. Melchiorre, *J. Am. Chem. Soc.* **2022**, *144*, 1113−1118.

(32) Z. Zuo, D. T. Ahneman, L. Chu, J. A. Terrett, A. G. Doyle, D. W. C. MacMillan, *Science* **2014**, *345*, 437–440.



Scheme 2.14. (a) Mechanism I (previous page): proposed manifold leading to product **2.4a** via radical cross-coupling. (b) Mechanism II: proposed manifold leading to product **2.4a** via a sequence of oxidative addition and reductive elimination.

To examine the operating mechanism, some control experiments were performed (Scheme 2.15). Addition of TEMPO to a standard reaction mixture fully shuts down catalysis with only traces (at most) of **2.4a** being detected (Scheme 2.15a). The presence of a suitable Ni-catalyst is crucial towards the formation of **2.4a** (cf., the occurrence of an oxidative addition step involving vinyl cyclic carbonate **2.1**) as in its absence only the radical addition product **2.5a** (Table 2.5, entry 3) was observed in 78% yield (see Table 2.5). Finally, formation of a benzylic anion after radical addition of the alkyl radical to **2.3a** seems unlikely as in the presence of protic compounds such as H_2O and HFIP,[33] **2.4a** is still formed in similar amounts (67-71% versus 74% under the standard conditions). The presence of triethylamine as a reductant in the absence of **2.2a**/**2.3a** under standard condition affords the HAT products **2.5d** and **2.5e** (Scheme 2.15b) due to the relatively low bond dissociation energy (BDE, ~42 kcal/mol) of an *α*-CH bond of an amino radical

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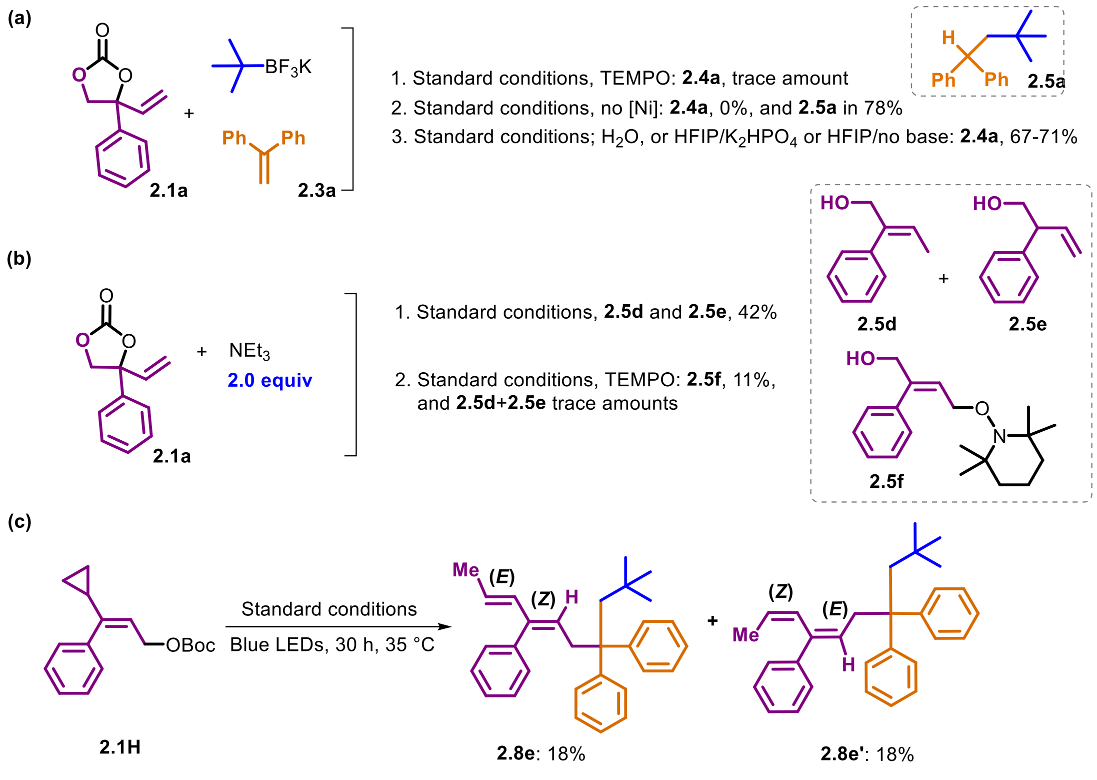
(33) Y. Shen, Z.-Y. Dai, C. Zhang, P.-S. Wang, *ACS Catal*. **2021**, *11*, 6757−6762.

cation.[34] The formation of a TEMPO adduct **2.5f** from **2.1a** also supports the intermediacy of an allylic radical species generated during this process. Together with the observation of homo-dimerized bisallylic products **2.5b** and **2.5c** generated during the synthesis of **2.7i** and the outcome of a radical clock experiment leading to the ring-opening products **2.8e** and **2.8e'** (36%, Scheme 2.15, see details in Experimental section), we conclude that generation of free allylic radical species during the process is feasible. Radical metal crossover affording a Ni(III) intermediate from which the product is released via reductive elimination may be challenging in some cases due to the steric character of the tertiary radical. An outer-sphere attack of the latter, however, onto a Ni(II)allyl species (**2-G**, Scheme 2.14a) provides an alternative pathway towards the 3CR product.



(a)
1. Standard conditions, TEMPO: **2.4a**, trace amount
2. Standard conditions, no [Ni]: **2.4a**, 0%, and **2.5a** in 78%
3. Standard conditions; H_2O, or HFIP/K_2HPO_4 or HFIP/no base: **2.4a**, 67-71%

(b)
1. Standard conditions, **2.5d** and **2.5e**, 42%
2. Standard conditions, TEMPO: **2.5f**, 11%, and **2.5d**+**2.5e** trace amounts

Scheme 2.15. (a) Radical capture experiment and support for the formation of a radical/anionic species. (b) Support for the formation of an allylic radical species; (c) Radical clock experiment.

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(34) Oxidative photoredox catalysis: a) J. W. Beatty, C. R. J. Stephenson, *Acc. Chem. Res.* **2015**, *48*, 1474−1484; b) L. Furst, B. S. Matsuura, J. M. R. Narayanam, J. W. Tucker, C. R. J. Stephenson, *Org. Lett.* **2010**, *12*, 3104–3107.

2.3. Conclusions

In this chapter, we present a versatile three-component coupling reaction based on a dual photo/Ni catalysis process involving allylic precursors, olefins and various radical precursors. The developed process expands the potential of radical-based allylic alkylation to multi-component approaches under high regio- and stereocontrol with ample variation of the individual reagents, and offers access to compounds featuring sterically congested and functionalized quaternary carbon centers. The stereoselectivity of the catalytic protocol is reversed by simply changing the photocatalyst.

This work exemplifies the potential value of multicomponent strategies in radical based methodologies to rapidly access allylic skeleton complexity through carbon-carbon bond formation reactions. These results indicate that Ni/photo-catalyzed allylic alkylation is not restricted to two-components processes, and thus paves the way to the transformation of more complex substrate combinations under catalytic control.

2.4. Experimental section

2.4.1. General information

Air- and water-sensitive reactions were carried out in heat-gun-dried glassware under an Ar or N_2 atmosphere using standard Schlenk techniques. Reactions were monitored by TLC and/or ^{1}H NMR. TLC was carried out on 0.25 mm Merck aluminum backed sheets coated with 60 F_{254} silica gel. Visualization of the silica plates was achieved using a UV lamp (λ = 254 nm) and/or by using the stain solutions of a $KMnO_4$ or ceric ammonium molybdate. Flash chromatography was carried out on Sigma-Aldrich silica gel 60 (70-230 mesh) using the indicated eluent system. Commercially available reagents and solvents were purchased from Sigma-Aldrich, TCI, Fluorochem, Strem Chemicals, ABCR GmbH, Acros Organics or Alfa Aesar, and were used without further purification. Starting materials were synthesized by following procedures as stated, $[Ir(dFCF_3ppy)_2(bpy)]PF_6$ was synthesized according to a previously reported procedure.[35] Solvents were dried using an Innovative Technology PURE SOLV solvent purification system. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded at room temperature on a Bruker AV-300, AV-400 or AV-500 spectrometer and referenced to their residual deuterated solvent signals. All reported NMR values are given in parts per million (ppm). UV-Vis measurements were carried out on an Agilent Cary 60 UV-Vis spectrophotometer equipped with two silicon diode detectors, double beam optics and Xenon pulse light. Mass spectrometric analyses were performed by the Research Support Group at ICIQ. Fluorescence measurements were carried out on an Aminco-Bowman Series 2 Luminescence spectrofluorimeter equipped with a high voltage PMT detector and continuum Xe light source. Cyclic voltammetry (CV) studies and square wave voltammograms (SWVs) were carried out on a Princeton Applied Research PARSTAT 2273 potentiostat.

Photocatalysis set-up

Photoreactions were performed in a parallel photoreactor with 8 spots using flat-bottom J-young Schlenk flasks (see Figure 2.1). The reactions were thermostated using a Heidolph rotacool. OSRAM Oslon SSL 80 royal-blue LEDs mounting on a star PCB were

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(35) J. C. Tellis, D. N. Primer, G. A. Molander, *Science* **2014**, *345*, 433–436.

used and cooled passively by a common heatsink. The LEDs were powered in series using a current limited power supply (RS Pro RS-3005D).

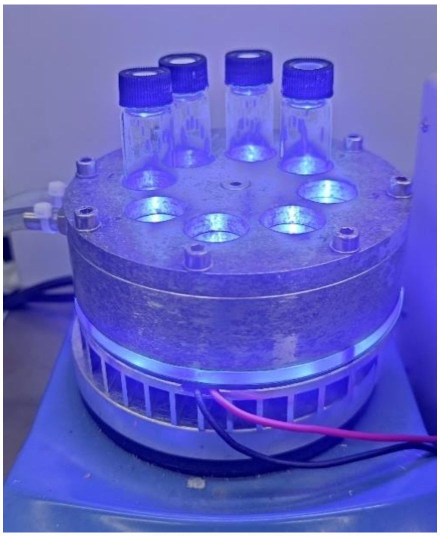


Figure 2.1. Photoreactor setup with 8 parallel reactors.

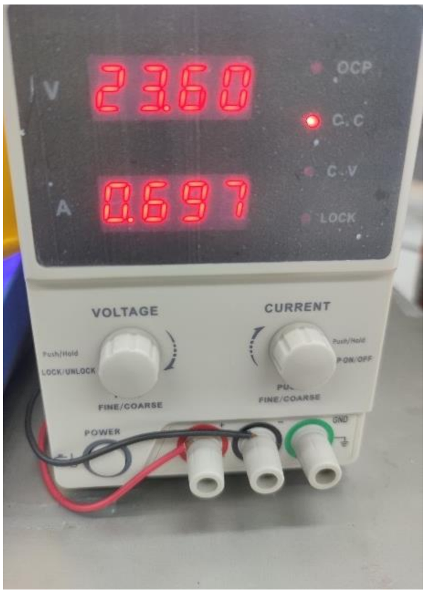
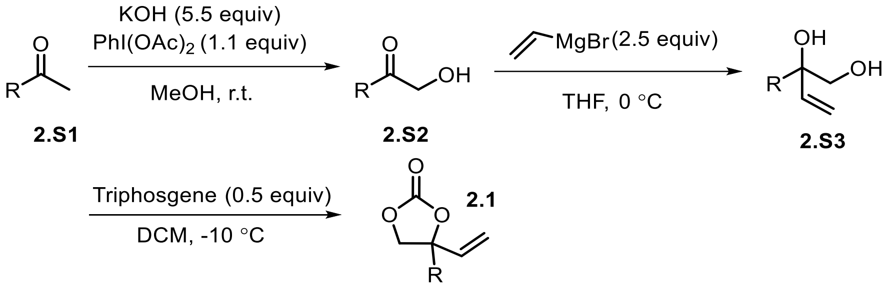


Figure 2.2. Photograph of the current-limited power supply used in this chapter.

2.4.2. General procedure for the preparation of starting materials

<u>General procedure for synthesis of the vinyl cyclic carbonates 2.1</u>:



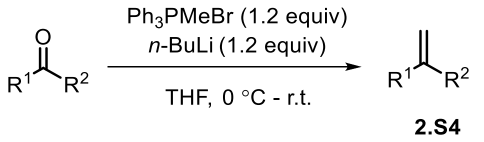
Step 1: To a cold solution of the ketone **2.S1** (15 mmol, 1 equiv) in MeOH was added the KOH (4.629 g, 82.5 mmol, 5.5 equiv) in portions, and then was added the $PhI(OAc)_2$ (diacetoxyiodobenzene) (5.314 g, 16.5 mmol, 1.1 equiv) slowly. After being stirred at 0 °C to room temperature for 2-3 hours, the reaction mixture was concentrated under the reduced pressure and the residue was extracted with H_2O (30 mL) and Et_2O (30 mL). The organic phase was separated, dried over Na_2SO_4 and filtered. After concentrated, the obtained residue was dissolved in MeOH (30 ml) and 2 N HCl (30 mL), and then stirred overnight at the room temperature. Next, a saturated aqueous solution of $NaHCO_3$ was added to the reaction mixture until pH 7 and diluted with DCM (30 mL). The organic phase was separated and dried with anhydrate Na_2SO_4, then the filtrate was concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (hexanes/EtOAc= 30:1 to 20:1) to yield **2.S2** (typically in 60-70% yield).

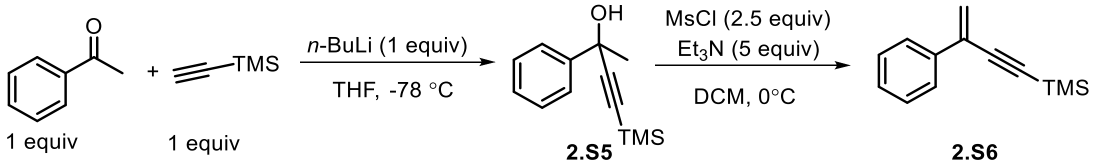
Step 2: An oven-dried Schlenk tube containing a magnetic stirring bar charged with **2.S2** (10 mmol, 1 equiv) before evacuating and back-filling with N_2, and then was added THF (20 mL) and Grignard reagent (1.0 M in THF, 25 mL, 2.5 equiv) by syringe at 0 °C. After being stirred at room temperature for 4-5 hours, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate (3×15 mL). The combined organic phases were dried over Na_2SO_4, concentrated under reduced pressure, then the obtained residue was purified by column chromatography on silica gel (hexanes/EtOAc= 10:1 to 5:1) to afford the pure product (typically in 50-70% yield).

Step 3: An oven-dried Schlenk tube containing a magnetic stirring bar charged with diol **2.S2** (7 mmol, 1 equiv) before evacuating and back-filling with N_2, then sequentially added pyridine (2.215 g, 28 mmol, 4 equiv) and a solution of triphosgene (1.036 g, 3.5

mmol, 0.5 equiv) in 10 mL DCM by syringe at -10 ºC. After being stirred at -10 ºC to room temperature for 1-2 hours, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and diluted with DCM (30 mL). The organic phase was washed with 1N HCl (3×20 mL), $NaHCO_3$ (3 × 20 mL) and brine (3 × 20 mL). The combined organic phases were dried over Na_2SO_4, concentrated under reduced pressure, then the obtained residue was purified by column chromatography on silica gel (hexanes/EtOAc= 15:1 to 10:1) to afford the pure product as a light-yellow oil (typically 60-70% yield). All vinyl compounds **2.3** were known and prepared according to a previously reported procedure.[36]

General procedure for synthesis of the vinyl compounds 2.3:





Synthesis of 2.S4: An oven-dried Schlenk tube containing a magnetic stirring bar charged with Ph_3PMeBr (2.143 g, 6 mmol, 1.2 equiv) before evacuating and back-filling with N_2, and then was added THF (20 mL) and *n*-BuLi (1.6 M in hexane, 3.75 mL, 6 mmol, 1.2 equiv) by syringe slowly at 0 ºC. After 1 h, ketone (5 mmol, 1 equiv) was added, then being stirred at room temperature for another 4-5 hours. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate (3×15 mL). The combined organic phases were dried over Na_2SO_4, concentrated under reduced pressure, then the obtained residue was purified by column chromatography on silica gel (hexanes/EtOAc= 100:1) to afford the pure product (typically in 90-95% yield).

Synthesis of 2.S6: An oven-dried Schlenk tube containing a magnetic stirring bar charged with alkyne (960 mg, 10 mmol, 1 equiv) before evacuating and back-filling with N_2, and then was added THF (20 mL) and *n*-BuLi (1.6 M in hexane, 6.25 mL, 10 mmol, 1 equiv) by syringe slowly at -78 ºC. After 1 h, ketone (10 mmol, 1 equiv) was added, then being

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(36) a) Q.-Y. Meng, S. Wang, B. König, *Angew. Chem. Int. Ed.* **2017**, *56*, 13426–13430; b) Y.-Y. Cheng, J.-X. Yu, T. Lei, H.-Y. Hou, B. Chen, C.-H. Tung, L.-Z. Wu, *Angew. Chem. Int. Ed.* **2021**, *60*, 26822–26828; c) Y. Chen, K. Zhu, Q. Huang, Y. Lu, *Chem. Sci.* **2021**, *12*, 13564–13571.

stirred at -78 ºC to room temperature for another 3 hours. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate (3 × 15 mL). The combined organic phases were dried over Na_2SO_4, concentrated under reduced pressure, then the obtained residue was purified by column chromatography on silica gel (hexanes/EtOAc= 30:1 to 20:1) to afford the pure product (typically in 80-90% yield).

To a cold solution of the resulting propargyl alcohol **S5** (8 mmol, 1 equiv) in DCM (30 mL) was added the Et_3N (40 mmol, 5 equiv) and methylsulfonyl chloride (20 mmol, 2.5 equiv) sequentially. After one hour the reaction was monitored by TLC for completion. The mixture was quenched with saturated aqueous NH_4Cl and extracted with DCM (3 × 15 mL). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure at low temperature, then the obtained residue was purified by column chromatography on silica gel (hexanes/EtOAc= 30:1 to 20:1) to afford the pure product **2.S7** and keep in the freezer (typically in 80-90% yield).

All organotrifluoroborates are known and were prepared from the pinacol boronate esters according to following previously reported procedures.[37] Pinacol boronate esters were prepared following **General Procedure A**, **General Procedure B** and other reported procedures. Analytical data were consistent with the literature values.

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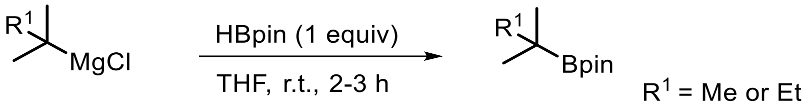
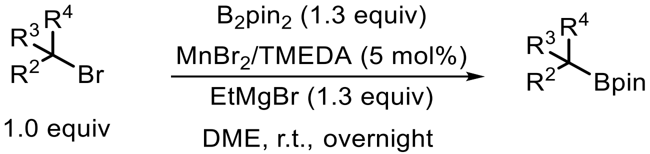
(37) a) B. Verbelen, L. C. D. Rezende, S. Boodts, J. Jacobs, L. Van Meervelt, J. Hofkens, W. Dehaen, *Chem. Eur. J.* **2015**, *21*, 12667–12675; b) B. Chen, C.-S. Kuai, J.-X. Xu, X.-F. Wu, *Adv. Synth. Catal.* **2022**, *364*, 487–492.

General procedure for the synthesis of pinacol boronate esters:



2.S7

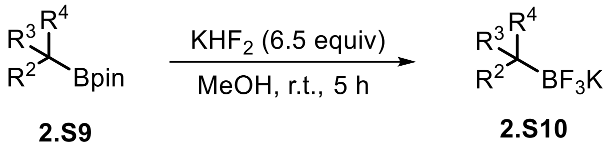
General Procedure A: An oven-dried Schlenk tube containing a magnetic stirring bar before evacuating and back-filling with N_2, charged with Grignard reagent (2.0 M in Et_2O, 5 mL, 1 equiv), pinBH (10 mmol, 1 equiv.) and THF (10 mL). After being stirred at room temperature for 2-3 hours, the reaction mixture was quenched with 1 N HCl and extracted with Et_2O, then washed with brine. The combined organics were dried over Na_2SO_4, concentrated under reduced pressure at low temperature. Then the obtained residue was purified by column chromatography on silica gel (pentane/Et_2O= 100:1) to afford the pure product **2.S7** as a colorless oil (typically 50-60% yield).



2.S8 **2.S9**

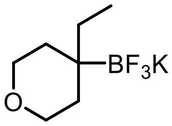
General Procedure B: A reaction flask was charged with $MnBr_2$ (5 mol%) and $(Bpin)_2$ (3.3 g, 1.3 equiv) before evacuating and back-filling with Ar. DME (10 mL, 1.0 M) was added, followed by TMEDA (75 µL, 5 mol%). Next, ethylmagnesium bromide **2.S8** (3 M in Et_2O, 4.5 mL, 1.3 equiv) was added dropwise to the reaction mixture. Finally, alkyl bromide (10 mmol, 1 equiv) was added to the reaction mixture at once. The reaction mixture was stirred at room temperature overnight. The reaction was quenched with 1 N HCl, extracted with Et_2O, then washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (hexanes/EtOAc= 50: 1) to yield **2.S9** as a colorless oil.

General procedure for the synthesis of organotrifluoroborates 2.2:



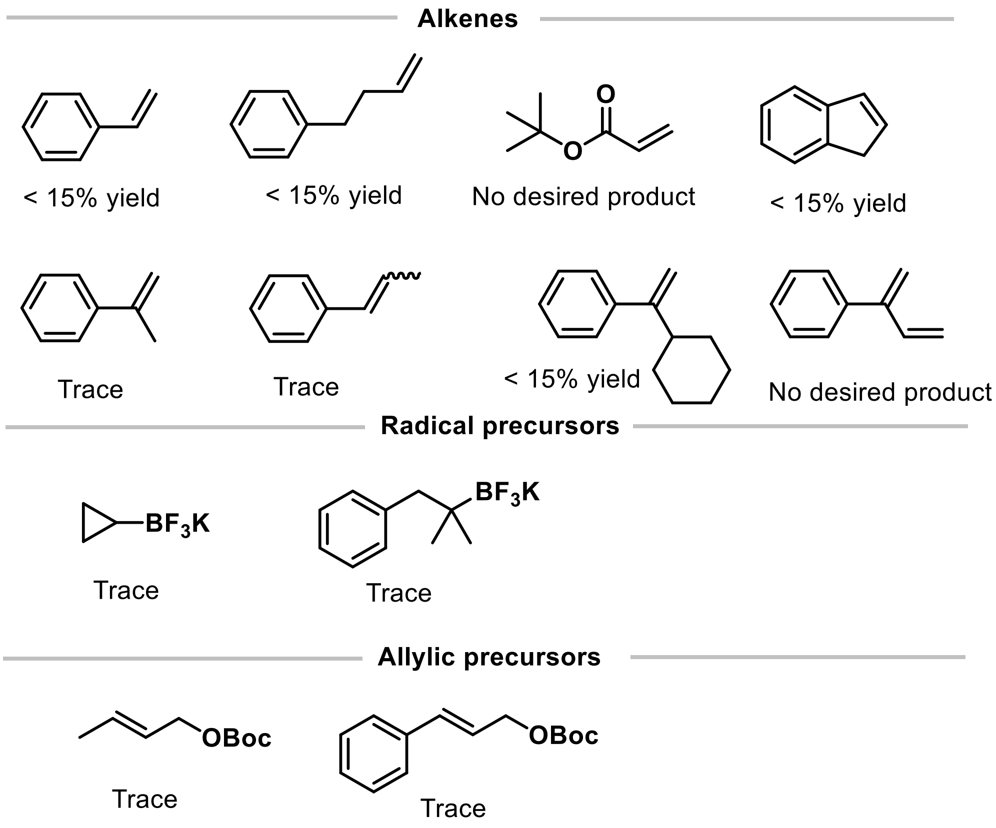
General Procedure: To the solution of pinacol boronate esters **2.S9** (5 mmol) in MeOH (10 mL) was added saturated aqueous KHF_2 (2.54 g, 32.5 mmol, 6.5 equiv). The resulting suspension was stirred for 5 h and then concentrated to dryness *via* rotary evaporation. The residue, a white solid, was washed with hot acetone (3 × 30 mL), then filtered through a fritted glass funnel to remove inorganic salts. The filtrate was concentrated to afford the crude solid, and then was washed with mixture solvent (hexanes/Et_2O = 1:1) to give the pure organotrifluoroborate **2.S10**.

Potassium (4-ethyltetrahydro-2*H*-pyran-4-yl)trifluoroborate (2.2e)



White solid (General Procedure B); **^{1}H NMR** (400 MHz, CD_3CN) 3.60 – 3.51 (m, 4H), 1.61-1.55 (m, 2H), 1.28 – 1.24 (m, 2H), 1.05 – 1.02 (m, 2H), 0.81 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, CD_3CN) δ 65.3, 34.1, 25.1, 10.1; **^{19}F NMR** (376 MHz, CD_3CN) δ -145.36; **^{11}B NMR** (128 MHz, CD_3CN) δ 5.15 ($^1J^{B\text{-}F}$ = 62.7 Hz); **HRMS** (ESI/TOF) *m/z*: $[M - K]^-$ Calcd for. $C_7H_{13}{}^{11}BF_3O^-$ 181.1017; found 181.1017.

Overview of moderately successful and unsuccessful substrates (categories 2.1, 2.2 and 2.3):



Recorded ^{1}H NMR (CDCl$_3$) spectra of unsucceful reactions of catergories 1-3 shown above:

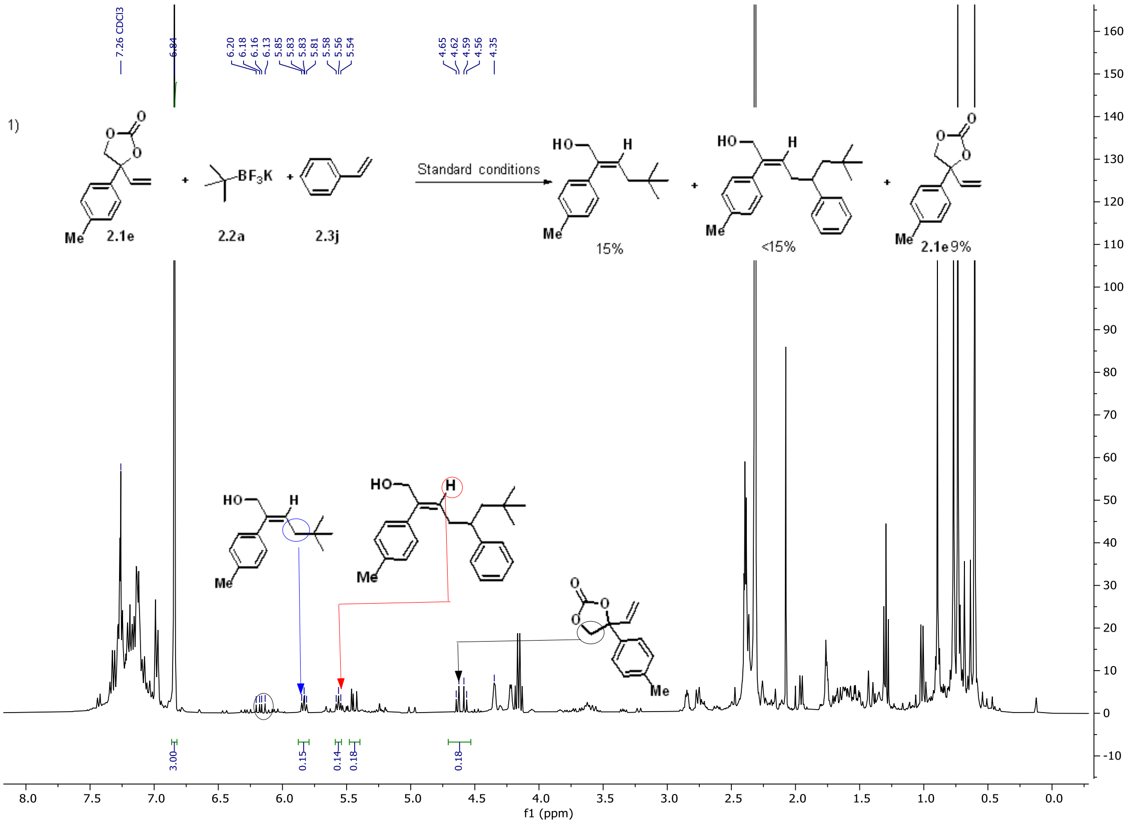


Figure 2.3a. Unsuccessful synthesis of product **2.3j**. Note that here **2.1e** (0.1 mmol) and mesitylene (0.1 mmol) are present. The singlet peak at 6.8 ppm is from mesitylene.

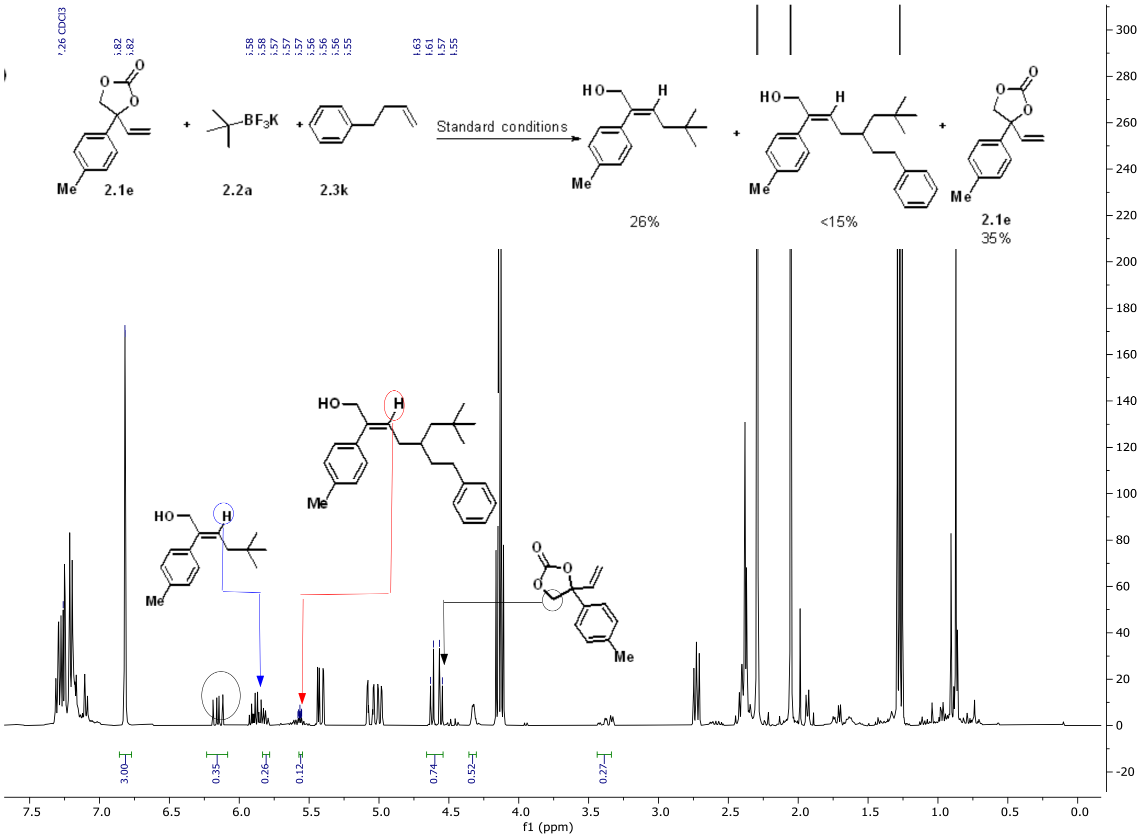


Figure 2.3b. Unsuccessful synthesis of product **2.3k**. Note that here **2.1e** (0.1 mmol) and mesitylene (0.1 mmol) are also present. The singlet peak at 6.8 ppm is from mesitylene.

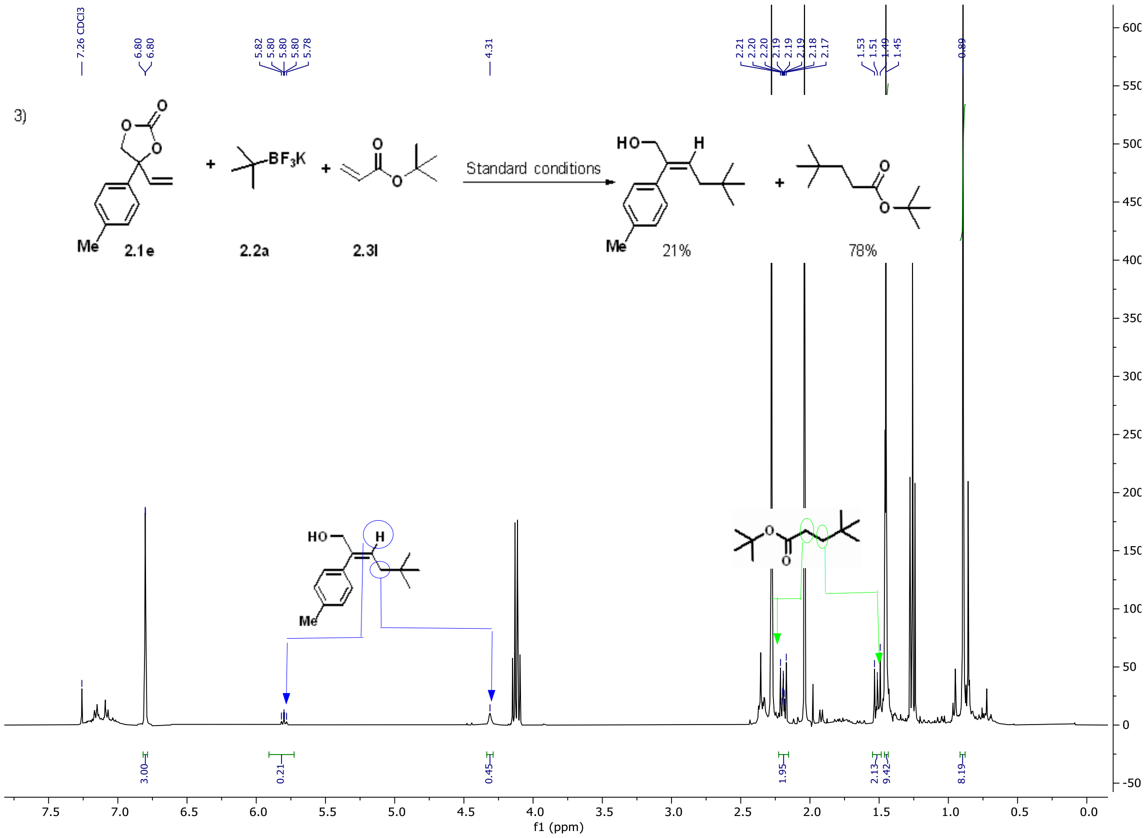
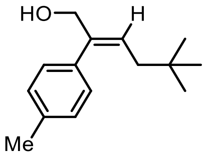


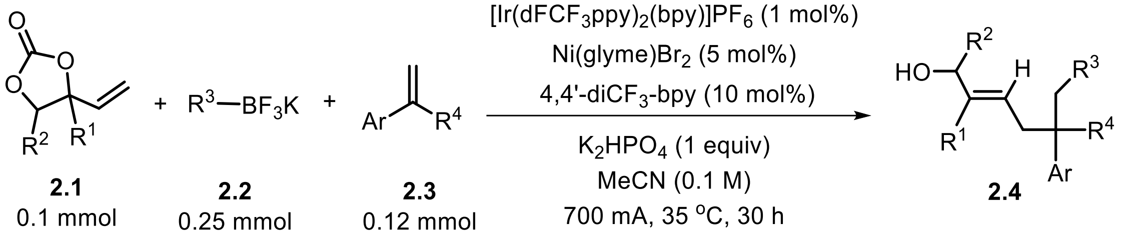
Figure 2.3c. Unsuccessful synthesis of product **2.3i**. Note that here **2.1e** (0.1 mmol) and mesitylene (0.1 mmol) are also present. The singlet peak at 6.8 ppm is from mesitylene.

Isolated product after column purification:

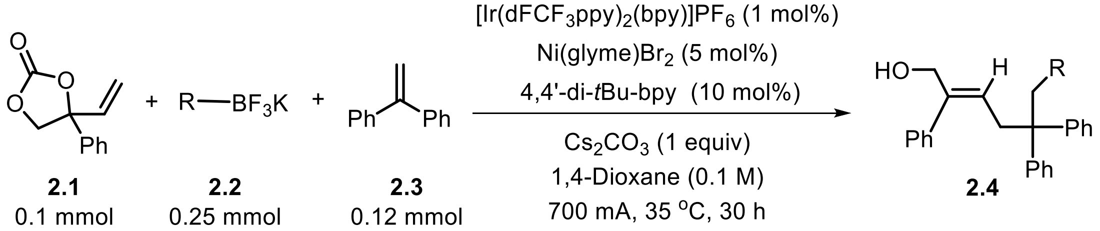


(*E*)-5,5-dimethyl-2-(*p*-tolyl)hex-2-en-1-ol). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.21 – 7.04 (m, 5H), 5.85 – 5.75 (m, 1H), 4.32 (s, 2H), 2.36 (s, 3H), 1.91 (d, *J* = 7.5 Hz, 2H), 0.85 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 141.5, 136.4, 135.5, 129.1, 128.9, 125.9, 68.7, 42.3, 31.2, 29.5, 21.3; **HRMS** (APCI/TOF) m/z: [M + H]+ Calcd. for $C_{15}H_{21}^{+}$ 201.1638; found 201.1635.

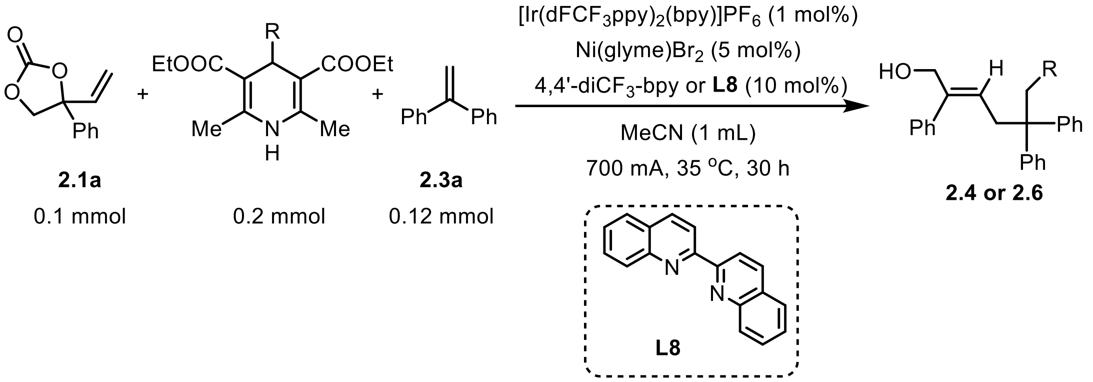
2.4.3. Typical procedure for the formation of highly functionalized compounds featuring quaternary stereocenters



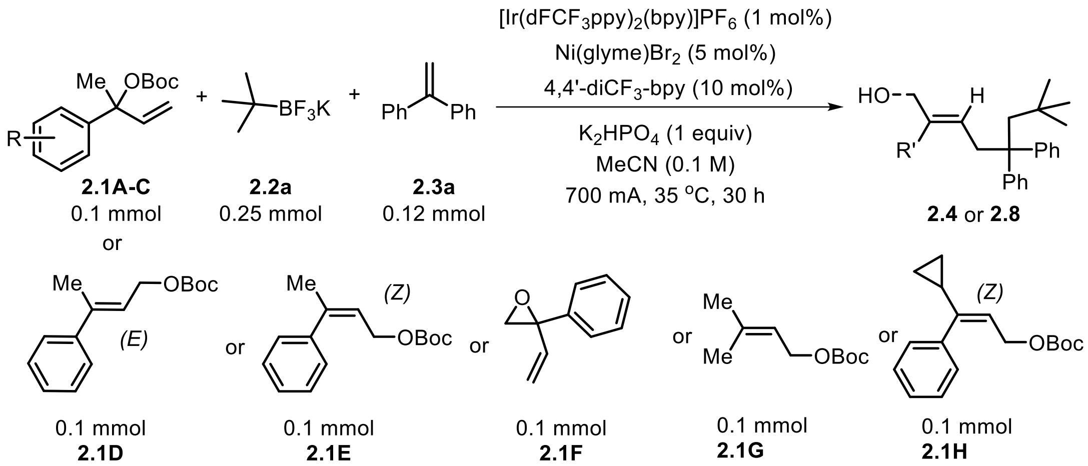
Method A: [Ir(dFCF$_3$ppy)$_2$(bpy)]PF$_6$ (1.1 mg, 1.0 mol%), 4,4'-diCF$_3$-bpy (2.9 mg, 10 mol%) and organotrifluoroborate **2.2** (41 mg, 0.25 mmol, 2.5 equiv) were weighed in a 10 mL screw-cap vial. The vial moved to a nitrogen-filled glove-box and was charged with Ni(glyme)Br$_2$ (1.5 mg, 5 mol%), K$_2$HPO$_4$ (17.4 mg, 0.10 mmol, 1 equiv) and CH$_3$CN (1 mL, 0.10 M). The liquid or solid **2.1** (0.10 mmol) and **2.3** (0.12 mmol) were added affording a light-yellow solution. The reaction system was capped, removed from the glove box and was irradiated for 30 hours at 35 °C using a single high-power blue LED (λ_{em} = 445 nm, 700 mA) from the bottom. After completion, the mixture was evaporated to dryness and the residue was purified by column chromatography (SiO$_2$, hexanes/EtOAc) to afford product **2.4**



Method B: [Ir(dFCF$_3$ppy)$_2$(bpy)]PF$_6$ (1.1 mg, 1.0 mol%), 4,4'-di-*t*Bu-bpy (2.7 mg, 10 mol%), organotrifluoroborate **2.2** (41 mg, 0.25 mmol, 2.5 equiv) and Cs$_2$CO$_3$ (32.6 mg, 0.10 mmol, 1 equiv) were weighed in a 10 mL screw-cap vial. The vial moved to a nitrogen-filled glove-box and was charged with Ni(glyme)Br$_2$ (1.5 mg, 5.0 mol%) and 1,4-Dioxane (1 mL, 0.10 M). The liquid or solid **2.1** (0.10 mmol) and **2.3** (0.12 mmol) were added affording a light-yellow solution. The reaction system was capped, removed from the glove box and was irradiated for 30 hours at 35 °C using a single high-power blue LED (λ_{em} = 445 nm, 700 mA) from the bottom. After completion, the mixture was evaporated to dryness and the residue was purified by column chromatography (SiO_2, hexanes/EtOAc) to afford product **2.4**.



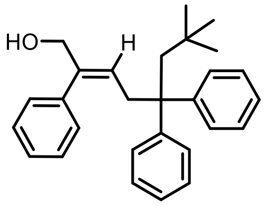
<u>Method C:</u> [Ir(dFCF$_3$ppy)$_2$(bpy)]PF$_6$ (1.1 mg, 1.0 mol%), Ligand (10 mol%) and DHP (0.20 mmol, 2 equiv) were weighed in a 10 mL screw-cap vial. The vial moved to a nitrogen-filled glove-box and was charged with Ni(glyme)Br$_2$ (1.5 mg, 5 mol%) and MeCN (1 mL, 0.10 M). The liquid **2.1a** (17.5 µL, 0.10 mmol, 1 equiv) and **2.3a** (21.8 µL, 0.12 mmol, 1.2 equiv) were added affording a light-yellow solution. The reaction system was capped, removed from the glove box and was irradiated for 30 hours at 35 °C using a single high-power blue LED (λ_{em} = 445 nm, 700 mA) from the bottom. After completion, the mixture was evaporated to dryness and the residue was purified by column chromatography (SiO_2, hexanes/EtOAc) to afford products **2.4** and **2.6**.



Method D: [Ir(dFCF$_3$ppy)$_2$(bpy)]PF$_6$ (1.1 mg, 1.0 mol%), 4,4'-diCF$_3$-bpy (2.9 mg, 10 mol%) and organotrifluoroborate **2.2a** (41 mg, 0.25 mmol, 2.5 equiv) were weighed in a 10 mL screw-cap vial. The vial moved to a nitrogen-filled glove-box and was charged with Ni(glyme)Br$_2$ (1.5 mg, 5.0 mol%), K$_2$HPO$_4$ (17.4 mg, 0.10 mmol, 1 equiv) and CH$_3$CN (1 mL, 0.10 M). The liquid or solid **2.1A-2.1H** (0.1 mmol) and **2.3a** (0.12 mmol) were added affording a light-yellow solution. The reaction system was capped, removed from the glove box and was irradiated for 30 hours at 35 °C using a single high-power blue LED (λ_{em} = 445 nm, 700 mA) from the bottom. After completion, the mixture was evaporated to dryness and the residue was purified by column chromatography (SiO$_2$, hexanes/EtOAc) to afford products **2.4** or **2.8**.

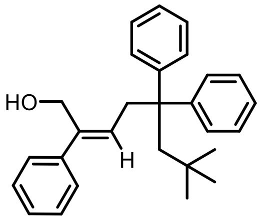
2.4.4. Characterization data for all new compounds

(*E*)-7,7-dimethyl-2,5,5-triphenyloct-2-en-1-ol (2.4a)



Yellowish oil (Method A, 28.5 mg, 74% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) (major) δ 7.36 – 7.30 (m, 2H), 7.30 – 7.26 (m, 1H), 7.24 – 7.18 (m, 4H), 7.17 – 7.11 (m, 6H), 7.02 – 6.97 (m, 2H), 5.52 (t, *J* = 6.8 Hz, 1H), 4.15 (s, 2H), 3.02 (d, *J* = 6.7 Hz, 2H), 2.21 (s, 2H), 0.57 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.2, 142.0, 138.6, 128.8, 128.7, 128.3, 127.7, 127.2, 125.75, 125.74, 68.4, 50.1, 37.9, 32.3, 31.7; **HRMS** (APCI/TOF) *m/z*: $[M - OH]^+$ Calcd for. $C_{28}H_{31}^+$ 367.2420; found 367.2421.

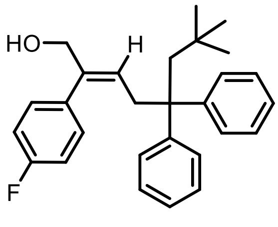
(*Z*)-7,7-dimethyl-2,5,5-triphenyloct-2-en-1-ol (2.4a)



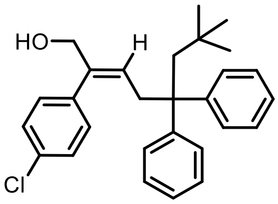
Yellowish oil (Method A, 27.3 mg, 71% yield, *E/Z* = 83:17); ***Z*-2.4a** was prepared according to the Method A with the following modifications: 4CzIPN (0.8 mg, 1 mol%) was used in place of $[Ir(dFCF_3ppy)_2(bpy)]PF_6$; **^{1}H NMR** (400 MHz, $CDCl_3$) **(major *Z*-isomer)** δ 7.30 – 7.15 (m, 15H), 5.87 (t, *J* = 7.6 Hz, 1H), 4.16 (s, 2H), 3.26 (d, *J* = 7.6 Hz, 2H), 2.38 (s, 2H), 0.78 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) **(major *Z*-isomer)** δ 149.2, 141.6, 140.9, 128.7, 128.5, 128.2, 127.8, 127.2, 126.5, 126.0, 59.7, 50.9, 49.8, 37.8, 32.5, 31.9; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd for. $C_{28}H_{32}NaO^+$ 407.2345; found 407.2358.

(*E*)-2-(4-fluorophenyl)-7,7-dimethyl-5,5-diphenyloct-2-en-1-ol (2.4b)

Yellowish oil (Method A, 26.6 mg, 66% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.24 – 7.18 (m, 4H), 7.17 – 7.10 (m, 6H), 7.04 – 6.97 (m, 2H), 6.94 – 6.88 (m, 2H), 5.56 (t, *J* = 6.8 Hz, 1H), 4.11 (d, *J* = 5.1 Hz, 2H), 2.98 (d, *J* = 6.9 Hz, 2H), 2.21 (s, 2H), 0.58 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.1 (d, *J* = 245.7 Hz), 149.1, 141.1, 134.5 (d, *J* = 3.3 Hz), 130.4 (d, *J* = 7.9 Hz), 128.7, 127.7, 126.3, 125.8, 115.2 (d, *J* = 21.2 Hz), 68.5, 50.14, 50.09, 37.9, 32.3, 31.8; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -114.92; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd for. $C_{28}H_{31}FNaO^+$ 425.2251; found 425.2261.

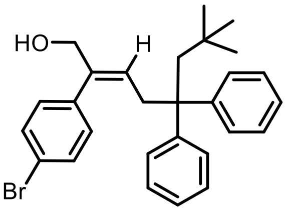


(*E*)-2-(4-chlorophenyl)-7,7-dimethyl-5,5-diphenyloct-2-en-1-ol (2.4c)



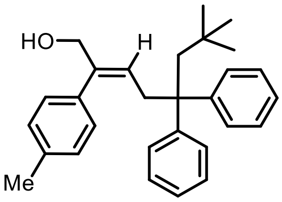
Yellowish oil (Method A, 28.5 mg, 68% yield); **2.4c** was prepared according to the Method A with the following modifications: Ligand bipyridine(1.6 mg, 10 mol%) was used in place of 4,4'-diCF$_3$bpy; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.30 – 7.26 (m, 3H), 7.24 – 7.16 (m, 4H), 7.15 – 7.09 (m, 5H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.58 (t, *J* = 6.8 Hz, 1H), 4.11 (s, 2H), 2.98 (d, *J* = 6.9 Hz, 2H), 2.21 (s, 2H), 0.59 (s, 9H); **^{13}C NMR** (101 MHz, CDCl$_3$) δ 149.1, 141.0, 137.1, 133.1, 130.2, 128.6, 128.5, 127.7, 126.6, 125.8, 68.3, 50.2, 50.9, 37.9, 32.3, 31.8; **HRMS** (ESI/TOF) *m/z*: [M + Na]$^+$ Calcd. for $C_{28}H_{31}ClNaO^+$ 441.1956; found 441.1954.

(*E*)-2-(4-bromophenyl)-7,7-dimethyl-5,5-diphenyloct-2-en-1-ol (2.4d)



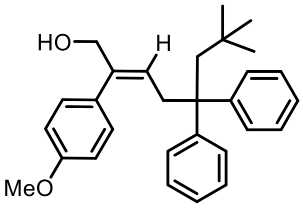
Yellowish oil (Method A, 23.2 mg, 50% yield); **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.49 – 7.40 (m, 2H), 7.24 – 7.18 (m, 4H), 7.17 – 7.10 (m, 6H), 6.86 – 6.77 (m, 2H), 5.59 (t, *J* = 6.8 Hz, 1H), 4.11 (s, 2H), 2.98 (d, *J* = 6.8 Hz, 2H), 2.21 (s, 2H), 0.59 (s, 9H); **^{13}C NMR** (101 MHz, CDCl$_3$) δ 149.0, 141.0, 137.6, 131.4, 130.5, 128.6, 127.7, 126.6, 125.9, 121.3, 68.3, 50.2, 50.1, 38.0, 32.3, 31.8; **HRMS** (ESI/TOF) *m/z*: [M + Na]$^+$ Calcd. for $C_{28}H_{31}BrNaO^+$ 485.1450; found 485.1439.

(*E*)-7,7-dimethyl-5,5-diphenyl-2-(*p*-tolyl)oct-2-en-1-ol (2.4e)



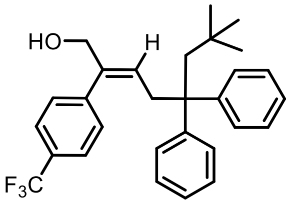
Yellowish oil (Method A, 32.3 mg, 81% yield); **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.24 – 7.17 (m, 4H), 7.17 – 7.11 (m, 8H), 6.95 – 6.83 (m, 2H), 5.49 (t, *J* = 6.7 Hz, 1H), 4.14 (s, 2H), 3.04 (d, *J* = 6.7 Hz, 2H), 2.36 (s, 3H), 2.22 (s, 2H), 0.58 (s, 9H); **^{13}C NMR** (101 MHz, CDCl$_3$) δ 149.3, 141.8, 136.9, 135.6, 129.1, 128.7, 127.7, 125.7, 125.5, 68.5, 50.10, 50.08, 37.9, 32.3, 31.8, 21.4; **HRMS** (ESI/TOF) *m/z*: [M + Na]$^+$ Calcd. for $C_{29}H_{34}NaO^+$ 421.2502; found 421.2505.

(*E*)-2-(4-methoxyphenyl)-7,7-dimethyl-5,5-diphenyloct-2-en-1-ol (2.4f)



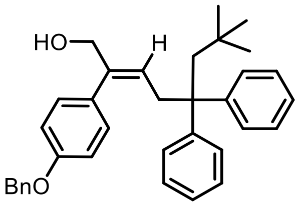
Yellowish oil (Method A, 19.1 mg, 46% yield); ^{1}**H NMR** (400 MHz, CDCl$_3$) δ 7.24 – 7.17 (m, 4H), 7.17 – 7.10 (m, 6H), 6.97 – 6.84 (m, 4H), 5.48 (t, *J* = 6.7 Hz, 1H), 4.13 (s, 2H), 3.83 (s, 3H), 3.03 (d, *J* = 6.7 Hz, 2H), 2.21 (s, 2H), 0.57 (s, 9H); ^{13}**C NMR** (101 MHz, CDCl$_3$) δ 158.8, 149.3, 141.5, 130.8, 130.0, 128.7, 127.7, 125.7, 125.5, 113.7, 68.6, 55.4, 50.10, 50.08, 37.9, 32.3, 31.8; **HRMS** (ESI/TOF) *m/z*: [M + Na]$^+$ Calcd. for $C_{29}H_{34}NaO_2^+$ 437.2451; found 437.2442.

(*E*)-7,7-dimethyl-5,5-diphenyl-2-(4-(trifluoromethyl)phenyl)oct-2-en-1-ol (2.4g)



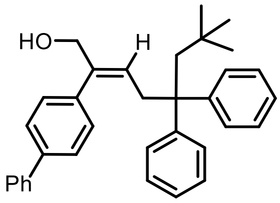
Yellowish oil (Method A, 22.7 mg, 50% yield); ^{1}**H NMR** (400 MHz, CDCl$_3$) δ 7.57 – 7.52 (m, 2H), 7.24 – 7.19 (m, 4H), 7.19 – 7.15 (m, 2H), 7.13 – 7.09 (m, 4H), 7.05 – 6.99 (m, 2H), 5.66 (t, *J* = 7.0 Hz, 1H), 4.14 (d, *J* = 4.7 Hz, 2H), 2.98 (d, *J* = 6.9 Hz, 2H), 2.22 (s, 2H), 0.59 (s, 9H); ^{13}**C NMR** (101 MHz, CDCl$_3$) 149.0, 142.5, 141.0, 129.3 (q, *J* = 32.3 Hz), 129.1, 128.6, 127.7, 127.1, 125.9, 125.2 (q, *J* = 3.8 Hz), 124.3 (q, *J* = 271.9 Hz), 68.1, 50.2, 50.0, 37.9, 32.3, 31.7; ^{19}**F NMR** (376 MHz, CDCl$_3$) δ -62.6; **HRMS** (ESI/TOF) *m/z*: [M + Na]$^+$ Calcd. for $C_{29}H_{31}F_3NaO^+$ 475.2219; found 475.2240.

(*E*)-2-(4-(benzyloxy)phenyl)-7,7-dimethyl-5,5-diphenyloct-2-en-1-ol (2.4h)



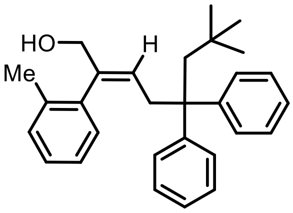
Yellowish solid (Method A, 28.5 mg, 58% yield); ^{1}**H NMR** (400 MHz, CDCl$_3$) 7.49 – 7.44 (m, 2H), 7.44 – 7.38 (m, 2H), 7.38 – 7.32 (m, 1H), 7.24 – 7.18 (m, 4H), 7.18 – 7.11 (m, 6H), 6.95 (s, 4H), 5.49 (t, *J* = 6.7 Hz, 1H), 5.09 (s, 2H), 4.14 (s, 2H), 3.04 (d, *J* = 6.7 Hz, 2H), 2.22 (s, 2H), 0.59 (s, 9H); ^{13}**C NMR** (101 MHz, CDCl$_3$) δ 158.0, 149.3, 141.5, 137.1, 131.1, 130.0, 128.72, 128.67, 128.1, 127.68, 127.65, 125.7, 125.5, 114.7, 70.2, 68.5, 50.10, 50.06, 37.9, 32.3, 31.8; **HRMS** (ESI/TOF) *m/z*: [M + Na]$^+$ Calcd. for $C_{35}H_{38}NaO_2^+$ 513.2764; found 513.2758.

(*E*)-2-([1,1'-biphenyl]-4-yl)-7,7-dimethyl-5,5-diphenyloct-2-en-1-ol (2.4i)



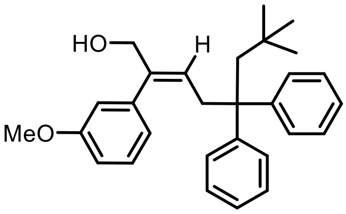
White solid (Method A, 32.3 mg, 70% yield, *E/Z* = 83:17); **^{1}H NMR** (400 MHz, CDCl$_3$) **(major *E*-isomer)** δ 7.65 – 7.63 (m, 2H), 7.59 – 7.56 (m, 2H), 7.49 – 7.44 (m, 2H), 7.39 – 7.33 (m, 1H), 7.30 – 7.28 (m, 1H), 7.25 – 7.19 (m, 4H), 7.19 – 7.15 (m, 5H), 7.08 (d, *J* = 8.1 Hz, 2H), 5.58 (t, *J* = 6.6 Hz, 1H), 4.20 (s, 2H), 3.09 (d, *J* = 6.7 Hz, 2H), 2.24 (s, 2H), 0.60 (s, 9H); **^{1}H NMR** (400 MHz, CDCl$_3$) **(minor *Z*-isomer, diagnostic peaks)** δ 5.94 (t, *J* = 7.6 Hz, 1H), 4.16 (s, 2H), 3.27 (d, *J* = 7.7 Hz, 2H), 2.38 (s, 2H), 0.77 (s, 9H); **^{13}C NMR** (101 MHz, CDCl$_3$) **(*E* + *Z*-isomer)** δ 149.3, 149.2, 141.6, 140.9, 140.5, 140.1, 140.0, 137.6, 129.2, 128.92, 128.88, 128.7, 128.3, 127.8, 127.7, 127.4, 127.34, 127.25, 127.2, 127.1, 127.0, 126.9, 126.2, 126.1, 125.8, 68.5, 59.6, 51.0, 50.2, 50.1, 49.8, 37.94, 37.87, 32.5, 32.3, 31.9, 31.8; **HRMS** (ESI/TOF) *m/z*: [M + Na]$^+$ Calcd. for $C_{34}H_{36}NaO^+$ 483.2658; found 483.2659.

(*E*)-7,7-dimethyl-5,5-diphenyl-2-(*o*-tolyl)oct-2-en-1-ol (2.4j)



Yellowish oil (Method A, 21.7 mg, 54% yield, *E/Z* = 70:30); **^{1}H NMR** (400 MHz, CDCl$_3$) **(major *E*-isomer)** δ 7.30 – 7.25 (m, 3H), 7.24 – 7.04 (m, 10H), 6.60 (d, *J* = 8.1 Hz, 1H), 5.60 (t, *J* = 6.7 Hz, 1H), 4.06-4.03 (m, 2H), 2.78 (d, *J* = 32.8 Hz, 2H), 2.23 (s, 2H), 2.11 (s, 3H), 0.60 (s, 9H); **^{1}H NMR** (400 MHz, CDCl$_3$) **(minor *Z*-isomer, diagnostic peaks)** δ 6.89 (d, *J* = 7.1 Hz, 1H), 5.60 (t, *J* = 6.7 Hz, 1H), 4.03 (s, 2H), 3.26 (d, *J* = 7.4 Hz, 2H), 2.31 (s, 2H), 2.07 (s, 3H), 0.73 (s, 9H); **^{13}C NMR** (101 MHz, CDCl$_3$) **(*E* + *Z*-isomer)** δ 149.5, 149.1, 141.9, 141.6, 141.5, 137.8, 136.1, 135.8, 130.2, 130.0, 129.5, 129.4, 128.7, 128.6, 127.8, 127.6, 127.4, 127.2, 126.0, 125.7, 125.62, 125.59, 124.9, 67.8, 61.0, 50.5, 50.4, 49.9, 49.5, 38.1, 37.3, 32.5, 32.3, 31.9, 31.8, 20.1, 19.5; **HRMS** (ESI/TOF) *m/z*: [M + Na]$^+$ Calcd. for $C_{29}H_{34}NaO^+$ 421.2502; found 421.2501.

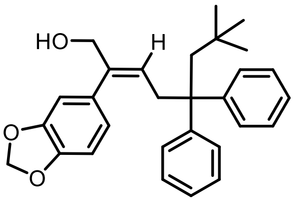
(*E*)-2-(3-methoxyphenyl)-7,7-dimethyl-5,5-diphenyloct-2-en-1-ol (2.4k)



Yellowish oil (Method A, 29.5 mg, 71% yield); **^{1}H NMR** (400 MHz, CDCl$_3$) 7.26 – 7.18 (m, 5H), 7.16 – 7.12 (m, 6H), 6.82 (dd, *J* = 8.3, 2.7 Hz, 1H), 6.64 – 6.52 (m, 2H), 5.51 (t, *J* = 6.8 Hz, 1H), 4.13 (d, *J* = 5.7 Hz, 2H), 3.81 (s, 3H), 3.03

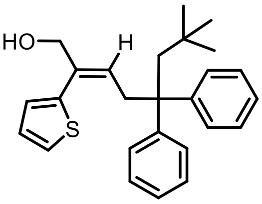
(d, *J* = 6.7 Hz, 2H), 2.21 (s, 2H), 0.58 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.5, 149.2, 141.8, 140.1, 129.3, 128.7, 127.7, 125.9, 125.8, 121.3, 114.4, 112.8, 68.4, 55.4, 50.2, 50.1, 37.9, 32.3, 31.8; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{29}H_{34}NaO_2^+$ 437.2451; found 437.2450.

(*E*)-2-(benzo[*d*][1,3]dioxol-5-yl)-7,7-dimethyl-5,5-diphenyloct-2-en-1-ol (2.4l)



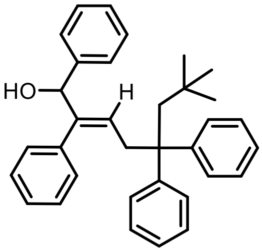
Yellowish oil (Method A, 24.9 mg, 58% yield, *E/Z* = 93:7); **^{1}H NMR** (400 MHz, $CDCl_3$) **(major *E*-isomer)** δ 7.26 (d, *J* = 2.5 Hz, 1H), 7.24 – 7.18 (m, 4H), 7.17 – 7.13 (m, 5H), 6.77 (d, *J* = 7.9 Hz, 1H), 6.48 – 6.41 (m, 2H), 5.96 (s, 2H), 5.50 (t, *J* = 6.8 Hz, 1H), 4.09 (s, 2H), 3.02 (d, *J* = 6.6 Hz, 2H), 2.22 (s, 2H), 0.60 (s, 9H); **^{1}H NMR** (400 MHz, $CDCl_3$) **(minor *Z*-isomer, diagnostic peaks)** δ 5.92 (s, 2H), 5.75 (t, *J* = 7.6 Hz, 1H), 3.19 (d, *J* = 7.7 Hz, 2H), 0.74 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) **(major *E*-isomer)** δ 149.2, 147.5, 146.7, 141.6, 132.3, 128.7, 127.7, 125.82, 125.77, 122.2, 109.2, 108.2, 101.1, 68.6, 50.1, 50.0, 37.9, 32.3, 31.8; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{29}H_{32}NaO_3^+$ 451.2244; found 451.2247.

(*Z*)-7,7-dimethyl-5,5-diphenyl-2-(thiophen-2-yl)oct-2-en-1-ol (2.4m)



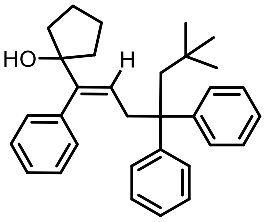
Yellowish oil (Method A, 17.6 mg, 45% yield, *Z/E* = 67:33); **2.4m** was prepared according to the Method A with the following modifications: Ligand bipyridine(1.6 mg, 10 mol%) was used in place of 4,4'-diCF$_3$bpy; **^{1}H NMR** (400 MHz, $CDCl_3$) **(major *E*-isomer)** δ 7.34 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.24 – 7.16 (m, 9H), 7.09 – 7.06 (m, 1H), 7.04 – 7.01 (m, 1H), 6.96 – 6.92 (m, 1H), 5.54 (t, *J* = 6.3 Hz, 1H), 4.23 (d, *J* = 4.9 Hz, 2H), 3.34 (d, *J* = 6.3 Hz, 2H), 2.26 (s, 2H), 0.62 (s, 9H); **^{1}H NMR** (400 MHz, $CDCl_3$) **(minor *E*-isomer, diagnostic peaks)** δ 6.04 (t, *J* = 7.8 Hz, 1H), 4.07 (d, *J* = 6.1 Hz, 2H), 3.21 (d, *J* = 7.8 Hz, 2H), 2.33 (s, 2H), 0.75 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) **(*E* + *Z*-isomer)** δ 149.2, 149.1, 145.2, 140.1, 134.8, 133.9, 128.7, 128.6, 128.2, 127.9, 127.8, 127.5, 127.2, 127.0, 126.4, 126.1, 125.9, 125.4, 123.7, 123.4, 68.8, 59.8, 51.0, 50.5, 50.0, 49.6, 38.3, 37.7, 32.5, 32.3, 31.9, 31.8; **HRMS** (APCI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{26}H_{31}OS^+$ 391.2090; found 391.2099.

(*E*)-7,7-dimethyl-1,2,5,5-tetraphenyloct-2-en-1-ol (2.4n)



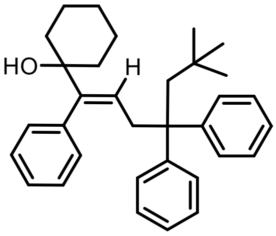
Yellowish oil (Method A, 34.7 mg, 75% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.24 – 7.16 (m, 12H), 7.15 – 7.11 (m, 4H), 7.06 – 7.00 (m, 2H), 6.67 – 6.62 (m, 2H), 5.71 (t, *J* = 7.3 Hz, 1H), 5.26 (s, 1H), 2.95 (d, *J* = 7.2 Hz, 2H), 2.26 (s, 2H), 0.62 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.3, 144.5, 142.0, 137.8, 129.5, 128.7, 128.1, 127.9, 127.7, 127.3, 127.1, 126.7, 126.3, 125.7, 78.7, 50.2, 50.1, 37.8, 32.3, 31.8; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{34}H_{36}NaO^+$ 483.2658; found 483.2647.

(*E*)-1-(6,6-dimethyl-1,4,4-triphenylhept-1-en-1-yl)cyclopentan-1-ol (2.4o)



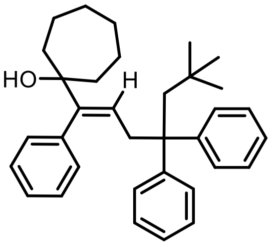
Yellowish oil (Method A, 33.7 mg, 77% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.26 – 7.18 (m, 7H), 7.18 – 7.13 (m, 2H), 7.14 – 7.08 (m, 4H), 6.77 – 6.69 (m, 2H), 5.76 (t, *J* = 6.8 Hz, 1H), 2.72 (d, *J* = 6.8 Hz, 2H), 2.24 (s, 2H), 1.79 – 1.69 (m, 2H), 1.60 – 1.51 (m, 4H), 1.48 – 1.42 (m, 2H), 0.62 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.1, 147.2, 139.4, 129.8, 128.9, 127.8, 127.6, 126.7, 125.7, 123.3, 84.5, 50.6, 50.4, 38.7, 38.3, 32.4, 31.9, 23.0; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{32}H_{38}NaO^+$ 461.2815; found 461.2817.

(*E*)-1-(6,6-dimethyl-1,4,4-triphenylhept-1-en-1-yl)cyclohexan-1-ol (2.4p)



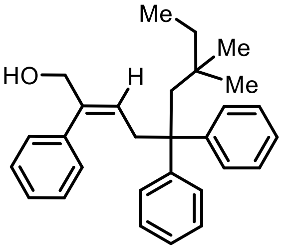
Yellowish solid (Method A, 36.5 mg, 81% yield); **2.4p** was prepared according to the Method A with the following modifications: the reaction time prolong to 48 h; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29 – 7.24 (m, 4H), 7.24 – 7.21 (m, 3H), 7.20 – 7.17 (m, 2H), 7.15 – 7.11 (m, 4H), 6.76 – 6.64 (m, 2H), 5.81 (t, *J* = 6.7 Hz, 1H), 2.69 (d, *J* = 6.7 Hz, 2H), 2.27 (s, 2H), 1.64 – 1.49 (m, 4H), 1.45 – 1.37 (m, 6H), 0.65 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.4, 149.2, 139.0, 130.0, 128.9, 127.7, 127.5, 126.6, 125.7, 122.9, 73.7, 50.6, 50.3, 38.4, 36.7, 32.4, 31.9, 25.6, 22.2; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{33}H_{40}NaO^+$ 475.2971; found 475.2974.

(*E*)-1-(6,6-dimethyl-1,4,4-triphenylhept-1-en-1-yl)cycloheptan-1-ol (2.4q)



Yellowish oil (Method A, 34.9 mg, 75% yield); **2.4q** was prepared according to the Method A with the following modifications: the reaction time prolong to 48 h; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.26 – 7.18 (m, 7H), 7.17 – 7.13 (m, 2H), 7.13 – 7.08 (m, 4H), 6.73 – 6.67 (m, 2H), 5.73 (t, *J* = 6.7 Hz, 1H), 2.65 (d, *J* = 6.7 Hz, 2H), 2.25 (s, 2H), 1.72 – 1.66 (m, 2H), 1.59 – 1.49 (m, 6H), 1.41 – 1.35 (m, 2H), 1.27 – 1.20 (m, 2H), 0.63 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.8, 149.2, 139.1, 130.1, 128.8, 127.8, 127.6, 126.7, 125.7, 122.2, 50.5, 50.3, 40.7, 38.3, 32.4, 31.9, 29.4, 22.4; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{34}H_{42}NaO^+$ 489.3128; found 489.3134.

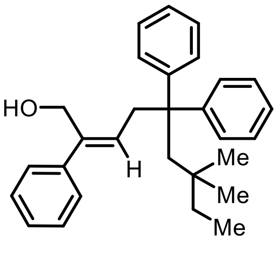
(*E*)-7,7-dimethyl-2,5,5-triphenylnon-2-en-1-ol (2.6a)



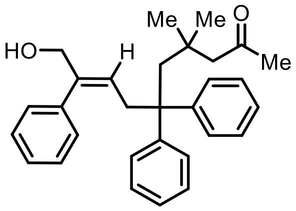
Yellowish oil (Method A, 22.7 mg, 57% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 – 7.30 (m, 2H), 7.30 – 7.26 (m, 1H), 7.24 – 7.18 (m, 4H), 7.17 – 7.11 (m, 6H), 7.04 – 6.95 (m, 2H), 5.51 (t, *J* = 6.7 Hz, 1H), 4.15 (d, *J* = 5.1 Hz, 2H), 3.02 (d, *J* = 6.6 Hz, 2H), 2.18 (s, 2H), 0.97 (q, *J* = 7.4 Hz, 2H), 0.70 (t, *J* = 7.4 Hz, 3H), 0.45 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.4, 141.9, 138.6, 128.8, 128.7, 128.3, 127.7, 127.3, 125.9, 125.8, 68.5, 50.0, 47.7, 38.1, 37.8, 34.7, 27.9, 8.6; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{29}H_{34}NaO^+$ 421.2502; found 421.2494.

(*Z*)-7,7-dimethyl-2,5,5-triphenylnon-2-en-1-ol (2.6a)

Yellowish oil (Method A, 19.1 mg, 48% yield, *Z/E* = 86:14); ***Z*-2.6a** was prepared according to the Method A with the following modifications: 4CzIPN (0.8 mg, 1 mol%) was used in place of $[Ir(dFCF_3ppy)_2(bpy)]PF_6$; **^{1}H NMR** (400 MHz, $CDCl_3$) **(major *Z*-isomer)** δ 7.28 – 7.12 (m, 15H), 5.85 (t, *J* = 7.6 Hz, 1H), 4.14 (d, *J* = 6.0 Hz, 2H), 3.24 (d, *J* = 7.6 Hz, 2H), 2.33 (s, 2H), 1.11 (q, *J* = 7.4 Hz, 2H), 0.78 (t, *J* = 7.4 Hz, 3H), 0.66 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) **(major *Z*-isomer)** δ 149.4, 141.6, 140.9, 128.7, 128.5, 128.3, 127.8, 127.2, 126.5, 126.0, 59.7, 50.8, 47.5, 38.1, 34.9, 28.0, 8.7; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{29}H_{34}NaO^+$ 421.2502; found 421.2511.

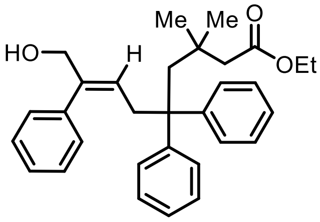


(*E*)-10-hydroxy-4,4-dimethyl-6,6,9-triphenyldec-8-en-2-one (2.6b)



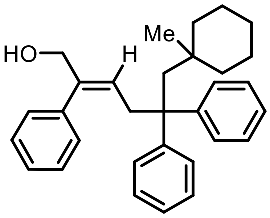
Yellowish oil (Method A, 17.5 mg, 41% yield); **2.6b** was prepared according to the Method A with the following modifications: DMA as the solvent in place of MeCN; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.36 – 7.30 (m, 2H), 7.29 – 7.26 (m, 1H), 7.24 – 7.18 (m, 4H), 7.17 – 7.11 (m, 6H), 7.07 – 7.03 (m, 2H), 5.51 (t, *J* = 6.7 Hz, 1H), 4.16 (s, 2H), 3.01 (d, *J* = 6.7 Hz, 2H), 2.43 (s, 2H), 1.85 (s, 3H), 1.83 (s, 2H), 0.66 (s, 6H); **^{13}C NMR** (101 MHz, CDCl$_3$) δ 209.0, 149.1, 142.1, 138.8, 128.8, 128.7, 128.3, 127.8, 127.3, 125.9, 125.8, 68.5, 55.4, 50.0, 46.4, 38.2, 34.9, 32.1, 29.2; **HRMS** (ESI/TOF) *m/z*: [M + Na]$^+$ Calcd. for $C_{30}H_{34}NaO_2^+$ 449.2451; found 449.2443.

Ethyl-(*E*)-9-hydroxy-3,3-dimethyl-5,5,8-triphenylnon-7-enoate (2.6c)



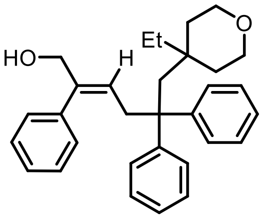
Yellowish oil (Method A, 23.2 mg, 51% yield); **2.6c** was prepared according to the Method A with the following modifications: DMA as the solvent in place of MeCN; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.46 – 7.40 (m, 2H), 7.40 – 7.35 (m, 2H), 7.35 – 7.30 (m, 4H), 7.29 – 7.26 (m, 2H), 7.26 – 7.23 (m, 3H), 7.19 – 7.12 (m, 2H), 5.63 (t, *J* = 6.7 Hz, 1H), 4.26 (s, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.14 (d, *J* = 6.6 Hz, 2H), 2.53 (s, 2H), 1.95 (s, 2H), 1.34 (t, *J* = 7.1 Hz, 3H), 0.73 (s, 6H); **^{13}C NMR** (101 MHz, CDCl$_3$) δ 172.5, 149.0, 142.1, 138.7, 128.8, 128.6, 128.3, 127.8, 127.3, 125.9, 125.7, 68.5, 60.0, 49.9, 48.8, 47.4, 38.0, 34.9, 28.6, 14.4; **HRMS** (ESI/TOF) *m/z*: [M + Na]$^+$ Calcd. for $C_{31}H_{36}NaO_3^+$ 479.2557; found 479.2561.

(*E*)-6-(1-methylcyclohexyl)-2,5,5-triphenylhex-2-en-1-ol (2.6d)



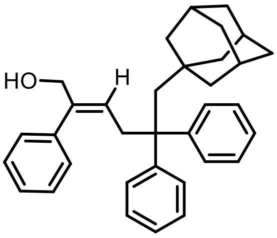
Yellowish oil (Method A, 28.5 mg, 67% yield); **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.37 – 7.31 (m, 2H), 7.30 – 7.26 (m, 1H), 7.23 – 7.17 (m, 4H), 7.17 – 7.12 (m, 6H), 7.04 – 7.00 (m, 2H), 5.52 (t, *J* = 6.7 Hz, 1H), 4.16 (s, 2H), 3.05 (d, *J* = 6.7 Hz, 2H), 2.21 (s, 2H), 1.37 – 1.17 (m, 6H), 0.99 – 0.93 (m, 4H), 0.45 (s, 3H); **^{13}C NMR** (101 MHz, CDCl$_3$) δ 149.6, 141.9, 138.7, 128.8, 128.6, 128.3, 127.6, 127.2, 125.9, 125.7, 68.4, 50.3, 50.0, 40.1, 38.3, 34.8, 26.4, 24.2, 22.1; **HRMS** (ESI/TOF) *m/z*: [M + Na]$^+$ Calcd. for $C_{31}H_{36}NaO^+$ 447.2658; found 447.2667.

(*E*)-6-(4-ethyltetrahydro-2*H*-pyran-4-yl)-2,5,5-triphenylhex-2-en-1-ol (2.6e)



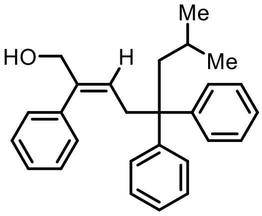
Yellowish oil (Method A, 22.9 mg, 52% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.31 (m, 2H), 7.31 – 7.27 (m, 1H), 7.24 – 7.18 (m, 4H), 7.18 – 7.12 (m, 6H), 7.06 – 7.02 (m, 2H), 5.50 (t, *J* = 6.6 Hz, 1H), 4.14 (s, 2H), 3.45 – 3.31 (m, 4H), 3.04 (d, *J* = 6.5 Hz, 2H), 2.21 (s, 2H), 1.25 – 1.17 (m, 2H), 1.09 (q, *J* = 7.4 Hz, 2H), 1.04 – 0.97 (m, 2H), 0.58 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.0, 142.1, 138.6, 128.8, 128.6, 128.3, 127.7, 127.4, 126.0, 125.6, 68.2, 63.5, 50.0, 45.3, 38.3, 36.3, 35.3, 26.3, 7.7; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{31}H_{36}NaO_2^+$ 463.2608; found 463.2614.

(*E*)-6-((3*r*,5*r*,7*r*)-adamantan-1-yl)-2,5,5-triphenylhex-2-en-1-ol (2.6f)



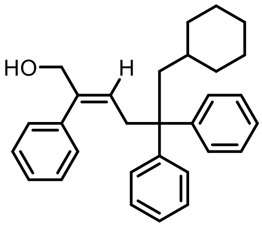
Yellowish oil (Method A, 32.4 mg, 70% yield); **2.6f** was prepared according to the Method A with the following modifications: Ligand 1,10-phenanthroline (1.8 mg, 10 mol%) was used in place of 4,4'-diCF_3bpy and a mixture of CH_3CN and DMF (1 mL + 0.5 mL) in place of CH_3CN (1 mL); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.31 (m, 2H), 7.29 – 7.26 (m, 1H), 7.23 – 7.18 (m, 4H), 7.16 – 7.10 (m, 6H), 7.04 – 6.98 (m, 2H), 5.50 (t, *J* = 6.8 Hz, 1H), 4.16 (s, 2H), 3.04 (d, *J* = 6.8 Hz, 2H), 2.05 (s, 2H), 1.68 – 1.64 (m, 3H), 1.53 – 1.47 (m, 3H), 1.41 – 1.35 (m, 3H), 1.15 (d, *J* = 2.9 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.7, 142.0, 138.7, 128.9, 128.5, 128.3, 127.6, 127.2, 125.9, 125.7, 68.4, 51.6, 49.6, 43.9, 38.2, 36.9, 34.6, 28.9; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{34}H_{38}NaO^+$ 485.2815; found 485.2819.

(*E*)-7-methyl-2,5,5-triphenyloct-2-en-1-ol (2.6g)



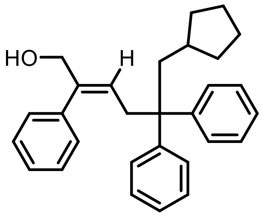
Yellowish oil (Method B, 24.4 mg, 66% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 2H), 7.31 – 7.27 (m, 1H), 7.25 – 7.20 (m, 4H), 7.18 – 7.14 (m, 2H), 7.14 – 7.09 (m, 4H), 7.04 – 6.99 (m, 2H), 5.47 (t, *J* = 6.9 Hz, 1H), 4.16 (s, 2H), 2.89 (d, *J* = 6.8 Hz, 2H), 2.01 (d, *J* = 5.1 Hz, 2H), 1.27 – 1.23 (m, 1H), 0.52 (d, *J* = 6.7 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.4, 142.3, 138.6, 128.8, 128.4, 128.3, 127.8, 127.3, 125.8, 125.3, 68.4, 50.2, 47.1, 37.3, 24.9, 24.1; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{27}H_{30}NaO^+$ 393.2189; found 393.2193.

(*E*)-6-cyclohexyl-2,5,5-triphenylhex-2-en-1-ol (2.6h)



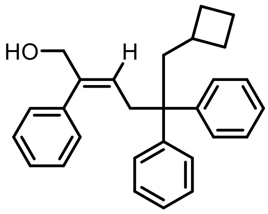
Yellowish oil (Method B, 23.8 mg, 58% yield); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.41 – 7.34 (m, 2H), 7.34 – 7.29 (m, 1H), 7.27 – 7.21 (m, 4H), 7.21 – 7.15 (m, 2H), 7.15 – 7.10 (m, 4H), 7.07 – 7.02 (m, 2H), 5.47 (t, *J* = 6.8 Hz, 1H), 4.18 (s, 2H), 2.91 (d, *J* = 6.9 Hz, 2H), 1.98 (d, *J* = 4.6 Hz, 2H), 1.50 – 1.40 (m, 3H), 1.32 – 1.25 (m, 1H), 1.05 – 0.87 (m, 5H), 0.79 – 0.68 (m, 2H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 148.6, 142.2, 138.6, 128.8, 128.33, 128.29, 127.8, 127.3, 125.8, 125.4, 68.4, 50.0, 45.6, 37.2, 35.3, 33.6, 26.5, 26.3; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{30}H_{34}NaO^+$ 433.2502; found 433.2505.

(*E*)-6-cyclopentyl-2,5,5-triphenylhex-2-en-1-ol (2.6i)



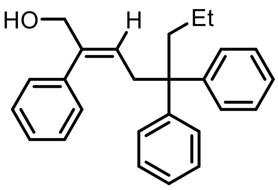
Yellowish oil (Method B, 16.2 mg, 41% yield); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.33 (m, 2H), 7.33 – 7.29 (m, 1H), 7.28 – 7.22 (m, 4H), 7.21 – 7.17 (m, 2H), 7.16 – 7.11 (m, 4H), 7.07 – 7.03 (m, 2H), 5.47 (t, *J* = 7.0 Hz, 1H), 4.18 (s, 2H), 2.92 (d, *J* = 6.8 Hz, 2H), 2.20 (d, *J* = 5.7 Hz, 2H), 1.46 – 1.40 (m, 2H), 1.38 – 1.31 (m, 2H), 1.24 – 1.18 (m, 3H), 0.81 – 0.71 (m, 2H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 148.6, 142.3, 138.7, 128.9, 128.4, 128.3, 127.8, 127.3, 125.8, 125.3, 68.4, 50.1, 44.8, 37.3, 36.4, 34.4, 24.8; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{29}H_{32}NaO^+$ 419.2345; found 419.2335.

(*E*)-6-cyclobutyl-2,5,5-triphenylhex-2-en-1-ol (2.6j)



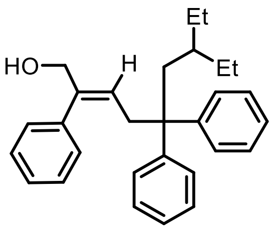
Yellowish oil (Method B, 18.0 mg, 47% yield); **2.6j** was prepared according to the Method B with the following modifications: a mixture of CH_3CN (1 mL) and 1,4-Dioxane (0.5 mL) in place of 1,4-Dioxane (1 mL); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.37 – 7.32 (m, 2H), 7.31 – 7.26 (m, 1H), 7.24 – 7.19 (m, 4H), 7.16 – 7.12 (m, 2H), 7.09 – 7.06 (m, 4H), 7.04 – 7.01 (m, 2H), 5.40 (t, *J* = 7.0 Hz, 1H), 4.15 (s, 2H), 2.81 (d, *J* = 7.0 Hz, 2H), 2.16 (d, *J* = 6.5 Hz, 2H), 1.88 – 1.81 (m, 1H), 1.54 – 1.47 (m, 2H), 1.46 – 1.39 (m, 2H), 1.32 – 1.26 (m, 2H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 148.3, 142.4, 138.7, 128.8, 128.4, 128.3, 127.8, 127.3, 125.8, 125.3, 68.4, 49.8, 45.8, 36.8, 32.6, 30.0, 19.2; **HRMS** (APCI/TOF) *m/z*: $[M - OH]^+$ Calcd. for $C_{28}H_{29}^+$ 365.2264; found 365.2263.

(*E*)-2,5,5-triphenyloct-2-en-1-ol (2.6k)



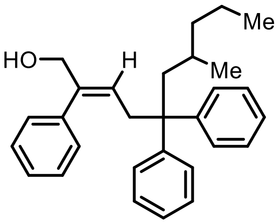
Yellowish oil (Method B, 11.1 mg, 31% yield); **2.6k** was prepared according to the Method B with the following modifications: 2,6-lutidine (1 equiv) in place of $CsCO_3$ and DMF (1 mL) in place of 1,4-Dioxane; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.31 (m, 2H), 7.30 – 7.27 (m, 1H), 7.25 – 7.20 (m, 4H), 7.18 – 7.12 (m, 2H), 7.12 – 7.08 (m, 4H), 7.06 – 7.02 (m, 2H), 5.39 (t, *J* = 7.1 Hz, 1H), 4.17 (d, *J* = 5.0 Hz, 2H), 2.82 (d, *J* = 7.1 Hz, 2H), 2.01 – 1.94 (m, 2H), 0.81 – 0.65 (m, 5H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.3, 142.6, 138.7, 128.8, 128.4, 128.1, 127.9, 127.3, 125.8, 125.1, 68.5, 49.9, 40.6, 36.6, 17.4, 14.8; **HRMS** (APCI/TOF) *m/z*: $[M - OH]^+$ Calcd. for $C_{26}H_{27}^+$ 339.2107; found 339.2104.

(*E*)-7-ethyl-2,5,5-triphenylnon-2-en-1-ol (2.6l)



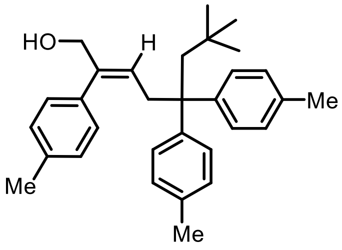
Yellowish oil (Method C, 15.9 mg, 40% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 – 7.32 (m, 2H), 7.31 – 7.27 (m, 1H), 7.24 – 7.18 (m, 4H), 7.18 – 7.13 (m, 2H), 7.13 – 7.08 (m, 4H), 7.06 – 7.01 (m, 2H), 5.49 (t, *J* = 6.7 Hz, 1H), 4.15 (s, 2H), 2.87 (d, *J* = 6.8 Hz, 2H), 1.98 (d, *J* = 4.5 Hz, 2H), 1.36 – 1.24 (m, 1H), 0.93 – 0.86 (m, 4H), 0.55 (t, *J* = 7.3 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.6, 142.1, 138.6, 128.8, 128.5, 128.3, 127.8, 127.3, 125.8, 125.6, 68.4, 50.3, 41.9, 36.8, 35.6, 26.4, 10.5; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{29}H_{34}NaO^+$ 421.2502; found 421.2505.

(*E*)-7-methyl-2,5,5-triphenyldec-2-en-1-ol (2.6m)



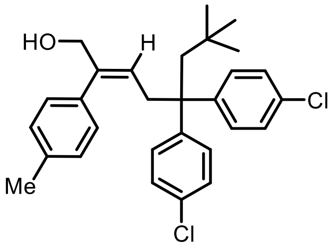
Yellowish oil (Method C, 22.3 mg, 56% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.26 (m, 3H), 7.25 – 7.18 (m, 4H), 7.18 – 7.13 (m, 2H), 7.13 – 7.05 (m, 4H), 7.05 – 6.99 (m, 2H), 5.47 (t, *J* = 6.8 Hz, 1H), 4.15 (s, 2H), 2.88 (d, *J* = 6.8 Hz, 2H), 2.10 – 2.02 (m, 1H), 1.98 – 1.87 (m, 1H), 1.17 – 1.05 (m, 2H), 1.00 – 0.91 (m, 1H), 0.87 – 0.82 (m, 2H), 0.65 (t, *J* = 7.2 Hz, 3H), 0.43 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.49, 148.47, 142.2, 138.6, 128.8, 128.5, 128.44, 128.35, 127.82, 127.81, 127.3, 125.8, 125.5, 68.4, 50.3, 45.8, 41.4, 37.2, 28.5, 21.5, 20.0, 14.3; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{29}H_{34}NaO^+$ 421.2502; found 421.2507.

(*E*)-7,7-dimethyl-2,5,5-tri-*p*-tolyloct-2-en-1-ol (2.7a)



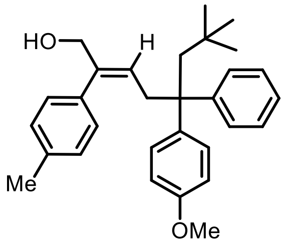
Yellowish solid (Method A, 30.3 mg, 71% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.14 (d, *J* = 7.8 Hz, 2H), 7.04 – 6.99 (m, 8H), 6.93 (d, *J* = 7.8 Hz, 2H), 5.48 (t, *J* = 6.9 Hz, 1H), 4.15 (d, *J* = 4.2 Hz, 2H), 2.99 (d, *J* = 6.8 Hz, 2H), 2.37 (s, 3H), 2.31 (s, 6H), 2.17 (s, 2H), 0.57 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.3, 141.5, 136.8, 135.7, 135.0, 129.0, 128.7, 128.5, 128.3, 125.9, 68.6, 50.2, 49.4, 38.0, 32.3, 31.8, 21.3, 21.0; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{31}H_{38}NaO^+$ 449.2815; found 449.2818.

(*E*)-5,5-bis(4-chlorophenyl)-7,7-dimethyl-2-(*p*-tolyl)oct-2-en-1-ol (2.7b)



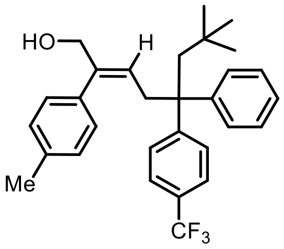
Yellowish oil (Method A, 38.8 mg, 83% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.19 – 7.12 (m, 6H), 7.05 – 6.99 (m, 4H), 6.86 (d, *J* = 8.2 Hz, 2H), 5.45 (t, *J* = 6.8 Hz, 1H), 4.14 (s, 2H), 2.97 (d, *J* = 6.8 Hz, 2H), 2.36 (s, 3H), 2.15 (s, 2H), 0.59 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.4, 142.6, 137.1, 135.2, 131.8, 129.9, 129.1, 128.5, 127.9, 123.8, 68.2, 49.9, 49.6, 37.6, 32.3, 31.8, 21.3; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{29}H_{32}Cl_2NaO^+$ 489.1722; found 489.1720.

(*E*)-5-(4-methoxyphenyl)-7,7-dimethyl-5-phenyl-2-(*p*-tolyl)oct-2-en-1-ol (2.7c)



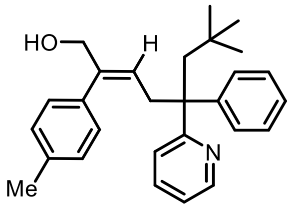
Yellowish oil (Method A, 20.3 mg, 47% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) 7.25 – 7.20 (m, 2H), 7.18 – 7.13 (m, 5H), 7.08 – 7.04 (m, 2H), 6.96 – 6.91 (m, 2H), 6.80 – 6.74 (m, 2H), 5.51 (t, *J* = 6.7 Hz, 1H), 4.16 (s, 2H), 3.81 (s, 3H), 3.02 (d, *J* = 6.7 Hz, 2H), 2.38 (s, 3H), 2.20 (s, 2H), 0.60 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.5, 149.5, 141.7, 141.3, 136.9, 135.6, 129.6, 129.0, 128.7, 128.6, 127.6, 125.7, 125.6, 113.0, 68.5, 55.3, 50.3, 49.5, 38.1, 32.3, 31.8, 21.4; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{30}H_{36}NaO_2^+$ 451.2608; found 451.2598.

(*E*)-7,7-dimethyl-5-phenyl-2-(*p*-tolyl)-5-(4-(trifluoromethyl)phenyl)oct-2-en-1-ol (2.7d)



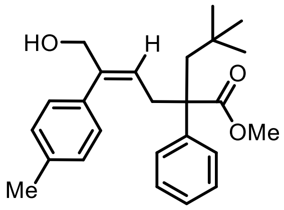
Yellowish oil (Method A, 34.1 mg, 73% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 – 7.40 (m, 2H), 7.25 – 7.16 (m, 5H), 7.14 – 7.08 (m, 4H), 6.86 – 6.77 (m, 2H), 5.49 (t, *J* = 6.8 Hz, 1H), 4.14 (s, 2H), 3.08 – 3.02 (m, 2H), 2.36 (s, 3H), 2.23 (d, *J* = 4.0 Hz, 2H), 0.60 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.7, 148.3, 142.5, 137.0, 135.2, 129.1, 128.9, 128.60, 128.57, 128.0 (q, *J* = 32.3 Hz), 127.9, 126.1, 124.53 (q, *J* = 3.7 Hz), 124.45 (q, *J* = 272.7 Hz), 124.1, 68.3, 50.4, 49.8, 37.6, 32.3, 31.8, 21.3; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.3; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{30}H_{33}F_3NaO^+$ 489.2376; found 489.2353.

(*E*)-7,7-dimethyl-5-phenyl-5-(pyridin-2-yl)-2-(*p*-tolyl)oct-2-en-1-ol (2.7e)



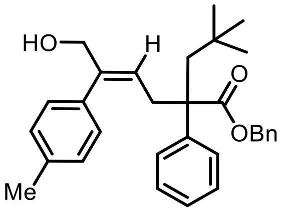
Yellowish oil (Method A, 26.1 mg, 65% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.56 – 8.50 (m, 1H), 7.48 – 7.41 (m, 1H), 7.24 – 7.17 (m, 2H), 7.17 – 7.08 (m, 5H), 7.08 – 7.03 (m, 1H), 7.00 – 6.91 (m, 1H), 6.90 – 6.82 (m, 2H), 5.54 (t, *J* = 6.9 Hz, 1H), 4.11 (s, 2H), 3.15 (d, *J* = 6.9 Hz, 2H), 2.41 – 2.30 (m, 5H), 0.60 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.7, 148.4, 148.0, 141.8, 136.7, 135.53, 135.46, 129.0, 128.7, 128.4, 127.8, 125.9, 125.4, 124.2, 121.0, 68.5, 52.9, 49.4, 37.2, 32.1, 31.7, 21.3; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{28}H_{34}NO^+$ 400.2635; found 400.2625.

Methyl-(*E*)-6-hydroxy-2-neopentyl-2-phenyl-5-(*p*-tolyl)hex-4-enoate (2.7f)



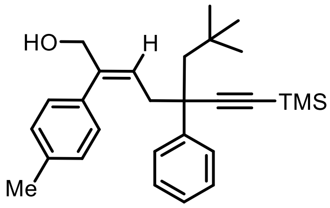
Yellowish oil (Method A, 12.2 mg, 32% yield); **7f** was prepared according to the Method A with the following modifications: 3 equiv of vinyl compound was used in place of 1.2 equivalent; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30 – 7.26 (m, 1H), 7.26 – 7.24 (m, 1H), 7.23 – 7.17 (m, 3H), 7.15 – 7.10 (m, 2H), 6.93 – 6.88 (m, 2H), 5.47 (t, *J* = 6.9 Hz, 1H), 4.15 (s, 2H), 3.60 (s, 3H), 2.98 – 2.79 (m, 2H), 2.35 (s, 3H), 2.10 (d, *J* = 1.5 Hz, 2H), 0.77 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.7, 143.3, 142.6, 137.0, 135.2, 129.1, 128.6, 128.2, 127.0, 126.7, 123.9, 68.3, 53.8, 51.8, 47.6, 36.2, 31.8, 31.2, 21.4; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{25}H_{32}NaO_3^+$ 403.2244; found 403.2232.

Benzyl-(*E*)-6-hydroxy-2-neopentyl-2-phenyl-5-(*p*-tolyl)hex-4-enoate (2.7g)



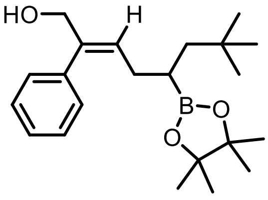
Yellowish oil (Method A, 22.8 mg, 50% yield); **2.7g** was prepared according to the Method A with the following modifications: 3.5 equiv of vinyl compound was used in place of 1.2 equivalent and the reaction time prolong to 48 h; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30 – 7.25 (m, 4H), 7.24 – 7.19 (m, 4H), 7.17 – 7.13 (m, 2H), 7.13 – 7.09 (m, 2H), 6.93 – 6.90 (m, 2H), 5.44 (t, *J* = 6.7 Hz, 1H), 5.13 – 4.97 (m, 2H), 4.12 (d, *J* = 6.1 Hz, 2H), 3.02 – 2.84 (m, 2H), 2.34 (s, 3H), 2.13 (d, *J* = 1.8 Hz, 2H), 0.74 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.9, 142.9, 142.5, 137.0, 135.9, 135.2, 129.1, 128.6, 128.5, 128.19, 128.15, 128.1, 127.2, 126.6, 123.8, 68.3, 66.5, 53.9, 47.7, 36.1, 31.8, 31.3, 21.3; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{31}H_{36}NaO_3^+$ 479.2557; found 479.2566.

(*E*)-7,7-dimethyl-5-phenyl-2-(*p*-tolyl)-5-((trimethylsilyl)ethynyl)oct-2-en-1-ol (2.7h)



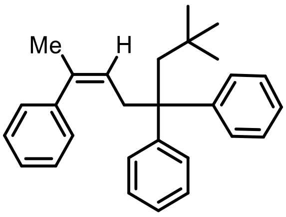
Yellowish oil (Method A, 16.7 mg, 40% yield); **2.7h** was prepared according to the Method A with the following modifications: 1.8 equiv of vinyl compound was used in place of 1.2 equivalent; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.43 – 7.39 (m, 2H), 7.26 – 7.23 (m, 2H), 7.20 – 7.14 (m, 3H), 7.02 – 6.99 (m, 2H), 5.62 (t, *J* = 7.0 Hz, 1H), 4.15 (d, *J* = 5.0 Hz, 2H), 2.60 – 2.45 (m, 2H), 2.37 (s, 3H), 1.89 – 1.72 (m, 2H), 0.72 (s, 9H), 0.24 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 143.3, 142.2, 136.8, 135.7, 129.1, 128.8, 128.0, 127.4, 126.3, 125.1, 110.8, 91.6, 68.5, 54.5, 45.2, 44.9, 32.4, 31.4, 21.4, 0.2; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{28}H_{38}NaOSi^+$ 441.2584; found 441.2587.

(*E*)-7,7-dimethyl-2-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oct-2-en-1-ol (2.7i)



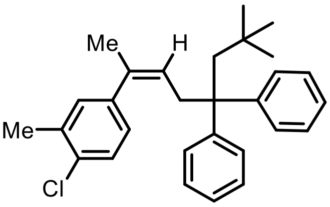
Yellowish oil (Method A, 11.1 mg, 31% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.31 (m, 2H), 7.29 – 7.26 (m, 1H), 7.25 – 7.20 (m, 2H), 5.74 (t, *J* = 7.2 Hz, 1H), 4.32 (s, 2H), 2.19 – 2.01 (m, 2H), 1.53 – 1.40 (m, 2H), 1.22 (d, *J* = 2.7 Hz, 12H), 1.10 – 1.03 (m, 2H), 0.83 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.5, 138.6, 129.1, 128.8, 128.4, 127.2, 83.2, 68.4, 45.7, 32.3, 31.1, 29.8, 25.0, 24.9; ^{11}B NMR (128 MHz, $CDCl_3$) δ 34.88; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{22}H_{35}BNaO_3^+$ 381.2571; found 381.2580.

(*Z*)-(7,7-dimethyloct-2-ene-2,5,5-triyl)tribenzene (2.8a)



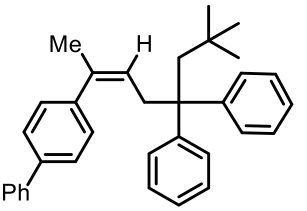
Yellowish oil (Method D, 28.4 mg, 77% yield); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.35 – 7.29 (m, 2H), 7.25 – 7.19 (m, 5H), 7.18 – 7.11 (m, 6H), 7.03 – 6.98 (m, 2H), 5.31 – 5.16 (m, 1H), 3.00 (d, *J* = 3.8 Hz, 2H), 2.21 (s, 2H), 1.91 (s, 3H), 0.55 (s, 9H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 149.6, 142.4, 137.8, 128.7, 128.2, 128.0, 127.6, 126.5, 125.6, 123.9, 50.1, 49.9, 38.4, 32.2, 31.7, 25.9; **HRMS** (APCI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{28}H_{33}^+$ 369.2577; found 369.2574.

(*Z*)-(7-(4-chloro-3-methylphenyl)-2,2-dimethyloct-6-ene-4,4-diyl)dibenzene (2.8b)



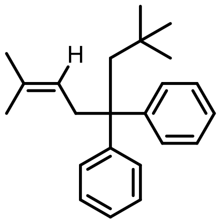
Yellowish oil (Method D, 33.8 mg, 81% yield); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.27 – 7.23 (m, 2H), 7.22 – 7.19 (m, 3H), 7.18 – 7.11 (m, 6H), 6.74 – 6.67 (m, 2H), 5.29 (t, *J* = 6.0 Hz, 1H), 2.94 (d, *J* = 6.8 Hz, 2H), 2.35 (s, 3H), 2.22 (s, 2H), 1.86 (d, *J* = 1.5 Hz, 3H), 0.59 (s, 9H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 149.4, 140.9, 137.0, 135.5, 132.4, 130.6, 128.8, 128.6, 127.6, 126.9, 125.6, 124.2, 50.2, 50.0, 38.5, 32.3, 31.8, 25.9, 20.2; **HRMS** (APCI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{29}H_{34}Cl^+$ 417.2344; found 417.2350.

(*Z*)-4-(7,7-dimethyl-5,5-diphenyloct-2-en-2-yl)-1,1'-biphenyl (2.8c)



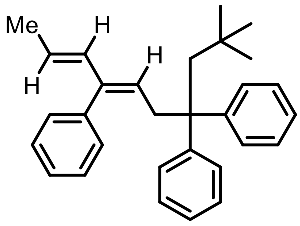
Yellowish oil (Method D, 26.7 mg, 60% yield); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.66 – 7.61 (m, 2H), 7.58 – 7.52 (m, 2H), 7.49 – 7.43 (m, 2H), 7.38 – 7.33 (m, 1H), 7.25 – 7.18 (m, 4H), 7.18 – 7.12 (m, 6H), 7.09 – 7.04 (m, 2H), 5.30 – 5.24 (m, 1H), 3.05 (d, *J* = 6.7 Hz, 2H), 2.22 (s, 2H), 1.94 (s, 3H), 0.56 (s, 9H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 149.6, 141.4, 141.1, 139.3, 137.4, 128.9, 128.7, 128.6, 127.6, 127.3, 127.1, 126.7, 125.6, 124.2, 50.2, 49.9, 38.4, 32.3, 31.7, 25.9; **HRMS** (APCI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{34}H_{37}^+$ 445.2890; found 445.2883.

(2,2,7-trimethyloct-6-ene-4,4-diyl)dibenzene (2.8d)



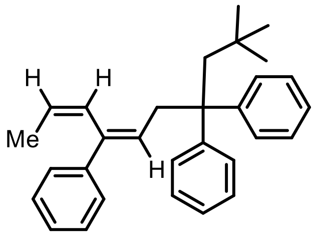
Yellowish oil (Method D, 12.3 mg, 40% yield); **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.21 (d, *J* = 4.2 Hz, 8H), 7.17 – 7.10 (m, 2H), 4.92 (t, *J* = 6.6 Hz, 1H), 2.95 (d, *J* = 6.7 Hz, 2H), 2.23 (s, 2H), 1.55 (s, 3H), 1.33 (s, 3H), 0.68 (s, 9H); **^{13}C NMR** (101 MHz, CDCl$_3$) δ 149.9, 133.4, 128.7, 127.5, 125.5, 120.7, 50.1, 49.6, 37.4, 32.4, 31.9, 26.1, 18.0; **HRMS** (APCI/TOF) *m/z*: [M + H]$^+$ Calcd. for $C_{23}H_{31}^+$ 307.2420; found 307.2408.

(6*Z*,8*E*)-2,2-Dimethyldeca-6,8-diene-4,4,7-triyl)tribenzene (2.8e)



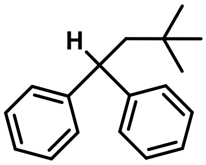
Yellowish oil (Method D, 7.1 mg, 18% yield); **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.33 – 7.28 (m, 2H), 7.18 (dd, *J* = 7.2, 1.3 Hz, 4H), 7.15 – 7.10 (m, 7H), 6.87 – 6.83 (m, 2H), 6.10 (d, *J* = 15.4 Hz, 1H), 5.35 (t, *J* = 6.8 Hz, 1H), 5.07 – 4.96 (m, 1H), 2.89 (d, *J* = 6.8 Hz, 2H), 2.20 (s, 2H), 1.62 (d, *J* = 6.7 Hz, 3H), 0.55 (s, 9H); **^{13}C NMR** (101 MHz, CDCl$_3$) 149.4, 142.4, 138.9, 135.8, 129.7, 128.7, 128.0, 127.6, 127.2, 126.7, 126.1, 125.7, 50.2, 50.1, 38.5, 32.3, 31.8, 18.2; **HRMS** (APCI/TOF) *m/z*: [M + H]$^+$ Calcd. for $C_{30}H_{35}^+$ 395.2733; found 395.2733.

(6*E*,8*Z*)-2,2-dimethyldeca-6,8-diene-4,4,7-triyl)tribenzene (2.8e´)



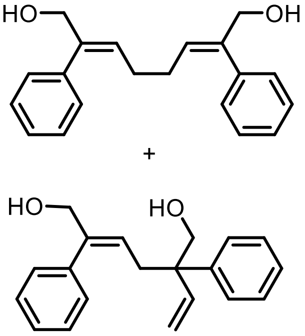
Yellowish oil (Method D, 7.1 mg, 18% yield); **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.25 – 7.20 (m, 10H), 7.16 – 7.10 (m, 3H), 7.07 – 7.01 (m, 2H), 6.26 (d, *J* = 15.5 Hz, 1H), 5.41 – 5.31 (m, 1H), 5.19 (t, *J* = 6.8 Hz, 1H), 3.27 (d, *J* = 6.9 Hz, 2H), 2.30 (s, 2H), 1.78 – 1.64 (m, 3H), 0.71 (s, 9H); **^{13}C NMR** (126 MHz, CDCl$_3$) δ 149.5, 143.1, 140.9, 129.7, 128.9, 128.7, 128.4, 127.9, 127.7, 126.7, 126.4, 125.7, 50.3, 50.0, 37.2, 32.4, 32.0, 18.7; **HRMS** (APCI/TOF) *m/z*: [M + H]$^+$ Calcd. for $C_{30}H_{35}^+$ 395.2733; found 395.2730.

(3,3-dimethylbutane-1,1-diyl)dibenzene (2.5a)[38]



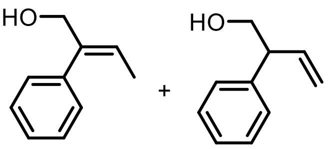
Yellowish oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 – 7.23 (m, 8H), 7.16 – 7.10 (m, 2H), 4.06 (t, *J* = 6.7 Hz, 1H), 2.10 (d, *J* = 6.6 Hz, 2H), 0.83 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.9, 128.5, 127.9, 126.0, 49.6, 48.6, 31.7, 30.4. ^{1}H NMR and ^{13}C NMR data are consistent with that reported in ref. 38.

(*2E,6E*)-2,7-diphenylocta-2,6-diene-1,8-diol and (*E*)-2,5-diphenyl-5-vinylhex-2-ene-1,6-diol (product 2.5b + 2.5c)



Yellowish oil (6.2 mg, 21% yield, **2.5b**/**2.5c** = 60:40); **^{1}H NMR** (400 MHz, $CDCl_3$) (major **2.5b**, *selected characteristic peaks*) δ 5.67 – 5.63 (m, 2H), 4.26 (s, 4H), 2.08 – 2.04 (m, 4H); **^{1}H NMR** (400 MHz, $CDCl_3$) (minor **2.5c**, *selected characteristic peaks*) δ 5.98 (dd, *J* = 17.8, 11.0 Hz, 1H), 5.62 – 5.58 (m, 1H), 5.32 (dd, *J* = 11.1, 1.1 Hz, 1H), 5.10 (dd, *J* = 17.8, 1.1 Hz, 1H), 4.19 (s, 2H), 3.77 (s, 2H), 2.58 (d, *J* = 7.1 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) **(2.5b+2.5c)** δ 142.7, 142.6, 142.1, 140.9, 138.6, 138.5, 128.7, 128.51, 128.48, 128.4, 128.0, 127.8, 127.4, 127.3, 126.7, 126.4, 124.0, 116.0, 68.1, 68.0, 67.8, 50.6, 34.3, 28.8; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{20}H_{22}NaO_2^+$ 317.1512; found 317.1509.

(*E*)-2-phenylbut-2-en-1-ol and 2-phenylbut-3-en-1-ol (products 2.5d + 2.5e)[39]



Yellowish oil (6.2 mg, 42% yield, **2.5d/2.5e** = 64:36); **^{1}H NMR** (400 MHz, $CDCl_3$) **(major 2.5d)** δ 7.41 – 7.26 (m, 3H), 7.25 – 7.22 (m, 2H), 5.88 – 5.80 (m, 1H), 4.34 (s, 2H), 1.65 (d, *J* = 6.9 Hz, 3H), 1.57 (s, 1H); **^{1}H NMR** (400 MHz, $CDCl_3$) **(minor 2.5e)** δ 7.41 – 7.26 (m, 3H), 7.25 – 7.22 (m, 2H), 6.07 – 5.96 (m, 1H), 5.28 – 5.14 (m, 2H), 3.87 – 3.80 (m, 2H), 3.54 (q, *J* = 7.3 Hz, 1H), 1.48 (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) **(2.5d+2.5e)** δ 141.1, 140.8, 138.4, 138.4, 128.9, 128.9, 128.5, 128.1, 127.2, 127.1, 123.6, 117.3, 68.3, 66.2, 52.7, 14.5. ^{1}H NMR and ^{13}C NMR data are consistent with that reported in ref. 39.

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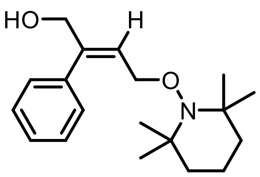
[38] S. Nii, J. Terao, N. Kambe, *J. Org. Chem.* **2004**, *69*, 573–576.

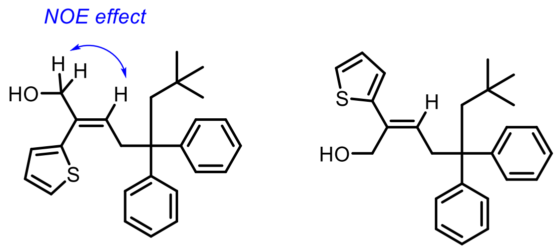
[39] a) C. C. Bausch, R. L. Patman, B. Breit, M. J. Krische, *Angew. Chem. Int. Ed.* **2011**, *50,* 5687 –5690; b) N. Selander, K. J. Szabó, *Chem. Commun.* **2008**, 3420–3422.

(*E*)-2-phenyl-4-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)but-2-en-1-ol (2.5f)



Yellowish oil (3.3 mg, 11% yield); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.36 – 7.32 (m, 2H), 7.31 – 7.27 (m, 1H), 7.23 – 7.20 (m, 2H), 5.93 (t, *J* = 6.9 Hz, 1H), 4.39 (s, 2H), 4.24 (d, *J* = 6.8 Hz, 2H), 1.44 – 1.34 (m, 4H), 1.30 – 1.26 (m, 2H), 1.09 (s, 6H), 1.05 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 143.4, 137.7, 128.6, 128.4, 127.7, 123.4, 74.4, 67.5, 59.8, 39.8, 33.0, 20.3, 17.3; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{19}H_{30}NO_2^+$ 304.2271; found 304.2275.

NOESY analysis of product 2.4m:



Major (*Z*)

Minor (*E*)

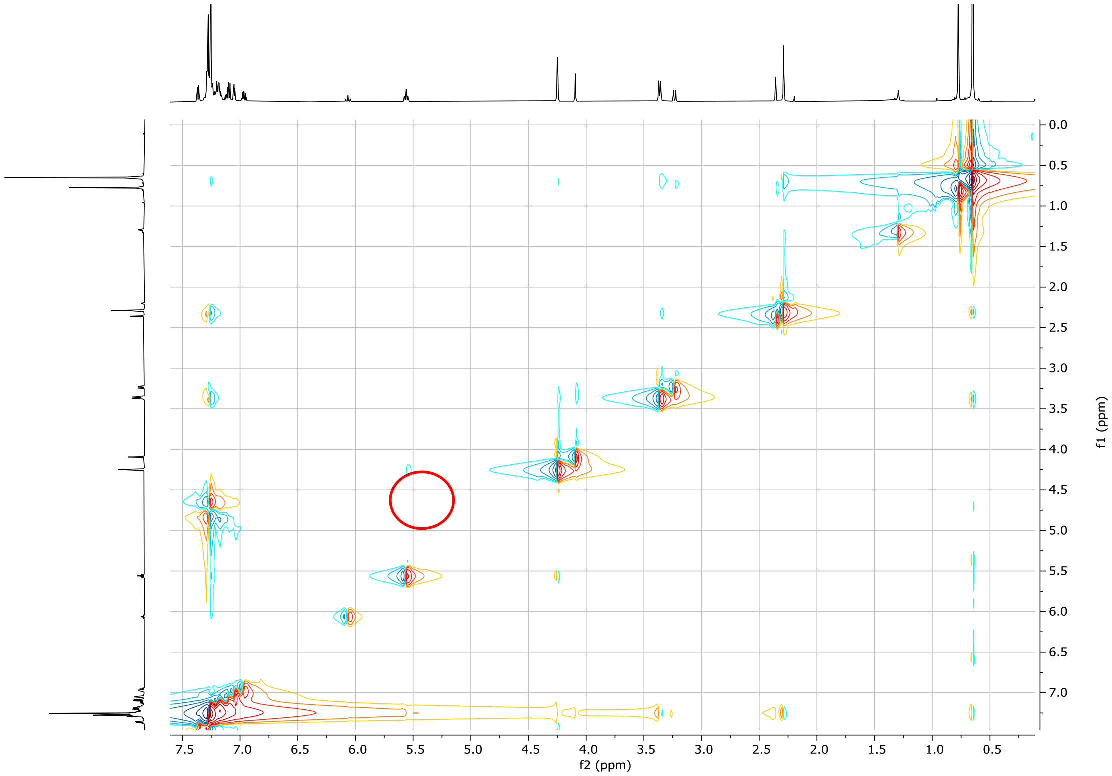
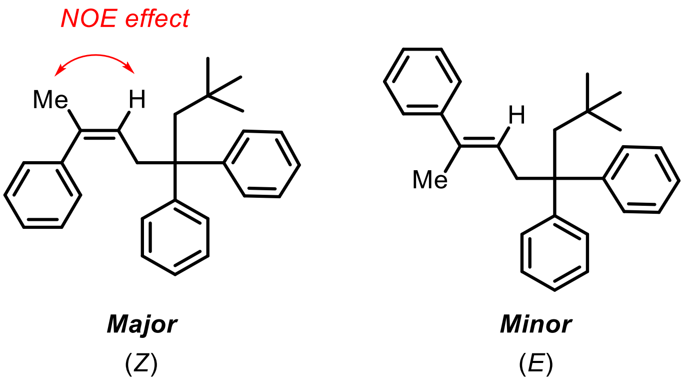


Figure 2.4. ^{1}H-^{1}H NOESY NMR spectra of product **2.4m**.

GOESY analysis of product 2.8a:



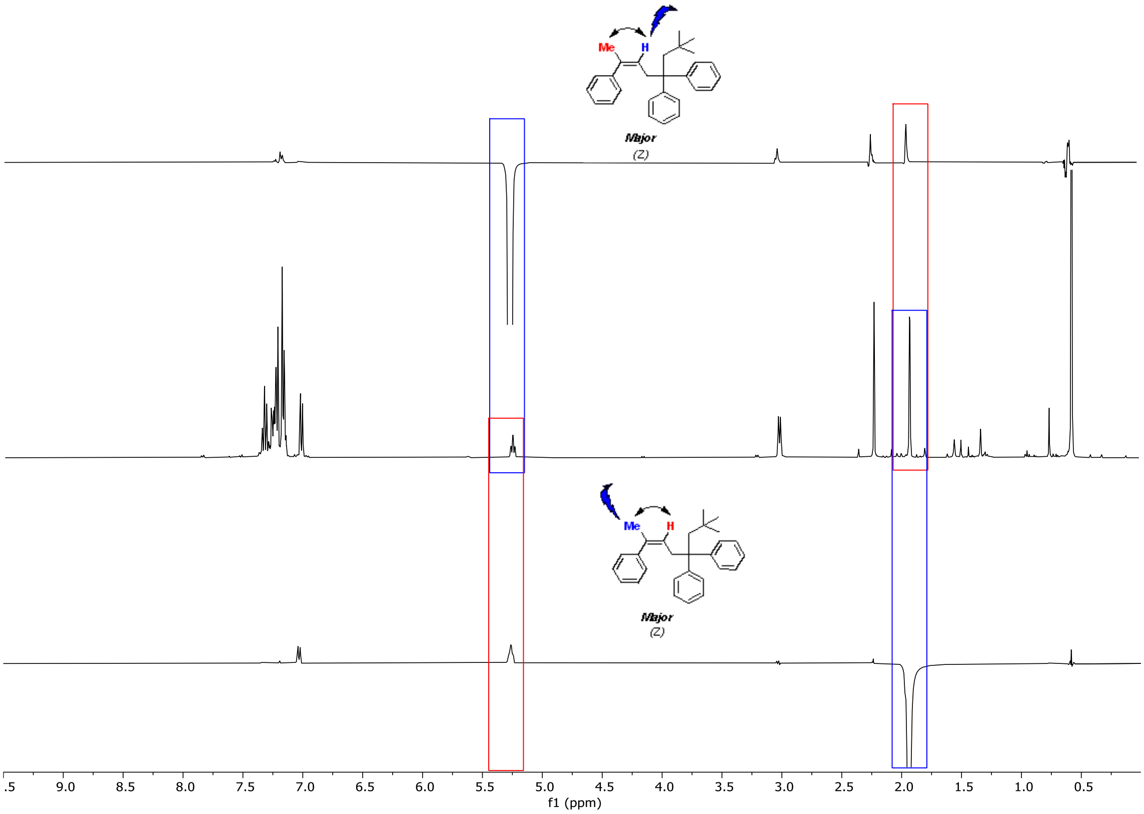
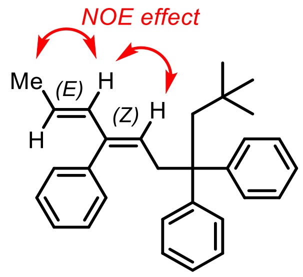


Figure 2.5. ^{1}H-^{1}H GOESY NMR spectra of product **2.8a**.

GOESY analysis of products 2.8e and 2.8e´:



((6*Z*,8*E*)-2,2-dimethyldeca-6,8-diene-4,4,7-triyl)tribenzene

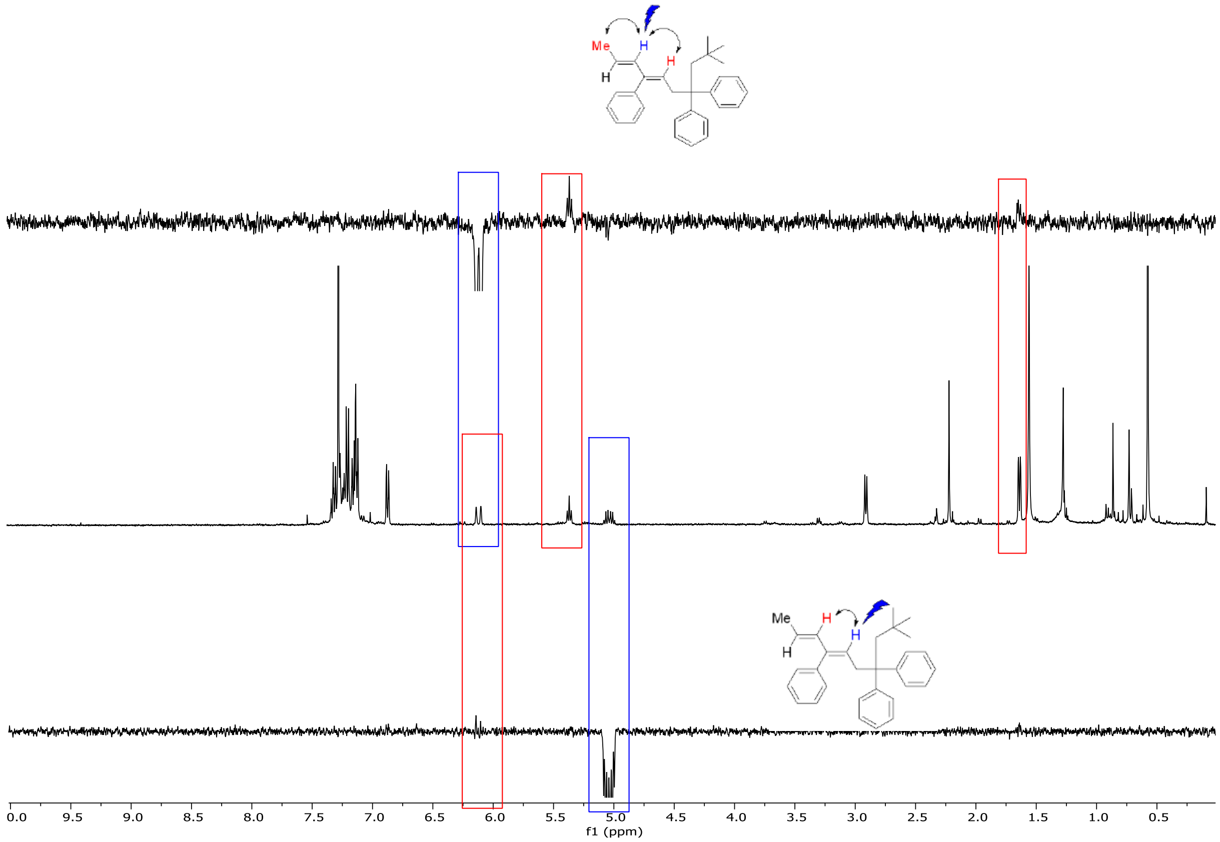
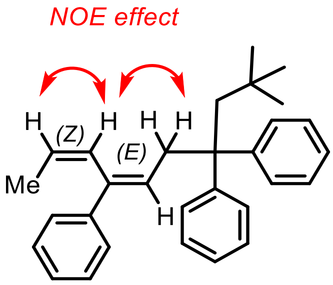


Figure 2.6. ^{1}H-^{1}H GOESY NMR spectra of product **2.8e**.



((6*E*,8*Z*)-2,2-dimethyldeca-6,8-diene-4,4,7-triyl)tribenzene

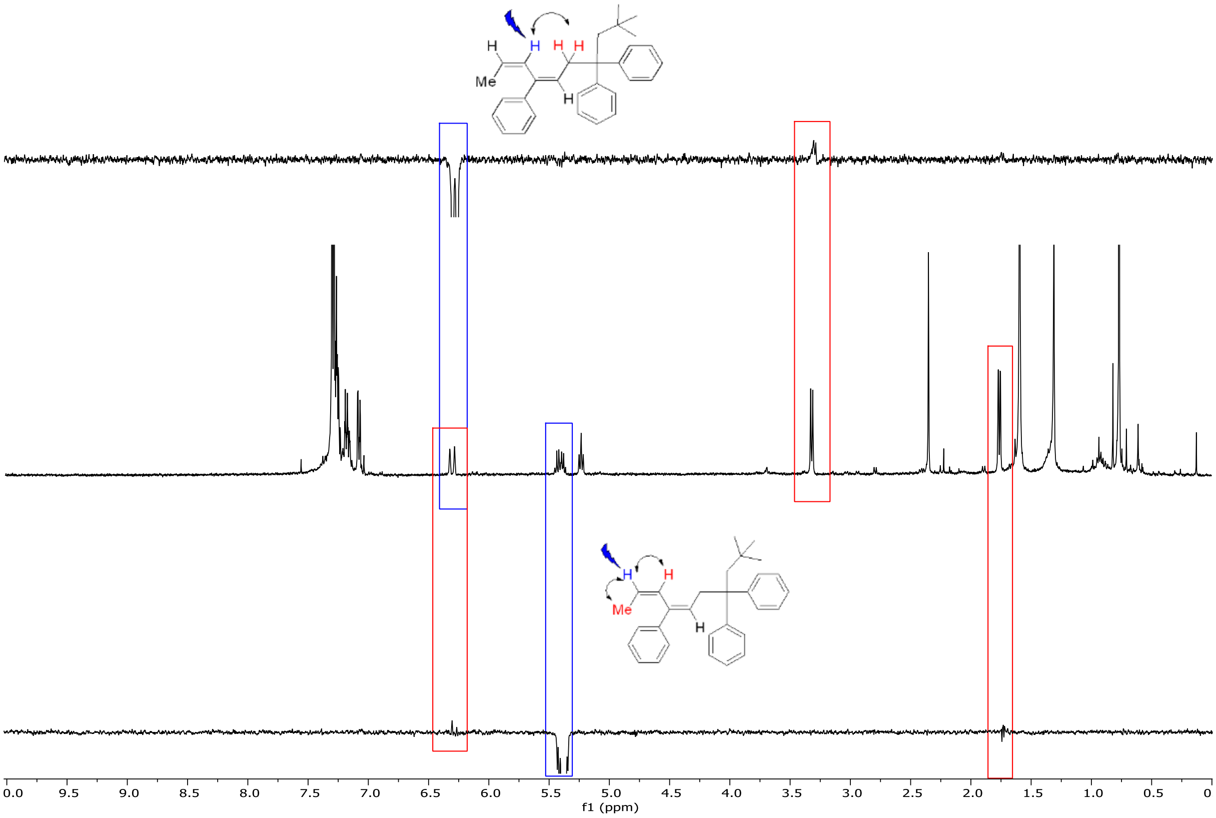
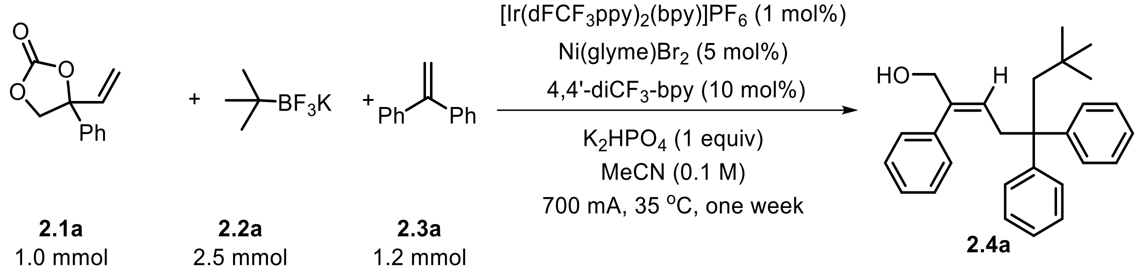


Figure 2.7. ^{1}H-^{1}H GOESY NMR spectra of product **2.8e’**.

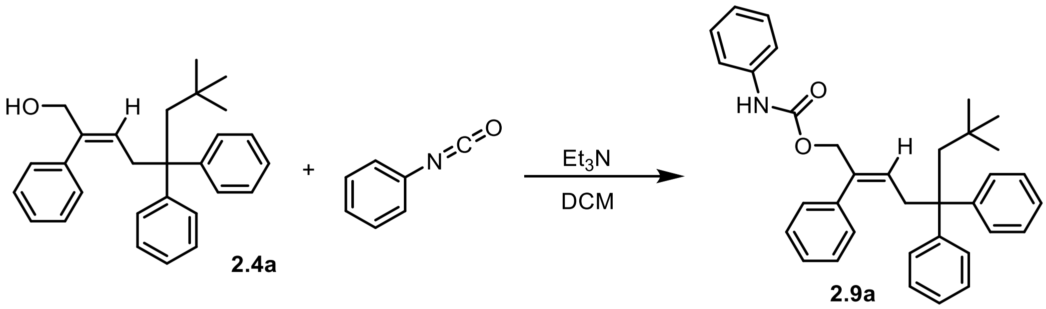
2.4.5. Scale up of the synthesis of 2.4a



The [Ir(dFCF$_3$ppy)$_2$(bpy)]PF$_6$ (10 mg, 1.0 mol%), 4,4'-diCF$_3$-bpy (29 mg, 10 mol%) and organotrifluoroborate **2.2a** (410 mg, 2.5 mmol, 2.5 equiv) were weighed in a 10 mL screw-cap vial. The vial moved to a nitrogen-filled glove-box and was charged with Ni(glyme)Br$_2$ (15 mg, 5.0 mol%), K_2HPO_4 (174 mg, 1.0 mmol, 1 equiv) and CH_3CN (10 mL, 0.10 M). The liquid **2.1a** (175 µL, 1.0 mmol, 1 equiv) and **2.3a** (218 µL, 1.2 mmol, 1.2 equiv) were added affording a light-yellow solution. The reaction system was capped, removed from the glove box and was irradiated for almost one week at 35 °C using a single high-power blue LED (λ_{em} = 445 nm, 700 mA) from the bottom. After completion, the mixture was evaporated to dryness and the residue was purified by column chromatography (SiO_2, hexanes/EtOAc= 15:1) to afford product **2.4a** (71%, 272 mg).

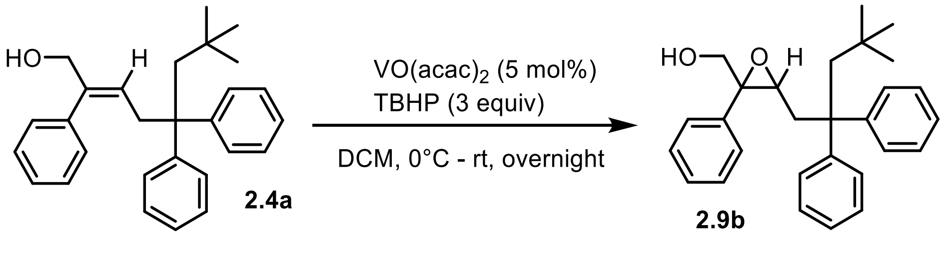
2.4.6. Post-synthetic transformations

(*E*)-7,7-dimethyl-2,5,5-triphenyloct-2-en-1-yl phenyl carbamate (2.9a)



To a solution of **2.4a** (0.1 mmol) in DCM (1 mL) was added phenyl isocyanate (13.1 µL, 0.12 mmol, 1.2 equiv) followed by Et$_3$N (27.7 µL, 0.2 mmol, 2 equiv) at room temperature. After stirring the mixture for 8 h, the solvent was removed under reduced pressure and the crude product was purified by flash chromatography on silica gel (hexanes/EtOAc= 30:1 to 15:1) to afford the pure product **2.9a** as a yellowish oil (46.8 mg, 93% yield); **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.40 – 7.27 (m, 7H), 7.24 – 7.19 (m, 4H), 7.18 – 7.12 (m, 6H), 7.10 – 7.05 (m, 3H), 6.53 (s, 1H), 5.63 (t, *J* = 7.0 Hz, 1H), 4.76 (s, 2H), 3.08 (d, *J* = 6.7 Hz, 2H), 2.21 (s, 2H), 0.57 (s, 9H); **^{13}C NMR** (101 MHz, CDCl$_3$) δ 153.3, 149.1, 138.2, 138.0, 137.2, 129.1, 128.80, 128.75, 128.6, 128.2, 127.7, 127.4, 125.8, 123.5, 118.7, 69.8, 50.0, 49.9, 38.0, 32.2, 31.7; **HRMS** (ESI/TOF) *m/z*: [M + Na]$^+$ Calcd. for $C_{35}H_{37}NNaO_2^+$ 526.2717; found 526.2735.

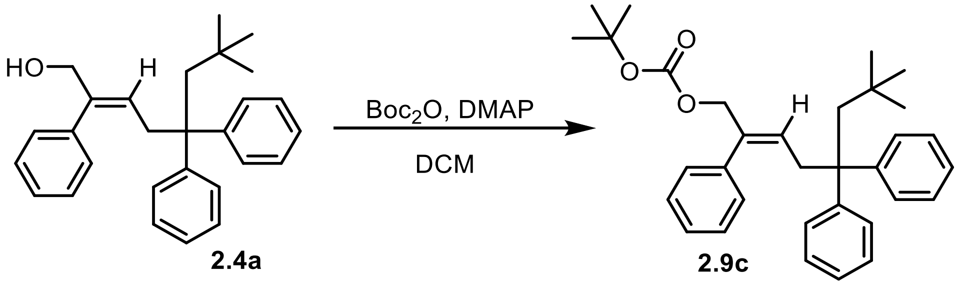
(3-(4,4-dimethyl-2,2-diphenylpentyl)-2-phenyloxiran-2-yl)methanol (2.9b)



To a cooled (0 °C) solution of **2.4a** (0.1 mmol) and VO(acac)$_2$ (1.3 mg, 0.005 mmol, 5 mol%) in DCM was added TBHP (*tert*-butyl hydroperoxide solution, 5.5 µL of a 5.0-6.0 M solution in decane). After stirring the mixture at 0 °C to room temperature for an additional 5 h, the solvent was removed under reduced pressure and the crude product was purified by flash chromatography on silica gel (hexanes/EtOAc= 20:1 to 10:1) to afford the pure product **2.9b** as a yellowish oil (20.4 mg, 51% yield); **^{1}H NMR** (400 MHz,

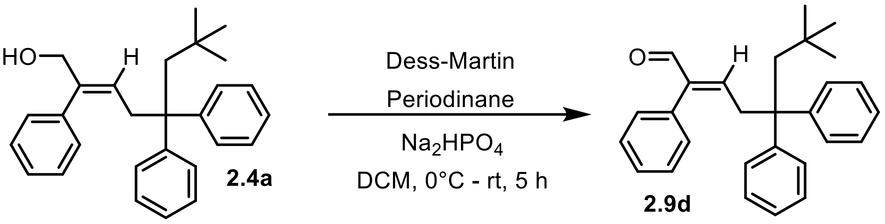
$CDCl_3$) δ 7.35 – 7.28 (m, 3H), 7.25 – 7.13 (m, 8H), 7.07 – 7.01 (m, 4H), 3.77 – 3.59 (m, 2H), 3.21 (t, *J* = 5.1 Hz, 1H), 2.46 – 2.37 (m, 2H), 2.17 (d, *J* = 14.3 Hz, 1H), 1.94 (dd, *J* = 14.7, 4.9 Hz, 1H), 0.62 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.9, 148.7, 135.7, 128.6, 128.3, 127.99, 127.96, 127.7, 127.0, 126.0, 65.4, 64.7, 59.0, 51.0, 49.2, 37.5, 32.4, 31.8; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{28}H_{32}NaO_2^+$ 423.2295; found 423.2301.

(*E*)-*tert*-butyl (7,7-dimethyl-2,5,5-triphenyloct-2-en-1-yl) carbonate (2.9c)



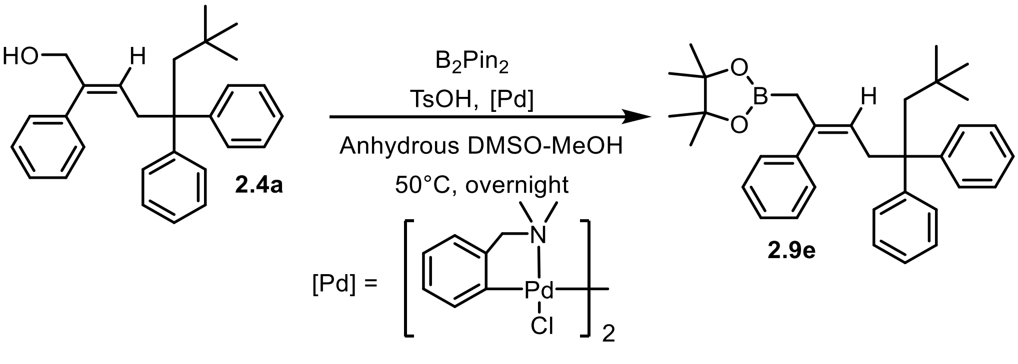
To a solution of **2.4a** (0.2 mmol, 1 equiv) and Boc_2O (di-*tert*-butyl dicarbonate) (50.6 µL, 0.22 mmol, 1.1 equiv) in THF (2 mL) was added DMAP (2.4 mg, 0.02 mmol, 1 mol%) at room temperature, then the solution was gently heated using a heat gun until effervescence was observed. After stirring the mixture for 2 h, it was filtered and the solvent was removed under reduced pressure. The crude product were purified by column chromatography on silica gel (Pentane/EtOAc= 150:1 to 100:1) to afford the pure product **2.9c** as a yellowish oil (67.9 mg, 70% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33 – 7.25 (m, 3H), 7.24 – 7.17 (m, 4H), 7.16 – 7.08 (m, 6H), 7.02 – 6.97 (m, 2H), 5.57 (t, *J* = 6.7 Hz, 1H), 4.60 (s, 2H), 3.01 (d, *J* = 6.8 Hz, 2H), 2.18 (s, 2H), 1.41 (s, 9H), 0.54 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.5, 149.1, 138.1, 137.2, 128.9, 128.7, 128.2, 127.7, 127.3, 125.8, 81.9, 71.4, 49.99, 49.95, 38.0, 32.2, 31.7, 27.9; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{33}H_{40}NaO_3^+$ 507.2870; found 507.2879.

(*E*)-7,7-dimethyl-2,5,5-triphenyloct-2-enal (2.9d)



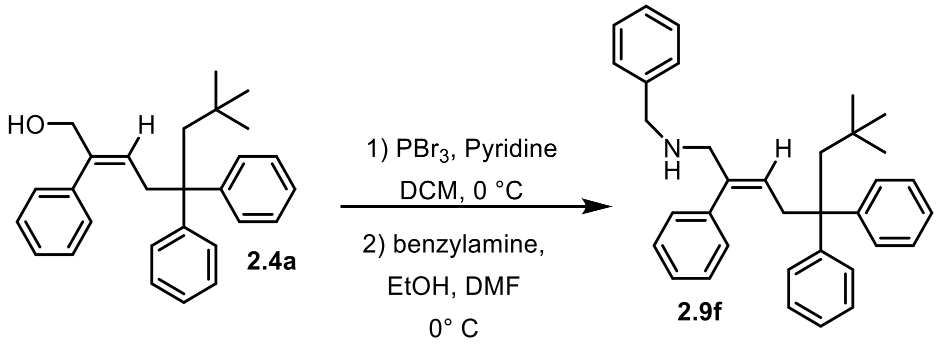
To a cooled (0 °C) solution of **2.4a** (0.1 mmol) in anhydrous DCM (1 mL), dry Na_2HPO_4 (7.9 mg, 0.05 mmol, 0.5 equiv) and Dess-Martin periodinane (45 mg, 0.11 mmol, 1.05 equiv) was added at once at 0 °C. After the resulting suspension was warmed to room temperature, the mixture was stirred for an additional 3 h. The reaction mixture was then quenched with saturated aqueous $NaHCO_3$ and saturated aqueous Na_2SO_3 solutions (both 1 mL), the aqueous layer was extracted with DCM, dried over Na_2SO_4 and the filtrate was concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (hexanes/EtOAc= 100:1 to 50:1) to afford the pure product **2.9d** as a yellowish oil (28.7 mg, 75% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.41 (s, 1H), 7.43 – 7.34 (m, 3H), 7.28 – 7.23 (m, 4H), 7.22 – 7.15 (m, 6H), 7.03 – 6.93 (m, 2H), 6.51 (t, *J* = 6.8 Hz, 1H), 3.36 (d, *J* = 6.8 Hz, 2H), 2.26 (s, 2H), 0.57 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 193.6, 153.4, 148.2, 145.2, 132.8, 129.6, 128.4, 128.3, 128.1, 128.0, 126.3, 50.7, 50.1, 39.4, 32.3, 31.7; **HRMS** (APCI/TOF) *m/z*: $[M - CHO]^+$ Calcd. for $C_{27}H_{29}^+$ 353.2264; found 353.2256.

(*Z*)-2-(7,7-dimethyl-2,5,5-triphenyloct-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.9e)



A reaction flask was charged with **2.4a** (0.1 mmol), TsOH (0.9 mg, 0.005 mmol, 5 mol%), di-*μ*-chlorobis{2-[(dimethylamino)methyl]phenyl-C,N}dipalladium(II) (1.3 mg, 0.0025 mmol, 2.5 mol%) and $(Bpin)_2$ (51 mg, 0.2 mmol, 2 equiv) before evacuating and back-filling with N_2. Anhydrous DMSO (0.5 mL) and anhydrous MeOH (0.5 mL) were added. After stirring this mixture at 50 °C overnight, it was cooled to room temperature and water (4 mL) and Et_2O (10 mL) were added. Next, the aqueous layer was extracted with Et_2O (3×10 mL), the organics combined, dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure and the crude product was purified by flash chromatography on silica gel (hexanes/EtOAc = 100:1 to 50:1) to afford the pure product **2.9e** as a yellowish oil (15.3 mg, 31% yield); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.26 – 7.22 (m, 2H), 7.20 – 7.16 (m, 5H), 7.15 – 7.10 (m, 6H), 7.03 – 6.99 (m, 2H), 5.25 – 5.16 (m, 1H), 2.97 (d, *J* = 6.7 Hz, 2H), 2.17 (s, 2H), 1.88 (s, 2H), 1.09 (s, 12H), 0.50 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 149.7, 142.8, 138.3, 128.8, 128.5, 127.8, 127.5, 126.3, 125.5, 123.8, 83.2, 50.1, 49.8, 38.7, 32.2, 31.7, 24.81, 24.78; **^{11}B NMR** (160 MHz, $CDCl_3$) δ 33.1; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{34}H_{43}NaO_2{}^{11}B^+$ 517.3248; found 517.3249.

(*E*)-*N*-benzyl-7,7-dimethyl-2,5,5-triphenyloct-2-en-1-amine (2.9f)

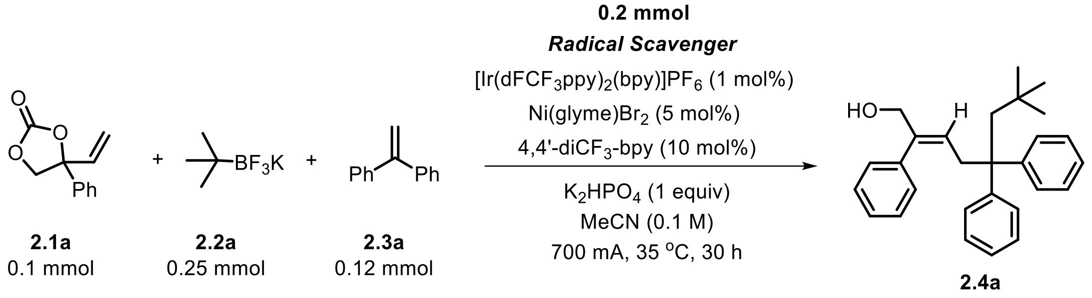


To a cooled (0 °C) solution of **2.4a** (0.5 mmol) in anhydrous Et_2O (1 mL) and pyridine (8 µL, 0.01 mmol, 0.2 equiv) was added dropwise a solution of PBr_3 (18.8 µL, 0.2 mmol, 0.4 equiv) in Et_2O (1 mL) under a N_2 atmosphere. After being stirred at room temperature for 2 h, the reaction mixture was quenched with water, the aqueous layer was extracted with Et_2O, and the collected organic phases were washed with saturated $NaHCO_3$, washed with water to neutral pH, dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and then used for the next step without further purification. To a cooled (0 °C) solution of $BnNH_2$ (874 µL, 8 mmol, 16 equiv) in EtOH (2 mL) was added dropwise to a solution of the alkyl bromidde derivative in anhydrous DMF (2 mL). After being stirred at 0 °C for 1 h, the mixture was allowed to stir at room temperature overnight. The solvent was removed under reduced pressure and the residue was quenched with water. The aqueous layer was basified to pH 9 with 1 N NaOH and then extracted several times with Et_2O. The combined organic phase was dried over Na_2SO_4 and the filtrate was concentrated under reduced pressure. The crude aminated derivative was purified by column chromatography on silica gel (hexanes/EtOAc= 20:1 to 10:1) to afford pure product **2.9f** as a yellowish oil (126 mg, 53% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.29 (m, 3H), 7.29 – 7.27 (m, 2H), 7.26 – 7.20 (m, 6H), 7.18 – 7.15 (m, 7H), 7.03 – 6.98 (m, 2H), 5.47 (t, *J* = 6.7 Hz, 1H), 3.57 (s, 2H), 3.38 (s, 2H), 3.05 (d, *J* = 6.7 Hz, 2H), 2.24 (s, 2H), 0.60 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.3, 140.5, 140.4, 139.8, 128.7, 128.4, 128.3, 128.2, 127.7, 127.0, 126.9, 125.9, 125.7, 56.4, 52.2, 50.07, 50.05, 38.0, 32.3, 31.8; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{35}H_{40}N^+$ 474.3155; found 474.3162.

2.4.7. Mechanistic studies

2.4.7.1. Confirming a radical process in the catalytic cycle

Control experiment 1: Radical scavenger experiment.

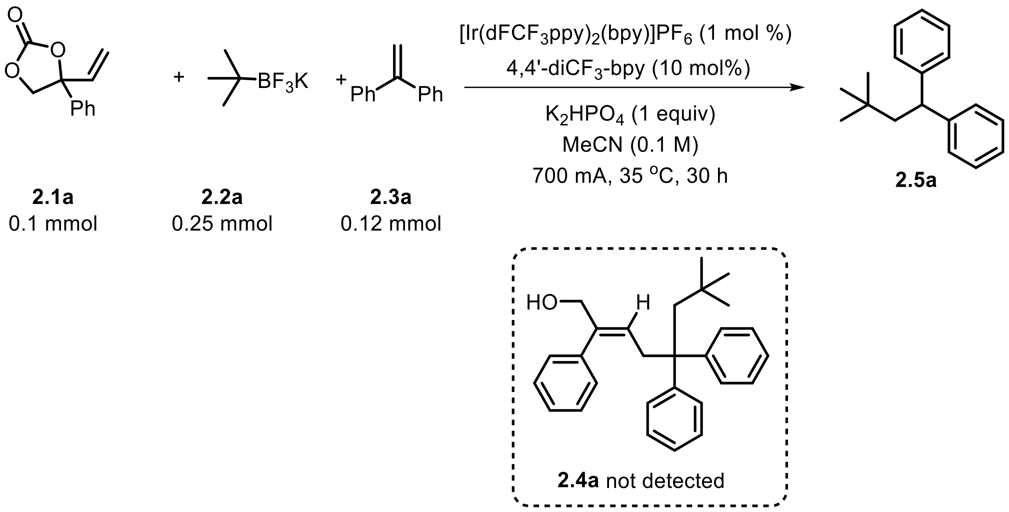


Procedure related to the standard conditions: [Ir(dFCF$_3$ppy)$_2$(bpy)]PF$_6$ (1.1 mg, 1.0 mol%), 4,4'-diCF$_3$-bpy (2.9 mg, 10 mol%), organotrifluoroborate **2.2a** (41 mg, 0.25 mmol, 2.5 equiv) and radical scavenger (TEMPO or BHT, 0.20 mmol) were weighed in a 10 mL screw-cap vial. The vial was transferred to a nitrogen-filled glove-box and was charged with Ni(glyme)Br$_2$ (1.5 mg, 5.0 mol%), K$_2$HPO$_4$ (17.4 mg, 0.10 mmol, 1 equiv) and CH$_3$CN (1 mL, 0.10 M). The liquid **2.1a** (0.1 mmol) and **2.3a** (0.12 mmol) were added affording a light-yellow solution. The reaction system was capped, removed from the glove box and was irradiated for 30 hours at 35 °C using a single high-power blue LED (λ_{em} = 445 nm, 700 mA) from the bottom. After completion, the mixture was evaporated to dryness and the residue was purified by column chromatography (SiO$_2$, Hexanes: EtOAc = 15:1) to afford product **2.4a**.

Table 2.6. Standard reaction in the presence of radical scavengers.

Entry	Radical Scavenger	Conversion of 2.1a (%)	Yield of 2.4a(%)
1	TEMPO	10	<5
2	BHT	>99	40

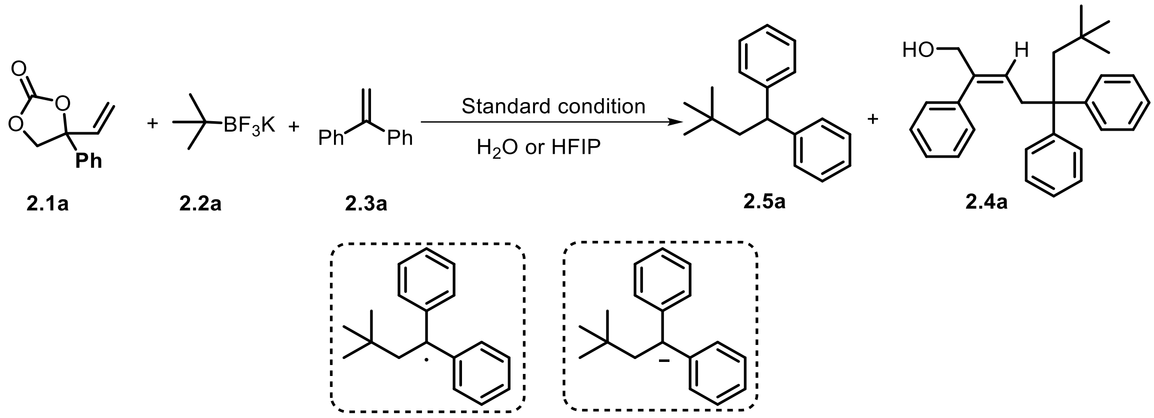
Control experiment 2: Deviation from the standard conditions for the formation of addition product **2.5a**



<u>Procedure related to the standard conditions:</u> [Ir(dFCF$_3$ppy)$_2$(bpy)]PF$_6$ (1.1 mg, 1.0 mol%), 4,4'-diCF$_3$-bpy (2.9 mg, 10 mol%) and organotrifluoroborate **2.2a** (41 mg, 0.25 mmol, 2.5 equiv) were weighed in a 10 mL screw-cap vial. The vial moved to a nitrogen-filled glove-box and was charged with K_2HPO_4 (17.4 mg, 0.10 mmol, 1 equiv) and CH_3CN (1 mL, 0.10 M). The liquid **2.1a** (0.10 mmol) and **2.3a** (0.12 mmol) were added affording a light-yellow solution. The reaction system was capped, removed from the glove box and was irradiated for 30 hours at 35 °C using a single high-power blue LED (λ_{em} = 445 nm, 700 mA) from the bottom. After completion, the mixture was evaporated to dryness and the residue was purified by column chromatography (SiO_2, hexanes/EtOAc) to afford product **2.5a**.

2.4.7.2. Investigation of a radical or carbanion intermediate

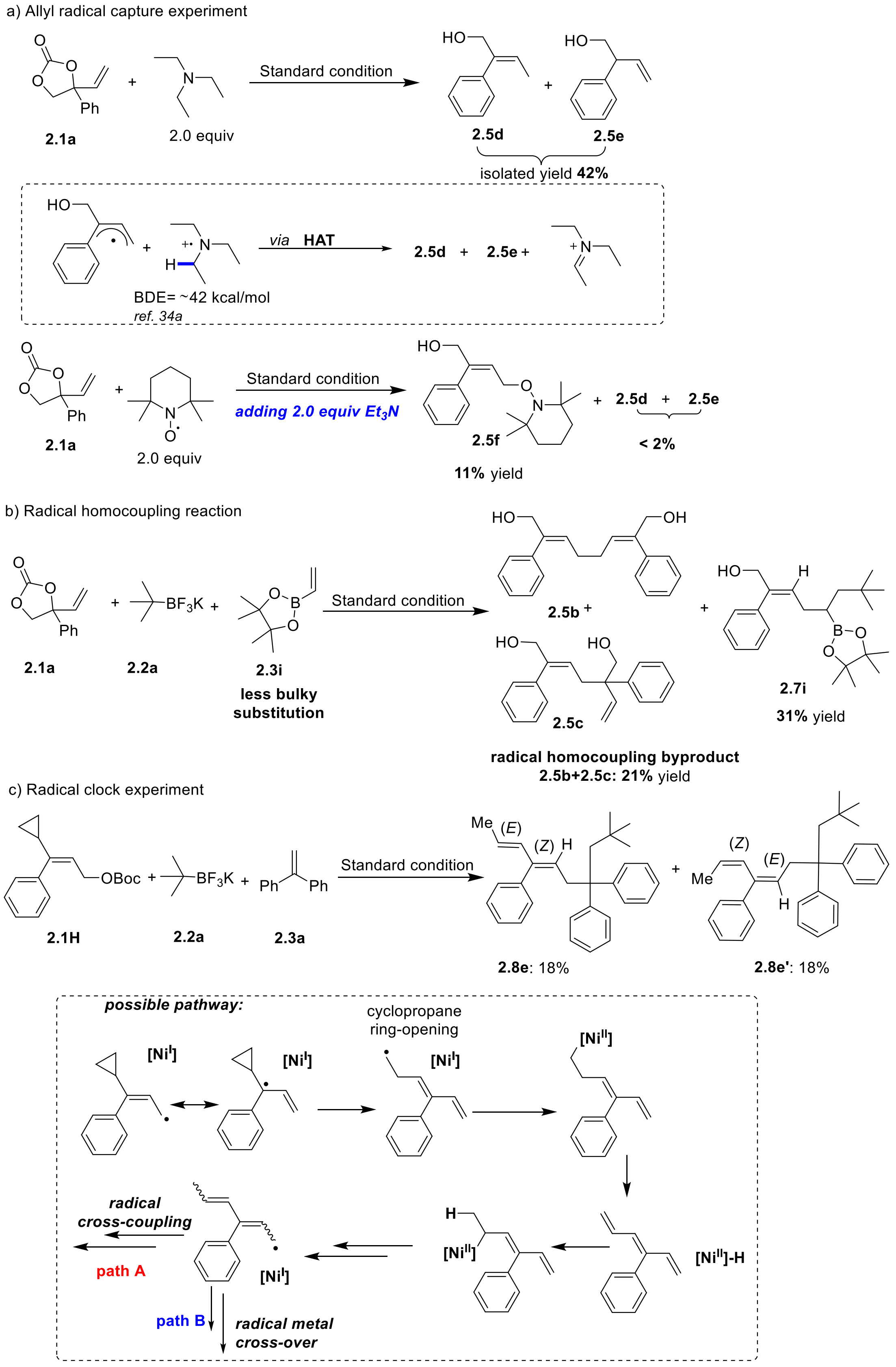
Table 2.7. Validation experiments for the presence of radical or carbanionic intermediates.



Entry	Deviation from the standard conditions	Additives	Yield of 2.4a (%)
1	no	H_2O (1.0 equiv)	71
2	no	HFIP (1.0 equiv)	67
3	without K_2HPO_4	HFIP (1.0 equiv)	70
4	without K_2HPO_4	HFIP (3.0 equiv)	68

General procedure: $[Ir(dFCF_3ppy)_2(bpy)]PF_6$ (1.1 mg, 1.0 mol%), 4,4'-diCF_3-bpy (2.9 mg, 10 mol%) and organotrifluoroborate **2.2a** (41 mg, 0.25 mmol, 2.5 equiv) were weighed in a 10 mL screw-cap vial. The vial moved to a nitrogen-filled glove-box and was charged with $Ni(glyme)Br_2$ (1.5 mg, 5.0 mol%), K_2HPO_4 (17.4 mg, 0.10 mmol, 1 equiv) and CH_3CN (1 mL, 0.10 M). The liquid **2.1a** (0.10 mmol), **2.3a** (0.12 mmol) and H_2O or HFIP were added affording a light-yellow solution. The reaction system was capped, removed from the glove box and was irradiated for 30 hours at 35 °C using a single high-power blue LED (λ_{em} = 445 nm, 700 mA) from the bottom. After completion, the mixture was evaporated to dryness and the residue was purified by column chromatography (SiO_2, hexanes/EtOAc = 15:1) to afford product **2.4a**.

2.4.7.3. Investigation of an allylic radical intermediate



Scheme 2.16: Experiments to support the presence of allylic radical species.

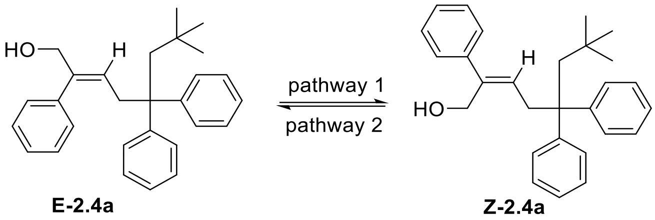
A series of control experiments were preformed to investigate the occurrence of allyl radical intermediates and the possibility of a radical cross-coupling process. First, we used triethylamine (2.0 equiv) as the reductant in place of other two component (**2.2a** and **2.3a**), and the generated isomeric products **2.5d** and **2.5e** support the view that an allylic radical species is responsible for the abstraction of a hydrogen atom from the amino radical cation (*under a*)[35a]. Based on the above experiment, the radical trapping reagent TEMPO was added to the reaction mixture containing **2.1a** and triethylamine. Notably, the adduct product **2.5f** was isolated and also suggests the formation of an allyl radical intermediate under the standard conditions (*under b*). Moreover, when the less bulky substituted vinyl compound **2.3i** instead of **2.3a** was used, the coupling procedure affords the product **2.7i** in low (31 %) yield along with homo-coupling bisallyl byproducts **2.5b** and **2.5c** in a combined 21% yield (*under c*). This classic radical clock experiment was performed under the standard condition to offer the ring-opening product **2.8e** and **2.8e'** in total yield 36%. Combined, the control experiments support the idea that an allylic radical and a tertiary radical generated in this catalytic process. However, we could not confirm the process through the radical cross-coupling and exclude the other possible pathway like radical metal crossover process.

General procedure

Control experiment a: [Ir(dFCF$_3$ppy)$_2$(bpy)]PF$_6$ (1.1 mg, 1.0 mol%), 4,4'-diCF$_3$-bpy (2.9 mg, 10 mol%) and TEMPO (31.2 mg, 2 equiv, for the eq. 2) were weighed in a 10 mL screw-cap vial. The vial moved to a nitrogen-filled glove-box and was charged with Ni(glyme)Br$_2$ (1.5 mg, 5.0 mol%), K$_2$HPO$_4$ (17.4 mg, 0.10 mmol, 1 equiv) and CH$_3$CN (1 mL, 0.10 M). The liquid **2.1a** (0.10 mmol) and triethylamine (27.7 µL, 0.2 mmol, 2 equiv) were added affording a light-yellow solution. The reaction was capped, removed from the glove box and was irradiated for 30 hours at 35 °C using a single high-power blue LED (λ_{em} = 445 nm, 700 mA) from the bottom. After completion, the mixture was evaporated to dryness and the residue was purified by column chromatography (SiO$_2$, hexanes/EtOAc = 15:1) to afford products **2.5d**+**2.5e**.

Control experiment b: procedure related to method A with the following modifications: vinyl boronate **2.3i** as the starting materials in place of **2.3a**. Products **2.7i** and bisallylic compounds **2.5b**+**2.5c** were isolated.

2.4.7.4. Investigation of the interconversion of *Z*- and *E*-isomers



Path 1: from ***E*-2.4a** to ***Z*-2.4a**

Condition 1: Blue light, CH_3CN: ***Z*-2.4a**, 0%;

Condition 2: Blue light, 4CzIPN, CH_3CN: ***Z*-2.4a**, 0%;

Condition 3: Blue light, 4CzIPN, Ni(glyme)Br_2, 4,4'-diCF$_3$-bpy, CH_3CN: ***Z*-2.4a**, 0%;

Condition 4: Blue light, Ir(ppy)$_3$, CH_3CN/DMSO: ***Z*-2.4a**, 0%; Path 2: from ***Z*-2.4a** to ***E*-2.4a**

Condition 5: Blue light, CH_3CN: ***E*-2.4a**, 100%;

Condition 6: Blue light, [Ir(dFCF$_3$ppy)$_2$(bpy)]PF$_6$, CH_3CN: ***E*-2.4a**, 100%;

Condition 7: No Blue light, 70ºC, CH_3CN, 48 h: ***E*-2.4a**, 0%;

Condition 8: No Blue light, rt, one week: ***E*-2.4a**, 0%;

In general: All the reactions above were conducted under 700 mA blue LED, 35 ºC for 24 h and standard amount of photocatalyst (1 mol%), Ni(glyme)Br_2 (5 mol%), 4,4'-diCF$_3$-bpy (10 mol%) and solvent (1 mL) if without further illustration.

In general, ***Z*-2.4a** can be transformed to the ***E*-4a** isomer. Even in the absence of the PC5 and other catalytic condition, it can still be transformed into ***E*-2.4a** under blue-LED light. On the contrary, if we start with ***E*-2.4a** and subject it to light or other catalytic conditions, no conversion occurred. We consider that it is not simply energy transfer from the photocatalyst that causes this difference. Then, we tested the UV absorbance of ***Z*-2.4a** and ***E*-2.4a** isomer (0.1 M), and they show light absorbtion at 450 nm. The corresponding spectra are as follows:

UV-Vis measurements were carried out on an Agilent Cary 60 UV-Vis spectrophotometer equipped with two silicon diode detectors, double beam optics and Xenon pulse light.

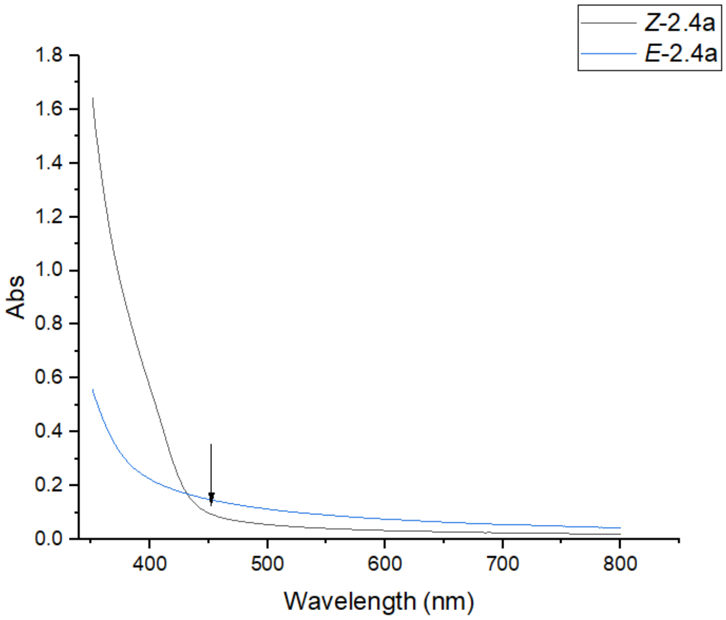
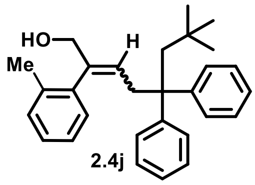


Figure 2.8. The UV-vis spectrum of ***E*-2.4a** and ***Z*-2.4a** in CH_3CN. The concentrations here are 0.1 M in both cases.

<u>*E*/*Z* isomerization studies with other substrates</u>:



2.4j

When using **2.1j** as the starting material under the optimized catalytic conditions in the presence of PC1, we measured its conversion at different time intervals and the *E/Z* value of product **2.4j**: 4 h, 8 h, 14h, 18 h, 22 h, 26 h, 30 h and 48 h. During the first 4 h, the *E*- and *Z*-isomers are generated in a 2:1 ratio and their combined yield was 10% based on NMR signal. After 30 h, **2.1j** was completely transformed and the final *E*/*Z* ratio was 2.38:1. From these experiments, we can conclude that the ratio does not significantly change.

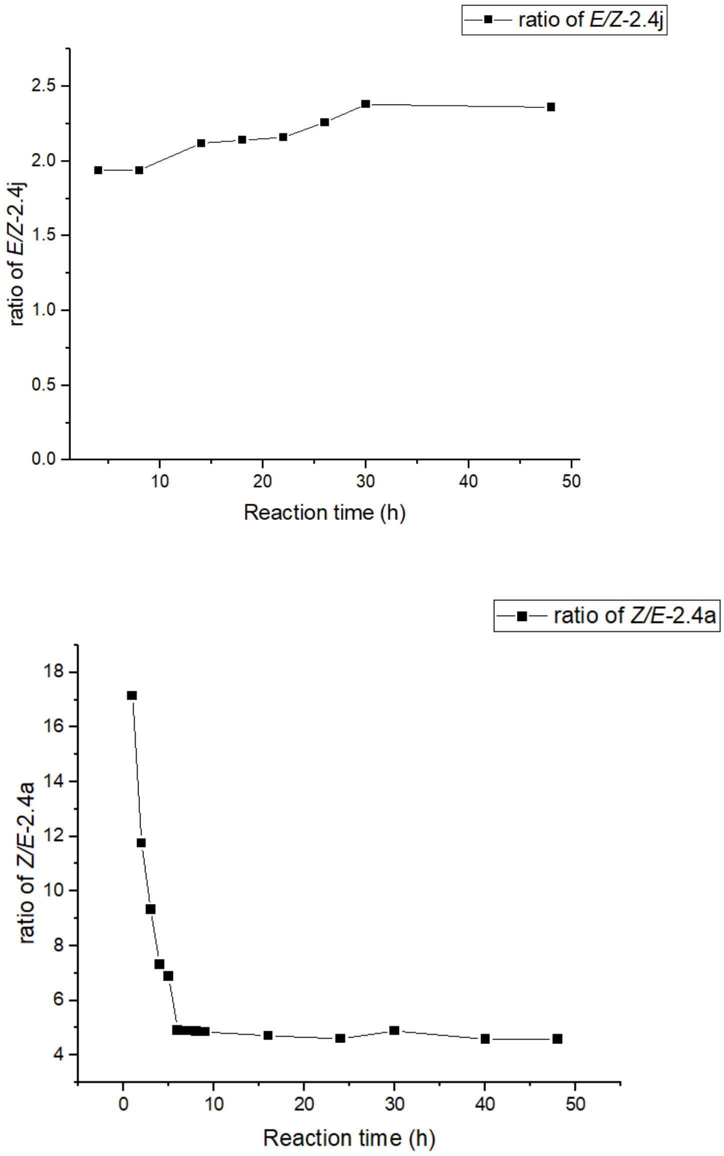
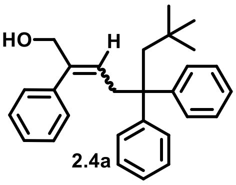


Figure 2.9. Kinetic experiments carried out for products ***E/Z*-2.4j** and ***Z/E*-2.4a**.



2.4a

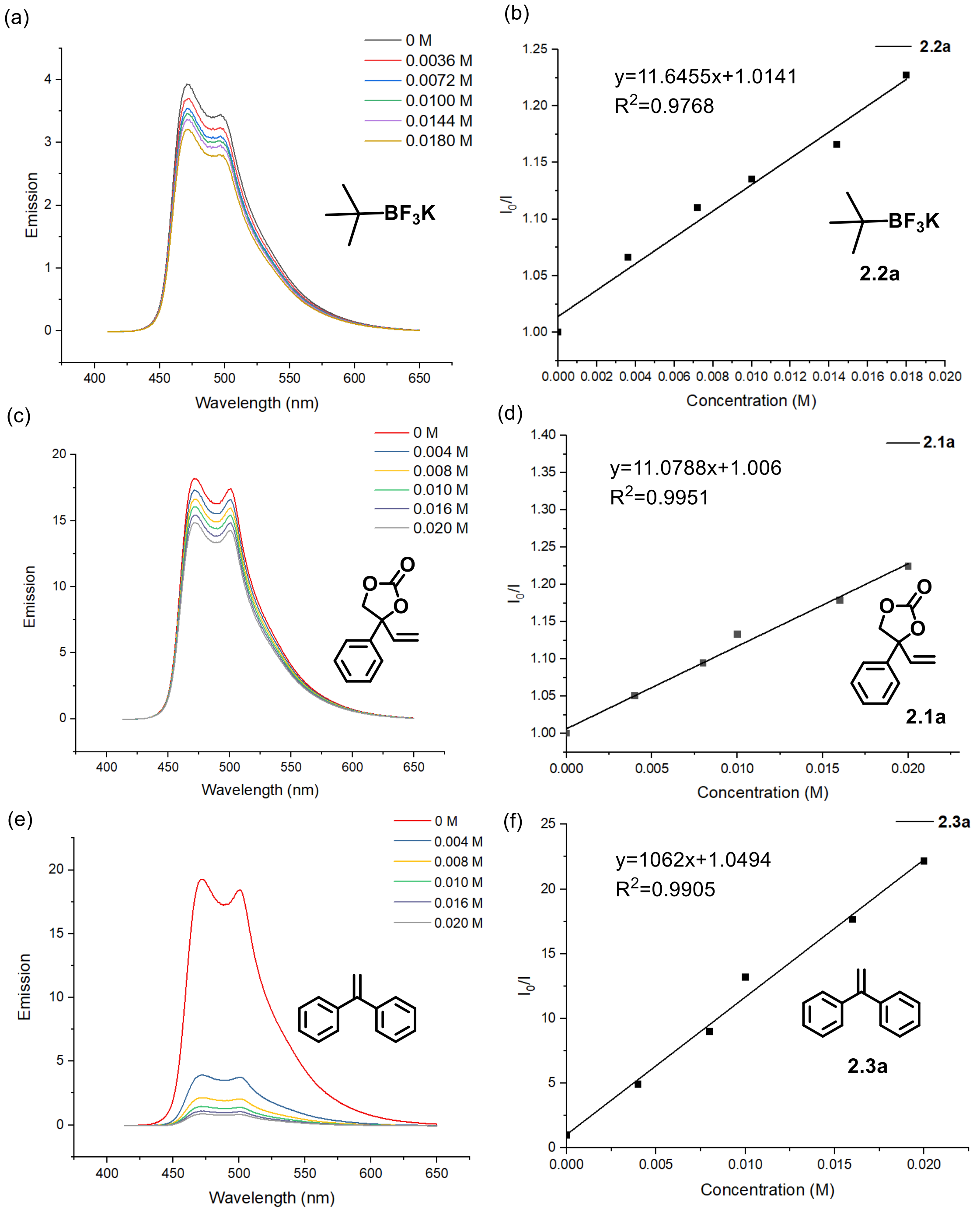
We also used substrate **2.1a** as starting material, and we measured the formation of ***E*-** and ***Z*-2.4a** over time. Substrate **2.1a** is fully converted after 7 h, but we prolonged the reaction time (up to 50 h) to see if there was any influence on the *E*/*Z* ratio. From the data, we can conclude that the ***Z*-2.4a** is first formed as the major isomer under the 4CzIPN photocatalyst but then is partially converted into the *E*-isomeric product. We also did some control experiments showing that ***Z*-2.4a** can be transformed into ***E*-2.4a** under blue light irradiation, but ***E*-2.4a** cannot be transformed back to the ***Z*-2.4a** under similar conditions, see the respective experimental details.

2.4.7.5. Stern-Volmer analysis

The Stern-Volmer plot for emission quenching of [Ir(dFCF$_3$ppy)$_2$(bpy)]PF$_6$ by **2.2a** is shown in CH$_3$CN in **Figure 2.10**. Fluorescence measurements were carried out on an Aminco-Bowman Series 2 Luminescence spectrofluorimeter equipped with a high voltage PMT detector and continuum Xe light source. Samples containing a solution of [Ir(dFCF$_3$ppy)$_2$(bpy)]PF$_6$ (1 mg photocatalyst in 50 mL degassed MeCN, to obtain concentration of 2 x 10^{-5} M) in total 2.2 mL of MeCN were deoxygenated through argon purge in a 10 x 10 mm light path quartz fluorescence cuvette equipped with Silicone/PTFE 3.2 mm septum under an argon atmosphere. Then, 4 μL of a 2.0 M solution of **2.2a** in MeCN was added to the solution of [Ir(dFCF$_3$ppy)$_2$(bpy)]PF$_6$ with 2.2 mL to give a final concentration of **2.2a.** Or 10 μL of a 0.9 M solution of **2.1a** (or **2.3a**) in MeCN was added to the solution of [Ir(dFCF$_3$ppy)$_2$(bpy)]PF$_6$ with 2.2 mL to give a final concentration of **2.1a** (or **2.3a**). The addition of **2.1a**, **2.2a, 2.3a** solution was repeated for five consecutive times. After each addition, the solution was mixed by sparging with argon for 60 s. The emission light was acquired from 410 nm to 650 nm. The results shown in **Figure 2.10** indicate that the components quench the excited state of [Ir(dFCF$_3$ppy)$_2$(bpy)]PF$_6$ and its emission. A small change in the emission spectra of the solution was observed upon the first addition (λ_{max} = 470 nm to 492 nm).

The maximum emission intensity 471 nm without quencher divided by the emission intensity with quencher (i.e., I_0/I) was then plotted as a function of the concentration of quencher to obtain the Stern-Volmer plot according to the following equation (equation 1):

$$\frac{I_0}{I} = 1 + I_0 k_q [Q] \qquad \text{(eq. 1)}$$



*For **2.2a** as a quencher, we calculated a Stern-Volmer quenching constant of 11.6 M^{-1}.*

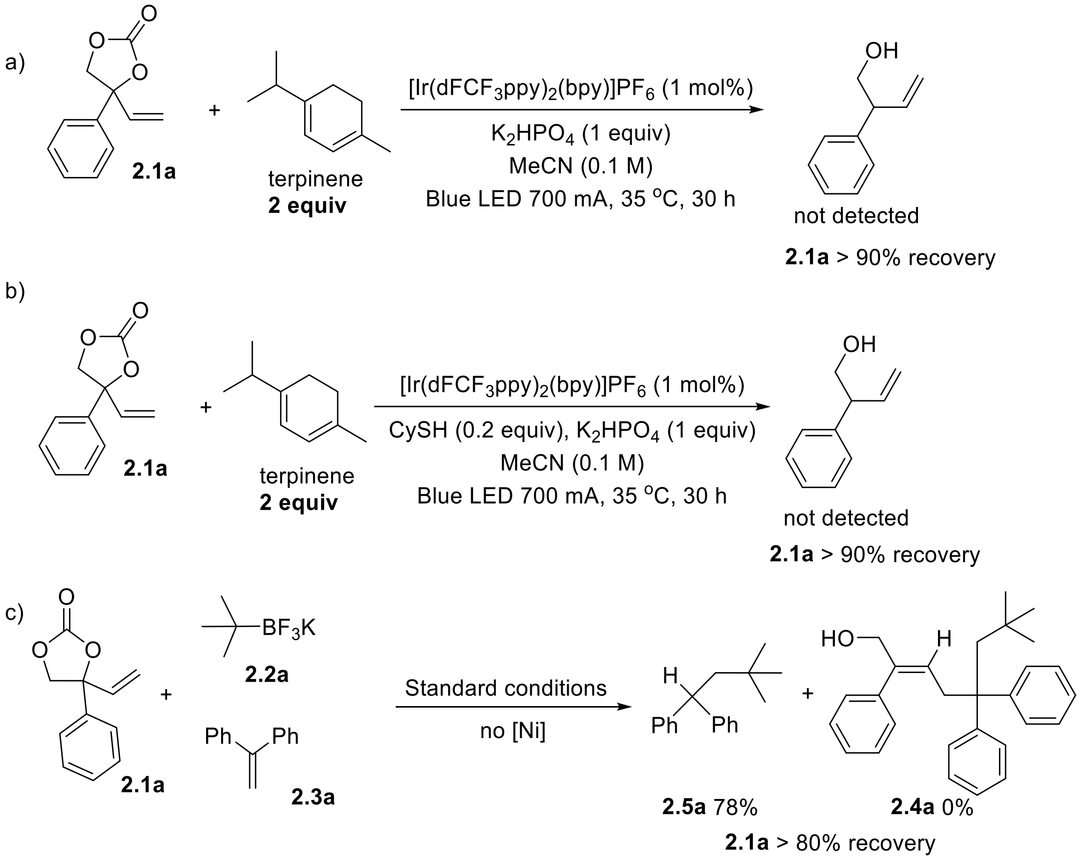
*For **2.1a** as a quencher, we calculated a Stern-Volmer quenching constant of 11.1 M^{-1}.*

*For **2.3a** as a quencher, we calculated a Stern-Volmer quenching constant of 1062 M^{-1}.*

Figure 2.10. Quenching experiments of various components **2.2a**, **2.1a** and **2.3a** (a, c, e); Stern-Volmer quenching plots using **2.2a**, **2.1a** and **2.3a** as a quencher (b, d, f).

From the Stern-Volmer quenching experiments, **2.3a** can be seen as an efficient quencher. There is a quenching phenomenon when using vcc **2.1a** and vinyl compound **2.3a**. To confirm that **2.1a** and **2.3a** can both undergo a SET process with the photocatalyst, we did the following experiments. Cyclic voltammetry (CV) measurements were performed as follows. From the spectrum, we can observe that significant reduction and oxidation of **2.1a** are not observed in the registered potential window (from 0 to -3.0 to 3.0 V). The single electron transfer between photocatalyst and **2.1a** seems unlikely as their redox potential are not matching ($E_{red}(Ir^{III}*/Ir^{II})$=+1.32 v and $E_{ox}(Ir^{IV}/Ir^{III}*)$= -1.0 v), and this is similar for **2.3a**. Next, we performed some other control experiments. We used terpinene and the CySH as hydrogen sources to investigate the HAT product generated from **2.1a** (see Scheme below under a and b) The remaining vinyl cyclic carbonate **2.1a** shows that there is no transformation between **2.1a** and photocatalyst. Moreover, one of the previous experiments we performed (cf. **Table 2.5**) also showed that 78% of **2.5a** is generated under these conditions in the absence of [Ni], and more than 80% of **2.1a** is recovered (Scheme below, under c). From these experiments, we believe that the excited photocatalyst first oxidizes *t*BuBF$_3$K as shown in our proposed mechanism. For the quenching phenomenon, we speculate that there might be an energy transfer process occurring between the vinyl compound and photocatalyst.

Control experiments:



2.4.7.6. Electrochemical studies

Cyclic voltammetry (CV) measurements were carried out on a Princeton Applied Research PARSTAT 2273 instrument with a glassy carbon disk electrode (diameter: 3 mm) as working electrode. A silver wire coated with AgCl immersed in a 3.0 M aqueous solution of NaCl and separated from the analyte by a fritted glass disk was employed as the reference electrode and a Pt wire counter-electrode completed the electrochemical setup. The scan rate was 100 mV/s. The substrates were measured at a concentration of 0.02 M in ACN with $TBAPF_6$ (0.1 M) as electrolyte. Potentials are quoted with the following notation: E_p^C (E_{Red}) refers to the cathodic peak potential, E_p^A (E_{Ox}) refers to the anodic peak potential.

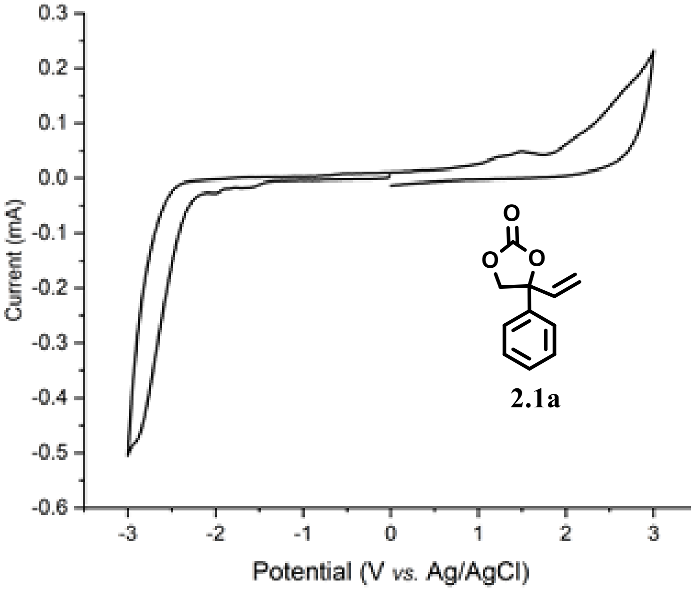


Figure 2.11: CV of VCC **2.1a** in MeCN starting with reduction, significant reduction and oxidation of **2.1a** were not observed in the registered potential window from 0 to −3.0 to 3.0 V.

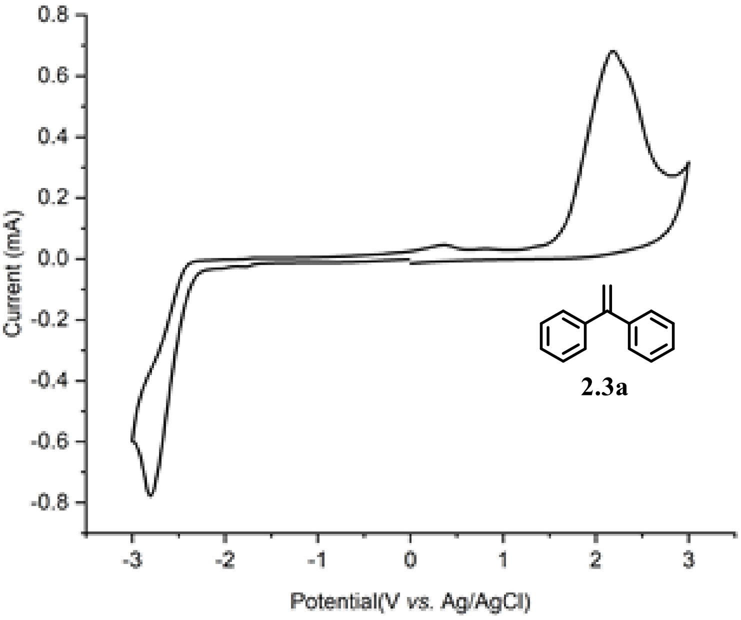


Figure 2.12: CV of 1,1-diphenylethylene **2.3a** in MeCN starting with reduction, irreversible reduction at E_p^C = -2.83 V and irreversible oxidation at E_p^A = 2.17 V.

2.4.8. X-ray crystallographic studies

Experimental procedure: The measured crystals of **2.7a** were stable under atmospheric conditions; nevertheless, they were treated under inert conditions immersed in perfluoro-polyether as protecting oil for manipulation. Data Collection: measurements were made on a Bruker-Nonius diffractometer equipped with an APPEX II 4K CCD area detector, a FR591 rotating anode with MoKα radiation, Montel mirrors and a Kryoflex low temperature device (T = −173 °C). Full-sphere data collection was used with ω and φ scans. Programs used: Data collection Apex2 V2011.3 (Bruker-Nonius 2008), data reduction Saint+Version 7.60A (Bruker AXS 2008) and absorption correction SADABS V. 2008−1 (2008). Structure Solution: SHELXTL Version 6.10 (Sheldrick, 2000)[40] was used. Structure Refinement: SHELXTL-97-UNIX VERSION. Details can be found in CCDC-2208334.

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(40) G. M. Sheldrick, SHELXTL Crystallographic System, version 6.10; Bruker AXS, Inc.: Madison, WI, 2000.

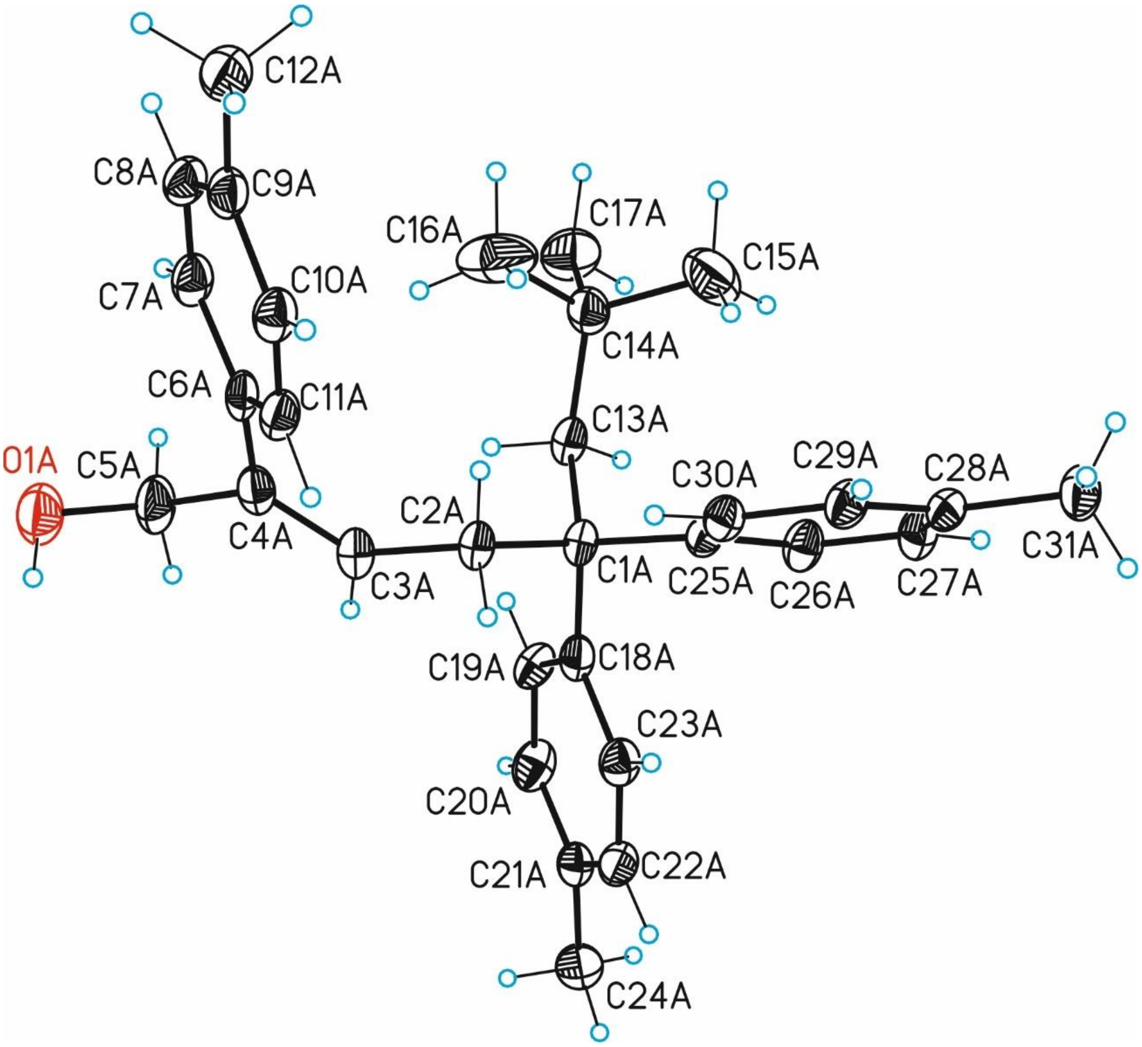


Figure 2.13: Molecular structure determined for **2.7a** (ORTEP) at 50% probability (ellipsoids) with the adopted numbering scheme.

Crystallographic data for 2.7a

Empirical formula	$C_{31}H_{38}O$	
Formula weight	426.61	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 10.6838(11)Å	α = 90°.
	b = 24.370(3)Å	β = 119.1415(17)°.
	c = 10.9016(11)Å	γ = 90°.
Volume	2479.1(4) $Å^3$	
Z	4	
Density (calculated)	1.143 Mg/m^3	
Absorption coefficient	0.067 mm^{-1}	
F(000)	928	
Crystal size	0.400 × 0.400 × 0.030 mm^3	
Theta range for data collection	1.671 to 32.898°.	
Index ranges	-16<=h<=16,-36<=k<=35,-15<=l<=16	
Reflections collected	30875	
Independent reflections	16264 [R(int) = 0.0544]	
Completeness to theta =32.898°	93.4%	
Absorption correction	Multi-scan	
Max. and min. transmission	0.74 and 0.56	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	16264/ 1/ 591	
Goodness-of-fit on F^2	1.031	
Final R indices [I>2sigma(I)]	R_1 = 0.0627, wR_2 = 0.1552	
R indices (all data)	R_1 = 0.0863, wR_2 = 0.1731	
Flack parameter	x = 0.0(10)	
Largest diff. peak and hole	1.055 and -0.364 $e·Å^{-3}$	

Chapter 3.

An Expedient Radical Approach for the Decarboxylative Synthesis of Stereodefined All-Carbon Tetrasubstituted Olefins

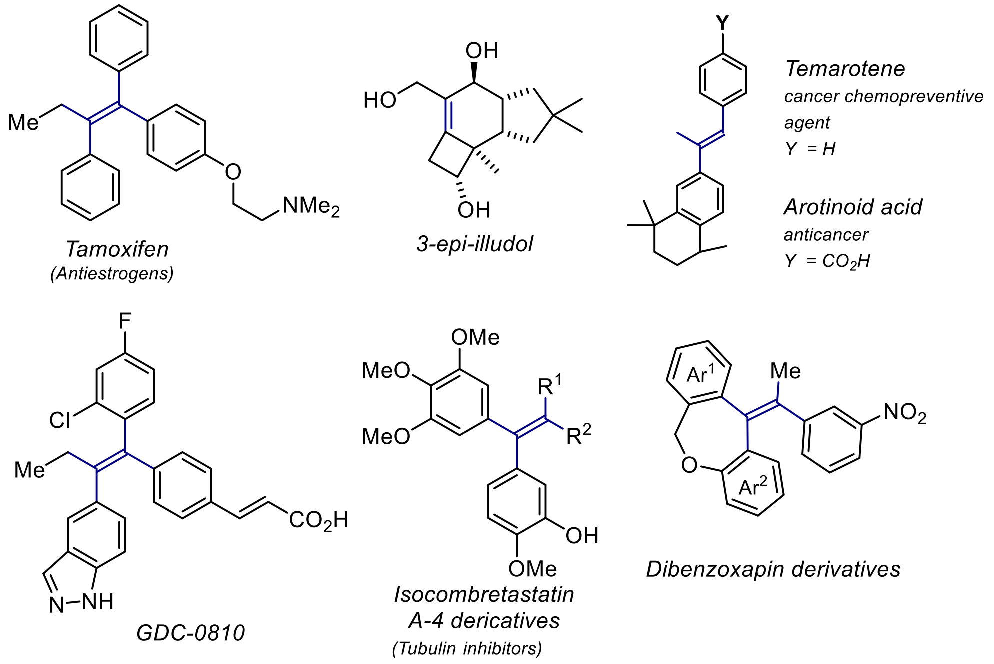
The results described in this chapter have been published in:

Q. Zeng, N. Yamini, J. Benet-Buchholz, A. W. Kleij, *Angew. Chem. Int. Ed.* **2024**, *63,* e202403651

3.1. Introduction

3.1.1. Multi-substituted olefins in traditional organic synthesis

Stereodefined tri- or tetra-substituted olefins are valuable motifs playing a significant role in natural products and pharmaceuticals due to their unique structural, physical and biological properties.[1] They serve as versatile and structurally diverse fragments in various drugs such as anticancer agents (e.g. Tamoxifen), tubulin inhibitors such as Isocombretastatin, and its analogues which are key to various medical treatments (Scheme 3.1).[2] Most of them are also suitable as precursors in numerous transformations allowing the preparation of more complex skeletons with contiguous and highly substituted *sp*^{2}- and *sp*^{3}-hybridized carbon centers, such as in (cyclo)alkanes and epoxides.[3]



Scheme 3.1. Bio-active compounds containing stereodefined tetrasubstituted olefins.

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(1) a) A. Takahashi, Y. Kirio, M. Sodeoka, H. Sasai, M. Shibasaki, *J. Am. Chem. Soc.* **1989**, *111*, 643–647; b) L. Zaman, O. Arakawa, A. Shimosu, Y. Onoue, S. Nishio, Y. Shida, T. Noguchi, *Toxicon* **1997**, *35*, 205–212; c) R. A. Pilli, M. C. Oliveira, *Nat. Prod. Rep*. **2000**, *17*, 117–127; a) H. Yu, R. N. Richey, M. W. Carson, M. J. Coghlan, *Org. Lett.* **2006**, *8*, 1685–1688; b) A. S. A. S. Levenson, V. C. Jordan, *Eur. J. Cancer*. **1999**, *35*, 1974–1985.

(2) a) R. McCague, G. Leclercq, N. Legros, J. Goodman, G. M. Blackburn, M. Jarman, A. B. Foster, *J. Med. Chem*. **1989**, *32*, 2527–2533; b) C. E. Connor, J. D. Norris, G. Broadwater, T. M. Willson, M. M. Gottardis, M. W. Dewhirst, D. P. McDonnell, *Cancer Res*. **2001**, *61*, 2917–2922.

(3) a) A. B. Flynn, W. W. Ogilvie, *Chem. Rev*. **2007**, *107*, 4698–4745; b) Q.-H. Xia, H.-Q. Ge, C.-P. Ye, Z.-M. Liu, K. X. Su, *Chem. Rev*. **2005**, *105*, 1603-1662.

However, the construction of multi-substituted alkenes remains a challenge in organic chemistry. Classical synthetic strategies towards these kinds of highly substituted olefins involve for instance Wittig and/or Horner-Wadsworth-Emmons olefination, olefin metathesis and alcohol-based elimination reactions.[4] These approaches have been shown to be generic strategies for the construction of the densely substituted alkenes,[5] however they typically encompass poor regio- and stereoselectivity control. For example, olefin metathesis strategies are a straightforward way towards tetra-substituted alkenes with good stereocontrol but are limited to endocyclic alkenes formed through ring-closing metathesis of the respective compounds.[6] Relevant research indicated that *endo*-and *exo*-cyclic alkenes tend to be easier substrates than acyclic ones in stereoselective synthesis as the cyclic ring restricts the position of the substituents on the newly formed double bond.

3.1.2. Transition metal catalysis promoted the synthesis of multi-substituted olefins

Conventional methods to construct C=C double bonds typically do not proceed well when high steric demand and good overall synthetic efficiency are crucial objectives. The cross-coupling of either alkynes or vinyl electrophiles catalyzed by transition metal (TM) catalysts derived from Pd,[7] Ni,[8] Cu[9] among others[5] has emerged as a useful and versatile alternative over the last decades. Among various metal-based approaches, the carbometallation of alkynes activated as in situ formed nucleophilic alkenyl metal species can be captured by various electrophiles, thus allowing difunctionalization. In 2005, Larock and coworkers reported that the synthesis of tetra-substituted olefins **4** can be achieved by combining alkynes **1**, aryl iodides **2** and arylboronic acids **3** enabled by

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(4) a) B. E. Maryanoff, A. B. Reitz, *Chem. Rev*. **1989**, *89*, 863; b) N. Calderon, *Acc. Chem. Res*. **1972**, *5*, 127–132; c) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem. Int. Ed*. **2005**, *44*, 4490–4527; d) N. Lim, P. Weiss, B. X. Li, C. H. McCulley, S. R. Hare, B. L. Bensema, T. A. Palazzo, D. J. Tantillo, H. Zhang, F. Gosselin, *Org. Lett*. **2017**, *19*, 6212–6215.

(5) a) F. Buttard, J. Sharma, P. A. Champagne, *Chem. Commun*. **2021**, *57*, 4071–4088; b) M. Li, S. Zhai, X. Nong, A. Gu, J. Li, G.-Q. Lin, Y.-B. Liu, *Sci. China. Chem*. **2023**, *66*, 1261–1287.

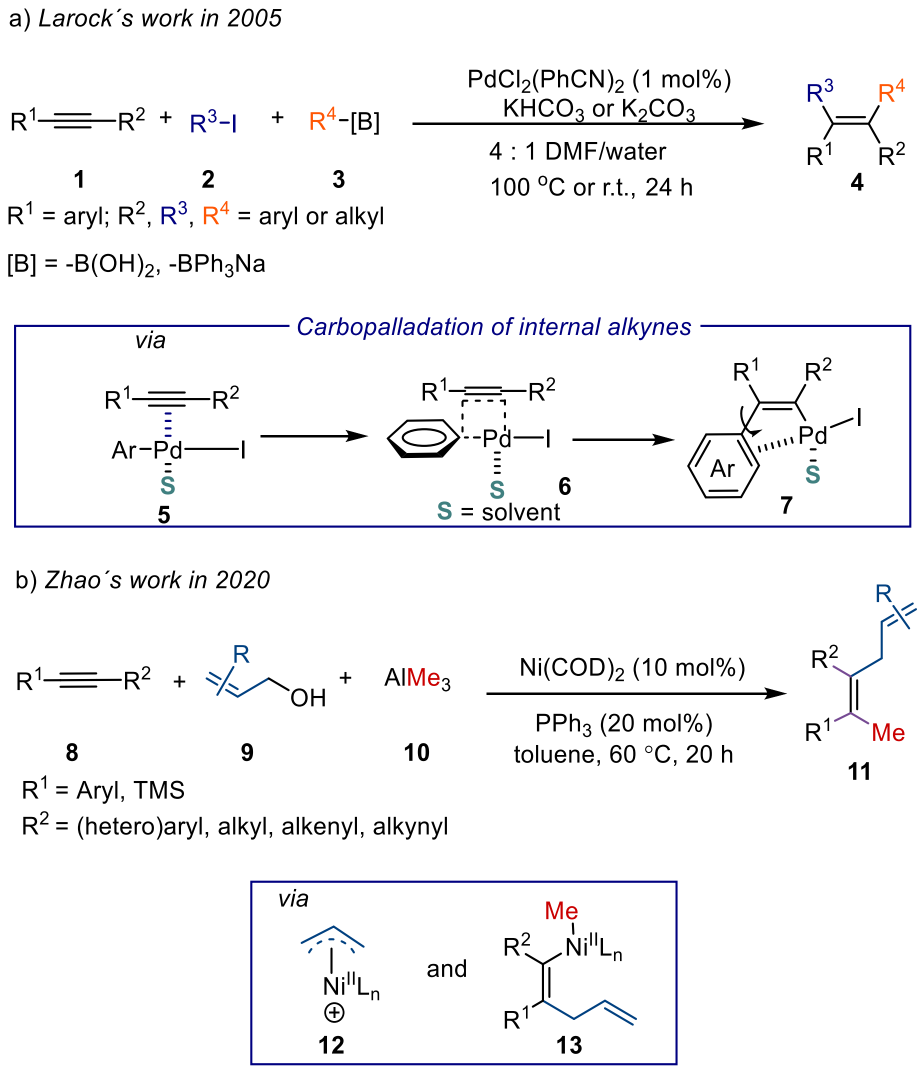
(6) N. Mukherjee, S. Planer, K. Grela, *Org. Chem. Front.* **2018**, *5*, 494–516.

(7) a) J. Wang, Z. Dong, C. Yang, G.-B. Dong, *Nat. Chem*. **2019**, *11*, 1106–1112; b) N. Ishida, T. Miura, M. Murakami, *Chem. Commun*. **2007**, 4381–4383.

(8) a) S. Arai, Y. Amako, X. Yang, A. Nishida, *Angew. Chem. Int. Ed*. **2013**, *52*, 8147–8150; b) W. Li, S. Yu, J. Li, Y. Zhao, *Angew. Chem. Int. Ed*. **2020**, *59*, 14404–14408.

(9) a) W.-Y. Xu, Y.-J. Li, T.-J. Gong, Y. Fu, *Org. Lett.* **2022**, *24*, 5884–5889; b) M. Luo, S. Zhu, C. Shi, Y. Du, C. Yang, L. Guo, W.-J. Xia, *Org. Lett.* **2022**, *24*, 6560−6565.

palladium-catalyzed cross-coupling.[10] The key intermediate iodide-Pd-alkenyl species **7**, generated from *cis*-carbopalladation on the internal alkyne via aryl-Pd-I species **5**, undergoes transmetalation with arylboronic acid **3** followed by reductive elimination, allowing to generate a highly substituted alkene **4**. Similarly, a Ni-catalyzed cross-coupling approach that utilizes allylic alcohols **9** and organometallic reagents **10** as coupling partners was reported by the Zhao group in 2020.[11] The 1,4-diene products **11** were prepared in good yields in the presence of $AlMe_3$. The intermediate π-allyl-Ni **12** and methyl-Ni-alkenyl **13** species are thought to be crucial to obtained the target products.



Scheme 3.2. Metal-catalyzed cross-coupling of a nucleophilic alkenyl metal species towards the formation of tetra-substituted alkenes.

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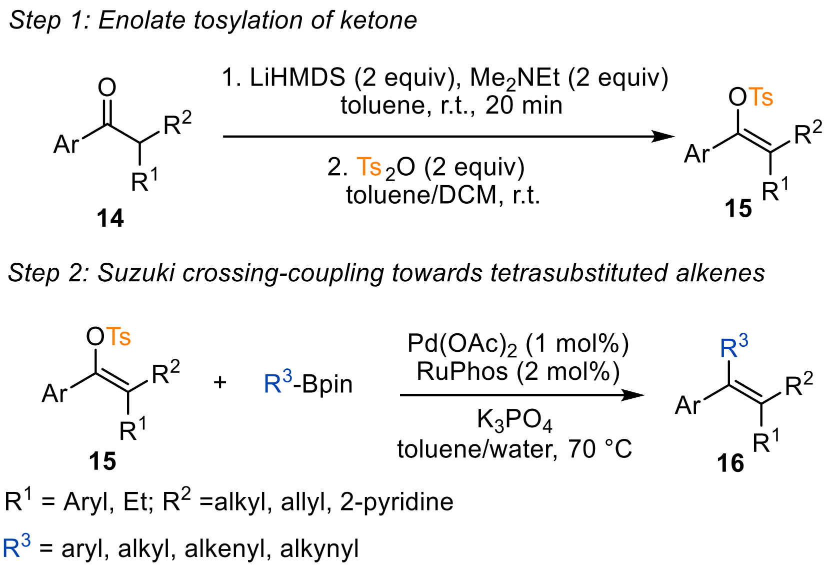
[10] C. Zhou, R. C. Larock, *J. Org. Chem.* **2005**, *70*, 3765–3777.

[11] W. Li, S. Yu, J. Li, Y. Zhao, *Angew. Chem. Int. Ed.* **2020**, *59*, 14404–14408.

A common way to generate productive vinyl electrophiles from alkynes is by trapping of carbometallated species by an electrophilic halide source,[12] or through enolization of a ketone and trapping the corresponding enolate with a sulfonate reagent. In 2017, a representative lithium *tert*-butoxide-mediated enolization-tosylation strategy was communicated by Gosselin,[13] who described the formation of tosylated alkenyl compounds **15** from ketone substrates **14** under excellent stereocontrol. The newly formed vinyl tosylates **15** subsequently undergo a Pd-catalyzed Suzuki-Miyaura coupling to furnish stereodefined olefins **16**. This latter strategy was devoted towards the construction of drug scaffolds such as the estrogen receptor degrader GDC-0810, which is under evaluation in medical trials for the treatment of relevant positive breast cancer tumors (see structure in Scheme 3.1).[14]



Scheme 3.3. Pd-catalyzed Suzuki-Miyaura cross-coupling reaction involving enolate-tosylated electrophiles towards the formation of tetra-substituted alkenes.

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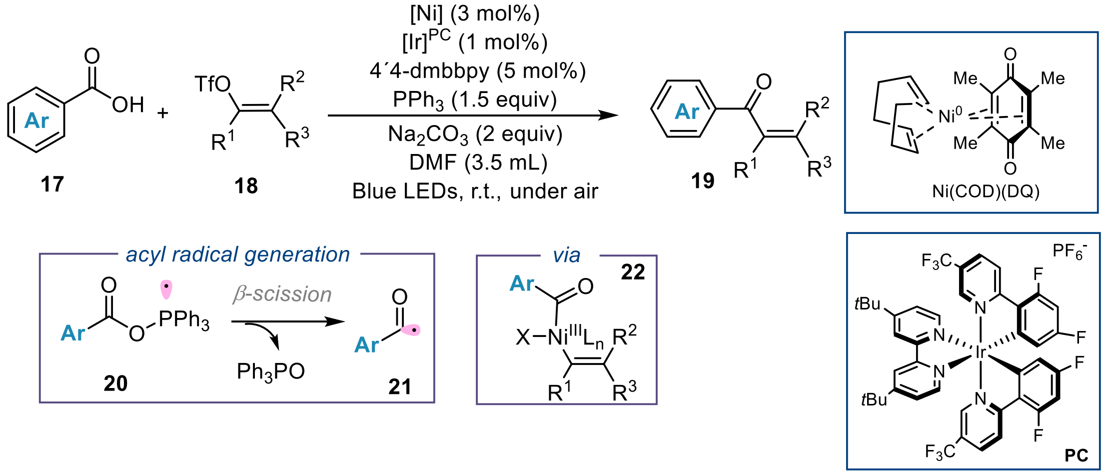
(12) a) T. Konno, T. Daitoh, A. Noiri, J. Chae, T. Ishihara, H. Yamanaka, *Org. Lett.* **2004**, *6*, 933–936; b) D. A. Rooke, E. M. Ferreira, *J. Am. Chem. Soc.* **2010**, *132*, 11926–11928; c) V. Kotek, P. Polák, H. Dvořáková, T. Tobrman, *Eur. J. Org. Chem.* **2016**, 5037–5044.

(13) B, X. Li, D. N. Le, K. A. Mack, A. McClory, N.-K. Lim, T. Cravillion, S. Savage, C. Han, D. B. Collum, H.-M. Zhang, F. Gosselin, J. *Am. Chem. Soc.* **2017**, *139*, 10777−10783.

(14) S. Savage, A. McClory, H. Zhang, T. Cravillion, N.-K. Lim, C. Masui, S. J. Robinson, C. Han, C. Ochs, P. D. Rege, F. Gosselin, *J. Org. Chem.* **2018**, *83*, 11571–11576.

3.1.3. Radical mediated approaches on construction of multi-substituted alkenes

Despite that the aforementioned TM-promoted transformations are powerful methods to build up multi-substituted olefins, they may undeniably suffer from demanding process conditions such as high temperature, the requirement of excess organometallic reagents and the presence of a strong base possibly affecting the level of user-friendliness and functional group tolerance.[5] Apart from classical organometallic process towards elaborate olefin synthesis, more recently it was demonstrated that radical-initiated protocols can also offer a practical tool for the late stage functionalization of tedious olefins and alkynes via photocatalytic methodologies.[15] In this context, the Xie group employed pre-defined alkenyl sulfonates **18** and carboxylic acids **17** as radical precursors to forge stereodefined tetra-substituted alkenes **19** enabled by dual Ni/photoredox catalysis (Scheme 3.4).[16] They proposed, based on DFT, that the key intermediate **22** may generated via a Ni(0)/Ni(II)/Ni(III) redox pathway. The Ni(COD)DQ/[Ir] enabled transformation proceeds well in air and thus extremely simplifies this Ni(0)-engaged metallaphotoredox catalysis.



Scheme 3.4. A metallaphotoredox based method to prepare multi-substituted olefins.

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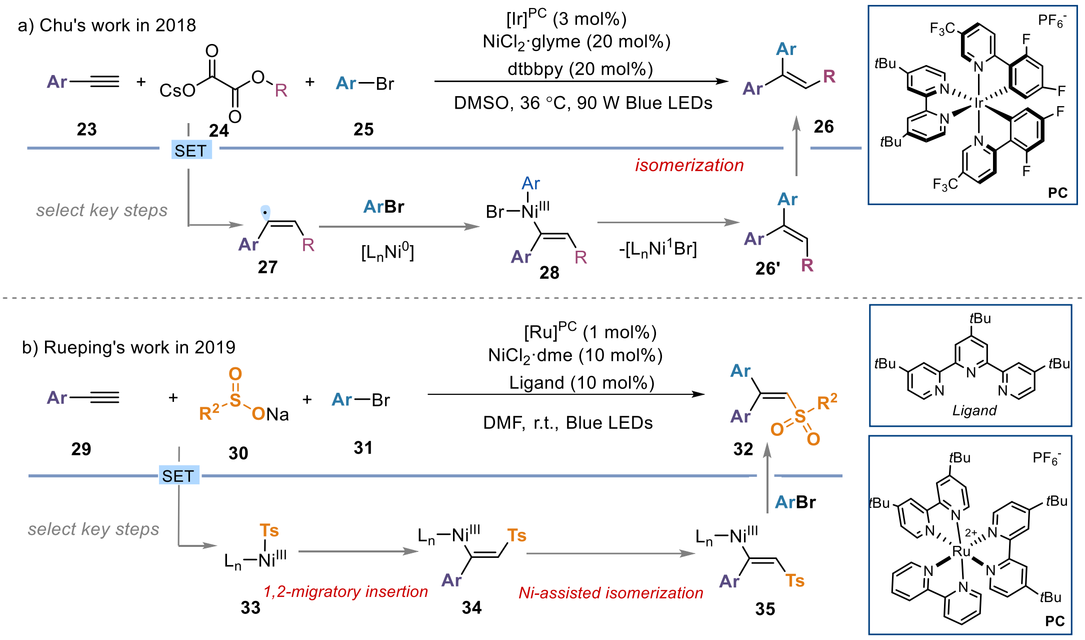
(15) a) Y. Chen, K. Zhu, Q. Huang, Y. Lu, *Chem. Sci*. **2021**, *12*, 13564−13571; a) J. D. Lasso, D. J. Castillo-Pazos, J. M. Salgado, C. Ruchlin, L. Lefebvre, D. Farajat, D. F. Perepichka, C.-J. Li, *J. Am. Chem. Soc*. **2024**, *146*, 2583–2592; b) Y. Chen, J. Wang, X.-X Wu, C. Zhu, *ACS Org. Inorg. Au* **2022**, *2*, 392−395.

(16) Y. Li, Q. Shao, H. He, C. Zhu, X.-S. Xue, J. Xie, *Nat. Commun*. **2022**, *13*, 10.

Metalla-photocatalytic cascade reactions of alkynes have been more frequently employed in the pursuit of novel, highly substituted alkene frameworks.[17] For instance, Chu[18] and Rueping[19] respectively reported on Ni-catalyzed processes towards mostly trisubstituted alkenes that are formed by alkyl-arylation and aryl-sulfonylation of alkynes (Scheme 3.5). Chu's work encompasses a radical addition, transition-metal-based coupling, and alkene isomerization sequence offering a regio-and *syn*-stereoselective synthetic strategy to tri-substituted alkenes **26** (Scheme 3.5a). Alternatively, Rueping proposed the generation of radical adduct Ni complex **33** via the 1,2-migratory insertion of alkyne **29** and Ni-assisted isomerization of **34** offering **35** as the primary steps (Scheme 3.5b).



Scheme 3.5. Ni/photoredox catalysis strategies for multi-substituted olefin synthesis via (a) alkyl-arylation of alkynes, and (b) aryl-sulfonylation of alkynes.

This reactivity paradigm involving radical addition onto olefin substrates has been well-established, and usually follows a sequence involving radical addition to the alkene promoted by a single-electron-transfer (SET) event following deprotonation.[20]

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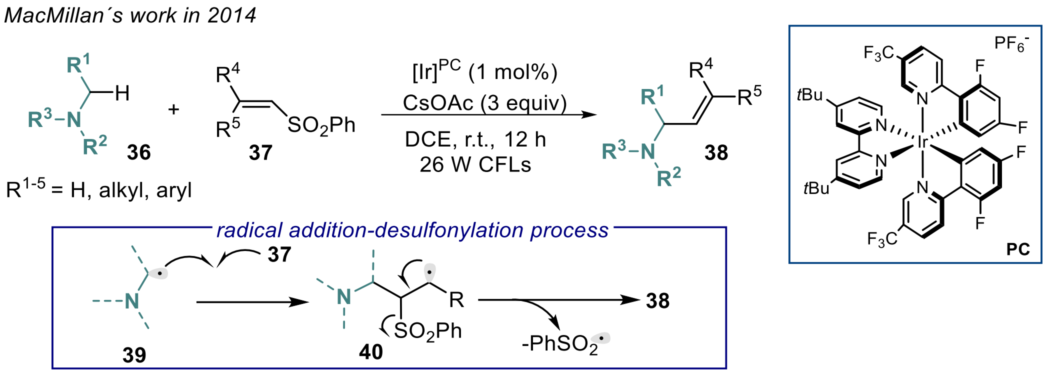
(17) a) U. Wille, *Chem. Rev*. **2013**, *113*, 813−853; b) F. Tang, Y.-S. Feng, Z.-F. Cheng, Q. Zhang, H.-J. Xu, *Org. Lett*. **2023**, *25*, 3916−3921.

(18) L. Guo, F. Song, S. Zhu, H. Li, L. Chu, *Nat. Commun*. **2018**, *9*, 4543.

(19) C. Zhu, H. F. Yue, B. Maity, I. Atodiresei, L. Cavallo, M. Rueping, *Nat. Catal.* **2019**, *2*, 678−687.

(20) a) Q.-Y. Lin, X.-H. Xu, F.-L. Qing, *J. Org. Chem*. **2014**, *79*, 10434−10446; b) T. Besset, T. Poisson, X. Pannecoucke, *Chem. Eur. J*. **2014**, *20*, 16830−16845; c) R. Tomita, Y. Yasu, T. Koike, M. Akita,

Alternatively, the adoption of radical-mediated desulfonylation of allyl sulfones **37** and similar approaches based on β-elimination of a suitable leaving group have marked a novel synthetic approach for the development of substituted, functional alkenes (Scheme 3.6).[21] For example, Macmillan and co-workers proposed a radical-mediated desulfonylation strategy that combines photoredox-generated α-amino radical species **39** and vinyl sulfones **37** offering access to diverse allylic amines **38**.[22] However, synthesis of all-carbon, tetra-substituted olefins through this latter approach remains challenging in terms of stereocontrol and alkene complexity.



Scheme 3.6. Photo-induced desulfonylation to access tri-substituted allylic amines.

3.1.4. Aims of the work in this chapter

In this chapter, we present a conceptually different photocatalytic approach enabling radical chemistry to foster the preparation of both stereodefined tri- and tetra-substituted olefins (Scheme 3.7) from vinyl cyclic carbonates (VCCs)[23] using decarboxylation as a driving force. These highly modular VCCs incorporate a terminal double bond, and we envisioned a manifold that would start with *in situ* radical addition using tertiary amines as convenient radical precursors. α-Amino radical addition would then provoke decarboxylation in the VCC under visible-light photo-irradiation without the need for a

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Beilstein. J. Org. Chem. **2014**, *10*, 1099–1106; d) Y. Zhang, C. Zhao, C. Ma, Z. Cai, S. Trienes, L. Ackermann, *Angew. Chem. Int. Ed.* **2023**, *62*, e202300166.

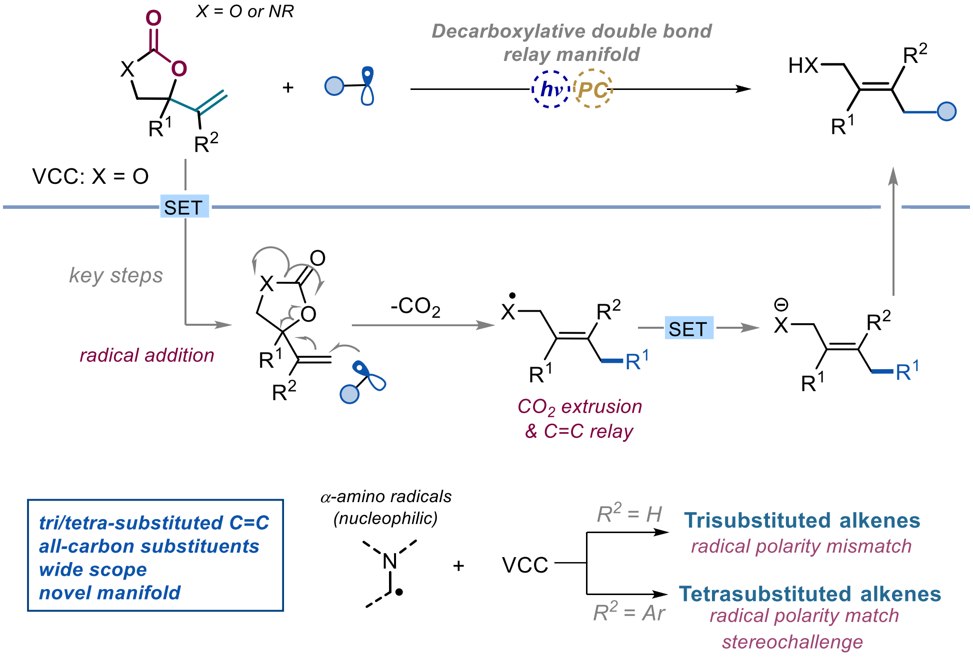
(21) a) X. Chu, D. Ge, Y. Cui, Z. Shen, C.-J. Li, *Chem. Rev.* **2021**, *121*, 12548−12680; b) T. Suga, R. Takada, S. Shimazu, M. Sakata, Y. Ukaji, *J. Org. Chem.* **2022**, *87*, 7487−7493; c) M. Schrempp, R. Wagner, H. Gleich, A. Gansäuer, D. Menche, *Org. Lett.* **2023**, *25*, 8089–8094.

(22) A. Noble, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2014**,*136*, 11602−11605.

(23) For a review on the use of VCCs and similar heterocycles in stereoselective synthesis see: W. Guo, J. E. Gómez, À. Cristòfol, J. Xie, A. W. Kleij, *Angew. Chem. Int. Ed.* **2018**, *57*, 13735-13747.

TM catalyst to stabilize the allyl species.[24] The challenge in using VCCs with R^2 = H would be to overcome the polar mismatch between the olefin and (nucleophilic) radical species.[25] In the case of R^2 being an aryl group, there is obviously a better polarity match between the reactants with the C=C bond being a much better acceptor, but here the stereocontrol over the mutual positional of the different carbon-substituents represents a crucial factor. These polarizing effects[26] enable nucleophilic radical addition of α-amino radical species with high regioselectivity onto the C=C bond of the VCC, and a formal relay of the latter within the final product. Our developed photocatalytic process shows wide scope in the target products, and can be extended to other sources of radicals, related heterocycles and can be combined with complex substrates such as drug molecules to build up advanced synthons. Further to this, mechanistic studies support the view that CO_2 extrusion in the VCC is key, and that the stereochemical configurations of the final products are retained under the process conditions.

This chapter:



Scheme 3.7. Radical-initiated decarboxylative formation of stereodefined olefins.

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(24) a) Q. Zeng, F. Gao, J. Benet-Buchholz, A. W. Kleij, *ACS Catal*. **2023**, *13*, 7514−7522; b) S. Xue, À. Cristofol, B. Limburg, Q. Zeng, A. W. Kleij, *ACS Catal.* **2022**, *12*, 3651−3659; c) H.-M. Huang, P. Bellotti, F. Glorius, *Chem. Soc. Rev*. **2020**, *49*, 6186−6197.

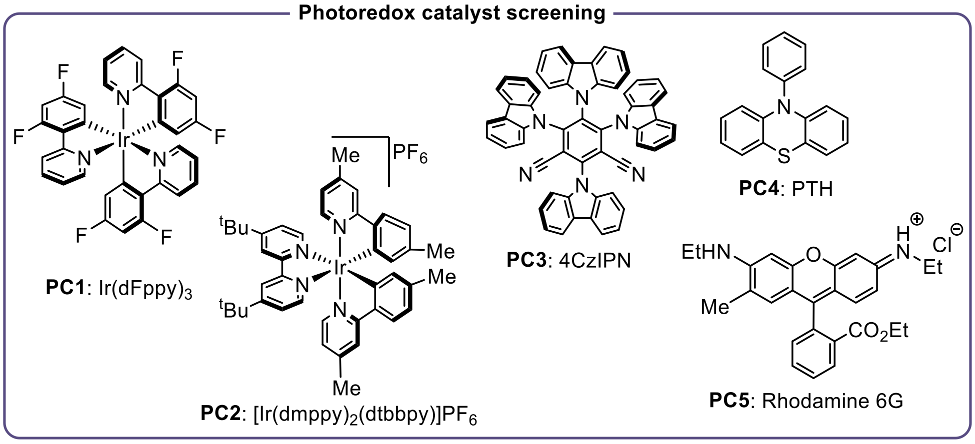
(25) a) B.P. Roberts, *Chem. Soc. Rev*. **1999**, *28*, 25−35; b) T. Constantin, M. Zanini, A. Regni, N. S. Sheikh, F. Juliá, D. Leonori, *Science* **2020**, *367*, 1021–1026; c) F. Parsaee, M. C. Senarathna, P. B. Kannangara, S. N. Alexander, P. D. E. Arche, E. R. Welin, *Nat. Rev. Chem*. **2021**, *5*, 486−499.

(26) J. Davies, T. D. Svejstrup, D. Fernandez Reina, N. S. Sheikh, D. Leonori, *J. Am. Chem. Soc*. **2016**, *138*, 8092–8095.

3.2. Results and Discussion

3.2.1. Optimization studies

Process screening. We started our studies by combining VCC **3.1a** and *N*-phenyl pyrrolidine **3.2a** as a substrate combination. Taking advantage of the ease of *α*-amino radical formation from suitable *N*-based precursors under appropriate photocatalytic conditions,[27] we first screened a small set of photocatalysts (**PCs** directly below and Table 3.1; entries 1-5). Among the five **PCs** tested, we found that the use of Ir-derived **PC2** (entry 2) gave the best results and promoted full conversion of **3.1a** with a 71% NMR yield of **3.2a** as a single stereoisomer (*E*). Next, some other bases such as Ph_3N, CsOAc and HCO_2Na were scrutinized under this reaction, but the yield of **3.3a** could not be improved. Further variations of this protocol (solvents and additives) showed that the system in the presence of a minimal amount of H_2O improves its efficiency (entry 2 vs. 9; 71 vs. 48% yield of **3.3a**) while increasing the amount of H_2O to 100 or 150 µL did not improve the yield any further. Performing the reaction in a polar solvent, such as CH_3CN or DMF resulted in moderate product yield, while the DMF-based system provided mostly byproduct **3.13** (**Table 3.1**). Neither the use of THF or 1,4-dioxane in this catalytic system was competitive (enough) likely due interference of the *O*-donor atoms present in these solvents (entry 10-15).



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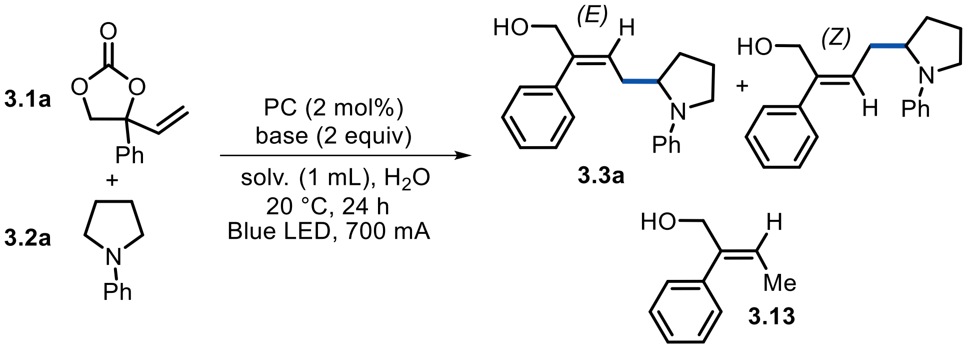
(27) See for an example of the recent use of this substrate: K. Ree Lee, S. Ahn, S.-G. Lee, *Org. Lett*. **2021**, *23*, 3735−3740.

Table 3.1. Screening of the PC, base, solvent and control experiments for the radical induced decarboxylative synthesis of tetra-substituted alkenes **3.3a**.[a]

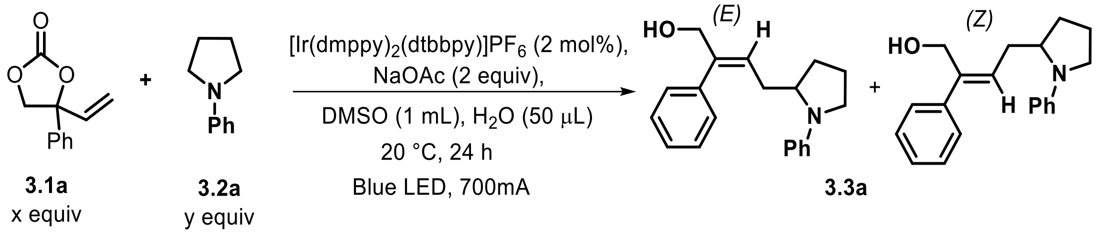


Entry	PC	Solv./base	Conv. **3.1a** [%][b]	Yield **3.3a** [%][b]	E/Z [b]
1	**PC1**	DMSO, NaOAc	>99	58	>99:1
2	**PC2**	**DMSO, NaOAc**	**>99**	**71**	**>99:1**
3	**PC3**	DMSO, NaOAc	94	49	65:35
4	**PC4**	DMSO, NaOAc	74	51	78:22
5	**PC5**	DMSO, NaOAc	32	20	30:70
6	**PC2**	DMSO, Ph_3N	82	35	>99:1
7	**PC2**	DMSO, CsOAc	>99	61	>99:1
8	**PC2**	DMSO, HCOONa	96	47	>99:1
9[c]	**PC2**	DMSO, NaOAc	95	48	>99:1
10[d]	**PC2**	DMSO, NaOAc	>99	52	>99:1
11[e]	**PC2**	DMSO, NaOAc	>99	68	>99:1
12	**PC2**	DMF, NaOAc	>99	27[f]	>99:1
13	**PC2**	CH_3CN, NaOAc	93	42	>99:1
14	**PC2**	THF, NaOAc	23	–	–
15	**PC2**	1,4-dioxane, NaOAc	22	–	–

[a] General conditions: **3.1a** (0.10 mmol), **3.2a** (0.25 mmol), **PC** (2.0 mol%), NaOAc (2 equiv), solvent (1.0 mL), H_2O (50 µL), 700 mA blue LED, 20 °C for 24 h. [b] Yields were determined by ^{1}H NMR using 1,3,5-tri-methoxybenzene as internal standard, the *E/Z* values were also determined by this method. [c] In the absence of added H_2O. [d] Adding 100 µL H_2O. [e] Adding 150 µL H_2O. [f] Byproduct **3.13** generated in 26% yield.

A further exploration of the reaction stoichiometry of this catalytic process indicated that both reducing and increasing the amount of radical precursor led to slightly decreased yield of product. Switching to the use of an excess of vinyl cyclic carbonate also gave poorer results. We suppose that the high reactivity of the double bond and ring strain of the VCC reagent could negatively affect its potential decomposition under the reaction conditions.

Table 3.2. Variation of the reaction stoichiometry in the allylic substitution process.[a]

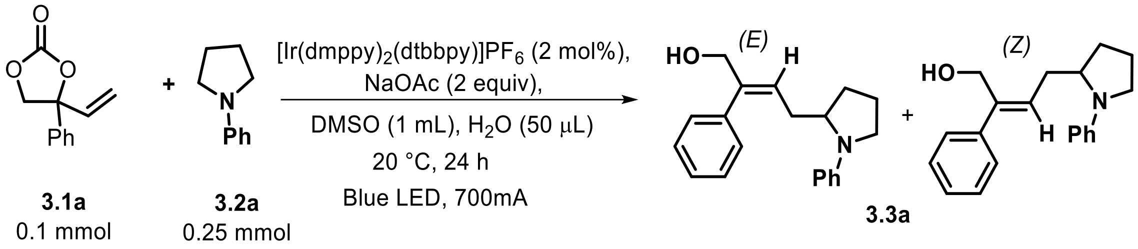


Entry	x (equiv) VCC	y (equiv) amine	Conv. **3.1a** (%)	Yield of **3.3a** (%)[b]	*E/Z* [b]
1	1	1.5	93	54	>99:1
2	1	2.0	>99	67	>99:1
3	**1**	**2.5**	**>99**	**71**	**>99:1**
4	1	3.0	>99	65	>99:1
5	1	5.0	95	60	>99:1
6	1.2	1	>99	26	>99:1
7	1.5	1	>99	37	>99:1

[a] General procedure A (Experimental section): **3.1a** (x mmol), **3.2a** (y mmol), [Ir(dmppy)$_2$(dtbbpy)]PF$_6$ (2 mol%), NaOAc (2 equiv), solvent (1 mL) and H_2O (50 μL), 700 mA blue LED, 20 ºC for 24 h. [b] Yields and *E/Z* values were determined by ^{1}H NMR using 1,3,5-trimethyloxybenzene as internal standard, and the ***Z*** isomer was not detected.

Before investigating the scope of substrates, further control experiments were conducted. The presence of light (entry 1), the **PC2** (entry 2) and base (entry 5) are indispensable. The reaction under air (entry 4) showed lower efficiency likely as a result of interference with the in situ formed *α*-amino radicals.

Table 3.3. Control reactions using the benchmark conversion of **3.1a** and **3.2a**.[a]

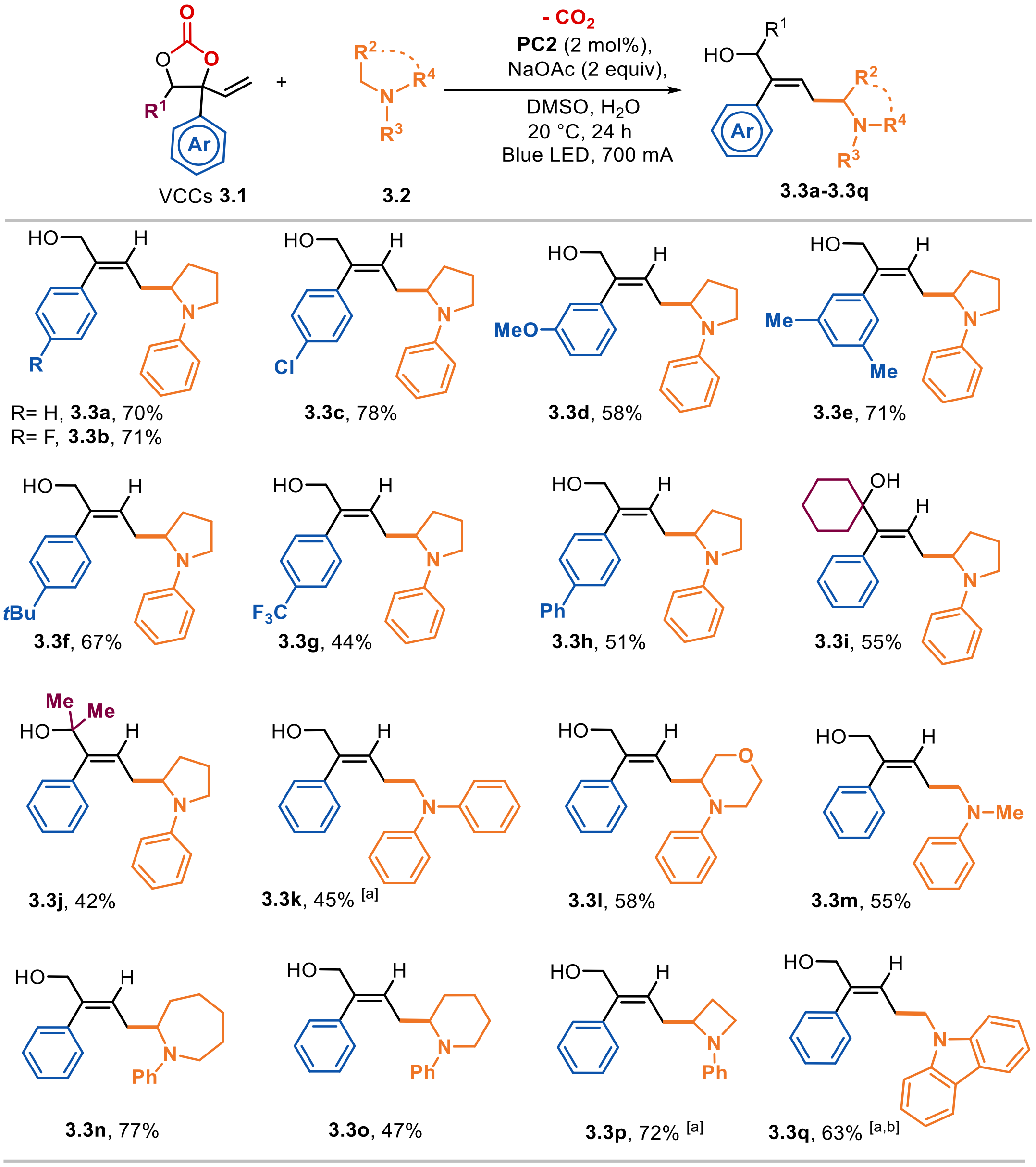


Entry	Change to standard conditions	Conv. **3.1a** (%)	Yield of **3.3a** (%)[b]	*E/Z* [b]
1	no light	0	0	–
2	no $[Ir]^{PC}$	26	18	33:67
3	no $[Ir]^{PC}$ + air	0	0	–
4	air	>99	19	>99:1
5	no base	0	0	–

[a] General procedure A (Experimental section): **3.1a** (0.1 mmol), **3.2a** (0.25 mmol), $[Ir(dmppy)_2(dtbbpy)]PF_6$ (2 mol%), NaOAc (2 equiv), DMSO (1 mL) and H_2O (50 μL), 700 mA blue LED, 20 ºC for 24 h. [b] Yields and *E/Z* values were determined by ^1H NMR using 1,3,5-trimethyloxybenzene as internal standard.

3.2.2. Scope of products

Scope of tri-substituted olefins. We first explored the preparation of trisubstituted olefins starting from VCCs **3.1** that are devoid of an activating substituent. The terminal C=C bonds are relatively unreactive but undergo the target transformation combining a variety of VCC and amine reagents (Scheme 3.8). Various aryl groups in the VCC can be employed providing olefin products **3.3a**-**3.3h** in yields of up to 78% and, importantly, as a single stereoisomer (*E*). More elaborate VCCs (at R^1) can also be used allowing to further structurally diversify the products (i.e., **3.3i** and **3.3j**). Apart from the VCC, the structure of the amine precursor can also be easily altered and examples of more functional acyclic and larger cyclic amines with ring sizes ranging from 4 to 7 can productively engage in this protocol leading to their trisubstituted olefin products (**3.3k**-**3.3q**) with appreciable yields. It should be noted that the protocol is highly robust, has a high level of user-friendliness and these photoreactions are easily set up making it thus attractive towards the formation of challenging stereodefined tetrasubstituted olefins (*vide infra*).



Scheme 3.8. Scope of trisubstituted olefins **3.3a-3.3q** derived from various VCCs **3.1** and amine precursors **3.2**. Conditions: **3.1a** (0.1 mmol), **3.2a** (0.25 mmol), [Ir(dmppy)$_2$(dtbbpy)]PF$_6$ (2 mol%), NaOAc (2 equiv), DMSO (1 mL) and H_2O (50 μL), 700 mA blue LED, 20 ºC for 24 h; all reported yields are of the isolated products with *E/Z* >99:1 unless stated otherwise. [a] 2 equiv of the amine were used. [b] Using [Ir(dFCF$_3$ppy)$_2$(dtbbpy)]PF$_6$ instead of [Ir(dmppy)$_2$(dtbbpy)]PF$_6$.

Scope of tetra-substituted olefins. Given the success of the formation of products **3.3a**-**3.3q**, we then focused on using VCCs with an aryl group introduced at the double bond. Obviously, this should more easily stabilize the initial radical addition product, and lead to the target products but simultaneously introduces a stereochemical challenge. The developed protocol could be, however, easily extended to the synthesis of complex olefin scaffolds (Scheme 3.9, **3.4a**-**3.4r**) with overall improved product yields compared to the trisubstituted products. The conversion of VCCs **3.1** with a simple phenyl on the C=C bond while varying the nature of the amine, provided products **3.4a**-**3.4e** with good yields of up to 90%. Moreover, they were isolated as single stereoisomers (note that in these specific compounds, the configurations are assigned as *Z*). Variation of the other aryl group in the VCC was also feasible creating a wider pool of aromatic substituents in the olefins **3.4g**-**3.4r** that were typically formed in yields >75% as stereodefined products (*Z/E* >99:1). In a few cases, though, lower *Z/E* values were obtained. The synthesis of **3.4f** (64%, *E/Z* = 60:40; R^3 = methyl) and **3.4s** (71%, *E/Z* = 53:47; R^3 = -$(CH_2)_2C_6H_5$) proceeded with lower process control and at this stage we believe that this is a result of a lower degree of steric discrimination between both sides of the C=C bond. In the case of products **3.4j** (95%, *E/Z* = 73:27) and **3.4o** (82%, *dr* = 74:26), the lower stereo-outcome of the process can be tentatively explained by the presence of a (photoactive) thiophene unit (**3.4j**). For **3.4o**, a possible intramolecular HO⋯Si interaction involving the pendent OTBS group may influence the reactive conformation along its formation pathway. Replacing the aryl group by a *tert*-butyl one in the VCC had no detrimental effect on the selectivity of the process, and product **3.4t** could be isolated in an appreciable yield of 75%. We also tested amine precursors with *α*-substituents (methyl groups; synthesis of **3.4u** and **3.4t**) providing **3.4u** in good yield and excellent regiocontrol (92%, *rr* >20:1). Product **3.4t**, however, was produced in only moderate yield (42%) likely because of a more sterically hindered radical being in situ formed when exposed to the photocatalyst slowing down its addition to the double bond of the VCC.

Apart from the cyclic amine precursors, the synthesis of **3.4n** (74%) shows that acyclic amines are also efficient reaction partners in this radical-based protocol towards tetrasubstituted olefins. Finally, the preparation of **3.4p** was performed at a 10-fold scale providing similar efficiency (81 *vs* 84% yield) and showing the process to be robust in this respect. In the case of **3.4g**, we were able to unambiguously confirm its molecular structure by single crystal structure determination using 3D electron diffraction (see insert at the top of Scheme 3.9),[28] which in combination with 2D NMR methods (GOESY-^{1}H NMR) were used to assign to stereochemical configurations of all products.

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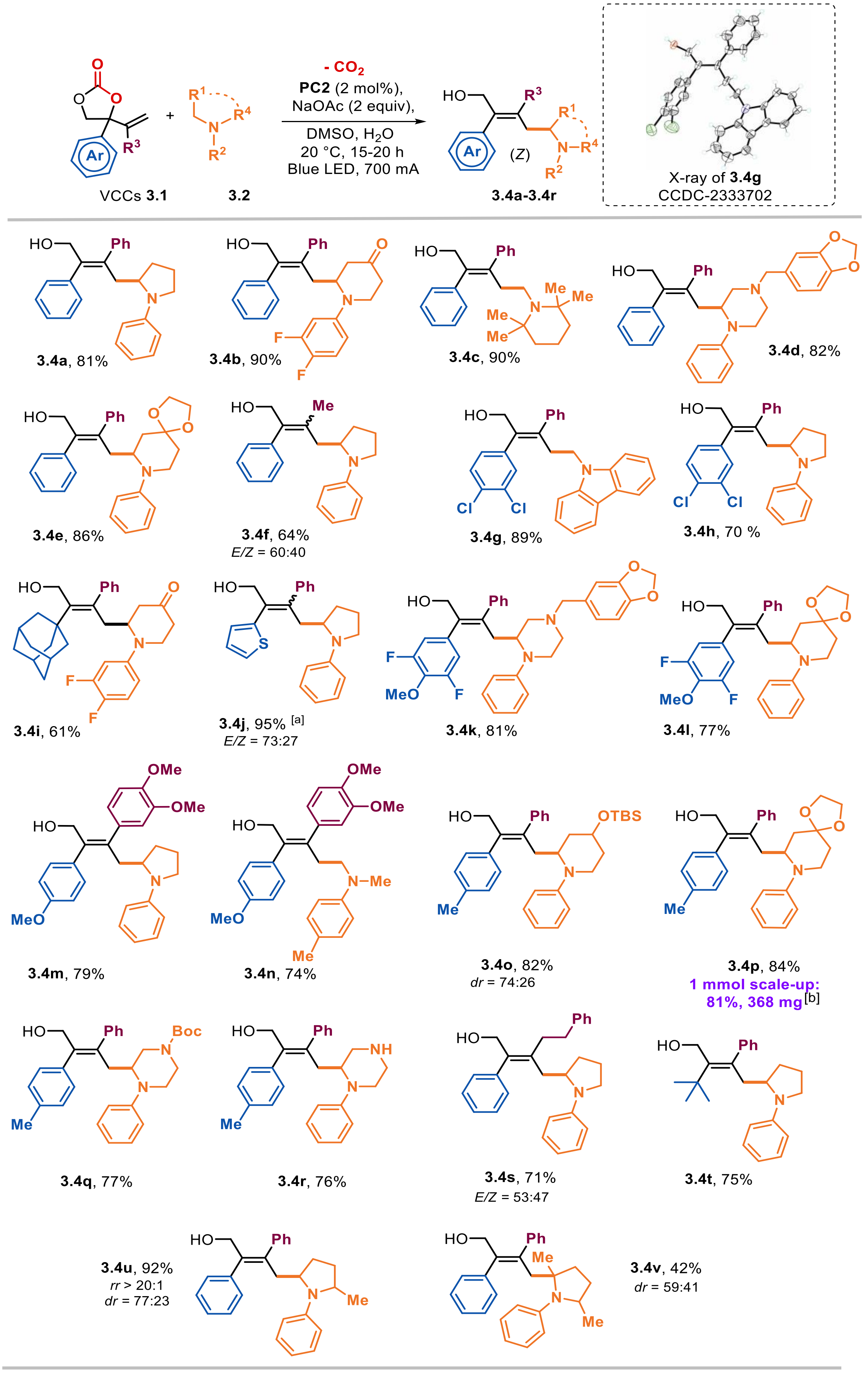
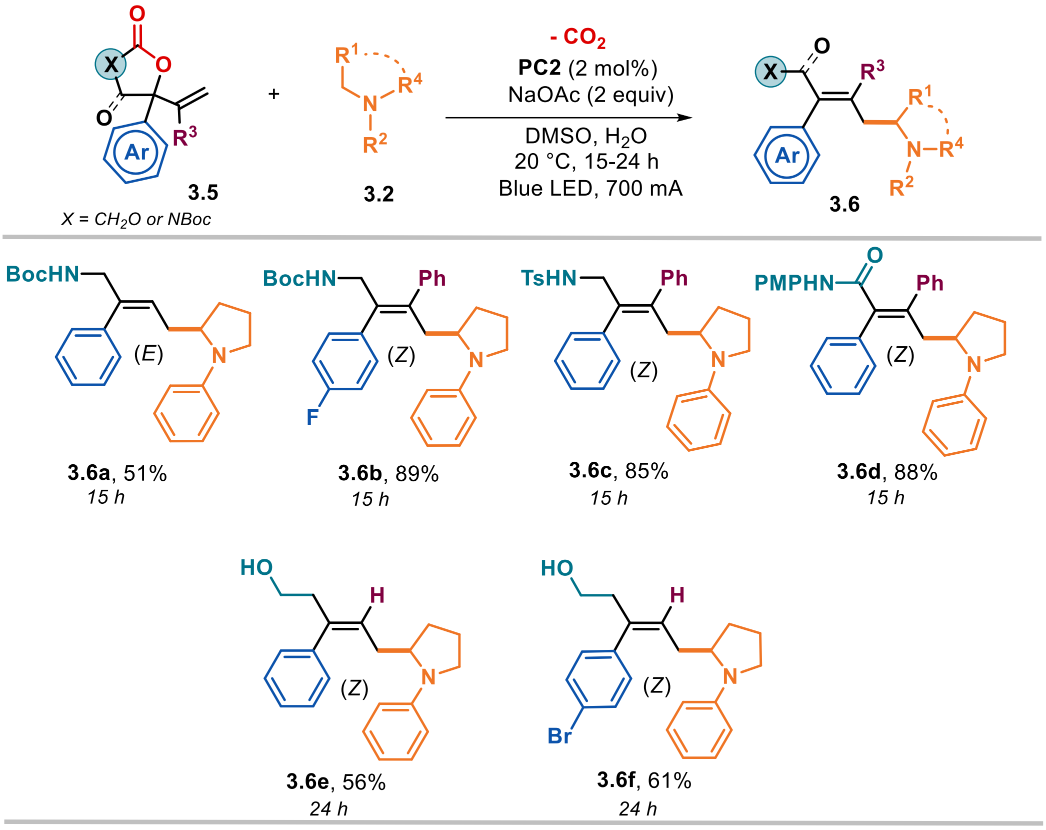
(28) Deposition number 2333702 contains the supplementary crystallographic data for compound **3.4g**. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service, see for more details: https://www.ccdc.cam.ac.uk/structures/?gad_source=1&gclid=CjwKCAjwt-OwBhBnEiwAgwzrUizhlitT71iN5AKpeRYJqq9lBH89VdJeRVIRjH8AdNye-h9Ejha6VBoCrJEQAvD_BwE.



(*details on the next page*)

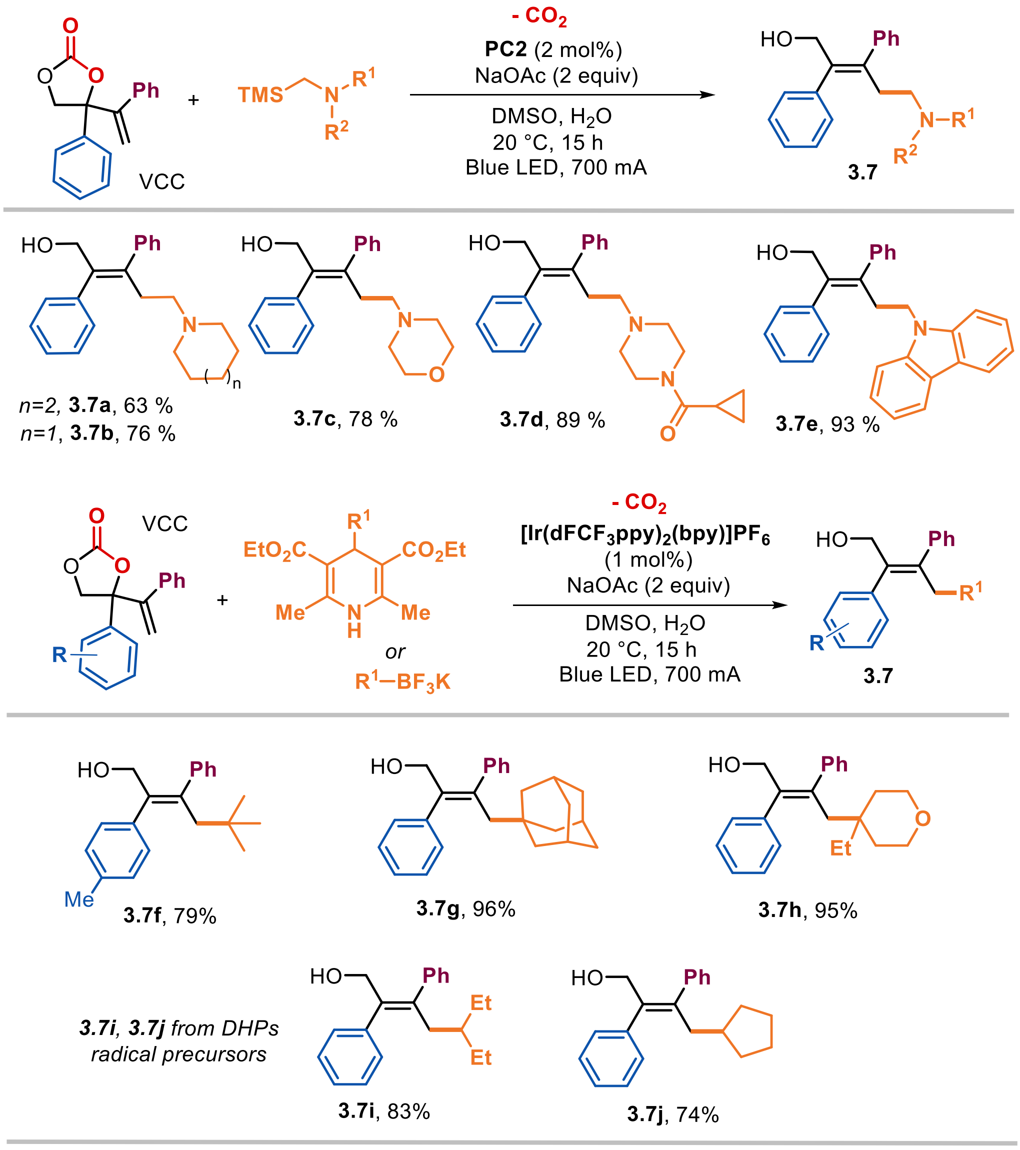
Scheme 3.9 *(previous page).* Scope of tetrasubstituted olefins **3.4a**-**3.4v** derived from various VCCs **3.1** and amine precursors **3.2**. Conditions: **3.1a** (0.1 mmol), **3.2a** (0.25 mmol), [Ir(dmppy)$_2$(dtbbpy)]PF$_6$ (2 mol%), NaOAc (2 equiv), DMSO (1 mL) and H_2O (50 µL), 700 mA blue LED, 20 ºC for 24 h; all reported yields are of the isolated products with *E/Z* >99:1 unless stated otherwise. The insert shows the X-ray molecular structure of **3.4g**. [a] The reaction time was 30 min. [b] 2 equiv of the amine were used.

Extending the reaction partners. We then set out to amplify the reaction partners in terms of the heterocyclic (Scheme 3.10) and radical precursors (Scheme 3.11). We considered both the use of two cyclic carbamates (X = NBoc) and a larger-ring, six-membered analogue of the VCCs **3.1** (X = CH_2O instead of "O") and combined these under the optimized reaction conditions (cf., Table 1, entry 2) with the benchmark amine *N*-phenyl pyrrolidine. The use of NBoc- and NTs-based, five-membered cyclic carbamates is also feasible and shows essentially the same reactivity patterns. The trisubstituted olefin (**3.6a**; *E/Z* >99:1) was isolated in 51% yield, whereas tetrasubstituted **3.6b** and **3.6c** were isolated in higher (89% and 85%, respectively) yield as exclusive *Z*-isomers. Other heterocyclic precursors with an additional carbonyl substituent (synthesis of **3.6d**) can also be effectively employed and allow products such as **3.6d** (88%) featuring an enamide fragment to be isolated. Apart from five-membered precursors such as cyclic carbonates/carbamates, six-membered vinyl cyclic carbonate analogues of **3.1a** are also productive substrates leading to the formation of stereodefined, trisubstituted olefins **3.6e** (56%) and **3.6f** (61%). These results help to establish that the reaction protocol is not necessarily limited to a specific kind of heterocyclic substrate.



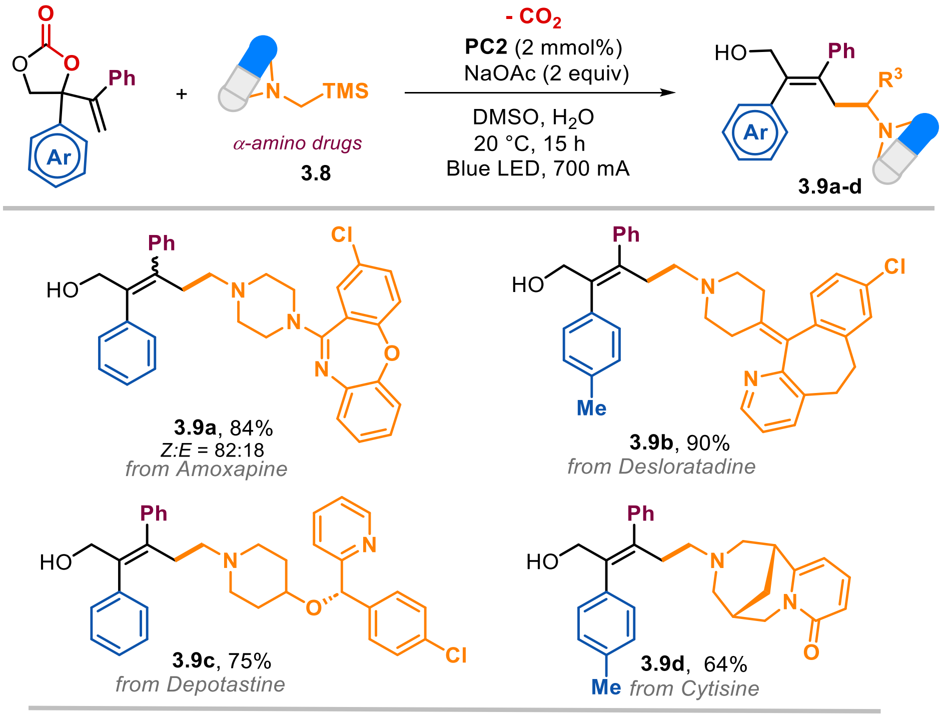
Scheme 3.10. Use of other heterocycles to expand the scope of the developed photocatalytic process.

We further assessed the use of (slightly) different radical precursors (Scheme 3.11) taking advantage of the availability and ease of *N*-based radical formation from TMS-based precursors, alkyl trifluoroborate salts and 1,4-dihydropyridines (DHPs). In the case of the TMS-containing *N*-reagents, in the presence of a VCC with a Ph-substituent on the C=C bond, the formation of tetrasubstituted olefins **3.7a-3.7e** was straightforward in up to 93% yield, and in all cases the products were isolated as exclusive *Z*-isomers. When various organotrifluoroborate salts were used as radical precursors, a similar photocatalytic protocol afforded **3.7f-3.7h** in 79-96% yield and again the products were isolated as single stereoisomers (*Z*). Similarly, the use of 1,4-dihydropyridines (DHPs) as radical precursors gave access to product **3.7i** (83%) and **3.7j** (74%) in good yields.



Scheme 3.11. Use of other radical precursors to expand the scope of the developed photocatalytic process. Here 2 equiv of the TMS-based amine, trifluoroborate salt or DHP radical precursor were used.

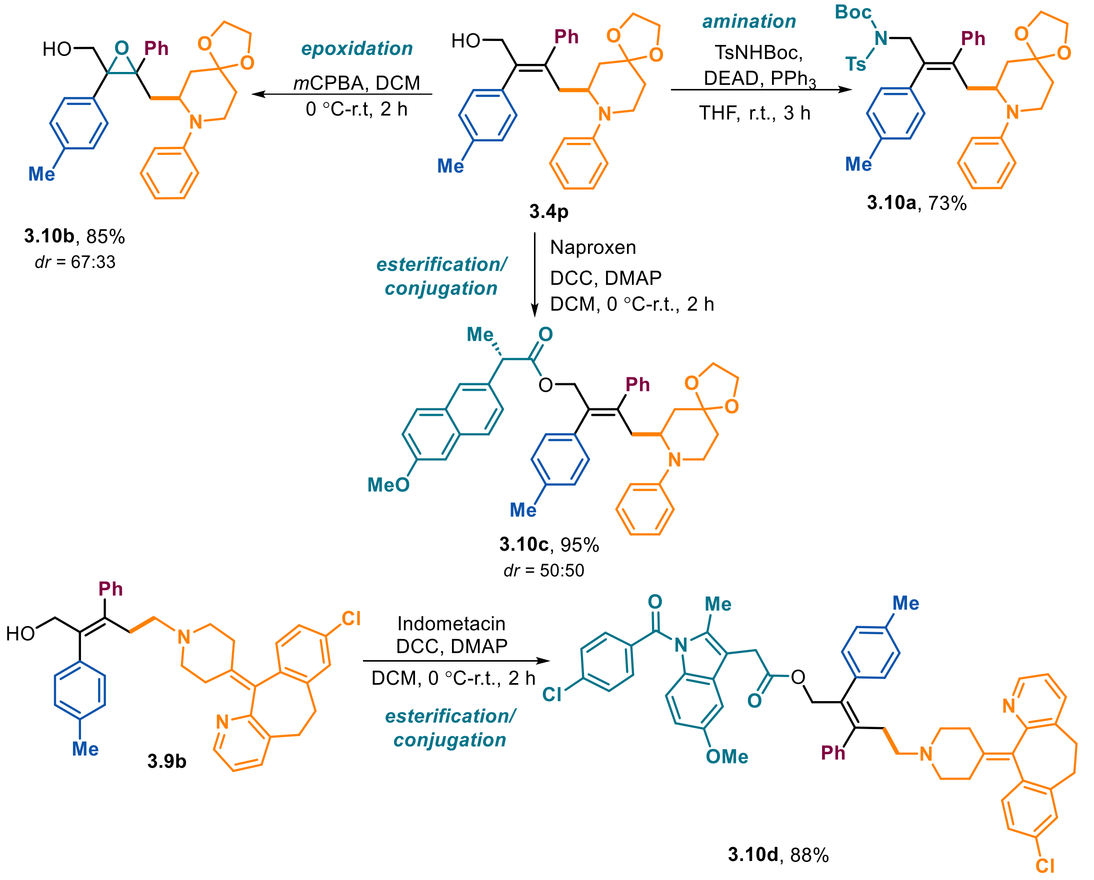
Drug-modification potential. Given the efficient nature of the use of TMS-derived *N*-based reagents as suitable radical precursors, we then examined four α-amino equipped drug molecules towards their functionalization using the optimized photocatalytic protocol (Scheme 3.12, compounds **3.9a-d**). Gratifyingly, we found that our procedure could also be successfully applied leading to good yields of these drug-modified scaffolds (64-90%) and generally with high stereofidelity.



Scheme 3.12. Functionalization of amine-based drug molecules under the optimized photocatalytic conditions. Here 2 equiv of the TMS-based radical precursor were used.

3.2.3. Post-synthetic use of olefinic products

In order to assess the suitability of stereodefined tetrasubstituted olefins as possible synthons, we examined some transformations of **3.4p** and **3.9b** that can create entries to further diversified products (Scheme 3.13). First **3.4p** was subjected to a formal amination by treating TsNHBoc in the presence of DEAD/PPh_3 (Mitsunobu reaction) delivering allylic amine product **3.10a** in 73% yield. Next, we examined the oxidation of the same starting material using *m*CPBA, which produced the epoxide **3.10b** in 85% as a mixture of two diastereoisomers (67:33 *dr*). The alcohol group within **3.4p** and **3.9b** were then both used to create conjugates with carboxylic acid-terminated drug molecules (naproxen and indomethacin) under standard Steglich esterification conditions. In both cases (products **3.10c** and **3.10d**), the corresponding esters were obtained in high yield (95 and 88% yield, respectively) thus showing further options to create increasing molecular complexity.



Scheme 3.13. Post-synthetic use of compounds **3.4p** and **3.9b**.

3.2.4. Mechanistic control experiments

We finally conducted a number of control experiments (Scheme 3.14) to support the mechanistic view expressed in Scheme 3.7. First (Scheme 3.14a), we subjected VCC **3.11a** (with two methyl groups on the terminal carbon of the vinyl fragment) and **3.11b** (with only one methyl substituent) to the optimized reaction conditions to sterically challenge the envisioned radical addition step. In both cases, we were not able to note any product formation, thus aligning with the view that the reaction starts with radical addition to the double bond of the VCC.

Second, to probe the idea that CO_2 extrusion is a crucial step, we performed the optimized procedure on to a vinyl epoxide substrate that cannot undergo decarboxylation but should lead to the same manifold after ring-opening (Scheme 3.14b). In this case we were not able to observe any formation of **3.3a** suggesting indeed that loss of CO_2 is driving the reaction forward. Further to this, when the optimized protocol is carried out in 1 atm of CO_2, we found a nearly similar yield (Scheme 3.14c: **3.4a**, 75 vs 81%)

clarifying that the decarboxylation is likely to be irreversible under the reaction conditions. Then competition experiments were designed to demonstrate the polarity mismatch between VCC and the a-amino radical derived from *N*-phenyl pyrrolidine (Scheme 3.14d). When equimolar amounts of the latter and the more activated olefin *N*-(*tert*-butyl)acrylamide were used, the product distribution showed mostly compound **3.12** (82%) as a product with a much lower amount of **3.3a** (34%). When switching to a VCC with a phenyl-substituent on the double bond (Scheme 3.14e), a different product ratio was found and a larger relative amount of the target product **3.4a** (45%) compared to **3.12** (60%) was isolated. This can be anticipated, taking into account the higher reactivity of these kind of heterocycles towards radical addition and intermediate stabilization.

In order to study the lower stereo-control in the synthesis of tetrasubstituted olefin products **3.4f** and **3.4j**, we decided to follow the reactions in time and monitor the *E/Z* ratio (see Experimental section for details). We found that for **3.4f** the initial *E/Z* ratio (60:40) was maintained throughout a total period of 30 h, excluding the possibility of unwanted post-synthetic photo-isomerization.[29] In the case of product **3.4j** (*E/Z* = 73:27), various conditions were then probed to examine potential post-isolation isomerization of pure ***E*-3.4j**, ***Z*-3.4j** and the synthetic mixture in the presence of light and the PC. For all three compositions, the reaction mixture showed after 12 h of irradiation an increase of the *E/Z* ratio in the range of 83:17 up to 86:14 (see full details in the Experimental section). The combined results suggest that undesired photo-isomerization may be a function of the level of conjugation present in the product and whether it contains a photoactive unit (cf., a thiophene in the case of **3.4j**).

Finally, we performed Stern-Volmer quenching studies (see Experimental section for details, see for a visual Scheme 3.14f) that showed that the excited **PC2** is efficiently quenched by the amine reagent **3.2a**, but not by the VCC substrate. This suggests that radical formation is primarily occurring from the amine reagent, initiating the entire manifold.

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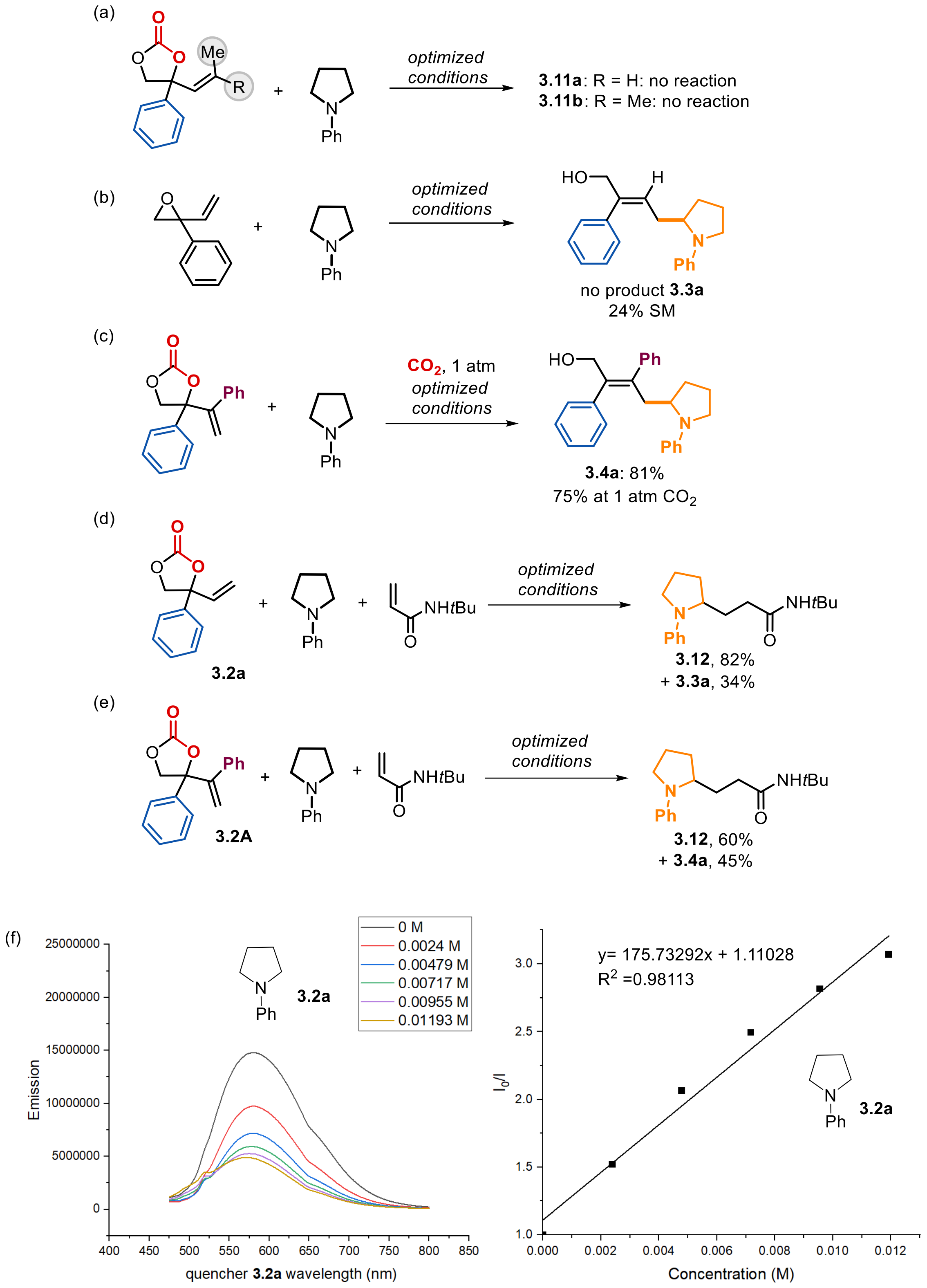
(29) T. Nevesely, M. Wienhold, J. J. Molloy, R. Gilmour, *Chem. Rev.* **2022**, *122*, 2650−2694.



Scheme 3.14. Mechanistic control experiments. The yields for **3.12** under (d-e) are based on the acrylamide reagent, while the ones reported for **3.3a** and **3.4a** are based on **3.2a** and **3.2A**, respectively. Under (f), the Stern-Volmer quenching experiment with amine **3.2a** is shown.

3.3. Conclusions

We here present an efficient, user-friendly and attractive radical-based method for the synthesis of stereodefined tri- and tetrasubstituted olefins with a wide structural diversity. The photocatalytic process enables the coupling between modular VCCs and related reagents. Furthermore, more complex substrates can be employed allowing the protocol to be adapted to various synthetic campaigns directed towards fine-chemical or pharmaceutical development. Mechanistic information has been obtained that shows that initial radical addition to the C=C bond of the VCC takes place, following a sequence of double bond migration and a key CO_2 extrusion driving the manifold forward.

3.4. Experimental section

3.4.1. General information

Air- and water-sensitive reactions were carried out in heat-gun-dried glassware under an Ar or N_2 atmosphere using standard Schlenk techniques. Reactions were monitored by TLC and/or ^{1}H NMR. TLC was carried out on 0.25 mm Merck aluminum backed sheets coated with 60 F_{254} silica gel. Visualization of the silica plates was achieved using a UV lamp (λ = 254 nm) and/or by using the stain solutions of a $KMnO_4$ or ceric ammonium molybdate. Flash chromatography was carried out on Sigma-Aldrich silica gel 60 (70-230 mesh) using the indicated eluent system.

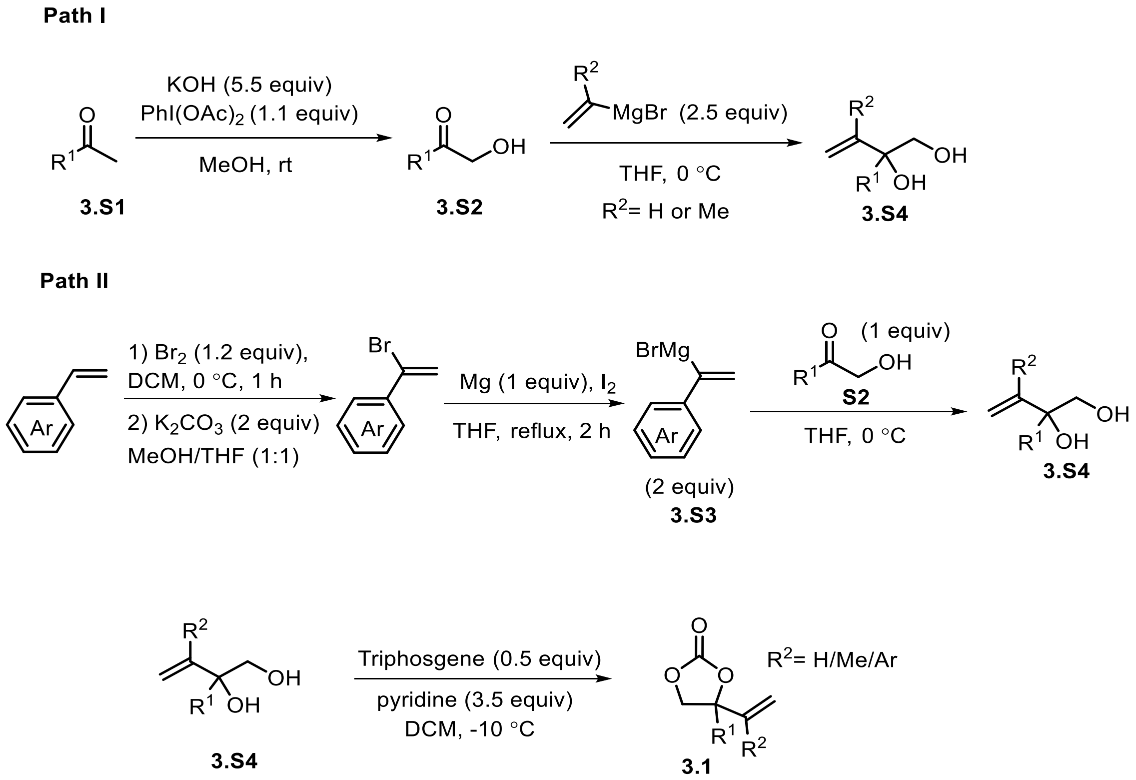
Commercially available reagents and solvents were purchased from Sigma-Aldrich, TCI, Fluorochem, Strem Chemicals, ABCR GmbH, Acros Organics or Alfa Aesar, and were used without further purification. Starting materials were synthesized by following procedures as stated, $[Ir(dmppy)_2(dtbbpy)]PF_6$ was synthesized according to a previously reported procedure.[1] Solvents were dried using an Innovative Technology PURE SOLV solvent purification system.

^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded at room temperature on a Bruker AV-300, AV-400 or AV-500 spectrometer and referenced to their residual deuterated solvent signals. Coupling constants (J) are reported in Hertz with the following splitting abbreviations: s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiples. All reported NMR values are given in parts per million (ppm). Mass spectrometric and electro diffraction analyses were performed by the Research Support Group at ICIQ. Fluorescence measurements were carried out on a Fluorolog Horiba Jobin Yvon spectrofluorimeter equipped with a photomultiplier detector, a double monochromator, and a 350W xenon light source.

Photoreactions were performed in a parallel photoreactor with 8 spots using flat-bottom 10-mL vial (see chapter 2, experimental section 2.3). The reactions were thermostated using a Heidolph rotacool. OSRAM Oslon SSL 80 royal-blue LEDs mounting on a star PCB were used and cooled passively by a common heatsink. The LEDs were powered in series using a current limited power supply (RS Pro RS-3005D).

3.4.2. General procedure for the preparation of starting materials

General procedure A for synthesis of the vinyl cyclic carbonates 3.1:



Two pathways were used to prepare compounds 3.S4:

Path I:

Step 1: To a cold solution of the ketone **3.S1** (15 mmol, 1 equiv) in MeOH was added the KOH (4.629 g, 82.5 mmol, 5.5 equiv) in portions, and then was added the $PhI(OAc)_2$ (diacetoxy iodobenzene) (5.314 g, 16.5 mmol, 1.1 equiv) slowly. After being stirred at 0 ºC to room temperature for 2-3 hours, the reaction mixture was concentrated under the reduced pressure and the residue was extracted with H_2O (30 mL) and Et_2O (30 mL). The organic phase was separated, dried over Na_2SO_4 and filtered. After concentrated, the obtained residue was dissolved in MeOH (30 ml) and 2 N HCl (30 mL), and then stirred overnight at room temperature. Next, a saturated aqueous solution of $NaHCO_3$ was added to the reaction mixture until pH 7 and diluted with DCM (30 mL). The organic phase was separated and dried with anhydrate Na_2SO_4, then the filtrate was concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (hexanes/EtOAc= 30:1 to 20:1) to yield **3.S2** (typically 60-70% yield).

Step 2: An oven-dried Schlenk tube containing a magnetic stirring bar charged with **3.S2** (10 mmol, 1 equiv) before evacuating and back-filling with N_2, and then was added THF (20 mL) and Grignard reagent (1.0 M in THF, 25 mL, 2.5 equiv) by syringe at 0 ºC. After being stirred at room temperature for 4-5 hours, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate (3 × 15 mL). The combined organic phases were dried over Na_2SO_4, concentrated under reduced pressure, then the obtained residue was purified by column chromatography on silica gel (hexanes/EtOAc= 10:1 to 5:1) to afford the pure product **3.S4** (typically in 50-70% yield).

Path II:

Step 1: To a 100 mL dry round flask, the respective styrene derivative (40 mmol) and DCM (80 mL, 0.5 M) was added. After cooling to 0 ºC, Br_2 was added dropwise and the reaction was stirred at 0 ºC to room temperature for 1 h. After the styrene was consumed and monitored by the thin layer chromatography (TLC), the solution was quenched with the aqueous $Na_2S_2O_3$ and filtered through Cite. The mixture was extracted with DCM and organic phase was collected. Then the solution was concentrated under the reduced pressure and residue was directly used in the next step without any purification. To a solution of above crude in THF/MeOH (80 mL: 80 mL, 0.25 M) was added the K_2CO_3 (1.103 g, 80 mmol, 2 equiv) at the room temperature. After being stirred for 16 h, the reaction mixture was quenched with water and organic solvent was removed volatiles on the rotary evaporator. The reaction residue was extracted with Et_2O (40 mL) and water 40 (mL). The organic phase was collected and dried over Na_2SO_4 and filtered. After concentrated under the reduced pressure, the residue was purified by silica gel chromatography (hexanes/EtOAc= 100:1) to provide the pure α-brominated alkenes (typically in 50-70% yield).

Step 2:[30] Mg chips (486 mg, 2 equiv), one granule I_2 and THF (30 mL) were added into a dry two-necked round flask under N_2. After the reaction temperature was increased to 80 ºC (refluxing), the above α-brominated styrene was added dropwise slowly (1 drop in 2 seconds) and monitored the reaction color changes (typically from brown to colorless) at the same time. After changing to colorless, the rest of the styrene was added into the system and refluxing about 2 hours. The Mg chips consumed and cooling down to 0 ºC,

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(30) L. Dai, W. Liu, Y. Q. Zhou, Z. Zeng, X. Y. Hu, W. D. Cao, X. M. Feng, *Angew. Chem. Int. Ed.* **2021**, *60*, 26599–26603.

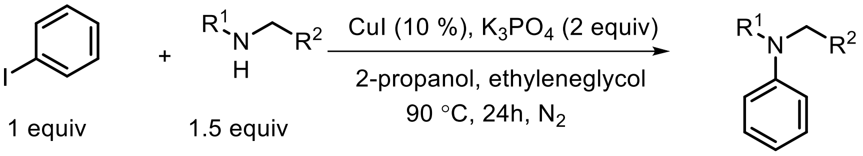
the **3.S2** (10 mmol dissolved in 10 mL THF, 1 equiv) was added to the prepared Grignard reagent **3.S3** (about 2 equiv). After being stirred at 0 ºC to room temperature for 16 h, the reaction mixture was extracted with EtOAc (30 mL) and H_2O (30 mL) three times. The organic phase was separated and dried with anhydrate Na_2SO_4, then the filtrate was concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (hexanes/EtOAc= 10:1 to 5:1) to yield **3.S4** (typically in 70-90% yield).

Synthesis 3.1: An oven-dried Schlenk tube containing a magnetic stirring bar charged with diol **3.S4** (7 mmol, 1 equiv) before evacuating and back-filling with N_2, then sequentially added pyridine (2.22 g, 24.5 mmol, 3.5 equiv) and a solution of triphosgene (1.04 g, 3.5 mmol, 0.5 equiv) in 10 mL DCM by syringe at -10 ºC. After being stirred at -10 ºC to room temperature for 1-2 hours, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and diluted with DCM (30 mL). The organic phase was washed with 1 N HCl (3×20 mL), $NaHCO_3$ (3 × 20 mL) and brine (3 × 20 mL). The combined organic phases were dried over Na_2SO_4, concentrated under reduced pressure, then the obtained residue was purified by column chromatography on silica gel (hexanes/EtOAc= 15:1 to 10:1) to afford the pure product as a light-yellow oil (typically in 80-90% yield).

General procedure for the preparation of substituted amines compounds:

All phenyl-substituted and TMS-substituted amines are known and were prepared from the amine according to following previously reported **General Procedure B** and **C**. Analytical data were consistent with the literature values.

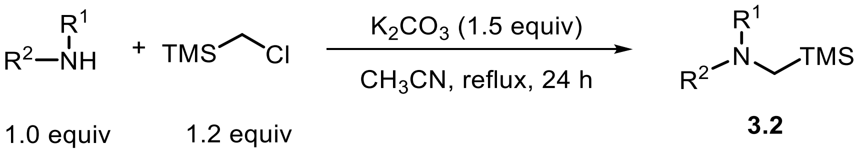
General procedure B for synthesis of phenyl-substituted amine compounds 3.2:



3.2

Synthesis of 3.2:[31] A 100 mL-round flask containing a magnetic stirring bar charged with CuI (95 mg, 0.5 mmol, 0.1 equiv) and K_3PO_4 (2.12 g, 10 mmol, 2 equiv) before evacuating and back-filling with N_2, and then was added 2-propanol (10 mL), ethyleneglycol (1.1 mL) and iodo-benzene (5 mmol, 1 equiv) by syringe slowly. After being stirring at 90 °C for 16 h, the reaction mixture was concentrated under reduced pressure. Then the mixture was quenched with saturated aqueous NH_4Cl and extracted with DCM (3 × 15 mL). The combined organic phases were dried over Na_2SO_4, then the obtained residue was purified by column chromatography on silica gel (hexanes/EtOAc= 20:1 to 10:1) to afford the pure product (typically in 80-90% yield).

General procedure C for the synthesis of TMS-substituted amines 3.2:



3.2

Synthesis of 3.2:[32] A 100 mL-round flask containing a magnetic stirring bar charged with K_2CO_3 (620 mg, 1.5 equiv) and amine (3 mmol, 1.0 equiv) before adding CH_3CN (20 mL). Then the (chloromethyl)trimethylsilane (0.5 mL, 440 mg, 1.2 equiv) was added by syringe. After being stirred at refluxing temperature 80° C for 16 h, the reaction mixture was filtered and extracted with CH_3CN. The combined organics were dried over Na_2SO_4, concentrated under reduced pressure. Then the obtained residue was purified by column

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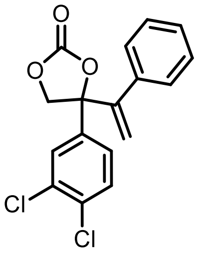
(31) K. Alagiri, P. Devadig, K. R. Prabhu, *Tetrahedron Lett.* **2012**, *53,* 1456–1459.

(32) S. Zheng, W. Wang, W. Yuan, *J. Am. Chem. Soc.* **2022**, *144*, 17776–17782.

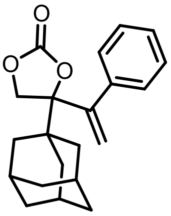
chromatography on silica gel to afford the pure product **3.2** as a light-yellow oil (typically in 70-80% yield).

4-(3,4-Dichlorophenyl)-4-(1-phenylvinyl)-1,3-dioxolan-2-one (3.1G)



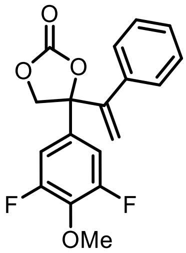
Yellow solid (General Procedure A); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 – 7.47 (m, 2H), 7.33 – 7.27 (m, 3H), 7.26 – 7.23 (m, 1H), 7.08 – 7.04 (m, 2H), 5.61 (d, *J* = 6.0 Hz, 2H), 4.74 (d, *J* = 8.9 Hz, 1H), 4.65 (d, *J* = 9.0 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) 153.3, 146.8, 138.8, 136.9, 133.8, 133.6, 131.1, 128.8, 128.7, 128.4, 128.2, 125.3, 118.8, 86.4, 73.3; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd for. $C_{17}H_{12}Cl_2NaO_3^+$ 357.0056; found 357.0055.

(4-((3*r*,5*r*,7*r*)-Adamantan-1-yl)-4-(1-phenylvinyl)-1,3-dioxolan-2-one (3.1I)



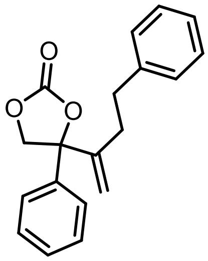
Yellow solid (General Procedure A); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29 – 7.32 (m, 5H), 5.44 (s, 1H), 5.32 (s, 1H), 4.73 (d, *J* = 8.6 Hz, 1H), 4.58 (d, *J* = 8.6 Hz, 1H), 2.02 – 1.96 (m, 3H), 1.69 – 1.64 (m, 3H), 1.60 – 1.54 (m, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.6, 147.7, 140.7, 129.0, 128.4, 128.0, 120.4, 91.5, 70.5, 40.1, 36.6, 36.2, 28.1; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd for. $C_{21}H_{24}NaO_3^+$ 347.1618; found 347.1624.

4-(3,5-Difluoro-4-methoxyphenyl)-4-(1-phenylvinyl)-1,3-dioxolan-2-one (3.1K)



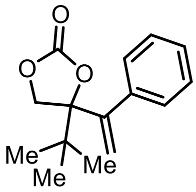
Yellow solid (General Procedure A); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31 – 7.25 (m, 3H), 7.10 – 7.04 (m, 2H), 7.01 – 6.97 (m, 2H), 5.62 (s, 2H), 4.71 – 4.60 (m, 2H), 4.04 (t, *J* = 1.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.7 (dd, *J* = 250.4, 6.3 Hz), 153.3, 146.6, 137.2 (t, *J* = 13.7, 13.7 Hz), 136.9, 133.4 (dd, *J* = 7.9, 7.9 Hz), 128.8, 128.7, 128.2, 118.6, 110.52 (dd, *J* = 17.3, 7.9 Hz), 86.3 (dd, *J* = 1.7, 1.7 Hz), 73.3, 61.9 (t, *J* = 3.6, 3.6 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -126.0; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd for. $C_{18}H_{14}F_2NaO_4^+$ 355.0752; found 355.0750.

4-Phenyl-4-(4-phenylbut-1-en-2-yl)-1,3-dioxolan-2-one (3.1S)



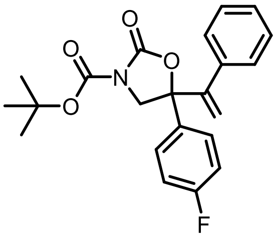
Yellow liquid (General Procedure A); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.42 – 7.35 (m, 5H), 7.25 – 7.22 (m, 2H), 7.20 – 7.15 (m, 1H), 7.08 – 7.05 (m, 2H), 5.35 (s, 1H), 5.26 (s, 1H), 4.78 – 4.73 (m, 1H), 4.64 – 4.58 (m, 1H), 2.73 – 2.64 (m, 2H), 2.37 – 2.20 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.1, 146.5, 141.1, 138.6, 129.08, 129.07, 128.6, 128.4, 126.3, 125.2, 113.0, 88.4, 73.4, 34.4, 32.8; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd for. $C_{19}H_{18}NaO_3^+$ 317.1148; found 317.1148.

4-(*tert*-Butyl)-4-(1-phenylvinyl)-1,3-dioxolan-2-one (3.1T)



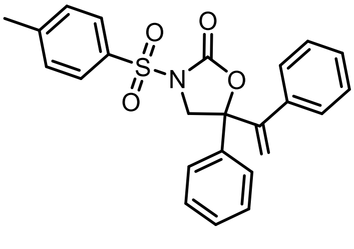
Yellow solid (General Procedure A); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.35 – 7.30 (m, 3H), 7.30 – 7.27 (m, 2H), 5.44 (s, 1H), 5.40 (s, 1H), 4.75 – 4.63 (m, 2H), 0.95 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.5, 148.2, 140.6, 129.0, 128.4, 128.1, 120.3, 91.5, 71.2, 38.6, 25.5; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd for. $C_{15}H_{18}NaO_3^+$ 269.1148; found 269.1146.

***tert*-Butyl-5-(4-fluorophenyl)-2-oxo-5-(1-phenylvinyl)oxazolidine-3-carboxylate (3.5b)**



Yellow solid (General Procedure A); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 – 7.35 (m, 2H), 7.27 – 7.20 (m, 3H), 7.10 – 7.00 (m, 4H), 5.57 (s, 1H), 5.44 (s, 1H), 4.29 (d, *J* = 10.7 Hz, 1H), 4.19 (d, *J* = 10.6 Hz, 1H), 1.51 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.9 (d, *J* = 248.7 Hz), 150.7, 149.4, 148.7, 137.8, 135.5 (d, *J* = 3.3 Hz), 128.7, 128.4, 128.3, 128.1 (d, *J* = 8.4 Hz), 117.8, 115.8 (d, *J* = 21.7 Hz), 84.4, 82.9, 53.4, 28.1; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -112.8; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd for. $C_{22}H_{22}FNNaO_4^+$ 406.1425; found 406.1422.

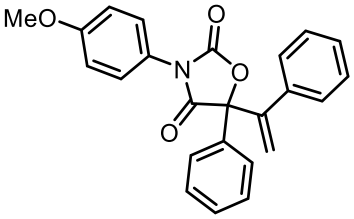
5-Phenyl-5-(1-phenylvinyl)-3-tosyloxazolidin-2-one (3.5c)



Yellow solid (General Procedure A); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.4 Hz, 2H), 7.38 – 7.33 (m, 5H), 7.31 – 7.27 (m, 2H), 7.25 – 7.21 (m, 1H), 7.21 – 7.15 (m, 2H), 6.97 – 6.90 (m, 2H), 5.51 (s, 1H), 5.41 (s, 1H), 4.33 (d, *J* = 1.1 Hz, 2H), 2.45 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.8, 148.1, 145.8, 138.7, 137.7, 134.1, 130.0, 129.1, 128.9, 128.6, 128.4, 128.3, 126.0,

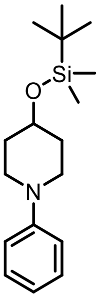
118.3, 84.7, 54.2, 21.9; **HRMS** (ESI/TOF) *m/z*: [M + Na] + Calcd for. $C_{24}H_{21}NNaO_4S^+$ 442.1083; found 442.1090.

3-(4-Methoxyphenyl)-5-phenyl-5-(1-phenylvinyl)oxazolidine-2,4-dione (3.5d)



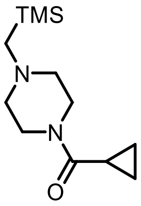
Yellow solid (General Procedure A);[33] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.81 – 7.74 (m, 2H), 7.49 – 7.43 (m, 3H), 7.36 – 7.29 (m, 5H), 7.01 – 6.95 (m, 2H), 6.94 – 6.86 (m, 2H), 5.57 (s, 1H), 5.45 (s, 1H), 3.79 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.1, 160.0, 153.6, 145.7, 137.4, 133.8, 129.5, 129.1, 128.8, 128.5, 128.4, 127.4, 126.5, 123.3, 122.7, 114.7, 89.6, 55.6; **HRMS** (ESI/TOF) *m/z*: [M + Na] + Calcd for. $C_{24}H_{19}NNaO_4^+$ 408.1206; found 408.1207.

4-((*tert*-Butyldimethylsilyl)oxy)-1-phenylpiperidine (3.2o)



Yellow solid (General Procedure B); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.28 – 7.22 (m, 2H), 6.96 (d, *J* = 8.1 Hz, 2H), 6.83 (t, *J* = 7.3 Hz, 1H), 3.93 – 3.83 (m, 1H), 3.53 – 3.40 (m, 2H), 3.07 – 2.95 (m, 2H), 1.94 – 1.81 (m, 2H), 1.75 – 1.64 (m, 2H), 0.91 (s, 9H), 0.08 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.6, 129.2, 119.3, 116.5, 67.6, 46.9, 34.4, 26.0, 18.3, -4.5; **HRMS** (ESI/TOF) *m/z*: [M + H] + Calcd for. $C_{17}H_{30}NOSi^+$ 292.2091; found 292.2110.

Cyclopropyl(4-((trimethylsilyl)methyl)piperazin-1-yl)methanone (3.2d)



Yellow solid (General Procedure C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.68 – 3.47 (m, 4H), 2.42 – 2.21 (m, 4H), 1.86 (s, 2H), 1.69 – 1.62 (m, 1H), 0.91 – 0.86 (m, 2H), 0.69 – 0.64 (m, 2H), 0.00 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.8, 57.1, 56.4, 50.7, 45.5, 42.2, 10.8, 7.3, -1.2; **HRMS** (ESI/TOF) *m/z*: [M + H] + Calcd for. $C_{12}H_{25}N_2OSi^+$ 241.1731; found 241.1736.

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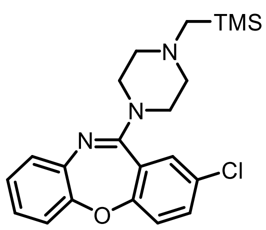
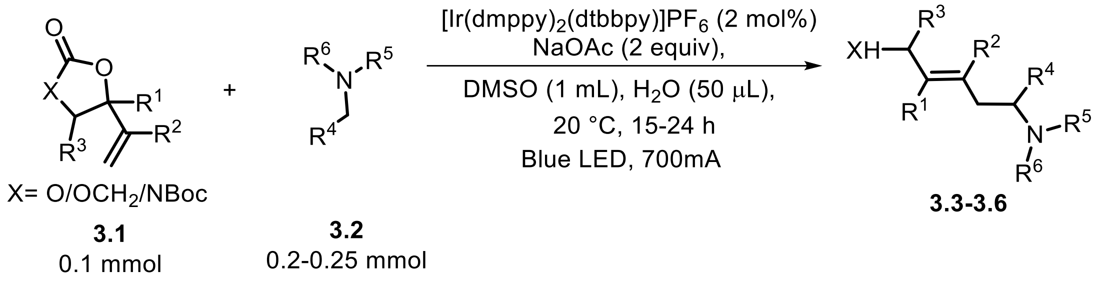
(33) A. Roblin, N. Casaretto, A. Archambeau, *Org. Lett.* **2023**, *25*, 6453–6458.

2-Chloro-11-(4-((trimethylsilyl)methyl)piperazin-1-yl)dibenzo[*b,f*][1,4]oxazepine (3.8a)

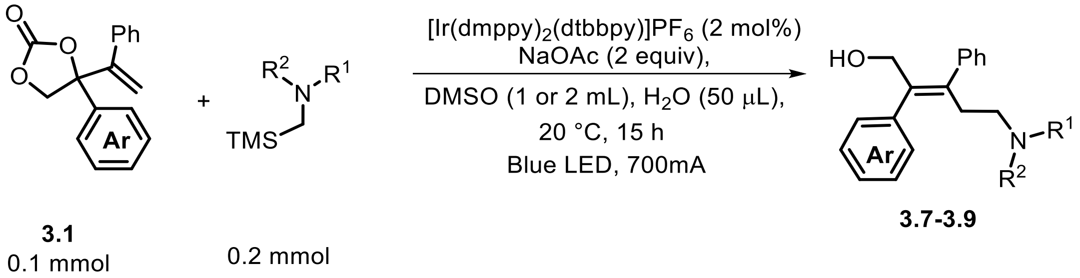


Yellow solid (General Procedure C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.35 (m, 1H), 7.31 – 7.29 (m, 1H), 7.20 – 7.16 (m, 1H), 7.15 – 7.11 (m, 1H), 7.10 – 7.05 (m, 2H), 7.00 – 6.94 (m, 1H), 3.54 (s, 4H), 2.53 (s, 4H), 1.99 (s, 2H), 0.09 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.4, 159.0, 152.0, 140.4, 132.6, 130.3, 129.3, 127.2, 125.9, 125.2, 124.5, 122.8, 120.2, 56.8, 50.9, -1.0; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd for. $C_{21}H_{27}ClN_3OSi^+$ 400.1606; found 400.1603.

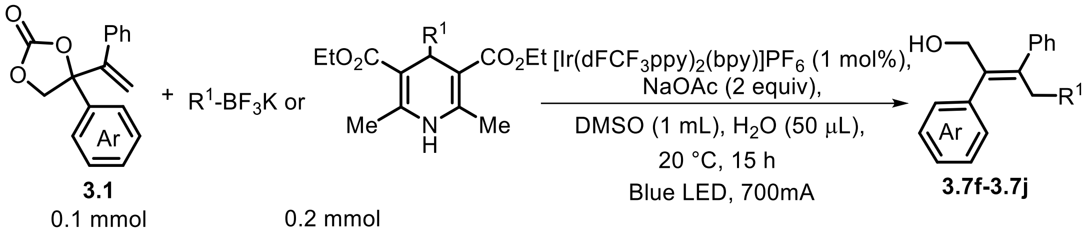
3.4.3. General procedure for the synthesis of the tri- and tetra-substituted alkenes



Method A: [Ir(dmppy)$_2$(dtbbpy)]PF$_6$ (1.9 mg, 2.0 mol%) and NaOAc (16.4 mg, 0.20 mmol, 2.0equiv) were weighed into a 10 mL screw-cap vial. The vial was sealed with a cap containing a silicone septum, evacuated, and filled with argon three times. The degassed solvent DMSO (1 mL, 0.1 M), H_2O (50 µL), VCC (0.1 mmol), and amine **3.2a** (0.2-0.25 mmol) were added, affording a light-yellow solution under Ar atmosphere. The reaction system was further sealed with Parafilm® and irradiated for 15-24 hours at 20 °C using a single high-power blue LED (λ_{em} = 445 nm, 700 mA) from the bottom. After completion, the mixture was directly extracted with EtOAc (20 mL). The organic phase was evaporated to dryness and the residue was purified by column chromatography (SiO_2, hexanes/EtOAc) to afford products **3.3-3.6**.



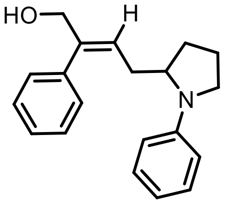
Method B: [Ir(dmppy)$_2$(dtbbpy)]PF$_6$ (1.9 mg, 2.0 mol%), NaOAc (16.4 mg, 0.20 mmol, 2.0 equiv), VCC (0.1 mmol) and TMS-based amine (0.2 mmol, 2 equiv) were weighed into a 10 mL screw-cap vial. The vial was sealed with a cap containing a silicone septum, evacuated, and filled with argon three times. Degassed solvent DMSO (1 mL of DMSO for generating product **3.7a-3.7e** and 2 mL of DMSO for generating product **3.9**) and H_2O (50 µL) were added, affording a light-yellow solution under Ar atmosphere. The reaction system was further sealed with Parafilm® and irradiated for 15 hours at 20 °C using a single high-power blue LED (λ_{em} = 445 nm, 700 mA) from the bottom. After completion, the mixture was directly extracted with EtOAc (20 mL). The organic phase was evaporated to dryness and the residue was purified by column chromatography (SiO_2, hexanes/EtOAc) to afford product **3.7-3.9**.



<u>Method C:</u> [Ir(dFCF$_3$ppy)$_2$(bpy)]PF$_6$ (1.0 mg, 1.0 mol%), NaOAc (16.4 mg, 0.20 mmol, 2.0 equiv), VCC (0.1 mmol) and *t*BuBF$_3$K or DHPs (0.2 mmol, 2 equiv) were weighed into a 10 mL screw-cap vial. The vial was sealed with a cap containing a silicone septum, evacuated, and filled with argon three times. Degassed solvent (DMSO, 1 mL, 0.1 M) and H_2O (50 µL) were added, affording a light-yellow solution under Ar atmosphere. The reaction system was further sealed with Parafilm® and irradiated for 15 hours at 20 °C using a single high-power blue LED (λ_{em} = 445 nm, 700 mA) from the bottom. After completion, the mixture was directly extracted with EtOAc (20 mL). The organic phase was evaporated to dryness and the residue was purified by column chromatography (SiO_2, hexanes/EtOAc) to afford product **3.7f-3.7j**.

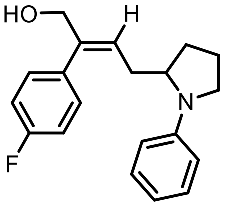
3.4.4. Characterization data for all new compounds

(*E*)-2-Phenyl-4-(1-phenylpyrrolidin-2-yl)but-2-en-1-ol (3.3a)



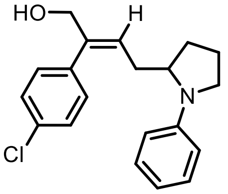
Yellowish oil (Method A, 20.5 mg, 70% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 – 7.35 (m, 2H), 7.34 – 7.30 (m, 1H), 7.24 – 7.20 (m, 2H), 7.15 – 7.10 (m, 2H), 6.61 (t, *J* = 7.3 Hz, 1H), 6.37 (d, *J* = 7.7 Hz, 2H), 5.79 (t, *J* = 7.6 Hz, 1H), 4.34 (s, 2H), 3.75 – 3.62 (m, 1H), 3.37 – 3.26 (m, 1H), 3.14 – 3.08 (m, 1H), 2.54 – 2.47 (m, 1H), 2.04 – 1.80 (m, 4H), 1.58 – 1.53 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.0, 142.9, 138.5, 129.2, 128.8, 128.6, 127.4, 124.9, 115.4, 111.9, 68.1, 58.6, 48.2, 31.6, 30.1, 23.3; **HRMS** (ESI/TOF) *m/z*: [M + H]$^+$ Calcd for. $C_{20}H_{24}NO^+$ 294.1852; found 294.1852.

(*E*)-2-(4-Fluorophenyl)-4-(1-phenylpyrrolidin-2-yl)but-2-en-1-ol (3.3b)



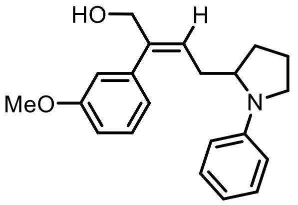
Yellowish oil (Method A, 21.8 mg, 71% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.20 – 7.12 (m, 4H), 7.09 – 7.03 (m, 2H), 6.63 (t, *J* = 7.3 Hz, 1H), 6.38 (d, *J* = 7.7 Hz, 2H), 5.80 (t, *J* = 7.6 Hz, 1H), 4.31 (s, 2H), 3.71 – 3.67 (m, 1H), 3.36 – 3.31 (m, 1H), 3.15 – 3.09 (m, 1H), 2.50– 2.44 (m, 1H), 2.03 – 1.78 (m, 4H), 1.65 – 1.56 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.2 (d, *J* = 246.2 Hz), 147.0, 141.8, 134.4 (d, *J* = 3.5 Hz), 130.5 (d, *J* = 8.0 Hz), 129.2, 125.6, 115.6 (d, *J* = 5.3 Hz), 115.4, 111.9, 68.1, 58.5, 48.3, 31.7, 30.2, 23.3; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -115.14; **HRMS** (ESI/TOF) *m/z*: [M + H]$^+$ Calcd for. $C_{20}H_{23}FNO^+$ 312.1758; found 312.1768.

(*E*)-2-(4-Chlorophenyl)-4-(1-phenylpyrrolidin-2-yl)but-2-en-1-ol (3.3c)



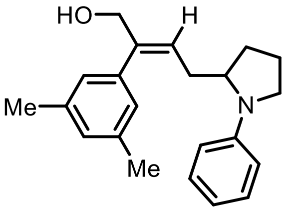
Yellowish oil (Method A, 25.6 mg, 78% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 – 7.32 (m, 2H), 7.18 – 7.09 (m, 4H), 6.63 (t, *J* = 7.3 Hz, 1H), 6.37 (d, *J* = 7.6 Hz, 2H), 5.80 (t, *J* = 7.6 Hz, 1H), 4.31 (s, 2H), 3.72 – 3.59 (m, 1H), 3.36 – 3.26 (m, 1H), 3.16 – 3.04 (m, 1H), 2.53 – 2.42 (m, 1H), 2.05 – 1.77 (m, 4H), 1.65 – 1.54 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.0, 141.7, 137.0, 133.4, 130.2, 129.2, 128.8, 125.9, 115.6, 111.9, 68.0, 58.5, 48.3, 31.8, 30.2, 23.3; **HRMS** (ESI/TOF) *m/z*: [M + H]$^+$ Calcd for. $C_{20}H_{23}ClNO^+$ 328.1463; found 328.1472.

(*E*)-2-(3-Methoxyphenyl)-4-(1-phenylpyrrolidin-2-yl)but-2-en-1-ol (3.3d)



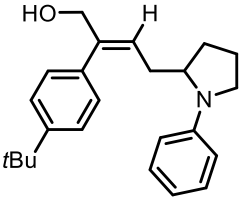
Yellowish oil (Method A, 18.7 mg, 58% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 – 7.26 (m, 1H), 7.15 – 7.11 (m, 2H), 6.88 – 6.85(m, 1H), 6.81 – 6.76 (m, 2H), 6.61 (t, *J* = 7.3 Hz, 1H), 6.39 (d, *J* = 7.7 Hz, 2H), 5.77 (t, *J* = 7.6 Hz, 1H), 4.33 (s, 2H), 3.81 (s, 3H), 3.72 – 3.63 (m, 1H), 3.36 – 3.31 (m, 1H), 3.14 – 3.08 (m, 1H), 2.54 – 2.48 (m, 1H), 2.03 – 1.81 (m, 5H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.8, 147.1, 142.7, 140.0, 129.6, 129.2, 125.0, 121.2, 115.4, 114.6, 112.8, 111.9, 68.1, 58.6, 55.3, 48.3, 31.7, 30.1, 23.3; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{21}H_{26}NO_2^+$ 324.1958; found 324.1970.

(*E*)-2-(3,5-Dimethylphenyl)-4-(1-phenylpyrrolidin-2-yl)but-2-en-1-ol (3.3e)



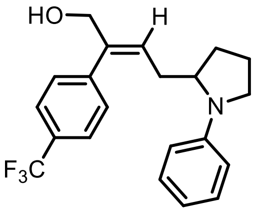
Yellowish oil (Method A, 22.8 mg, 71% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.15 – 7.11 (m, 2H), 6.97 (s, 1H), 6.83 (s, 2H), 6.62 (t, *J* = 7.3 Hz, 1H), 6.37 (d, *J* = 8.8 Hz, 2H), 5.75 (t, *J* = 7.6 Hz, 1H), 4.32 (s, 2H), 3.70 – 3.65 (m, 1H), 3.37 – 3.32 (m, 1H), 3.16 – 3.09 (m, 1H), 2.55 – 2.48 (m, 1H), 2.33 (s, 6H), 2.01 – 1.84 (m, 4H), 1.63 – 1.53 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.1, 143.2, 138.4, 138.1, 129.2, 129.1, 126.5, 124.4, 115.4, 111.9, 68.2, 58.7, 48.3, 31.6, 30.1, 23.3, 21.5; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{22}H_{28}NO^+$ 322.2165; found 322.2174.

(*E*)-2-(4-(*tert*-Butyl)phenyl)-4-(1-phenylpyrrolidin-2-yl)but-2-en-1-ol (3.3f)



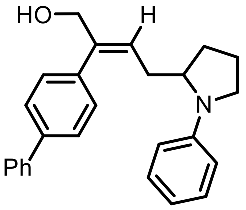
Yellowish oil (Method A, 23.4 mg, 67% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.37 (m, 2H), 7.17 – 7.09 (m, 4H), 6.60 (t, *J* = 7.3 Hz, 1H), 6.40 (d, *J* = 7.7 Hz, 2H), 5.76 (t, *J* = 7.5 Hz, 1H), 4.33 (s, 2H), 3.70 – 3.66 (m, 1H), 3.36 – 3.32 (m, 1H), 3.12 – 3.10 (m, 1H), 2.56 – 2.49 (m, 1H), 2.04 – 1.96 (m, 1H), 1.94 – 1.78 (m, 4H), 1.34 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.3, 147.1, 142.7, 135.4, 129.2, 128.5, 125.5, 124.8, 115.4, 112.0, 68.3, 58.7, 48.3, 34.7, 31.7, 31.5, 30.1, 23.3; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{24}H_{32}NO^+$ 350.2478; found 350.2485.

(*E*)-4-(1-phenylpyrrolidin-2-yl)-2-(4-(trifluoromethyl)phenyl)but-2-en-1-ol (3.3g)



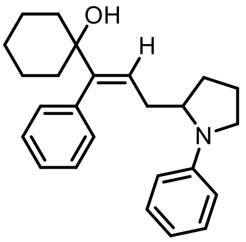
Yellowish oil (Method A, 15.8 mg, 44% yield); **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.62 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.6 Hz, 2H), 7.14 – 7.10 (m, 2H), 6.62 (t, *J* = 7.3 Hz, 1H), 6.37 (d, *J* = 7.8 Hz, 2H), 5.86 (t, *J* = 7.6 Hz, 1H), 4.34 (s, 2H), 3.72 – 3.68 (m, 1H), 3.36 – 3.31 (m, 1H), 3.15 – 3.09 (m, 1H), 2.49 – 2.43 (m, 1H), 2.05 – 1.77 (m, 5H); **^{13}C NMR** (101 MHz, CDCl$_3$) δ 147.0, 142.5, 141.6, 129.6 (q, J = 32.66 Hz), 129.3, 129.2, 126.5, 125.5 (q, *J* = 3.7 Hz), 124.3 (q, *J* = 271.9 Hz), 115.7, 111.9, 67.9, 58.4, 48.3, 31.9, 30.3, 23.3; **^{19}F NMR** (376 MHz, CDCl$_3$) δ -62.6; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{21}H_{23}F_3NO^+$ 362.1726; found 362.1736.

(*E*)-2-([1,1'-Biphenyl]-4-yl)-4-(1-phenylpyrrolidin-2-yl)but-2-en-1-ol (3.3h)



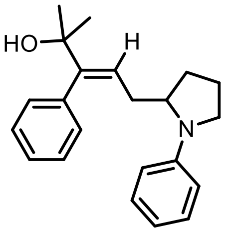
Yellowish oil (Method A, 18.8 mg, 51% yield); **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.64 – 7.60 (m, 4H), 7.48 – 7.45 (m, 2H), 7.40 – 7.36 (m, 1H), 7.31 – 7.29 (m, 2H), 7.13 – 7.09 (m, 2H), 6.59 (t, *J* = 7.3 Hz, 1H), 6.40 (d, *J* = 7.7 Hz, 2H), 5.83 (t, *J* = 7.6 Hz, 1H), 4.39 (s, 2H), 3.74 – 3.70 (m, 1H), 3.37 – 3.32 (m, 1H), 3.16 – 3.12 (m, 1H), 2.61 – 2.55 (m, 1H), 2.10 – 2.02 (m, 1H), 1.94 – 1.84 (m, 4H); **^{13}C NMR** (101 MHz, CDCl$_3$) δ 147.0, 142.4, 140.9, 140.3, 137.5, 129.3, 129.2, 128.9, 127.5, 127.3, 127.2, 125.3, 115.5, 111.9, 68.1, 58.6, 48.3, 31.7, 30.1, 23.3; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{26}H_{28}NO^+$ 370.2165; found 370.2175.

(*E*)-1-(1-Phenyl-3-(1-phenylpyrrolidin-2-yl)prop-1-en-1-yl)cyclohexan-1-ol (3.3i)



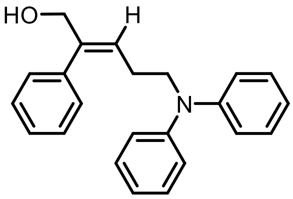
Yellowish oil (Method A, 19.9 mg, 55% yield); **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.37 – 7.29 (m, 3H), 7.12 – 7.08 (m, 4H), 6.59 (t, *J* = 7.3 Hz, 1H), 6.30 (d, *J* = 7.7 Hz, 2H), 5.90 (t, *J* = 7.6 Hz, 1H), 3.67 – 3.62 (m, 1H), 3.31 – 3.26 (m, 1H), 3.12 – 3.07 (m, 1H), 2.26 – 2.19 (m, 1H), 1.90 – 1.86 (m, 4H), 1.77 – 1.69 (m, 1H), 1.67 – 1.51 (m, 10H); **^{13}C NMR** (101 MHz, CDCl$_3$) δ 150.8, 147.1, 139.1, 130.2, 129.2, 128.1, 126.9, 122.6, 115.3, 111.9, 73.7, 58.5, 48.2, 36.8, 36.7, 32.2, 30.0, 25.6, 23.3, 22.2, 22.1; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{25}H_{32}NO^+$ 362.2478; found 362.2492.

(*E*)-2-Methyl-3-phenyl-5-(1-phenylpyrrolidin-2-yl) pent-3-en-2-ol (3.3j)



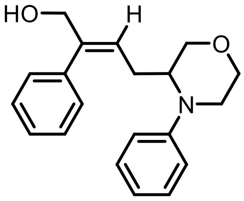
Yellowish oil (Method A, 13.5 mg, 42% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.31 (m, 3H), 7.12 – 7.08 (m, 4H), 6.59 (t, *J* = 7.3 Hz, 1H), 6.31 (d, *J* = 7.7 Hz, 2H), 5.90 (t, *J* = 7.6 Hz, 1H), 3.67 – 3.63 (m, 1H), 3.31 – 3.27 (m, 1H), 3.12 – 3.08 (m, 1H), 2.25 – 2.18 (m, 1H), 1.93 – 1.82 (m, 4H), 1.76 – 1.69 (m, 1H), 1.35 (d, *J* = 6.0 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.4, 147.1, 139.1, 130.0, 129.2, 128.2, 127.0, 121.9, 115.3, 111.9, 73.2, 58.4, 48.2, 32.2, 30.1, 29.7, 29.6, 23.3; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{22}H_{28}NO^+$ 322.2165; found 322.2167.

(*E*)-5-(Diphenylamino)-2-phenylpent-2-en-1-ol (3.3k)



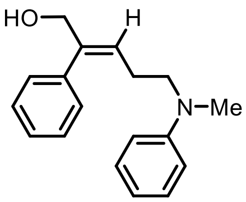
Yellowish oil (Method A, 14.8 mg, 45% yield); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38 – 7.31 (m, 3H), 7.22 – 7.18 (m, 6H), 6.94 – 6.92 (m, 2H), 6.88 – 6.86 (m, 4H), 5.75 (t, *J* = 7.6 Hz, 1H), 4.30 (s, 2H), 3.72 – 3.69 (m, 2H), 2.43 – 2.37 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 147.8, 142.9, 138.3, 129.3, 128.7, 128.6, 127.5, 124.8, 121.3, 120.9, 68.0, 52.0, 26.8; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{23}H_{23}NNaO^+$ 352.1672; found 352.1677.

(*E*)-2-Phenyl-4-(4-phenylmorpholin-3-yl)but-2-en-1-ol (3.3l)



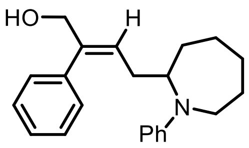
Yellowish oil (Method A, 17.9 mg, 58% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.26 (m, 3H), 7.21 – 7.12 (m, 4H), 6.83 – 6.80 (m, 1H), 6.73 – 6.69 (m, 2H), 5.63 (t, *J* = 7.6 Hz, 1H), 4.19 (s, 2H), 3.90 – 3.83 (m, 2H), 3.76 – 3.72 (m, 1H), 3.66 – 3.60 (m, 2H), 3.07 – 2.96 (m, 2H), 2.42 – 2.29 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.91 142.6, 138.2, 129.3, 128.63, 128.56, 127.4, 124.8, 119.3, 115.9, 69.2, 68.0, 67.0, 56.0, 43.6, 25.1; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{20}H_{24}NO_2^+$ 310.1802; found 310.1806.

(*E*)-5-(Methyl(phenyl)amino)-2-phenylpent-2-en-1-ol (3.3m)



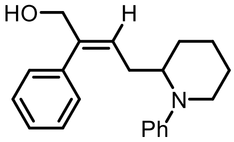
Yellowish oil (Method A, 14.7 mg, 55% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.31 (m, 3H), 7.21 – 7.15 (m, 4H), 6.69 – 6.65 (m, 1H), 6.59 – 6.56 (m, 2H), 5.75 (t, *J* = 7.6 Hz, 1H), 4.30 (s, 2H), 3.35 – 3.31 (m, 2H), 2.83 (s, 3H), 2.32 – 2.26 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.2, 142.7, 138.3, 129.2, 128.7, 128.5, 127.4, 125.2, 116.2, 112.3, 68.0, 52.6, 38.2, 26.0; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{18}H_{22}NO^+$ 268.1696; found 268.1704.

(*E*)-2-Phenyl-4-(1-phenylazepan-2-yl)but-2-en-1-ol (3.3n)



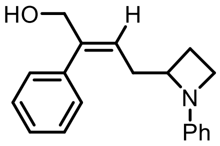
Yellowish oil (Method A, 24.8 mg, 77% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.33 (m, 2H), 7.33 – 7.28 (m, 1H), 7.22 – 7.17 (m, 2H), 7.15 – 7.09 (m, 2H), 6.60 – 6.54 (m, 1H), 6.52 – 6.47 (m, 2H), 5.81 (t, *J* = 7.7 Hz, 1H), 4.30 (s, 2H), 3.67 – 3.52 (m, 1H), 3.41 – 3.30 (m, 1H), 3.10 – 2.98 (m, 1H), 2.48 – 2.34 (m, 1H), 2.22 – 2.03 (m, 2H), 1.84 – 1.71 (m, 2H), 1.64 – 1.58 (m, 2H), 1.36 – 1.16 (m, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.4, 142.4, 138.6, 129.3, 128.9, 128.6, 127.4, 125.1, 114.7, 110.5, 68.3, 57.3, 43.1, 35.0, 32.3, 30.0, 27.3, 25.5; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{22}H_{28}NO^+$ 322.2165; found 322.2175.

(*E*)-2-Phenyl-4-(1-phenylpiperidin-2-yl)but-2-en-1-ol (3.3o)



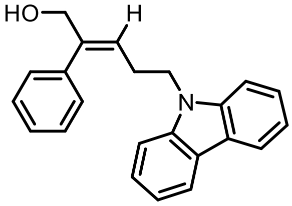
Yellowish oil (Method A, 14.4 mg, 47% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 – 7.27 (m, 3H), 7.22 – 7.16 (m, 2H), 7.16 – 7.11 (m, 2H), 6.84 – 6.72 (m, 3H), 5.61 (t, *J* = 7.6 Hz, 1H), 4.20 (s, 2H), 3.89 – 3.81 (m, 1H), 3.26 – 3.18 (m, 1H), 2.80 – 2.70 (m, 1H), 2.30 – 2.17 (m, 2H), 1.70 – 1.52 (m, 4H), 1.37 – 1.25 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.3, 141.8, 138.5, 129.1, 128.7, 128.5, 127.3, 126.1, 118.6, 116.8, 68.1, 56.4, 44.1, 28.3, 26.8, 25.7, 19.3; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{21}H_{26}NO^+$ 308.2009; found 308.2015.

(*E*)-2-Phenyl-4-(1-phenylazetidin-2-yl)but-2-en-1-ol (3.3p)



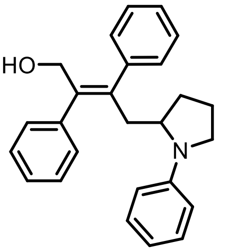
Yellowish oil (Method A, 20.1 mg, 72% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 – 7.37 (m, 2H), 7.35 – 7.30 (m, 1H), 7.25 – 7.23 (m, 2H), 7.18 – 7.14 (m, 2H), 6.74 – 6.70 (m, 1H), 6.39 (d, *J* = 8.6 Hz, 2H), 5.84 (t, *J* = 7.5 Hz, 1H), 4.37 (s, 2H), 4.03 – 3.96 (m, 1H), 3.92 – 3.88 (m, 1H), 3.59 – 3.53 (m, 1H), 2.67 – 2.61 (m, 1H), 2.49 – 2.42 (m, 1H), 2.35 – 2.27 (m, 1H), 2.17 – 2.07 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.2, 143.3, 138.5, 129.0, 128.8, 128.6, 127.5, 123.0, 117.8, 111.9, 68.0, 64.4, 50.0, 35.6, 23.1; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{19}H_{22}NO^+$ 280.1696; found 280.1693.

(*E*)-5-(9*H*-Carbazol-9-yl)-2-phenylpent-2-en-1-ol (3.3q)



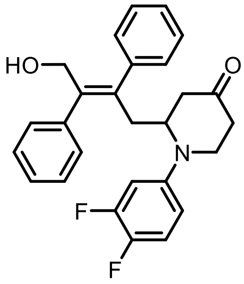
Yellowish solid (Method A, 20.6 mg, 63% yield); **3.3q** was prepared according to the Method A with the following modifications: Using the [Ir(dFCF$_3$ppy)$_2$dtbbpy)]PF$_6$ instead of [Ir(dmppy)$_2$(dtbbpy)]PF$_6$ and 2.0 equiv of the amine was used; **^{1}H NMR** (500 MHz, CDCl$_3$) δ 8.09 – 8.07 (m, 2H), 7.41 – 7.37 (m, 2H), 7.24 – 7.19 (m, 7H), 6.93 – 6.91 (m, 2H), 5.80 (t, *J* = 7.7 Hz, 1H), 4.29 (t, *J* = 7.3 Hz, 2H), 4.19 (s, 2H), 2.55 (q, *J* = 7.4 Hz, 2H); **^{13}C NMR** (126 MHz, CDCl$_3$) δ 143.9, 140.4, 137.9, 128.50, 128.45, 127.4, 125.7, 123.9, 123.0, 120.5, 119.0, 108.8, 67.8, 42.7, 28.1; **HRMS** (ESI/TOF) *m/z*: [M + Na]$^+$ Calcd. for $C_{23}H_{21}NNaO^+$ 350.1515; found 350.1517.

(*Z*)-2,3-Diphenyl-4-(1-phenylpyrrolidin-2-yl)but-2-en-1-ol (3.4a)



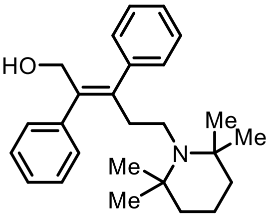
Yellowish oil (Method A, 30.1 mg, 81% yield); **^{1}H NMR** (500 MHz, CDCl$_3$) δ 7.49 – 7.43 (m, 4H), 7.40 – 7.33 (m, 6H), 7.08 – 7.05 (m, 2H), 6.58 – 6.55 (m, 1H), 6.13 (d, *J* = 8.6 Hz, 2H), 4.27 – 4.21 (m, 2H), 3.51 – 3.47 (m, 1H), 3.17 – 3.13 (m, 1H), 3.01 – 2.96 (m, 1H), 2.78 – 2.75 (m, 1H), 2.29 – 2.23 (m, 1H), 1.80 – 1.72 (m, 2H), 1.72 – 1.64 (m, 1H), 1.52 – 1.48 (m, 1H); **^{13}C NMR** (126 MHz, CDCl$_3$) δ 146.7, 140.8, 140.2, 139.3, 139.2, 129.4, 129.1, 128.72, 128.68, 128.5, 127.5, 127.2, 115.2, 111.6, 64.4, 56.8, 47.7, 36.5, 28.9, 22.8; **HRMS** (ESI/TOF) *m/z*: [M + H]$^+$ Calcd. for $C_{26}H_{28}NO^+$ 370.2165; found 370.2179.

(*Z*)-1-(3,4-Difluorophenyl)-2-(4-hydroxy-2,3-diphenylbut-2-en-1-yl)piperidin-4-one (3.4b)



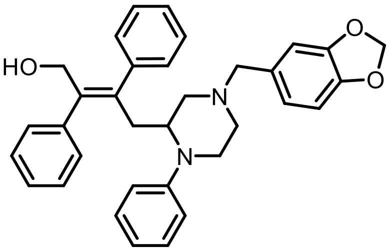
Yellowish oil (Method A, 38.9 mg, 90% yield); **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.43 – 7.31 (m, 6H), 7.26 – 7.23 (m, 2H), 7.20 – 7.14 (m, 2H), 6.95 – 6.85 (m, 1H), 6.29 – 6.22 (m, 1H), 6.19 – 6.11 (m, 1H), 4.16 (s, 2H), 3.77 – 3.67 (m, 1H), 3.44 – 3.32 (m, 1H), 3.02 – 2.90 (m, 1H), 2.61 – 2.53 (m, 1H), 2.49 – 2.41 (m, 2H), 2.40 – 2.32 (m, 1H), 2.27 – 2.20 (m, 1H), 2.18 – 2.10 (m, 1H); **^{13}C NMR** (101 MHz, CDCl$_3$) δ 207.4, 150.62 (dd, *J* = 245.9, 13.3 Hz), 145.8 (dd, *J* = 7.8, 1.9 Hz), 140.2, 139.7, 139.4, 137.0, 129.1, 128.8, 128.68, 128.66, 127.8, 127.6, 117.4 (dd, *J* = 17.7, 1.6 Hz), 111.23 (dd, *J* = 5.5, 3.0 Hz), 105.3 (d, *J* = 20.5 Hz), 64.3, 56.0, 43.7, 43.3, 39.7, 36.6; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -136.4 (d, *J* = 22.1 Hz), -150.0 (d, *J* = 22.2 Hz); **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{27}H_{26}F_2NO_2^+$ 434.1926; found 434.1924.

(*Z*)-2,3-Diphenyl-5-(2,2,6,6-tetramethylpiperidin-1-yl)pent-2-en-1-ol (3.4c)



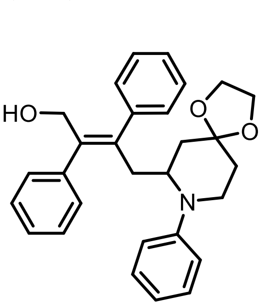
Yellowish solid (Method A, 34.0 mg, 90% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.35 (m, 4H), 7.33 – 7.27 (m, 6H), 4.16 (s, 2H), 2.39 – 2.30 (m, 2H), 2.25 – 2.18 (m, 2H), 1.42 – 1.37 (m, 2H), 1.25 – 1.21 (m, 4H), 0.67 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.5, 140.6, 140.5, 137.7, 129.2, 128.7, 128.5, 128.2, 127.11, 127.05, 64.5, 54.6, 43.4, 41.2, 41.1, 27.1, 17.8; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{26}H_{36}NO^+$ 378.2791; found 378.2799.

(*Z*)-4-(4-(Benzo[d][1,3]dioxol-5-ylmethyl)-1-phenylpiperazin-2-yl)-2,3-diphenylbut-2-en-1-ol (3.4d)



Yellowish oil (Method A, 42.8 mg, 82% yield**)**; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 – 7.33 (m, 6H), 7.32 – 7.28 (m, 2H), 7.24 – 7.18 (m, 2H), 7.07 – 7.00 (m, 2H), 6.75 – 6.68 (m, 2H), 6.55 – 6.50 (m, 1H), 6.48 (d, *J* = 1.3 Hz, 1H), 6.29 (d, *J* = 7.8 Hz, 2H), 6.03 – 5.93 (m, 2H), 4.18 (s, 2H), 3.59 – 3.50 (m, 1H), 3.41 (d, *J* = 12.7 Hz, 1H), 3.12 – 3.01 (m, 2H), 2.97 (d, *J* = 12.7 Hz, 1H), 2.81 – 2.71 (m, 2H), 2.58 – 2.50 (m, 1H), 2.36 – 2.21 (m, 2H), 1.91 – 1.81 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.2, 147.6, 146.6, 140.9, 140.0, 139.23, 139.19, 132.3, 129.3, 129.1, 128.9, 128.8, 128.4, 127.33, 127.32, 122.1, 118.6, 115.7, 109.7, 107.7, 101.0, 64.7, 62.5, 55.5, 53.8, 51.7, 43.7, 31.9; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{34}H_{35}N_2O_3^+$ 519.2642; found 519.2661.

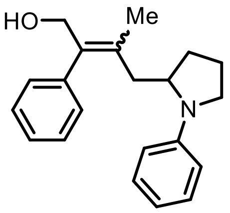
(*Z*)-2,3-Diphenyl-4-(8-phenyl-1,4-dioxa-8-azaspiro[4.5]decan-7-yl)but-2-en-1-ol (3.4e)



Yellowish oil (Method A, 38 mg, 86% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 – 7.36 (m, 4H), 7.35 – 7.30 (m, 2H), 7.30 – 7.26 (m, 2H), 7.22 – 7.16 (m, 2H), 7.13 – 7.07 (m, 2H), 6.84 – 6.76 (m, 1H), 6.55 – 6.44 (m, 2H), 4.21 – 4.08 (m, 2H), 3.83 – 3.73 (m, 2H), 3.72 – 3.64 (m, 1H), 3.63 – 3.56 (m, 1H), 3.55 – 3.48 (m, 1H), 3.15 – 3.05 (m, 1H), 2.91 – 2.83 (m, 1H), 2.74 – 2.65 (m, 1H), 2.63 – 2.54 (m, 1H), 1.85 – 1.75

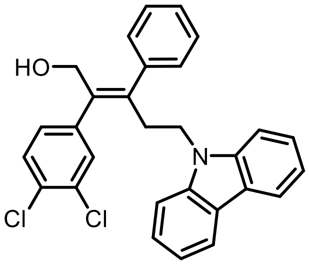
(m, 1H), 1.64 – 1.58 (m, 2H), 1.54 – 1.46 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.2, 141.0, 140.1, 139.2, 139.1, 129.5, 129.0, 128.9, 128.5, 128.3, 127.2, 127.1, 119.9, 118.6, 107.2, 64.7, 64.4, 63.9, 54.3, 45.0, 36.8, 35.7, 34.4; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{29}H_{32}NO_3^+$ 442.2377; found 442.2385.

(*E/Z*)-3-Methyl-2-phenyl-4-(1-phenylpyrrolidin-2-yl)but-2-en-1-ol (3.4f)



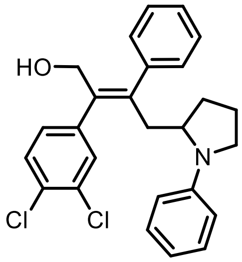
Yellowish oil (Method A, 19.7 mg, 64% yield, *E/Z* = 60:40); **^{1}H NMR** (400 MHz, $CDCl_3$) **(major *E*-isomer)** δ 7.39 – 7.34 (m, 2H), 7.32 – 7.29 (m, 1H), 7.17 – 7.11 (m, 4H), 6.59 (t, *J* = 7.3 Hz, 1H), 6.33 (d, *J* = 8.1 Hz, 2H), 4.41 (q, *J* = 12.0 Hz, 2H), 3.87 – 3.83 (m, 1H), 3.17 – 3.13 (m, 1H), 3.06– 2.99 (m, 1H), 2.49 – 2.44 (m, 1H), 2.04 (s, 3H), 2.00 – 1.94 (m, 1H), 1.79 – 1.74 (m, 2H), 1.57 – 1.50 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.0, 141.2, 137.6, 133.5, 129.6, 129.3, 128.7, 126.9, 115.3, 111.6, 63.7, 57.0, 47.8, 37.4, 29.2, 22.9, 18.8; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{21}H_{26}NO^+$ 308.2009; found 308.2021; **^{1}H NMR** (400 MHz, $CDCl_3$) **(minor *Z*-isomer)** δ 7.36 – 7.30 (m, 2H), 7.28 – 7.21 (m, 3H), 7.09 – 7.02 (m, 2H), 6.72 – 6.61 (m, 3H), 4.39 – 4.29 (m, 2H), 4.12 – 4.04 (m, 1H), 3.56 – 3.47 (m, 1H), 3.26 – 3.16 (m, 1H), 2.68 – 2.59 (m, 1H), 2.42 – 2.34 (m, 1H), 2.21 – 2.12 (m, 1H), 2.10 – 2.03 (m, 1H), 1.99 – 1.92 (m, 2H), 1.72 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.7, 141.4, 137.6, 133.3, 129.4, 129.1, 128.5, 126.8, 116.0, 112.2, 63.3, 57.2, 48.7, 37.7, 30.2, 23.6, 21.0; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{21}H_{26}NO^+$ 308.2009; found 308.2017.

(*Z*)-5-(9*H*-Carbazol-9-yl)-2-(3,4-dichlorophenyl)-3-phenylpent-2-en-1-ol (3.4g)



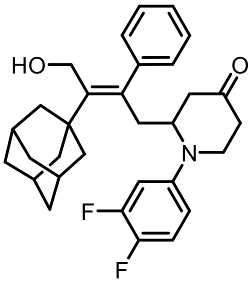
White solid (Method A, 42 mg, 89% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 7.7 Hz, 2H), 7.55 – 7.47 (m, 3H), 7.42 – 7.29 (m, 6H), 7.23 – 7.18 (m, 2H), 6.89 – 6.85 (m, 3H), 4.17 (s, 2H), 4.11 (t, *J* = 7.8 Hz, 2H), 2.79 (t, *J* = 7.8 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.0, 139.9, 139.7, 139.4, 137.9, 132.8, 131.6, 130.64, 130.61, 128.9, 128.7, 128.3, 128.2, 125.7, 123.0, 120.5, 119.1, 108.3, 64.1, 41.3, 34.4; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{29}H_{23}Cl_2NNaO^+$ 494.1049; found 494.1049.

(*Z*)-2-(3,4-Dichlorophenyl)-3-phenyl-4-(1-phenylpyrrolidin-2-yl)but-2-en-1-ol (3.4h)



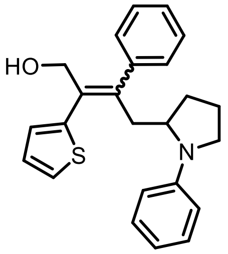
Yellowish oil (Method A, 30.8 mg, 70% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 – 7.43 (m, 4H), 7.42 – 7.37 (m, 1H), 7.36 – 7.30 (m, 2H), 7.20 – 7.15 (m, 1H), 7.11 – 7.05 (m, 2H), 6.58 (t, *J* = 7.1 Hz, 1H), 6.15 (d, *J* = 8.1 Hz, 2H), 4.18 (s, 2H), 3.53 – 3.42 (m, 1H), 3.26 – 3.15 (m, 1H), 3.06 – 2.96 (m, 1H), 2.82 – 2.72 (m, 1H), 2.29 – 2.12 (m, 1H), 1.87 – 1.77 (m, 1H), 1.77 – 1.68 (m, 2H), 1.61 – 1.53 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.6, 141.1, 140.7, 140.2, 137.0, 132.7, 131.39, 131.36, 130.6, 129.2, 128.9, 128.7, 128.5, 127.8, 115.5, 111.7, 64.1, 56.7, 47.8, 36.9, 29.1, 22.9; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{26}H_{26}Cl_2NO^+$ 438.1386; found 438.1401.

2-((*Z*)-3-((1*S*,3*S*)-Adamantan-1-yl)-4-hydroxy-2-phenylbut-2-en-1-yl)-1-(3,4-difluorophenyl)-piperidin-4-one (3.4i)



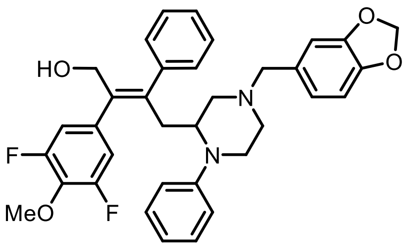
Yellowish oil (Method A, 29.9 mg, 61% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 – 7.27 (m, 3H), 7.04 – 6.94 (m, 2H), 6.94 – 6.87 (m, 1H), 6.26 – 6.21 (m, 1H), 6.18 – 6.14 (m, 1H), 3.96 (d, *J* = 11.7 Hz, 1H), 3.79 (d, *J* = 11.8 Hz, 1H), 3.77 – 3.70 (m, 1H), 3.56– 3.50 (m, 1H), 3.34 – 3.22 (m, 2H), 2.61 – 2.42 (m, 5H), 2.01 (s, 9H), 1.73 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 207.8, 151.9 150.64 (dd, *J* = 246.0, 13.2 Hz), 146.4, 143.1, 139.3, 128.8, 128.5, 127.8, 127.1, 117.4 (dd, *J* = 18.0, 1.7 Hz), 111.4, 105.4 (d, *J* = 20.6 Hz), 61.9, 56.2, 43.6, 43.2, 42.2, 40.3, 38.1, 37.0, 36.6, 29.2; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -136.3 (d, *J* = 22.2 Hz), -150.0 (d, *J* = 22.1 Hz); **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{31}H_{36}F_2NO_2^+$ 492.2709; found 492.2716.

(*E*/*Z*)-3-Phenyl-4-(1-phenylpyrrolidin-2-yl)-2-(thiophen-2-yl)but-2-en-1-ol (3.4j)



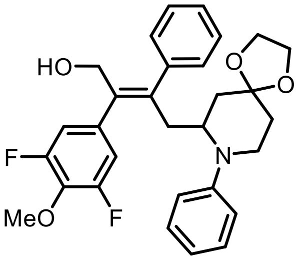
Yellowish oil (Method A, 35.7 mg, 95% yield, *E/Z* = 73:17); **^{1}H NMR** (400 MHz, $CDCl_3$) (major ***E***) δ 7.49 – 7.46 (m, 2H), 7.41 – 7.33 (m, 4H), 7.10 – 7.06 (m, 3H), 7.03 – 7.01 (m, 1H), 6.59 – 6.56 (m, 1H), 6.20 – 6.18 (m, 2H), 4.19 (s, 2H), 3.53 – 3.46 (m, 1H), 3.25 – 3.21 (m, 1H), 3.05 – 3.00 (m, 1H), 2.86 – 2.81 (m, 1H), 2.59 – 2.53 (m, 1H), 1.84 – 1.79 (m, 2H), 1.73 – 1.64 (m, 2H); **^{1}H NMR** (400 MHz, $CDCl_3$) (minor ***Z***, *selected characteristic peaks*) δ 6.84 – 6.80 (m, 1H), 6.75 – 6.72 (m, 1H), 6.64 (t, *J* = 7.2 Hz, 1H), 6.33 (d, *J* = 8.1 Hz, 2H), 4.67 (s, 2H), 3.73 – 3.66 (m, 1H), 3.50 – 3.45 (m, 1H), 3.22 – 3.12 (m, 1H), 3.00 – 2.93 (m, 1H), 2.83 – 2.74 (m, 1H), 2.20 – 2.04 (m, 2H); **^{13}C NMR** (101 MHz, CDCl$_3$) δ 147.0, 146.7, 143.4, 142.5, 141.8, 141.3, 141.0, 140.5, 131.9, 131.3, 129.27, 129.25, 129.2, 128.6, 128.5, 127.7, 127.41, 127.40, 127.3, 127.2, 126.5, 125.8, 125.6, 115.7, 115.3, 112.0, 111.7, 64.7, 63.6, 56.7, 56.6, 47.8, 37.5, 37.1, 29.4, 29.0, 23.4, 23.0; **HRMS** (ESI/TOF) *m/z*: [M + H]$^+$ Calcd. for $C_{24}H_{26}NOS^+$ 376.1730; found 376.1731.

(*Z*)-4-(4-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-1-phenylpiperazin-2-yl)-2-(3,5-difluoro-4-methoxy-phenyl)-3-phenylbut-2-en-1-ol (3.4k)



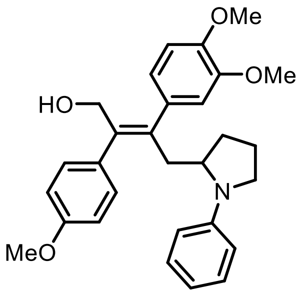
Yellowish oil (Method A, 47.3 mg, 81% yield); **^{1}H NMR** (500 MHz, CDCl$_3$) δ 7.41 – 7.34 (m, 3H), 7.15 – 7.07 (m, 4H), 6.88 – 6.86 (m, 2H), 6.76 – 6.74 (m, 2H), 6.61 – 6.58 (m, 2H), 6.41 – 6.38 (m, 2H), 5.96 (q, *J* = 1.5 Hz, 2H), 4.08 (s, 2H), 4.01 (s, 3H), 3.52 – 3.49 (m, 1H), 3.37 (d, *J* = 12.8 Hz, 1H), 3.11 – 2.99 (m, 3H), 2.87 – 2.81 (m, 1H), 2.63 – 2.58 (m, 2H), 2.35 – 2.22 (m, 2H), 1.98 – 1.93 (m, 1H); **^{13}C NMR** (126 MHz, CDCl$_3$) δ 155.5 (dd, *J* = 248.8, 6.5 Hz), 149.3, 147.7, 146.7, 140.9, 140.3, 136.9 (dd, *J* = 1.6, 1.6 Hz), 135.5 (dd, *J* = 13.9, 13.9 Hz), 135.2 (dd, *J* = 8.8, 8.8 Hz), 132.1, 129.1, 128.6, 128.5, 127.6, 122.2, 119.1, 116.2, 113.3 (dd, *J* = 16.1, 6.6 Hz), 109.5, 108.0, 101.0, 64.4, 62.6, 61.8 (dd, *J* = 3.2, 3.2 Hz), 55.5, 54.2, 52.0, 44.1, 32.1; **^{19}F NMR** (376 MHz, CDCl$_3$) δ -128.6; **HRMS** (ESI/TOF) *m/z*: [M + H]$^+$ Calcd. for $C_{35}H_{35}F_2N_2O_4^+$ 585.2559; found 585.2567.

(*Z*)-2-(3,5-Difluoro-4-methoxyphenyl)-3-phenyl-4-(8-phenyl-1,4-dioxa-8-azaspiro-[4.5]decan-7-yl)but-2-en-1-ol (3.4l)



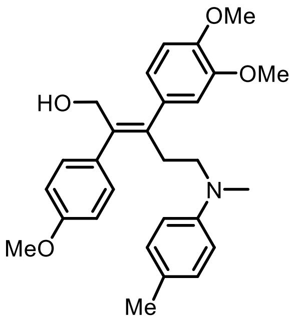
Yellowish oil (Method A, 39.1 mg, 77% yield); **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.40 – 7.32 (m, 3H), 7.15 – 7.11 (m, 4H), 6.86 – 6.79 (m, 3H), 6.56 – 6.53 (m, 2H), 4.07 (s, 2H), 4.03 (s, 3H), 3.86 – 3.73 (m, 3H), 3.73 – 3.65 (m, 1H), 3.58 – 3.52 (m, 1H), 3.20 – 3.08 (m, 1H), 2.93 – 2.84 (m, 1H), 2.76 – 2.68 (m, 1H), 2.59 – 2.50 (m, 1H), 1.82 – 1.77 (m, 1H), 1.63 – 1.60 (m, 2H), 1.51 – 1.47 (m, 1H); **^{13}C NMR** (101 MHz, CDCl$_3$) δ 155.48 (dd, *J* = 248.5, 6.4 Hz), 150.0, 140.9, 140.2, 136.9 (dd, *J* = 1.8, 1.8 Hz), 135.5 (dd, *J* = 8.7, 8.7 Hz), 135.3 (dd, *J* = 14.0, 14.0 Hz), 129.1, 128.6, 128.4, 127.5, 119.9, 118.2, 113.4 (dd, *J* = 16.14 Hz, 6.47 Hz), 107.1, 64.5, 64.3, 63.9, 62.0 (dd, *J* = 3.3, 3.3 Hz), 54.2, 44.1, 36.7, 35.3, 34.1; ^{19}**F NMR** (376 MHz, $CDCl_3$) δ -129.0; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{30}H_{32}F_2NO_4^+$ 508.2294; found 508.2293.

(*Z*)-3-(3,4-Dimethoxyphenyl)-2-(4-methoxyphenyl)-4-(1-phenylpyrrolidin-2-yl)but-2-en-1-ol (3.4m)



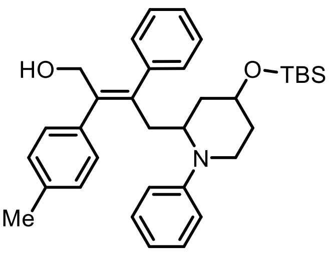
Yellowish oil (Method A, 36.5 mg, 79% yield); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.26 – 7.23 (m, 2H), 7.08 – 7.04 (m, 2H), 6.99 – 6.92 (m, 3H), 6.92 – 6.86 (m, 2H), 6.56 (t, *J* = 7.3 Hz, 1H), 6.17 (d, *J* = 7.8 Hz, 2H), 4.25 (s, 2H), 3.97 (s, 3H), 3.95 (s, 3H), 3.86 (s, 3H), 3.52 – 3.48 (m, 1H), 3.18 – 3.14 (m, 1H), 3.01 – 2.96 (m, 1H), 2.75 – 2.72 (m, 1H), 2.28 – 2.23 (m, 1H), 1.79 – 1.73 (m, 2H), 1.69 – 1.62 (m, 1H), 1.57 – 1.50 (m, 1H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 158.7, 148.9, 148.3, 146.7, 139.0, 138.6, 133.4, 132.4, 130.5, 129.1, 121.2, 115.2, 114.1, 111.7, 111.6, 111.0, 64.6, 56.9, 56.1, 56.0, 55.4, 47.7, 36.4, 28.9, 22.9; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{29}H_{34}NO_4^+$ 460.2482; found 460.2493.

(*Z*)-3-(3,4-Dimethoxyphenyl)-2-(4-methoxyphenyl)-5-(methyl(*p*-tolyl)amino)pent-2-en-1-ol (3.4n)



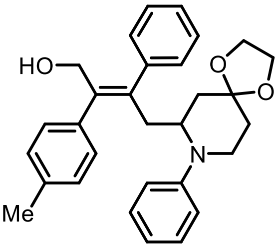
Yellowish oil (Method A, 33.1 mg, 74% yield); ^{1}**H NMR** (400 MHz, $CDCl_3$)) δ 7.26 – 7.25 (m, 1H), 7.24 – 7.23(m, 1H), 6.97 – 6.94 (m, 2H), 6.91 – 6.85 (m, 5H), 6.24 (d, *J* = 8.2 Hz, 2H), 4.22 (s, 2H), 3.94 (s, 3H), 3.91 (s, 3H), 3.86 (s, 3H), 3.17 – 3.13 (m, 2H), 2.64 (s, 3H), 2.48 – 2.44 (m, 2H), 2.20 (s, 3H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 159.0, 148.9, 148.3, 146.7, 138.9, 138.4, 133.7, 132.4, 130.2, 129.6, 121.0, 114.2, 112.4, 111.9, 111.1, 64.8, 56.1, 56.0, 55.4, 51.8, 38.2, 31.8, 20.3; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd for $C_{28}H_{34}NO_4^+$ 448.2482; found 448.2492.

(*Z*)-4-(4-((*tert*-Butyldimethylsilyl)oxy)-1-phenylpiperidin-2-yl)-3-phenyl-2-(*p*-tolyl)-but-2-en-1-ol (3.4o)



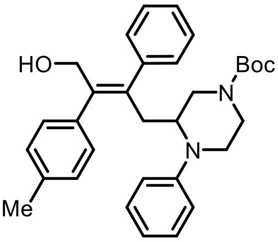
Yellowish solid (Method A, 30.3 mg, 82% yield, *dr* = 74:26); **^{1}H NMR** (400 MHz, $CDCl_3$) (major) δ 7.41 – 7.32 (m, 3H), 7.24 – 7.15 (m, 6H), 7.13 – 7.06 (m, 2H), 6.74 (t, *J* = 7.3 Hz, 1H), 6.43 (d, *J* = 8.8 Hz, 2H), 4.21-4.14 (m, 2H), 3.67 – 3.62 (m, 1H), 3.53 – 3.45 (m, 1H), 3.26 – 3.21 (m, 1H), 2.66 – 2.59 (m, 1H), 2.58 – 2.51 (m, 1H), 2.47 – 2.42 (m, 1H), 2.41 (s, 3H), 1.76 – 1.68 (m, 2H), 1.51 – 1.37 (m, 2H), 0.88 (s, 9H), 0.03 (s, 3H), -0.01 (s, 3H); **^{1}H NMR** (400 MHz, $CDCl_3$) (minor) δ 7.41 – 7.32 (m, 3H), 7.24 – 7.15 (m, 6H), 7.13 – 7.06 (m, 2H), 6.92 (t, *J* = 7.2 Hz, 1H), 6.66 (d, *J* = 7.6 Hz, 2H), 4.14 – 4.10 (m, 2H), 3.62 – 3.56 (m, 1H), 2.99 – 2.91 (m, 2H), 2.85 – 2.79 (m, 1H), 2.39 (s, 3H), 2.24 – 2.18 (m, 1H), 1.97 – 1.92 (m, 1H), 1.76 – 1.68 (m, 2H), 1.51 – 1.37 (m, 2H), 0.92 (s, 9H), 0.08 (s, 3H), 0.04 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.5, 149.9, 140.9, 140.5, 139.0, 138.98, 138.95, 138.6, 137.0, 136.8, 136.6, 129.5, 129.4, 129.3, 129.2, 129.0, 128.93, 128.90, 128.8, 128.4, 128.2, 127.3, 127.2, 121.6, 118.7, 116.7, 68.7, 65.8, 64.6, 64.5, 54.7, 53.4, 49.6, 42.5, 39.2, 39.1, 36.6, 35.1, 34.4, 33.9, 26.02, 25.96, 21.4, 21.3, 18.3, 18.1, -4.1, -4.2, -4.5, -4.5; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{34}H_{46}NO_2Si^+$ 528.3292; found 528.3289.

(*Z*)-3-Phenyl-4-(8-phenyl-1,4-dioxa-8-azaspiro[*4.5*]decan-7-yl)-2-(*p*-tolyl)but-2-en-1-ol (3.4p)



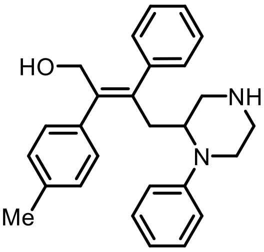
Yellowish oil (Method A, 38.2 mg, 84% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 – 7.35 (m, 2H), 7.34 – 7.29 (m, 1H), 7.22 – 7.14 (m, 6H), 7.13 – 7.07 (m, 2H), 6.81 (t, *J* = 7.3 Hz, 1H), 6.53 – 6.49 (m, 2H), 4.17 – 4.09 (m, 2H), 3.84 – 3.73 (m, 2H), 3.72 – 3.65 (m, 1H), 3.60 – 3.54 (m, 1H), 3.54 – 3.47 (m, 1H), 3.13 – 3.05 (m, 1H), 2.94 – 2.85 (m, 1H), 2.75 – 2.66 (m, 1H), 2.61 – 2.54 (m, 1H), 2.40 (s, 3H), 1.85 – 1.76 (m, 1H), 1.64 – 1.58 (m, 2H), 1.54 – 1.46 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.2, 141.2, 139.1, 138.9, 136.9, 136.6, 129.29, 129.26, 129.0, 128.9, 128.2, 127.1, 120.0, 118.7, 107.2, 64.7, 64.4, 63.9, 54.4, 45.2, 36.8, 35.7, 34.5, 21.4; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{30}H_{34}NO_3^+$ 456.2533; found 456.2541.

***tert*-Butyl-(*Z*)-3-(4-hydroxy-2-phenyl-3-(*p*-tolyl)but-2-en-1-yl)-4-phenylpiperazine-1-carboxylate (3.4q)**



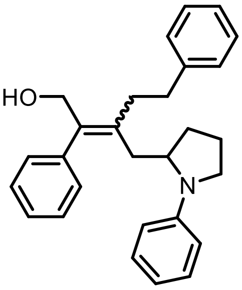
Yellowish oil (Method A, 38.2 mg, 77% yield); **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.42 – 7.32 (m, 3H), 7.23 – 7.10 (m, 8H), 6.89 – 6.80 (m, 1H), 6.58 – 6.48 (m, 2H), 4.17 – 4.10 (m, 2H), 3.59 (s, 1H), 3.40 – 3.27 (m, 2H), 3.22 – 2.99 (m, 3H), 2.82 – 2.78 (m, 1H), 2.65 – 2.52 (m, 1H), 2.50 – 2.43 (m, 1H), 2.38 (s, 3H), 1.56 – 1.44 (m, 9H); **^{13}C NMR** (101 MHz, CDCl$_3$) δ 155.4, 149.5, 140.3, 139.7, 137.6, 136.8, 129.4, 129.2, 129.1, 128.7, 128.4, 127.4, 119.5, 117.9, 116.6, 79.9, 64.5, 53.7, 45.8, 44.9, 43.7, 32.1, 28.6, 21.4; **HRMS** (ESI/TOF) *m/z*: [M + H]$^+$ Calcd. for C$_{32}$H$_{39}$N$_2$O$_3^+$ 499.2955; found 499.2966.

(*Z*)-3-phenyl-4-(1-phenylpiperazin-2-yl)-2-(*p*-tolyl)but-2-en-1-ol (3.4r)



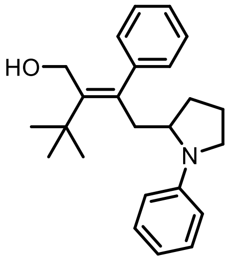
Yellowish oil (Method A, 30.4 mg, 76% yield); **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.43 – 7.33 (m, 3H), 7.25 – 7.14 (m, 6H), 7.11 – 7.04 (m, 2H), 6.74 (t, J = 7.2 Hz, 1H), 6.35 (d, J = 7.8 Hz, 2H), 4.20 – 4.13 (m, 2H), 3.35 – 3.30 (m, 1H), 3.01 – 2.92 (m, 2H), 2.83 – 2.79 (m, 2H), 2.76 – 2.66 (m, 2H), 2.60 – 2.54 (m, 1H), 2.41 (s, 3H), 2.23 – 2.19 (m, 1H), 1.75 (s, 1H); **^{13}C NMR** (101 MHz, CDCl$_3$) δ 149.6, 140.2, 139.4, 138.3, 137.0, 136.9, 129.6, 129.1, 129.0, 128.8, 128.4, 127.5, 118.8, 115.6, 64.3, 52.7, 46.5, 45.4, 44.1, 30.0, 21.4; **HRMS** (ESI/TOF) *m/z*: [M + H]$^+$ Calcd. for C$_{27}$H$_{31}$N$_2$O$^+$ 399.2431; found 399.2434.

(*E/Z*)-2,5-diphenyl-3-((1-phenylpyrrolidin-2-yl)methyl)pent-2-en-1-ol (3.4s)



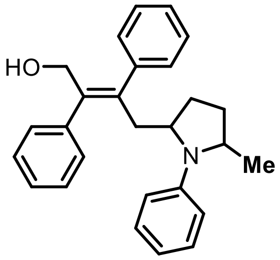
Yellowish oil (Method A, 28.2 mg, 71% yield, *E/Z* = 53:47); **^{1}H NMR** (500 MHz, CDCl$_3$) (mixture **E**+**Z**): δ 7.40 – 7.31 (m, 7H), 7.30 – 7.20 (m, 9H), 7.18 – 7.10 (m, 5H), 6.97 – 6.93 (m, 3H), 6.72 (t, J = 7.3 Hz, 1H), 6.67 (d, J = 7.8 Hz, 2H), 6.61 (t, J = 7.3 Hz, 1H), 6.25 (d, J = 7.7 Hz, 2H), 4.38 – 4.28 (m, 2H), 4.22 – 4.13 (m, 2H), 4.12 – 4.07 (m, 1H), 3.87 – 3.80 (m, 1H), 3.59 – 3.53 (m, 1H), 3.27 – 3.21 (m, 1H), 3.20 – 3.15 (m, 1H), 3.08 – 3.01 (m, 1H), 2.94 – 2.86 (m, 2H), 2.78 – 2.71 (m, 2H), 2.67 – 2.54 (m, 4H), 2.41 – 2.35 (m, 1H), 2.32 – 2.27 (m, 1H), 2.24 – 2.14 (m, 1H), 2.13 – 2.06 (m, 1H), 2.01 – 1.91 (m, 3H), 1.83 – 1.73 (m, 3H), 1.62 – 1.53 (m, 2H); **^{13}C NMR** (126 MHz, CDCl$_3$) δ 147.8, 146.9, 141.9, 141.6, 141.2, 140.9, 139.3, 139.0, 136.3, 136.1, 129.6, 129.4, 129.3, 128.91, 128.88, 128.7, 128.6, 128.5, 128.4, 127.0, 126.9, 126.5, 126.0, 116.1, 115.3, 112.3, 111.6, 63.5, 63.3, 57.4, 57.3, 48.9, 47.7, 36.2, 35.7, 35.6, 34.6, 34.4, 34.3, 30.5, 29.3, 23.6, 23.0; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{28}H_{32}NO^+$ 398.2478; found 398.2470.

(*Z*)-2-(*tert*-Butyl)-3-phenyl-4-(1-phenylpyrrolidin-2-yl)but-2-en-1-ol (3.4t)



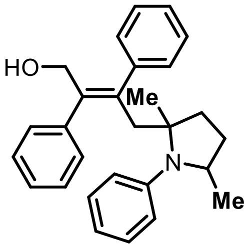
Yellowish oil (Method A, 26.1 mg, 75% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55 – 7.26 (m, 4H), 7.16 – 7.06 (m, 3H), 6.60 (t, *J* = 7.2 Hz, 1H), 6.24 (d, *J* = 8.4 Hz, 2H), 4.08 – 4.00 (m, 1H), 3.90 – 3.80 (m, 1H), 3.51 – 3.42 (m, 1H), 3.42 – 3.32 (m, 1H), 3.14 – 3.03 (m, 1H), 2.98 – 2.85 (m, 1H), 2.78 – 2.65 (m, 1H), 2.15 – 2.05 (m, 1H), 2.04 – 1.95 (m, 2H), 1.83 – 1.71 (m, 1H), 1.38 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.0, 144.7, 143.4, 141.3, 129.2, 126.9, 115.4, 111.8, 62.9, 56.8, 48.3, 37.2, 35.1, 31.8, 28.6, 23.4; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{24}H_{32}NO^+$ 350.2478; found 350.2488.

(*Z*)-4-(5-methyl-1-phenylpyrrolidin-2-yl)-2,3-diphenylbut-2-en-1-ol (3.4u)



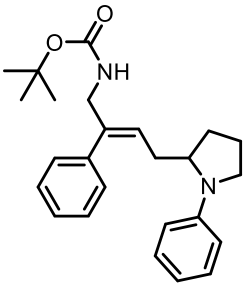
Yellowish oil (Method A, 35.4 mg, 92% yield, *dr* 77:23); **^{1}H NMR** (400 MHz, $CDCl_3$) (major) δ 7.52 – 7.28 (m, 10H), 7.09 – 7.02 (m, 2H), 6.59 – 6.50 (m, 1H), 6.17 – 6.13 (m, 2H), 4.28 – 4.17 (m, 2H), 3.80 – 3.70 (m, 1H), 3.63 – 3.52 (m, 1H), 2.82 – 2.73 (m, 1H), 2.16 – 2.08 (m, 1H), 1.91 – 1.73 (m, 2H), 1.62 – 1.56 (m, 1H), 1.43 – 1.37 (m, 1H), 0.96 (d, *J* = 6.1 Hz, 3H); (minor, *selected characteristic peaks*) 6.59 – 6.50 (m, 1H), 6.17 – 6.13 (m, 2H), 4.28 – 4.17 (m, 2H), 3.63 – 3.52 (m, 1H), 3.47 – 3.38 (m, 1H), 2.98 – 2.90 (m, 1H), 2.35 – 2.26 (m, 1H), 1.02 (d, *J* = 5.7 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.8, 141.4, 140.6, 137.4, 129.5, 128.7, 128.5, 128.2, 126.98, 126.95, 64.8, 40.8, 38.3, 32.3, 24.9; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{27}H_{30}NO^+$ 384.2322; found 384.2337.

(*Z*)-4-(2,5-Dimethyl-1-phenylpyrrolidin-2-yl)-2,3-diphenylbut-2-en-1-ol (3.4v)



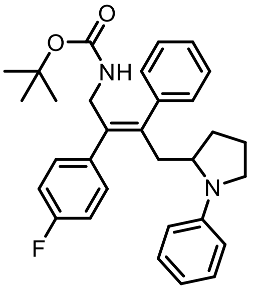
Yellowish oil (Method A, 16.7 mg, 42% yield, *dr* 59:41); **^{1}H NMR** (500 MHz, $CDCl_3$) (major) δ 7.51 – 7.30 (m, 10H), 6.94 – 6.89 (m, 2H), 6.57 – 6.48 (m, 1H), 6.17 – 6.15 (m, 2H), 4.26 – 4.21 (m, 2H), 3.60 (d, *J* = 13.9 Hz, 1H), 2.47 (d, *J* = 13.9 Hz, 1H), 1.78 – 1.72 (m, 1H), 1.61 – 1.54 (m, 1H), 1.47 – 1.36 (m, 2H), 1.30 – 1.25 (m, 1H), 1.07 (s, 3H), 0.98 (d, *J* = 6.0 Hz, 3H); (minor) δ 7.51 – 7.30 (m, 10H), 6.94 – 6.89 (m, 2H), 6.57 – 6.48 (m, 1H), 6.26 – 6.22 (m, 2H), 4.25-4.22 (m, 2H), 3.35 (d, *J* = 13.8 Hz, 1H), 2.35 (d, *J* = 13.8 Hz, 1H), 1.61 – 1.54 (m, 1H), 1.47 – 1.36 (m, 1H), 1.30 – 1.25 (m, 2H), 1.24 (s, 3H), 1.23 – 1.20 (m, 1H), 1.00 (d, *J* = 6.0 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 145.1, 144.8, 141.9, 141.8, 140.5, 140.3, 140.1, 140.0, 139.2, 139.0, 129.9, 129.8, 129.1, 129.0, 128.9, 128.7, 128.6, 128.38, 128.36, 128.3, 127.33, 127.27, 127.2, 115.6, 115.4, 115.3, 65.3, 65.1, 64.5, 64.4, 54.9, 54.7, 44.9, 39.9, 39.6, 38.7, 30.5, 29.9, 27.8, 22.9, 20.0, 19.8; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{28}H_{32}NO^+$ 398.2478; found 398.2493.

***tert*-Butyl-(*E*)-(2-phenyl-4-(1-phenylpyrrolidin-2-yl)but-2-en-1-yl)carbamate (3.6a)**



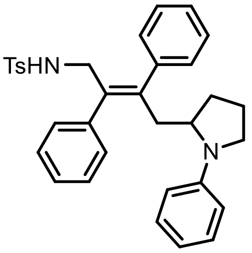
Yellowish oil (Method A, 20.1 mg, 51% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 – 7.33 (m, 2H), 7.31 – 7.28 (m, 1H), 7.17 – 7.16 (m, 2H), 7.13 – 7.09 (m, 2H), 6.59 (t, *J* = 7.4 Hz, 1H), 6.35 (d, *J* = 7.6 Hz, 2H), 5.65 (t, *J* = 7.5 Hz, 1H), 4.57 (s, 1H), 4.01 – 3.93 (m, 2H), 3.66 – 3.64(m, 1H), 3.32 – 3.29 (m, 1H), 3.12 – 3.07 (m, 1H), 2.48 – 2.43 (m, 1H), 2.09 – 1.74 (m, 5H), 1.42 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.9, 147.0, 140.2, 138.9, 129.2, 128.8, 128.5, 127.3, 125.0, 115.4, 111.9, 79.4, 58.6, 48.3, 47.8, 31.7, 30.0, 28.5, 23.3; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{25}H_{33}N_2O_2^+$ 393.2537; found 393.2525.

***tert*-Butyl-(*Z*)-(2-(4-fluorophenyl)-3-phenyl-4-(1-phenylpyrrolidin-2-yl)but-2-en-1-yl)carbamate (3.6b)**



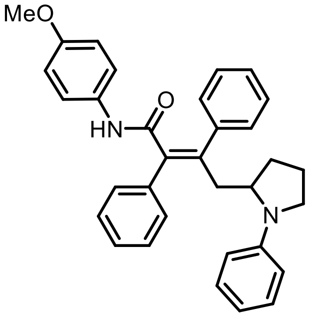
Yellowish oil (Method A, 43.4 mg, 89% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 – 7.45 (m, 2H), 7.39 – 7.35 (m, 1H), 7.32 – 7.30 (m, 2H), 7.24 – 7.21 (m, 2H), 7.12 – 7.03 (m, 4H), 6.56 (t, *J* = 7.3 Hz, 1H), 6.11 (d, *J* = 8.1 Hz, 2H), 4.22 (s, 1H), 4.03 – 3.86 (m, 2H), 3.48 – 3.43 (m, 1H), 3.18 – 3.13 (m, 1H), 3.01 – 2.95 (m, 1H), 2.71 – 2.67 (m, 1H), 2.20 (t, *J* = 12.2 Hz, 1H), 1.79 – 1.62 (m, 3H), 1.54 – 1.45 (m, 1H), 1.30 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.0 (d, *J* = 245.9 Hz), 155.5, 146.7, 140.7, 139.5, 136.0 (d, *J* = 32.6 Hz), 131.1 (d, *J* = 7.8 Hz), 129.1, 128.7, 128.6, 127.5, 115.6, 115.3 (d, *J* = 4.3 Hz), 111.7, 79.2, 56.7, 47.7, 43.8, 36.9, 29.0, 28.3, 22.9; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{31}H_{36}FN_2O_2^+$ 487.2755; found 487.2758.

(*Z*)-*N*-(2,3-Diphenyl-4-(1-phenylpyrrolidin-2-yl)but-2-en-1-yl)-4-methylbenzenesulfonamide (3.6c)



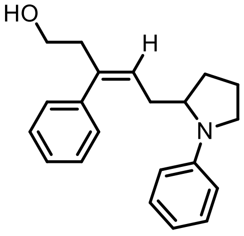
Yellowish solid (Method A, 44.3 mg, 85% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 – 7.30 (m, 8H), 7.25 – 7.19 (m, 2H), 7.18 – 7.12 (m, 2H), 7.12 – 7.07 (m, 2H), 7.07 – 7.00 (m, 2H), 6.59 – 6.51 (m, 1H), 6.15 – 6.04 (m, 2H), 4.37 (s, 1H), 3.77 (d, *J* = 6.0 Hz, 2H), 3.46 – 3.36 (m, 1H), 3.17 – 3.08 (m, 1H), 3.00 – 2.91 (m, 1H), 2.69 – 2.60 (m, 1H), 2.42 (s, 3H), 2.26 – 2.15 (m, 1H), 1.76 – 1.59 (m, 3H), 1.50 – 1.38 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.6, 143.1, 140.8, 140.2, 139.1, 136.5, 134.5, 129.5, 129.3, 129.1, 128.8, 128.7, 128.4, 127.5, 127.4, 127.2, 115.2, 111.6, 56.5, 47.6, 46.6, 36.7, 28.9, 22.8, 21.6; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{33}H_{35}N_2O_2S^+$ 523.2414; found 523.2416.

(*Z*)-*N*-(4-Methoxyphenyl)-2,3-diphenyl-4-(1-phenylpyrrolidin-2-yl)but-2-enamide (3.6d)



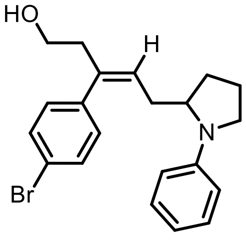
White solid (Method A, 43.0 mg, 88% yield); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.56 – 7.52 (m, 4H), 7.49 – 7.43 (m, 4H), 7.42 – 7.37 (m, 2H), 7.13 – 7.07 (m, 2H), 6.89 – 6.85 (m, 2H), 6.71 – 6.68 (m, 2H), 6.60 (t, *J* = 7.3 Hz, 1H), 6.19 (d, *J* = 7.7 Hz, 2H), 3.72 (s, 3H), 3.60 – 3.54 (m, 1H), 3.19 – 3.14 (m, 1H), 3.04 – 2.92 (m, 2H), 2.46 – 2.38 (m, 1H), 1.81 – 1.75 (m, 2H), 1.72 – 1.67 (m, 1H), 1.55 – 1.46 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.2, 156.6, 146.6, 141.9, 140.5, 138.6, 137.1, 130.5, 129.5, 129.2, 129.1, 128.6, 128.4, 127.9, 127.8, 122.2, 115.4, 113.9, 111.7, 56.7, 55.5, 47.7, 35.8, 29.0, 22.8; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{33}H_{32}N_2NaO_2^+$ 511.2356; found 511.2345.

(*Z*)-3-Phenyl-5-(1-phenylpyrrolidin-2-yl)pent-3-en-1-ol (3.6e)



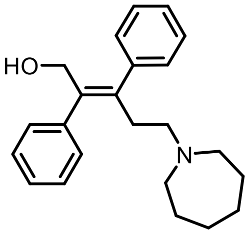
Yellowish oil (Method A, 17.2 mg, 56% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 – 7.26 (m, 3H), 7.16 – 7.09 (m, 4H), 6.60 (t, *J* = 7.3 Hz, 1H), 6.36 (d, *J* = 7.5 Hz, 2H), 5.62 (t, *J* = 7.6 Hz, 1H), 3.68 – 3.61 (m, 1H), 3.58 (t, *J* = 6.3 Hz, 2H), 3.35 – 3.30 (m, 1H), 3.13 – 3.07 (m, 1H), 2.64 (t, *J* = 6.2 Hz, 2H), 2.49 – 2.42 (m, 1H), 1.99 – 1.79 (m, 5H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.1, 140.3, 140.1, 129.2, 128.6, 128.5, 127.1, 126.8, 115.4, 111.9, 60.6, 58.6, 48.3, 42.9, 32.2, 30.1, 23.3; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{21}H_{26}NO^+$ 308.2009; found 308.2018.

(*Z*)-3-(4-Bromophenyl)-5-(1-phenylpyrrolidin-2-yl)pent-3-en-1-ol (3.6f)



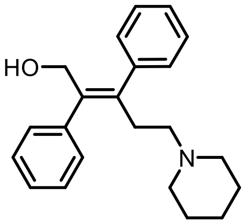
Yellowish oil (Method A, 23.5 mg, 61% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 – 7.45 (m, 2H), 7.16 – 7.12 (m, 2H), 7.03 – 6.99 (m, 2H), 6.63 (t, *J* = 7.3 Hz, 1H), 6.36 (d, *J* = 8.1 Hz, 2H), 5.63 (t, *J* = 7.6 Hz, 1H), 3.66 – 3.63 (m, 1H), 3.56 (t, *J* = 6.2 Hz, 2H), 3.36 – 3.32 (m, 1H), 3.13 – 3.10 (m, 1H), 2.60 (t, *J* = 6.4 Hz, 2H), 2.44 – 2.38 (m, 1H), 1.95 – 1.85 (m, 3H), 1.79 – 1.76 (m, 1H), 1.37 – 1.27 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.1, 139.2, 138.9, 131.7, 130.3, 129.3, 127.4, 121.1, 115.6, 111.9, 60.5, 58.5, 48.4, 42.6, 32.3, 30.2, 23.3; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{21}H_{25}BrNO^+$ 386.1114; found 386.1116.

(*Z*)-5-(Azepan-1-yl)-2,3-diphenylpent-2-en-1-ol (3.7a)



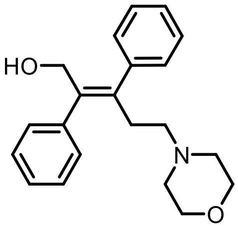
Yellowish oil (Method B, 21.1 mg, 63% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 – 7.35 (m, 5H), 7.32 – 7.27 (m, 5H), 4.15 (s, 2H), 2.46 – 2.43 (m, 6H), 2.00 – 1.99 (m, 2H), 1.49 – 1.48 (m, 8H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.8, 140.3, 139.6, 138.9, 129.0, 128.7, 128.6, 128.5, 127.4, 127.3, 64.6, 56.2, 54.8, 32.2, 27.0, 26.8; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{23}H_{30}NO^+$ 336.2322; found 336.2327.

(*Z*)-2,3-Diphenyl-5-(piperidin-1-yl)pent-2-en-1-ol (3.7b)



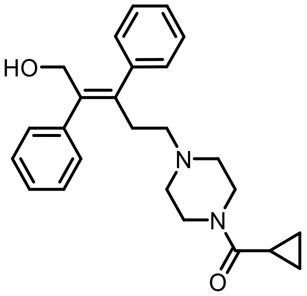
Yellowish oil (Method B, 24.3 mg, 76% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 – 7.27 (m, 10H), 4.16 (s, 2H), 2.48 – 2.44 (m, 2H), 2.24 – 2.14 (m, 6H), 1.51 – 1.45 (m, 4H), 1.36 – 1.32 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.0, 140.3, 139.6, 138.5, 129.1, 128.7, 128.6, 128.4, 127.3, 127.2, 64.7, 57.6, 54.3, 32.5, 25.8, 24.3; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{22}H_{28}NO^+$ 322.2165; found 322.2169.

(*Z*)-5-Morpholino-2,3-diphenylpent-2-en-1-ol (3.7c)



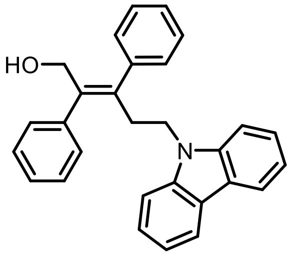
Yellowish oil (Method B, 25.1 mg, 78% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 – 7.35 (m, 4H), 7.34 – 7.26 (m, 6H), 4.16 (s, 2H), 3.57 (t, *J* = 4.7 Hz, 4H), 2.45 – 2.41 (m, 2H), 2.22 – 2.15 (m, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.9, 140.3, 139.6, 138.7, 129.1, 128.7, 128.6, 128.4, 127.4, 127.3, 66.9, 64.6, 57.3, 53.5, 32.3; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{21}H_{26}NO_2^+$ 324.1958; found 324.1961.

(*Z*)-Cyclopropyl(4-(5-hydroxy-3,4-diphenylpent-3-en-1-yl)piperazin-1-yl)methanone (3.7d)



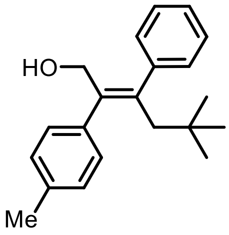
Yellowish oil (Method B, 34.6 mg, 89% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 – 7.38 (m, 4H), 7.36 – 7.27 (m, 6H), 4.17 (s, 2H), 3.55 – 3.50 (m, 4H), 2.46 – 2.42 (m, 2H), 2.25 – 2.13 (m, 6H), 1.68 – 1.62 (m, 1H), 0.96 – 0.92 (m, 2H), 0.73 – 0.69 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.9, 140.8, 140.2, 139.4, 138.8, 129.0, 128.7, 128.5, 127.4, 127.3, 64.6, 56.7, 53.3, 52.6, 45.3, 41.9, 32.4, 11.0, 7.5; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{25}H_{31}N_2O_2^+$ 391.2380; found 391.2382.

(*Z*)-5-(9*H*-Carbazol-9-yl)-2,3-diphenylpent-2-en-1-ol (3.7e)



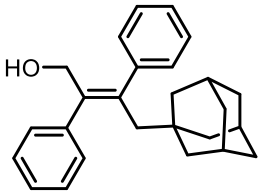
White solid (Method B, 37.7 mg, 93% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.03 – 8.01 (m, 2H), 7.54 – 7.50 (m, 2H), 7.47 – 7.40 (m, 6H), 7.32 – 7.26 (m, 4H), 7.18 – 7.14 (m, 2H), 6.76 (d, *J* = 8.3 Hz, 2H), 4.27 (s, 2H), 4.14 – 4.10 (m, 2H), 2.78 – 2.73 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.4, 140.1, 140.0, 139.9, 138.0, 129.01, 128.95, 128.8, 127.8, 127.6, 125.6, 122.9, 120.3, 118.9, 108.4, 64.5, 41.5, 34.5; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{29}H_{25}NNaO^+$ 426.1828; found 426.1835.

(*Z*)-5,5-Dimethyl-3-phenyl-2-(*p*-tolyl)hex-2-en-1-ol (3.7f)



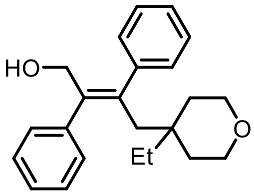
Yellowish oil (Method C, 23.3 mg, 79% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.26 (m, 5H), 7.23 – 7.15 (m, 4H), 4.19 (s, 2H), 2.39 (s, 3H), 2.36 (s, 2H), 0.58 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) 142.5, 140.0, 139.0, 137.7, 136.5, 129.5, 129.20, 129.17, 128.0, 126.9, 64.7, 47.5, 32.3, 30.6, 21.3; **HRMS** (APCI/TOF) *m/z*: $[M\text{-}OH]^+$ Calcd. for $C_{21}H_{25}^+$ 277.1951; found 277.1949.

(*Z*)-4-((3*r*,5*r*,7*r*)-Adamantan-1-yl)-2,3-diphenylbut-2-en-1-ol (3.7g)



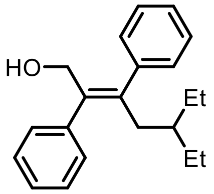
White solid (Method C, 34.5 mg, 96% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 – 7.38 (m, 2H), 7.36 – 7.26 (m, 8H), 4.20 (s, 2H), 2.22 (s, 2H), 1.75 – 1.71 (m, 3H), 1.56 – 1.50 (m, 3H), 1.43 – 1.37 (m, 3H), 1.16 – 1.13 (m, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.9, 141.0, 139.2, 139.1, 129.7, 129.1, 128.4, 128.0, 126.92, 126.88, 64.6, 48.7, 43.3, 36.9, 34.6, 28.9; **HRMS** (APCI/TOF) *m/z*: $[M\text{-}OH]^+$ Calcd. for $C_{26}H_{29}^+$ 341.2264; found 341.2263.

(*Z*)-4-(4-Ethyltetrahydro-2*H*-pyran-4-yl)-2,3-diphenylbut-2-en-1-ol (3.7h)



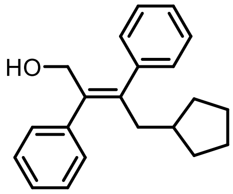
Yellowish oil (Method C, 32.0 mg, 95% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 – 7.37 (m, 2H), 7.37 – 7.26 (m, 8H), 4.17 (s, 2H), 3.40 – 3.19 (m, 4H), 2.51 (s, 2H), 1.17 – 1.07 (m, 4H), 1.06 – 0.98 (m, 2H), 0.35 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.4, 140.5, 140.2, 138.8, 129.7, 129.1, 128.6, 128.1, 127.11, 127.08, 64.4, 63.7, 41.1, 35.38, 35.37, 28.3, 7.2; **HRMS** (ESI/TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{23}H_{28}NaO_2^+$ 359.1982; found 359.1978.

(*Z*)-5-Ethyl-2,3-diphenylhept-2-en-1-ol (3.7i)



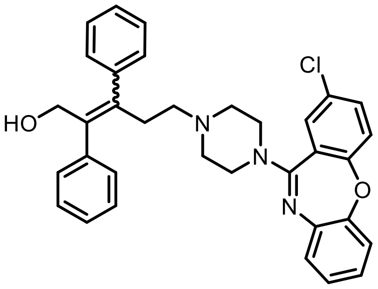
Yellowish oil (Method C, 24.3 mg, 83% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 – 7.34 (m, 4H), 7.33 – 7.25 (m, 6H), 4.18 (s, 2H), 2.22 (d, *J* = 7.0 Hz, 2H), 1.19 – 0.92 (m, 5H), 0.60 (t, *J* = 7.4 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.4, 141.3, 140.6, 138.1, 129.5, 128.6, 128.5, 128.2, 127.0, 126.9, 64.8, 38.6, 38.5, 25.0, 10.8; **HRMS** (APCI/TOF) *m/z*: $[M-OH]^+$ Calcd. for $C_{21}H_{25}^+$ 277.1951; found 277.1950.

(*Z*)-4-Cyclopentyl-2,3-diphenylbut-2-en-1-ol (3.7j)



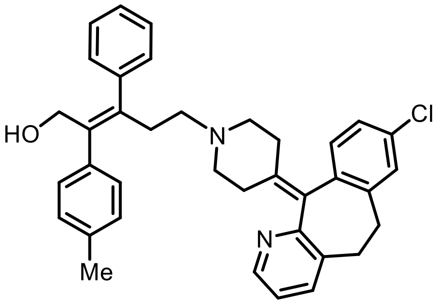
Yellowish oil (Method C, 21.6 mg, 74% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 – 7.36 (m, 4H), 7.35 – 7.26 (m, 6H), 4.16 (s, 2H), 2.28 (d, *J* = 7.1 Hz, 2H), 1.63 – 1.49 (m, 3H), 1.42 – 1.31 (m, 4H), 0.98 – 0.87 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.8, 141.4, 140.6, 137.4, 129.5, 128.7, 128.5, 128.2, 126.98, 126.95, 64.8, 40.8, 38.3, 32.3, 24.9; **HRMS** (APCI/TOF) *m/z*: $[M-OH]^+$ Calcd. for $C_{21}H_{23}^+$ 275.1794; found 275.1795.

(*Z/E*)-5-(4-(2-Chlorodibenzo[*b,f*][1,4]oxazepin-11-yl)piperazin-1-yl)-2,3-diphenylpent-2-en-1-ol (3.9a)



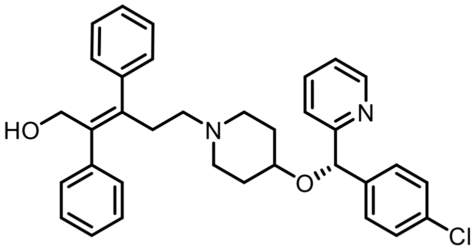
Yellowish oil (Method B, 46.2 mg, 84% yield, *Z/E* = 82:18); **^{1}H NMR** (400 MHz, $CDCl_3$) (major **Z**) δ 7.44 – 7.29 (m, 11H), 7.24 – 7.22 (m, 1H), 7.18 – 7.15 (m, 1H), 7.13 – 7.05 (m, 3H), 6.99 – 6.95 (m, 1H), 4.16 (s, 2H), 3.41 (s, 4H), 2.49 – 2.45 (m, 2H), 2.30 – 2.26 (m, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.3, 158.8, 151.9, 140.9, 140.3, 139.5, 138.7, 132.5, 130.3, 129.2, 129.0, 128.7, 128.6, 128.4, 127.3, 127.2, 127.1, 125.9, 125.1, 124.5, 122.8, 120.2, 64.5, 56.8, 52.7, 47.3, 32.4; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{34}H_{33}ClN_3O_2^+$ 550.2256; found 550.2247; Yellowish oil (minor **E**); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.37 (m, 1H), 7.29 – 7.28 (m, 1H), 7.20 – 7.16 (m, 1H), 7.16 – 7.03 (m, 11H), 7.03 – 6.95 (m, 3H), 4.43 (s, 2H), 3.69 (s, 4H), 2.85 (t, *J* = 5.6 Hz, 2H), 2.68 (s, 4H), 2.42 (t, *J* = 5.2 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.4, 158.6, 151.9, 142.8, 142.2, 140.9, 140.3, 140.0, 132.6, 130.4, 130.0, 129.2, 129.1, 128.1, 127.8, 127.2, 126.6, 126.2, 125.9, 125.1, 124.6, 122.8, 120.2, 63.9, 55.8, 54.1, 46.7, 33.3; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{34}H_{33}ClN_3O_2^+$ 550.2256; found 550.2245.

(*Z*)-5-(4-(8-Chloro-5,6-dihydro-11*H*-benzo[*5,6*]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidin-1-yl)-3-phenyl-2-(*p*-tolyl)pent-2-en-1-ol (3.9b)



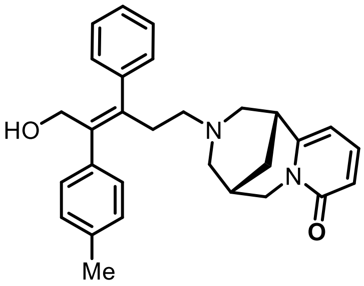
Yellowish oil (Method B, 50.6 mg, 90% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.37 – 8.35 (m, 1H), 7.41 – 7.38 (m, 1H), 7.37 – 7.31 (m, 2H), 7.30 – 7.26 (m, 2H), 7.25 – 7.24 (m, 1H), 7.18 (s, 4H), 7.13 – 7.11 (m, 1H), 7.09 – 7.04 (m, 3H), 4.13 (s, 2H), 3.39 – 3.28 (m, 2H), 2.83 – 2.72 (m, 2H), 2.51 – 2.40 (m, 5H), 2.36 (s, 3H), 2.31 – 2.16 (m, 5H), 1.96 – 1.88 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.7, 146.7, 141.0, 139.6, 138.5, 137.9, 137.3, 137.1, 136.9, 133.5, 132.7, 130.9, 129.9, 129.3, 129.0, 128.8, 128.7, 128.4, 128.3, 128.0, 127.1, 126.1, 122.2, 64.6, 56.6, 54.63, 54.55, 32.6, 31.9, 31.5, 30.8, 30.5, 21.3; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{37}H_{38}ClN_2O^+$ 561.2667; found 561.2661.

(*S*)-(*Z*)-5-(4-((4-Chlorophenyl)(pyridin-2-yl)methoxy)piperidin-1-yl)-2,3-diphenylpent-2-en-1-ol (3.9c)



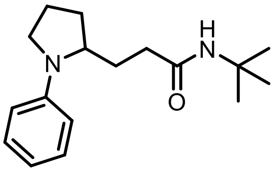
Yellowish oil (Method B, 40.4 mg, 75% yield); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.49 – 8.46 (m, 1H), 7.68 – 7.63 (m, 1H), 7.50 – 7.46 (m, 1H), 7.41 – 7.34 (m, 4H), 7.33 – 7.27 (m, 7H), 7.26 – 7.24 (m, 3H), 7.16 – 7.11 (m, 1H), 5.53 (s, 1H), 4.14 (s, 2H), 3.34 (s, 1H), 2.49 – 2.38 (m, 4H), 2.22 – 2.14 (m, 2H), 1.89 – 1.73 (m, 4H), 1.63 – 1.54 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.2, 149.0, 140.9, 140.5, 140.3, 137.0, 133.4, 129.1, 128.7, 128.62, 128.59, 128.4, 128.3, 127.3, 127.2, 122.6, 120.8, 80.9, 64.6, 56.7, 50.9, 41.1, 32.7, 31.4; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{34}H_{36}ClN_2O_2^+$ 539.2460; found 539.2459.

(1*R*,5*S*)-3-((*Z*)-5-Hydroxy-3-phenyl-4-(*p*-tolyl)pent-3-en-1-yl)-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (3.9d)



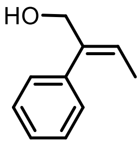
Yellowish oil (Method B, 28.3 mg, 64% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.33 (m, 1H), 7.29 (d, *J* = 7.8 Hz, 2H), 7.23 – 7.12 (m, 5H), 6.79 (s, 2H), 6.50 (d, *J* = 9.0 Hz, 1H), 6.03 – 5.98 (m, 1H), 4.21 – 4.08 (m, 2H), 3.93 – 3.78 (m, 2H), 2.85 (s, 1H), 2.62 – 2.44 (m, 3H), 2.38 (s, 3H), 2.32 – 2.28 (m, 1H), 2.22 – 2.11 (m, 2H), 2.00 – 1.91 (m, 2H), 1.88 – 1.78 (m, 2H), 1.70 – 1.62 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.0, 152.0, 140.4, 139.2, 138.7, 138.2, 137.3, 136.6, 129.4, 129.0, 128.5, 128.0, 126.6, 117.0, 105.0, 64.3, 61.0, 58.3, 54.8, 50.1, 35.7, 31.7, 27.9, 26.1, 21.4; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{29}H_{33}N_2O_2^+$ 441.2537; found 441.2536.

N-(*tert*-Butyl)-3-(1-phenylpyrrolidin-2-yl)propanamide (3.12)



White solid; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.25 – 7.19 (m, 2H), 6.66 (t, *J* = 7.3 Hz, 1H), 6.62 (d, *J* = 8.1 Hz, 2H), 5.29 (s, 1H), 3.79 – 3.72 (m, 1H), 3.49 – 3.40 (m, 1H), 3.18 – 3.11 (m, 1H), 2.18 – 2.11 (m, 2H), 2.08 – 1.94 (m, 4H), 1.84 – 1.78 (m, 1H), 1.69 – 1.60 (m, 1H), 1.34 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.9, 147.6, 129.3, 115.6, 112.1, 57.8, 51.3, 48.6, 34.6, 30.3, 29.4, 28.9, 23.6; **HRMS** (ESI/TOF) *m/z*: $[M +H]^+$ Calcd. for $C_{17}H_{27}N_2O^+$ 275.2118; found 275.2123.

(*E*)-2-Phenylbut-2-en-1-ol (3.13)[34]



Yellowish oil; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 – 7.35 (m, 2H), 7.31 – 7.27 (m, 1H), 7.25 – 7.21 (m, 2H), 5.84 (q, *J* = 6.9 Hz, 1H), 4.34 (s, 2H), 1.65 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 141.1, 138.4, 128.9, 128.5, 127.2, 123.7, 68.3, 14.5.

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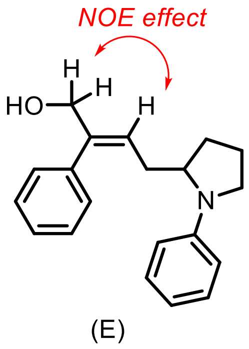
(34) A. V. Malkov, L. Czemerys, D. A. Malyshev, *J. Org. Chem.* **2009**, *74*, 3350-3355.

GOESY analysis of product 3.3a:



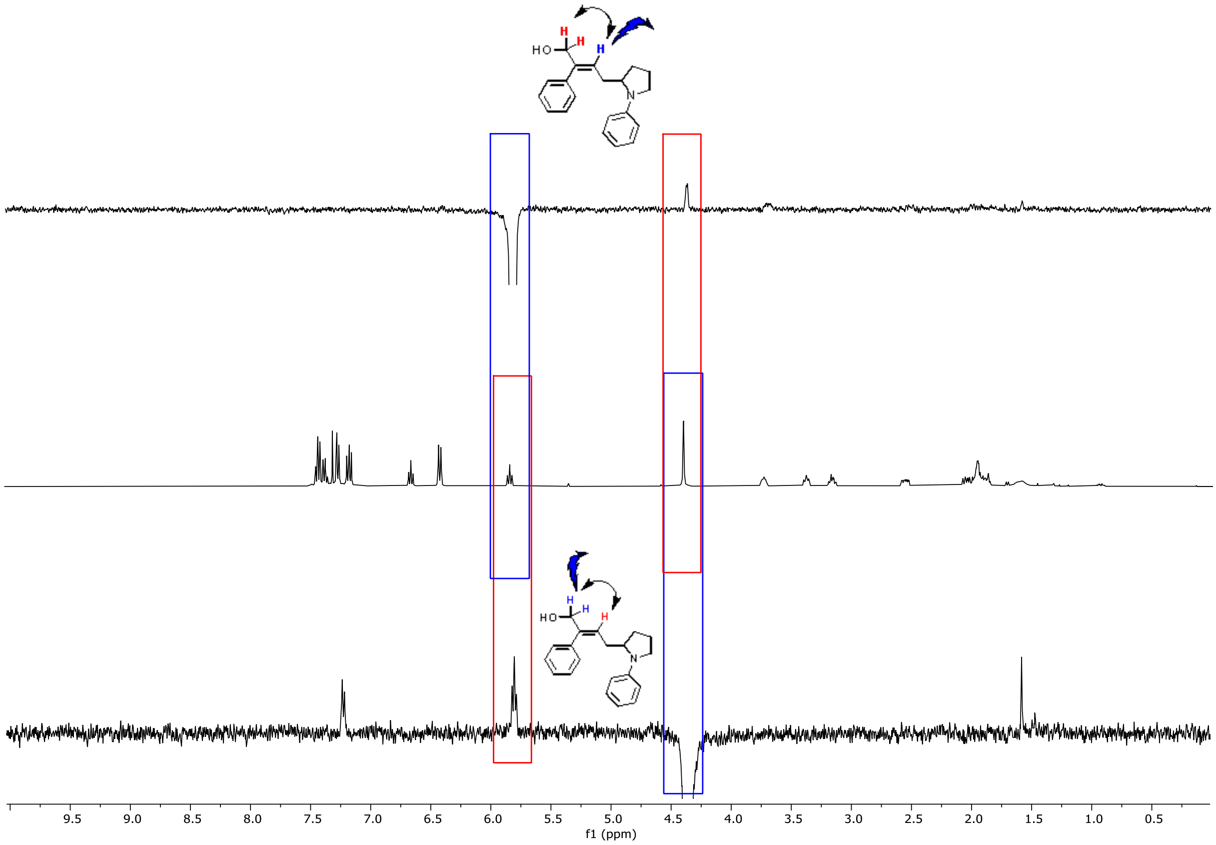
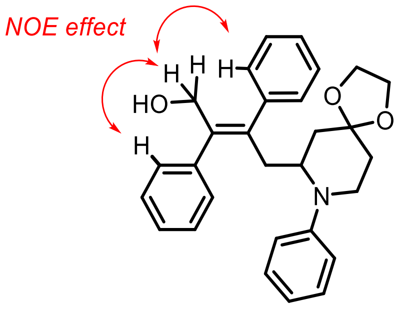


Figure 3.1. ^{1}H-^{1}H GOESY NMR spectrum of product **3.3a**.

GOESY analysis of product 3.4e:



(Z)

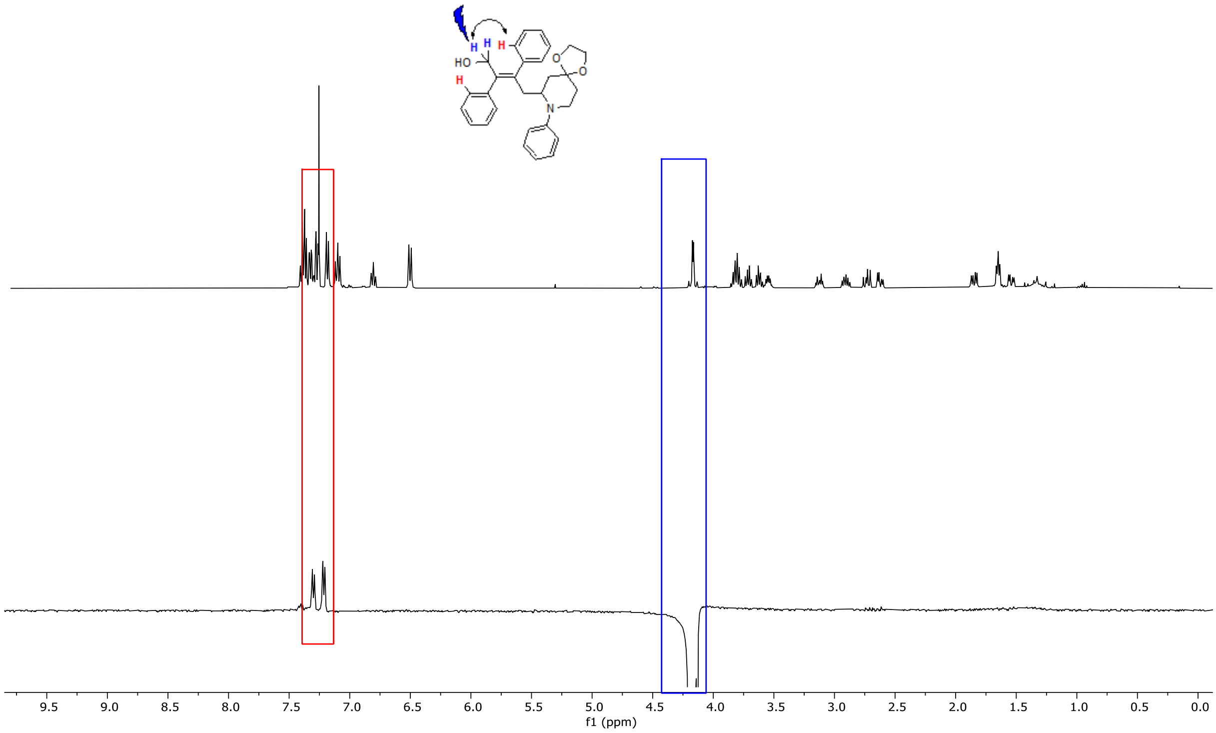
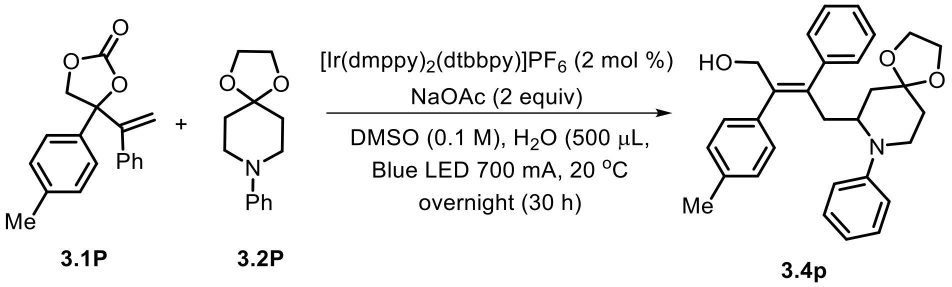


Figure 3.2. ^{1}H-^{1}H GOESY NMR spectra of product **3.4e**.

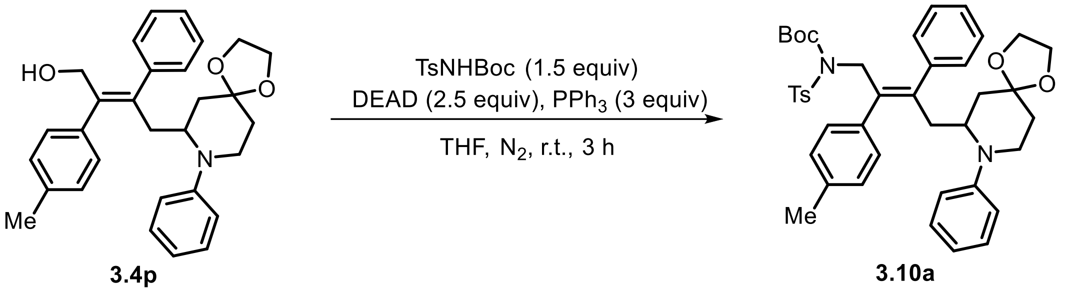
3.4.5. Scale up of the synthesis of 3.4p



The photocatalyst ([Ir(dmppy)$_2$(dtbbpy)]PF$_6$ (19 mg, 2 mmol%), NaOAc (164 mg, 2 mmol, 2 equiv), VCC **3.1P** (280 mg, 1 mmol, 1 equiv) and amine **3.2P** (548 mg, 2.5 mmol, 2.5 equiv) were weighed in a 10 mL screw-cap vial. The reaction vial was sealed with a cap containing a silicone septum, evacuated, and filled with argon three times. Degassed solvent (10 mL, 0.1 M) and H_2O (500 μL) was then added, affording a light-yellow solution under Ar atmosphere. The reaction system was further sealed with Parafilm® and irradiated for 30 hours at 20 °C using a single high-power blue LED (λ_{em} = 445 nm, 700 mA) from the bottom. After completion, the mixture was extracted with EtOAc (3 × 20 mL). The organic phase was evaporated to dryness and the residue was purified by column chromatography (SiO_2, hexanes/EtOAc = 10:1 – 5:1) to afford the colorless, oily product **3.4p** in 81% (368 mg).

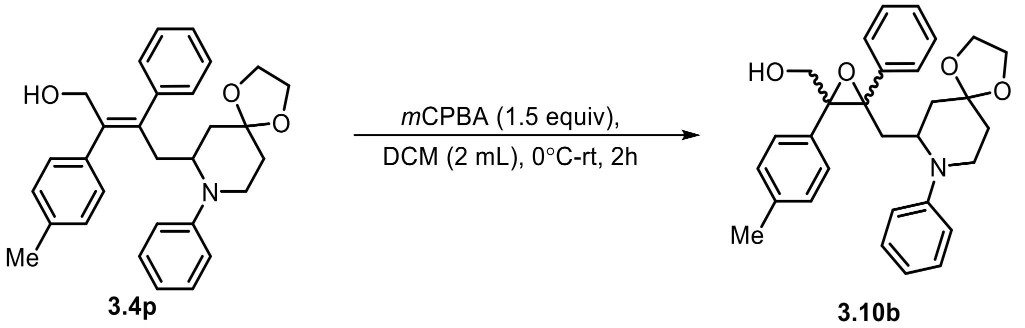
3.4.1. Post-synthetic transformations

tert-Butyl-(*Z*)-(3-phenyl-4-(8-phenyl-1,4-dioxa-8-azaspiro[4.5]decan-7-yl)-2-(*p*-tolyl)but-2-en-1-yl)(tosyl)carbamate (3.10a)



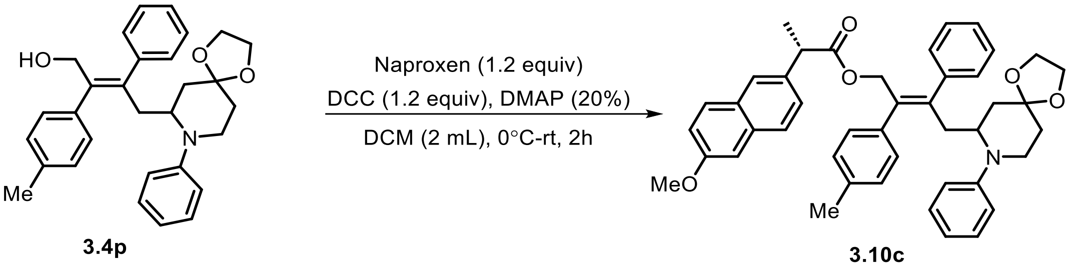
A reaction flask was charged with TsNHBoc (40.7 mg, 0.15 mmol, 1.5 equiv), PPh_3 (78.7 mg, 0.3 mmol, 3 equiv) before evacuating and back-filling with N_2. Anhydrous THF (0.5 mL) and **3.4p** (0.1 mmol) were added under N_2, followed by diethyl azodicarboxylate (43.5 mg, 0.25 mmol, 2.5 equiv). After stirring this mixture at room temperature for 3 hours, the mixture was concentrated under reduced pressure and the crude product was purified by flash chromatography on silica gel (hexanes/EtOAc= 20:1 to 10:1) to afford the pure product **3.10a** as a yellowish oil (51.9 mg, 73% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 – 7.38 (m, 2H), 7.38 – 7.32 (m, 1H), 7.30 – 7.27 (m, 2H), 7.25 – 7.21 (m, 2H), 7.16 – 7.06 (m, 8H), 6.84 – 6.79 (m, 1H), 6.52 – 6.46 (m, 2H), 4.71 (d, *J* = 15.9 Hz, 1H), 4.55 (d, *J* = 15.9 Hz, 1H), 3.85 – 3.80 (m, 2H), 3.76 – 3.62 (m, 2H), 3.46 – 3.39 (m, 1H), 3.06 – 3.01 (m, 1H), 2.92 – 2.83 (m, 1H), 2.60 – 2.48 (m, 2H), 2.40 (s, 3H), 2.35 (s, 3H), 1.90 – 1.81 (m, 1H), 1.65 – 1.58 (m, 2H), 1.51 – 1.42 (m, 1H), 1.12 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.6, 150.4, 143.5, 141.3, 138.1, 137.7, 136.3, 135.6, 135.5, 130.1, 129.3, 128.9, 128.8, 128.1, 127.8, 127.0, 120.3, 119.2, 107.3, 83.6, 64.4, 64.0, 54.4, 49.6, 46.2, 37.0, 36.5, 34.6, 27.7, 21.6, 21.4; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{42}H_{49}N_2O_6S^+$ 709.3306; found 709.3311.

(3-Phenyl-3-((8-phenyl-1,4-dioxa-8-azaspiro[4.5]decan-7-yl)methyl)-2-(*p*-tolyl)oxiran-2-yl)methanol (3.10b)



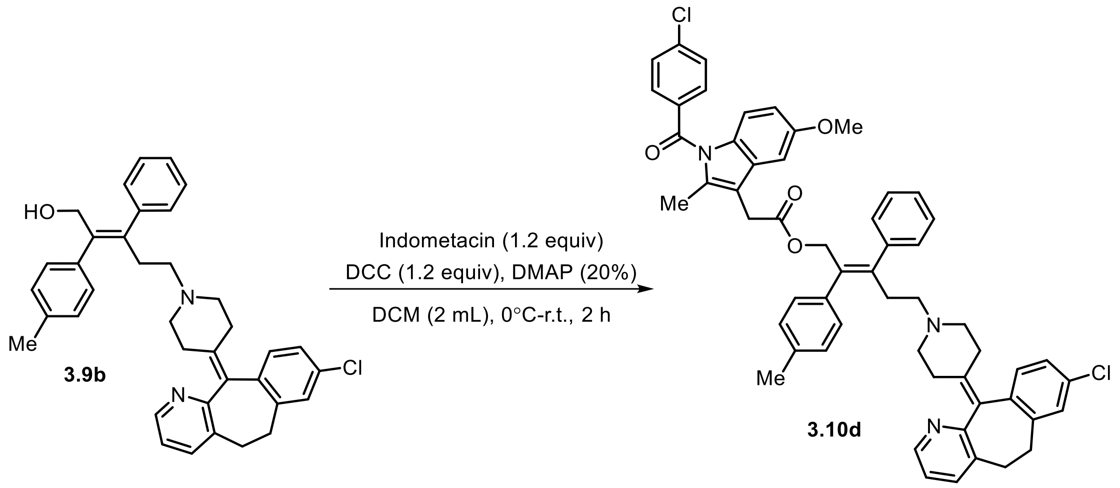
A cooled (0 °C) solution of **3.4p** (0.1 mmol) and *m*-CPBA (37 mg, 0.15 mmol, 1.5 equiv) in DCM was stirring for 1 h. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography on silica gel (DCM/Methanol= 50:1 to 20:1) to afford the isomer mixture product **3.10b** as a yellowish oil (40.2 mg, 85% yield, *dr* = 67:33); **^{1}H NMR** (400 MHz, $CDCl_3$) (major) δ 7.37 – 7.26 (m, 6H), 7.25 – 7.20 (m, 1H), 7.15 – 7.09 (m, 3H), 7.02 – 6.96 (m, 2H), 6.96 – 6.90 (m, 2H), 4.06 – 4.02 (m, 1H), 4.01 – 3.97 (m, 2H), 3.97 – 3.88 (m, 3H), 3.65 – 3.59 (m, 1H), 3.57 – 3.52 (m, 1H), 3.29 (d, *J* = 12.0 Hz, 1H), 2.79 – 2.69 (m, 1H), 2.69 – 2.58 (m, 1H), 2.33 (s, 3H), 2.31 – 2.25 (m, 1H), 1.99 (d, *J* = 13.9 Hz, 1H), 1.83 – 1.76 (m, 1H), 1.58 – 1.48 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.6, 140.9, 140.0, 137.0, 136.1, 135.7, 129.6, 128.8, 128.69, 128.67, 128.5, 127.4, 105.7, 71.2, 68.9, 64.8, 64.5, 64.3, 34.9, 34.3, 30.7, 21.3; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{30}H_{34}NO_4^+$ 472.2482; found 472.2476; **^{1}H NMR** (400 MHz, $CDCl_3$) (minor) δ 7.34 – 7.27 (m, 5H), 7.22 – 7.12 (m, 4H), 7.07 – 7.01 (m, 2H), 6.88 – 6.76 (m, 3H), 4.03 – 3.95 (m, 2H), 3.91 – 3.82 (m, 1H), 3.79 – 3.73 (m, 2H), 3.63 – 3.55 (m, 2H), 3.44 (d, *J* = 7.4 Hz, 1H), 3.30 – 3.22 (m, 1H), 3.14 – 3.07 (m, 1H), 2.86 – 2.75 (m, 2H), 2.38 (s, 3H), 2.11 (d, *J* = 12.3 Hz, 1H), 1.64 – 1.55 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.7, 140.9, 139.6, 136.8, 136.2, 135.5, 129.4, 129.1, 129.0, 128.5, 127.4, 121.1, 104.4, 76.2, 64.4, 64.3, 64.1, 57.6, 33.0, 31.5, 30.3, 21.4; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{30}H_{34}NO_4^+$ 472.2482; found 472.2479.

(*Z*)-3-Phenyl-4-(8-phenyl-1,4-dioxa-8-azaspiro[4.5]decan-7-yl)-2-(*p*-tolyl)but-2-en-1-yl-(2*S*)-2-(6-methoxynaphthalen-2-yl)propanoate (3.10c)



To a solution of **3.4p** (0.1 mmol, 1 equiv) and naproxen (27.6 mg, 0.12 mmol, 1.2 equiv) and DCC (24.8 mg, 0.12 mmol, 1.2 equiv) in DCM (2 mL) was added DMAP (2.4 mg, 0.02 mmol, 20 mol%) at 0 °C. After stirring the mixture for 2 h at 0 °C, it was filtered at r.t., and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (hexanes/EtOAc= 20 to 10:1) to afford the pure product **3.10c** as a yellowish oil (63.4mg, 95% yield, *dr* =50:50); **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.68 (t, *J* = 8.5 Hz, 2H), 7.55 (s, 1H), 7.27 (t, *J* = 1.9 Hz, 1H), 7.25 – 7.21 (m, 2H), 7.20 – 7.13 (m, 3H), 7.12 – 7.02 (m, 4H), 6.97 (d, *J* = 10.3 Hz, 4H), 6.84 – 6.77 (m, 1H), 6.50 – 6.43 (m, 2H), 4.66 – 4.48 (m, 2H), 3.94 (s, 3H), 3.79 – 3.70 (m, 2H), 3.69 – 3.57 (m, 2H), 3.52 – 3.37 (m, 2H), 3.14 – 3.03 (m, 1H), 2.93 – 2.83 (m, 1H), 2.78 – 2.67 (m, 1H), 2.58 – 2.50 (m, 1H), 2.33 (s, 3H), 1.82 – 1.70 (m, 2H), 1.63 – 1.55 (m, 2H), 1.46 (d, *J* = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, CDCl$_3$) δ 174.10, 174.08, 157.7, 150.14, 150.05, 142.2, 140.9, 140.7, 136.89, 136.87, 136.17, 136.15, 135.81, 135.78, 134.44, 134.36, 133.7, 129.4, 129.03, 128.96, 128.8, 128.7, 128.6, 128.1, 127.22, 127.20, 127.0, 126.53, 126.48, 126.0, 120.0, 119.7, 118.9, 118.6, 118.2, 107.1, 105.7, 66.9, 64.3, 63.88, 63.85, 55.4, 54.4, 54.3, 45.57, 45.55, 45.1, 44.5, 36.52, 36.47, 35.5, 35.3, 34.5, 34.4, 21.3, 18.19, 18.15; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{44}H_{46}NO_5^+$ 668.3371; found 668.3387.

(*Z*)-5-(4-(8-Chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)piperidin-1-yl)-3-phenyl-2-(*p*-tolyl)pent-2-en-1-yl-2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetate (3.10d)

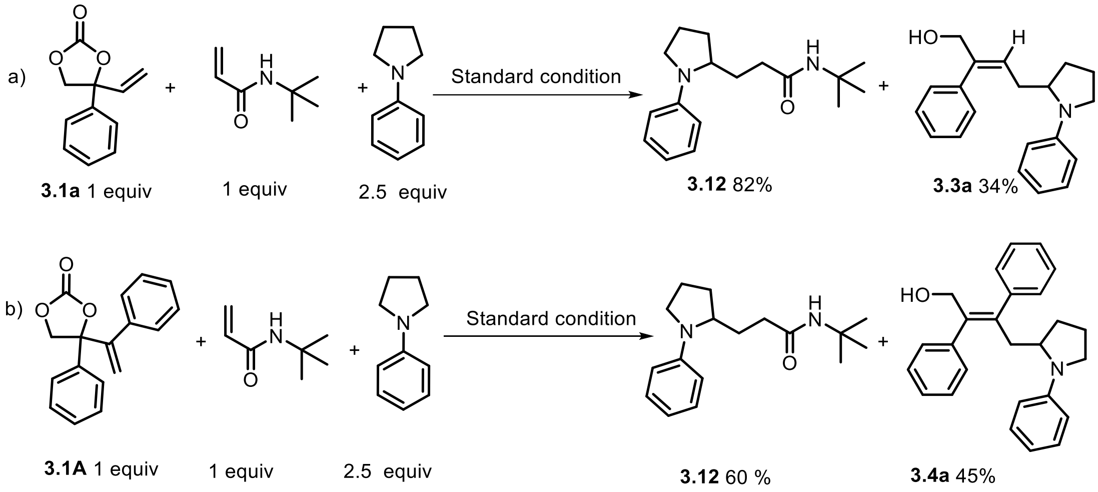


To a solution of **3.4p** (0.1 mmol, 1 equiv) and indometacin (42.9 mg, 0.12 mmol, 1.2 equiv) and DCC (24.8 mg, 0.12 mmol, 1.2 equiv) in DCM (2 mL) was added DMAP (2.4 mg, 0.02 mmol, 20 mol%) at 0 °C. After stirring the mixture for 2 h at 0 °C, it was filtered at r.t., and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (hexanes/EtOAc= 20 to 10:1) to afford the pure product **3.10d** as a yellowish oil (79.1 mg, 88% yield); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 8.37 (dd, *J* = 4.8, 1.7 Hz, 1H), 7.65 – 7.60 (m, 2H), 7.46 – 7.43 (m, 2H), 7.41 – 7.38 (m, 1H), 7.24 – 7.21 (m, 3H), 7.13 – 7.03 (m, 8H), 7.00 (d, *J* = 8.0 Hz, 2H), 6.89 (d, *J* = 9.0 Hz, 1H), 6.84 (d, *J* = 2.5 Hz, 1H), 6.70 – 6.65 (m, 1H), 4.60 (s, 2H), 3.79 (s, 3H), 3.49 (s, 2H), 3.39 – 3.27 (m, 2H), 2.83 – 2.73 (m, 2H), 2.48 – 2.36 (m, 5H), 2.30 (s, 3H), 2.29 – 2.24 (m, 1H), 2.23 (s, 3H), 2.23 – 2.08 (m, 4H), 1.95 – 1.86 (m, 2H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 170.4, 168.3, 157.7, 156.9, 156.1, 146.7, 142.9, 140.6, 139.6, 139.3, 137.9, 137.3, 136.8, 136.7, 135.8, 134.1, 133.6, 133.5, 132.7, 131.3, 131.0, 130.9, 130.8, 129.2, 129.03, 128.96, 128.6, 128.4, 128.3, 127.3, 126.1, 122.2, 115.0, 112.8, 111.7, 101.5, 66.9, 56.5, 55.8, 54.7, 54.6, 34.1, 31.9, 31.5, 30.4, 25.7, 25.1, 21.3, 13.3; HRMS (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{56}H_{52}Cl_2N_3O_4^+$ 900.3329; found 900.3356.

3.4.2. Mechanistic studies

3.4.2.1. Supporting a radical-mediated process in the catalytic cycle

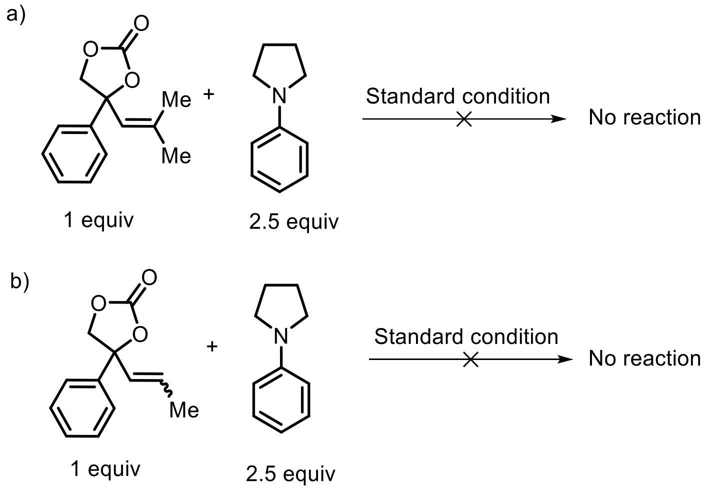
Experiment 1: Confirm radical generation



*Note: The yield of radical addition product **3.12** was calculated based on the *N*-(*tert*-butyl)acrylamide. The yield of targeted **3.3a** and **3.4a** were calculated based on the vinyl cyclic carbonate **3.1a** and **3.1A**.

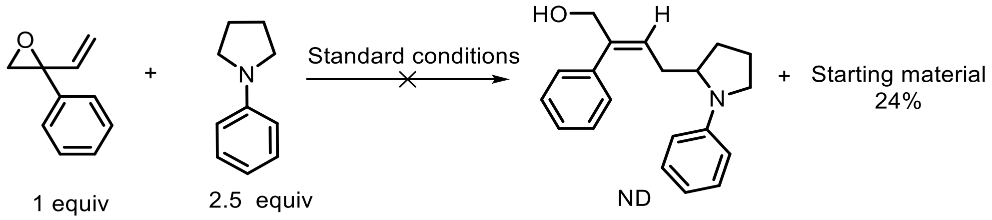
Procedure: The photocatalyst ([Ir(dmppy)$_2$(dtbbpy)]PF$_6$ (1.9 mg, 2 mmol%), NaOAc (16.4 mg, 0.2 mmol, 2 equiv), VCC (0.1 mmol, 1 equiv), *N*-(*tert*-butyl)acrylamide (0.1 mmol, 1 equiv) and amine **3.2a** (54.8 mg, 0.25 mmol, 2.5 equiv) were weighed in a 10 mL screw-cap vial. The reaction vial was sealed with a cap containing a silicone septum, evacuated, and filled with argon three times. The degassed solvent (1 mL, 0.1 M) and H_2O (50 µL) were added, affording a light-yellow solution under Ar atmosphere. The reaction system was further sealed with Parafilm® and irradiated for 15-24 hours at 20 °C using a single high-power blue LED (λ_{em} = 445 nm, 700 mA) from the bottom. After completion, the mixture was extracted with EtOAc (3 × 20 mL). The organic phase was evaporated to dryness and the residue was purified by column chromatography (SiO_2, hexanes/EtOAc = 10:1 – 5:1) to afford **3.12** as a white solid product in 82% (22.5 mg) and **3.3a** as a yellow oil 34% (10 mg) (***under a***); White solid product **3.12** in 60% (16.5 mg) and **3.4a** as a yellow oil in 45% (16.6 mg) (***under b***).

Experiment 2: Supporting a radical-triggered decarboxylation



<u>Procedure:</u> The photocatalyst ([Ir(dmppy)$_2$(dtbbpy)]PF$_6$ (1.9 mg, 2 mmol%), NaOAc (16.4 mg, 0.2 mmol, 2 equiv), VCC (0.1 mmol, 1 equiv) and amine **3.2a** (54.8 mg, 0.25 mmol, 2.5 equiv) were weighed in a 10 mL screw-cap vial. The reaction vial was sealed with a cap containing a silicone septum, evacuated, and filled with argon three times. The degassed solvent (1 mL, 0.1 M) and H_2O (50 µL) were added, affording a light-yellow solution under Ar atmosphere. The reaction system was further sealed with Parafilm® and irradiated for 15-24 hours at 20 °C using a single high-power blue LED (λ_{em} = 445 nm, 700 mA) from the bottom. After completion, the mixture was directly added 1,3,5-trimethyloxybenzene as internal standard then extraction with EtOAc (3 × 20 mL). The organic phase was evaporated to dryness and the residue was dissolved in $CDCl_3$ and analyzed by ^{1}H NMR.

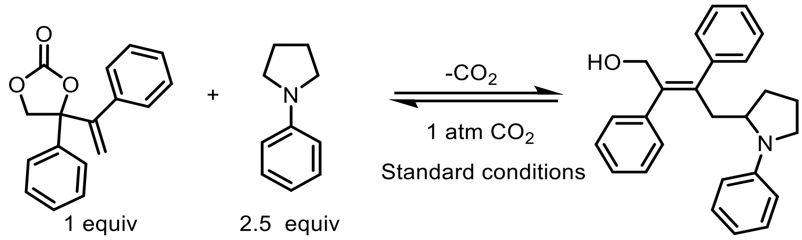
3.4.2.2. Investigation of a crucial CO_2 extrusion step



Procedure: The photocatalyst ([Ir(dmppy)$_2$(dtbbpy)]PF$_6$ (1.9 mg, 2 mmol%), NaOAc (16.4 mg, 0.2 mmol, 2 equiv), vinyl epoxide (0.1 mmol, 1 equiv) and amine **3.2a** (54.8 mg, 0.25 mmol, 2.5 equiv) were weighed in a 10 mL screw-cap vial. The reaction vial was sealed with a cap containing a silicone septum, evacuated, and filled with argon three times. The degassed solvent (1 mL, 0.1 M) and H_2O (50 µL) were added, affording a light-yellow solution under Ar atmosphere. The reaction system was further sealed with Parafilm® and irradiated for 24 hours at 20 °C using a single high-power blue LED (λ_{em} = 445 nm, 700 mA) from the bottom. After completion, the mixture was directly added 1,3,5-trimethyloxybenzene as internal standard then extraction with EtOAc (3 × 20 mL). The organic phase was evaporated to dryness and the residue was dissolved in $CDCl_3$ and analyzed by ^{1}H NMR. Here, we conclude that CO_2 extrusion seems a crucial step in the formation of the final product.

3.4.2.3. Investigation of the irreversibility of the CO_2 extrusion

Experiment: Equilibrium between VCC and allylic species:

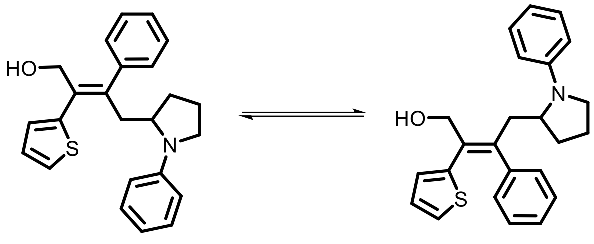


*Note: under standard conditions, Ar: 81% yield of product; under standard conditions, using 1 atm CO_2, 75% yield of product.

Procedure: The photocatalyst ([Ir(dmppy)$_2$(dtbbpy)]PF_6 (1.9 mg, 2 mmol%), NaOAc (16.4 mg, 0.2 mmol, 2 equiv), VCC compound (0.1 mmol, 1 equiv) and amine **3.2a** (54.8 mg, 0.25 mmol, 2.5 equiv) were weighed in a 10 mL screw-cap vial. The reaction vial was sealed with a cap containing a silicone septum, evacuated, and filled with CO_2 three times. The degassed solvent (1 mL, 0.1 M) and H_2O (50 µL) were added, affording a light-yellow solution under a CO_2 balloon atmosphere. The reaction system was further sealed with Parafilm® and irradiated for 24 hours at 20 °C using a single high-power blue LED (λ_{em} = 445 nm, 700 mA) from the bottom. After completion, the mixture was directly added 1,3,5-trimethyloxybenzene as internal standard then extraction with EtOAc (3 × 20 mL). The organic phase was evaporated to dryness and the residue was dissolved in $CDCl_3$ and analyzed by ^{1}H NMR. The isolated yield of product is 75% when using 1 atm CO_2, which is almost the same yield as before. We therefore suggest that the CO_2 extrusion is irreversible under the applied experimental conditions.

3.4.2.4. Investigation of the interconversion of *Z* and *E*-isomers

Table 3.4. *E/Z* photo-isomerization studies of product **3.4j**.



(*E*)-3.4j **(*Z*)-3.4j**

entry	SM	PC	Base	time (h)	Solvent	product
1	***E/Z*-3.4j**	–	–	5	DMSO	***E/Z*-3.4j**, 83:17
2	***E/Z*-3.4j**	–	–	24	DMSO	***E/Z*-3.4j**, 83:17
3	***E/Z*-3.4j**	PC1	–	24	DMSO	***E/Z*-3.4j**, 83:17
4	***E/Z*-3.4j**	PC2	NaOAc	12	DMSO/H_2O	<10% isomers
5	***E*-3.4j**	PC2	NaOAc	12	DMSO/H_2O	<5% isomers
6	***E*-3.4j**	PC2	–	12	DMSO	***E/Z*-3.4j**, 86:14
7	***E*-3.4j**	–	–	12	DMSO	***E/Z*-3.4j**, 83:17
8	***Z*-3.4j**	PC2	NaOAc	12	DMSO/H_2O	<5% isomers
9	***Z*-3.4j**	PC2	–	12	DMSO	***E/Z*-3.4j**, 86:14
10	***Z*-3.4j**	–	–	12	DMSO	***E/Z*-3.4j**, 76:24

The ratio of ***E*-3.4j/*Z*-3.4j** mixture was 73:27 before exposing to the conditions in the table. Entries 4,5 and 8 are based on the standard conditions. All the reactions were conducted under 700 mA blue LED, at 20 ºC and using a standard amount of ***E/Z*-3.4** (0.1 mmol), ***E*-3.4** (0.1 mmol) or ***Z*-3.4** (0.1 mmol) compound, photocatalyst (2 mol%), solvent (1 mL), H_2O (50 µL) unless stated otherwise. SM stands for starting materials. Blue light irradiation was used in all experiments. PCs used: here PC1 stands for 4CzIPN, PC2 stands for [Ir(dmppy)$_2$(dtbbpy)]PF$_6$.

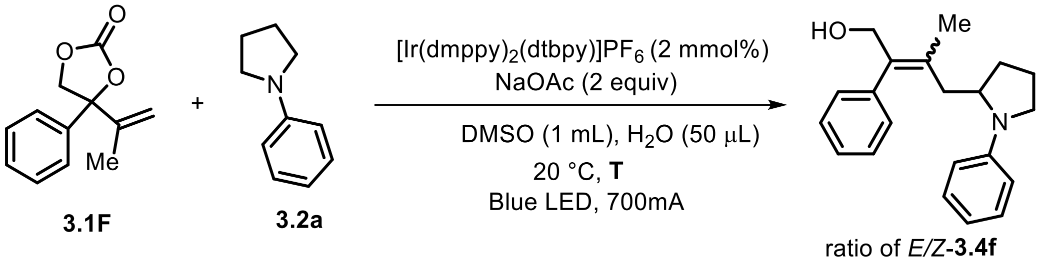
Table 3.5. *E/Z* photo-isomerization studies of **3.4f** and **3.4a**.

entry	SM	PC	Base	time (h)	Solvent	product
11	***E*-3.4f**	PC2	–	12	DMSO	***E/Z*-3.4j**, > 95:5
12	***Z*-3.4f**	PC2	–	12	DMSO	***E/Z*-3.4j**, 58:42
13	***Z*-3.4a**	PC2	–	12	DMSO	***Z*-3.4a**
14	***Z*-3.4a**	PC2	NaOAc	12	DMSO/H_2O	***Z*-3.4a**

Note: The ratio of ***E*-3.4f/*Z*-3.4f (**methyl-substituted substrate/product) mixture is 60:40 before exposing to the conditions mentioned in the Table. The ***Z*-3.4a** (standard phenyl-substituted substrate) was isolated by column purification. Entry 14 based on the standard conditions. SM stands for starting materials. Blue light irradiation was used in all experiments. PC2 stands for $[Ir(dmppy)_2(dtbbpy)]PF_6$.

Notes: Both pure isomers ***E*-3.4j** and ***Z*-3.4j** decompose under the standard conditions using prolonged reaction times. The actual reaction time to produce **3.4j** is only 30 min. To exclude any effect exerted by the base (NaOAc), we also used the isolated ***E*** and ***Z*** isomer in the presence of the photocatalyst and visible light only. In general, the results showed that both isomers of **3.4j** cannot be fully transformed into the other one. Compound **3.4j** can be photo-isomerized under the visible light even without a photocatalyst with a similar resultant *E/Z* ratio in the range of 76:24-86:14. All experiments combined show that light affects the structure of the alkene connected to a thiophene (**3.4j**, see entries 5-10) or a methyl group (**3.4f**) (see entries 11 and 12). If the alkene unit is connected to two phenyl groups (such as in **3.4a**), the olefin unit seems to be more stereochemically stable and is virtually not affected (see entries 13 and 14). We speculate that these alkene-based compound substituted by two phenyl groups need a higher energy to be photo-excited, and thus during their synthesis only one isomeric product is formed without any observable photo-isomerization.

3.4.2.5. Kinetic studies of the decarboxylative synthesis tetrasubstituted alkenes:



Using **3.1F** as the starting material under the optimized catalytic conditions in the presence of [Ir(dmppy)$_2$(dtbbpy)]PF$_6$, we measured its conversion at different time intervals (i.e., at 4, 8, 12, 16, 20, 24 and 28 h) together with the *E/Z* value of product **3.4f**. During the first 4 h, the *E*- and *Z*-isomers are generated in a 60:40 ratio and the conversion of VCC was 30% based on signal integration. After 24 h, **3.1F** was completely transformed and the final *E*/*Z* ratio remained 60:40. From these experiments, we conclude that the ratio virtually does not change.

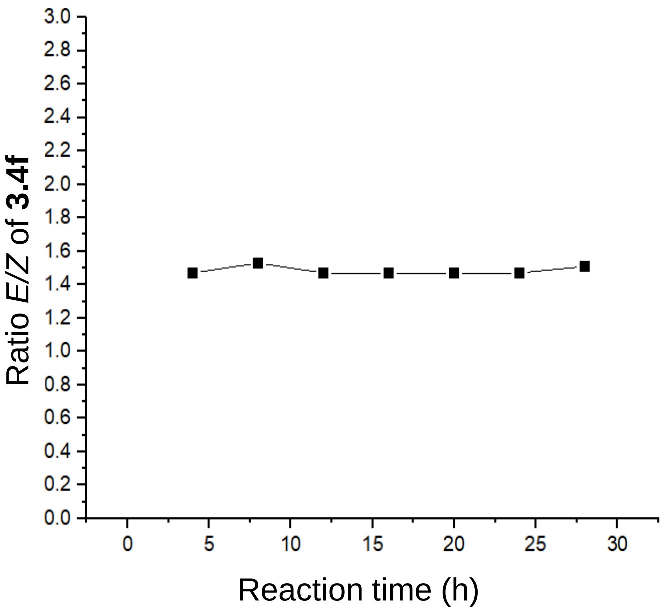


Figure 3.3. Photo-isomerization studies of **3.4f** followed by ^{1}H NMR analysis.

3.4.2.6. Stern-Volmer quenching studies

The Stern-Volmer plot for emission quenching of [Ir(dmppy)$_2$(dtbbpy)]PF$_6$ by **3.1a, 3.1A** and **3.2a** is shown in DMSO in **Figure 3.4**. The emission spectra were recorded on a Fluorolog Horiba Jobin Yvon spectrofluorimeter equipped with a photomultiplier detector, a double monochromator, and a 350W xenon light source. Samples containing a solution of [Ir(dmppy)$_2$(dtbbpy)]PF$_6$ (1 mg photocatalyst in 50 mL degassed DMSO to obtain a concentration of 2×10^{-5} M) in 2.5 mL of DMSO were deoxygenated by purging argon through a 10 × 10 mm light path quartz fluorescence cuvette equipped with a silicone/PTFE 3.2 mm septum under an argon atmosphere. Then, 5 μL of a 2.0 M solution of **3.1a** (or **3.1A**) in DMSO was added to the solution of [Ir(dmppy)$_2$(dtbbpy)]PF$_6$ to give a final concentration for **3.1a** (or **3.1A**). Alternatively, 3 μL of a 2.0 M solution of **3.2a** in DMSO was added to a solution of [Ir(dmppy)$_2$(dtbbpy)]PF$_6$ in 2.5 mL to give a final concentration of **3.2a**. The addition of **3.1a**, **3.1A** and **3.2a** solutions was repeated five consecutive times. The emission light was acquired from 350 nm to 650 nm. The results shown in **Figure 3.4** indicate that the components quench the excited state of [Ir(dmppy)$_2$(dtbbpy)]PF$_6$ and its emission. A small change in the emission spectra of the solution was observed upon the first addition (λ_{max} = 578 nm to 581 nm).

The maximum emission intensity at 581 nm without quencher divided by the emission intensity with quencher (i.e., I_0/I) was then plotted as a function of the concentration of quencher to obtain the Stern-Volmer plot according to the following equation:

$$\frac{I_0}{I} = 1 + I_0 k_q [Q]$$

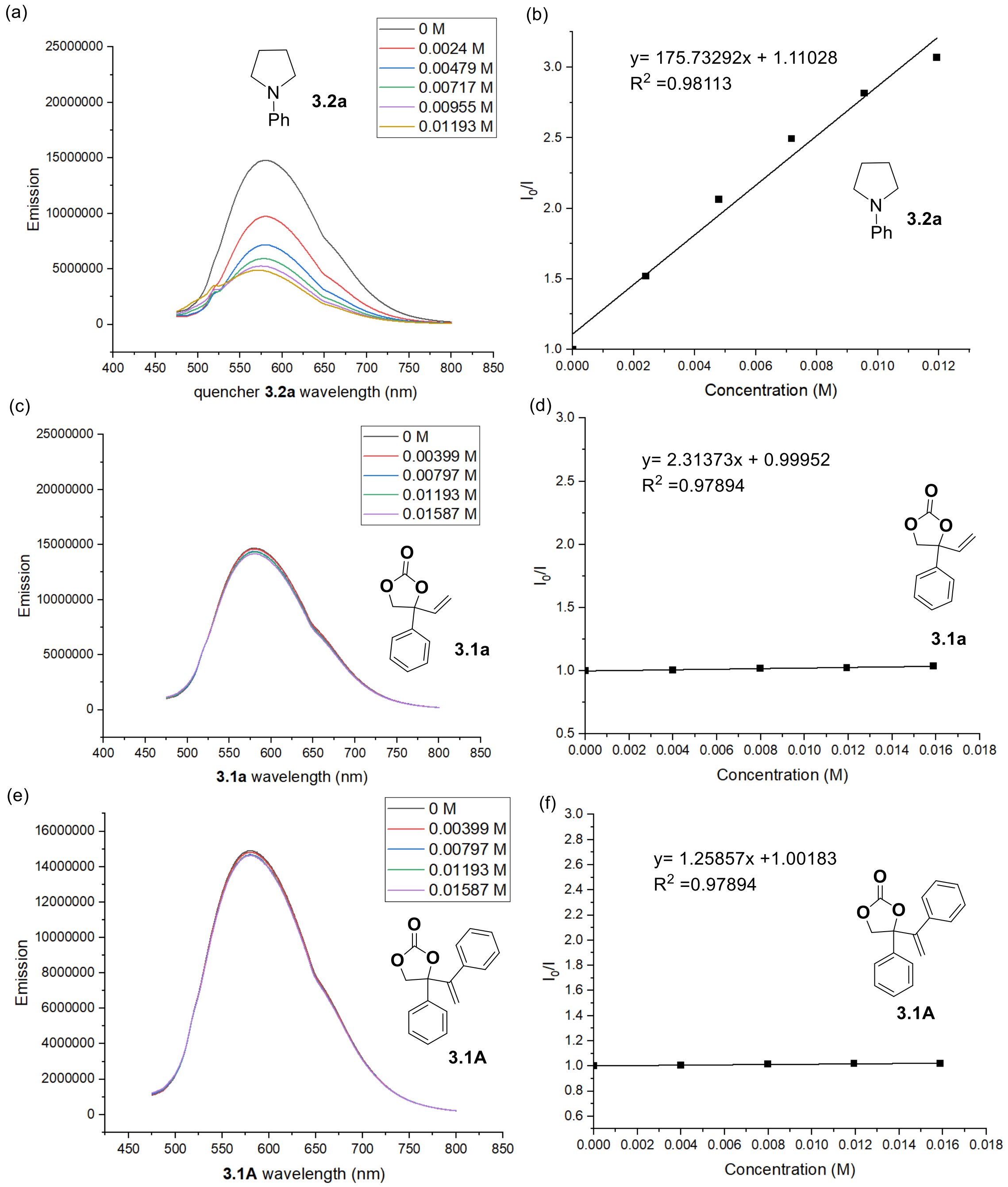


Figure 3.4. Quenching experiments using **3.1a, 3.1a** and **3.2A**.

For **3.2a** as a quencher, we calculated a Stern-Volmer quenching constant of 175.7 M^{-1}.
For **3.1a** as a quencher, we calculated a Stern-Volmer quenching constant of 2.31 M^{-1}.
For **3.1A** as a quencher, we calculated a Stern-Volmer quenching constant of 1.26 M^{-1}.

From these Stern-Volmer quenching experiments, **3.2a** can be as an efficient quencher. There is no significant quenching when using VCC **3.1a** or **3.1A**.

3.4.3. Crystallographic details for 3.4g

Single crystal structure determination via 3D electron diffraction

Electron radiation features very strong interacts with the electrostatic potential of matter. If monochromatic electron radiation is applied to crystals in the nanometer size range, single crystal diffraction can be observed. Due to the strong interaction, data collected by using electron radiation are affected by dynamical scattering effects and by the ionic scattering factors. In structures refined using a simplistic kinematic approximation, these effects can lead to seemingly bad *R*-values.

Sample preparation

The sample was gently grinded using two glass slides and prepared on copper-graphite grids (Cu200J from JEOL or Lacey C only 200 TH Cu TED PELLA INC.) by lightly contacting the grid with the pulverized sample and then removing the excess amount by shaking.

Cryo-preparation

The grid with the sample underwent cryo-preparation using an ELSA sample holder and the cryo-preparation stage from GATAN. The measurements were performed at 100 K (i.e., at low temperature). In order to remove ice formed during sample preparation at 100 K, the sample was warmed up for 15 minutes to 215 K in the specimen chamber and cooled back down to 100 K.

Device

The sample grains were measured using a XtalLAB Synergy-ED from Rigaku-JEOL provided with a HyPix-ED detector and a LiB6 200 kV electron source (200 kV, 101.20 µA) in shutter-less operation mode.[35] Wavelength: 0.0251 Å. Total dose for the eight selected crystal grains: 9.797 $e^-/Å^2$, condenser strength of 3. Magnification diffraction: 50 cm, IL1 projection focus: hex 52C1 (21185), CL 10 µm, SA 100 µm, distance (camera length): 644 mm, scan width: 0.25° and exposure time was depending on the crystal in the range 1-3 s/degree.

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(35) S. Ito, F. J. White, E. Okunishi, Y. Aoyama, A. Yamano, H. Sato, J. D. Ferrara, M. Jasnowski, M. Meyer, *CrystEngComm* **2021**, *23*, 8622–8630.

Accessories:

ELSA (GATAN) sample holder and sample preparation stage for preparation and measurement of samples at low temperatures.

Software:

Measurement and data processing: CrysAlis^{Pro} 43.107a (Rigaku).[36]

Structure processing: Olex2 Version 1.5-ac6-017 © OlexSys Ltd. 2004 – 2023.[37]

Measurement and refinement

The sample was explored on the XTalLAB Synergy-ED at r.t., and at 100 K.

- 2 crystals were measured at RT which did not diffract properly but could be indexed in a monoclinic cell with the space group $P2_1$.
- 34 crystals were measured at LT from which 32 gave the same monoclinic cell and the rest of crystals could not be indexed.

Initial indexing was performed with the AutoChem 6[38] software system in combination with Olex 2. No other crystalline phases could be detected in the crystals explored.

Monoclinic unit cell indexed:

	Unit cell parameters						Volume
Temperature	A (Å)	B (Å)	C (Å)	α (°)	β (°)	γ (°)	(Å^3)
295 K	18.8(7)	5.5(4)	23.8(7)	90	102(1)	90	2384(190)
100 K	18.6(2)	5.29(12)	23.60(18)	90	101.2(4)	90	2278(62)

A structure solution was successfully obtained from several crystals measured at 100 K. The best dataset measured corresponded to crystal 01(0202) which was used for structure solution using the program ShelXT.[39] The instrument was operated, and the diffraction data were processed in the program CrysAlis^{Pro}. Absorption correction was performed using spherical harmonics implemented in SCALE3 ABSPACK scaling algorithm in

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(36) Rigaku Oxford Diffraction, CrysAlisPro software system, Rigaku Corporation, Wrocław, Poland, **2023** (version 1.171.43.53a).

(37) O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard, H. Puschmann, OLEX2: A complete structure solution, refinement and analysis program. *J. Appl. Cryst*. **2009**, *42*, 339–341.

(38) Rigaku Oxford Diffraction, AutoChem 6 software system in conjunction with OLEX2, Rigaku Corporation, Wrocław, Poland, **2023** (version 1.5-ac6-009).

(39) Program for structure solution XT. G. M. Sheldrick, *Acta Cryst*. **2015**, *A71*, 3–8.

CrysAlis^{Pro}. To enhance the completeness and reflections-to-parameter ratio, the datasets of the 8 best selected crystals were merged resulting in a single improved data set [Crystals: 01 (measured on the 02/02/2024 and called 01(0202)), 06 (measured on the 30/01/2024 and called 06(3001)), 10(0202), 05(0202), 05(3001), 09(0202), 04(0202) and 07 (measured on the 29/01/2024 and called 07(2901))]. By merging data, a completeness of 100 % up to a resolution of 0.83 Å was achieved. Images and selected frames of the measured crystals are shown below. The merged dataset was used for structure refinement with a kinematical approximation using ShelXL[40] in the crystallographic program suite OLEX2. The structure refined to a final R_1-value of 17.10 %. An ORTEP-plot drawing showing the structure of the compound is represented below. The asymmetric unit contains two independent molecules of the organic compound showing different conformations (see below). The benzene and dichlorobenzene rings are disordered in both molecules in two orientations with a ratio of approximately 65:35. Non-hydrogen atoms were assigned anisotropic displacement parameters unless stated otherwise. The hydrogen atoms were placed in idealized positions and included as riding. Isotropic displacement parameters for all H atoms were constrained to multiples of the equivalent displacement parameters of their parent atoms with U_{iso}(H) = 1.2 (rigid H-atoms) or 1.5 (hydrogen atoms belonging to -OH) U_{eq}(parent atom). Enhanced rigid bond restraints[41,42] with standard uncertainties in the range of 0.01-0.003 Å^2 were applied. The experimental and refinement are given in the CCDC reference below.

CCDC 2333702 contains the supplementary crystallographic data for this publication. This data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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(40) Program for structure refinement XL. G. M. Sheldrick, *Acta Cryst.* **2015**, *C71*, 3–8.
(41) F. L. Hirshfeld, *Acta Cryst*. **1976**, *A32*, 239–244.
(42) A. Thorn, B. Dittrich, G. M. Sheldrick, *Acta Cryst*. **2012**, *A68*, 448–451.

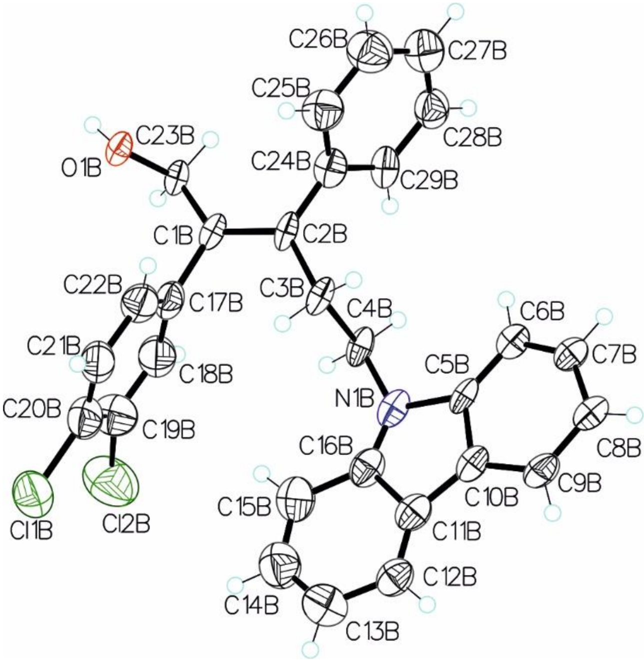


Figure 3.5. Molecular structure (ORTEP) determined of **3.4g** (*<u>note: disorder omitted</u>*).

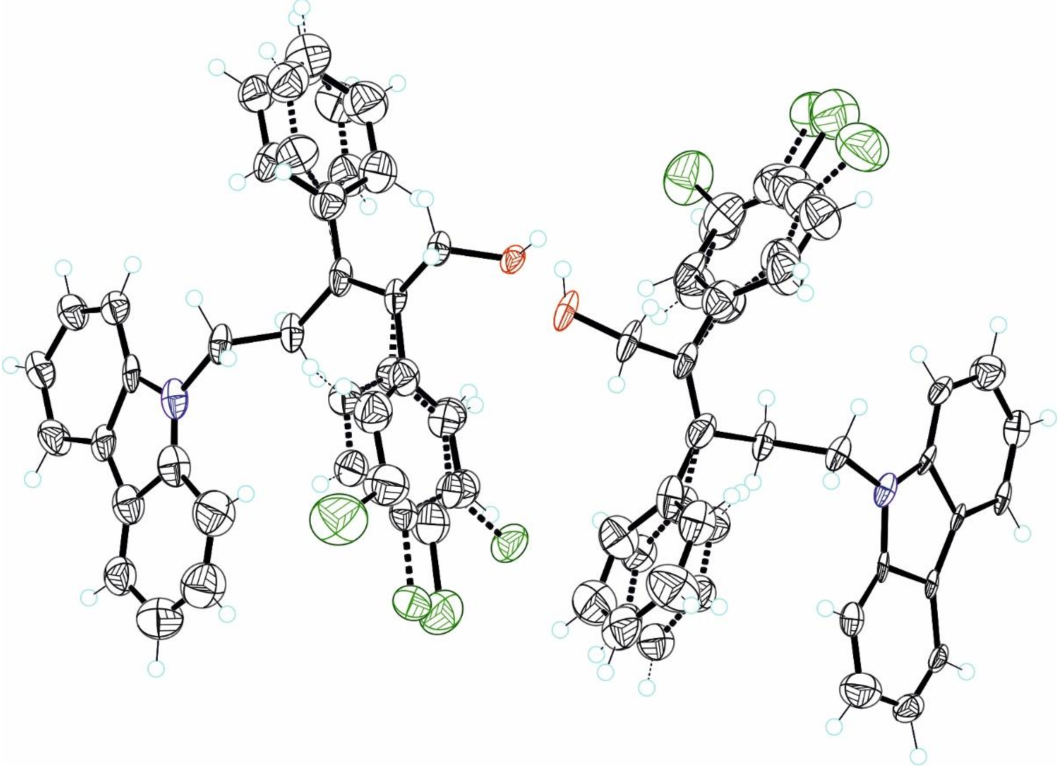


Figure 3.6. Unit cell representation for **3.4g** (*<u>with disorder</u>*).

Chapter 4.

Expanding Chemical Space of Highly Functionalized Bicyclo[1.1.1]Pentanes by Radical Initiated Three-Component Stereoselective Allylation

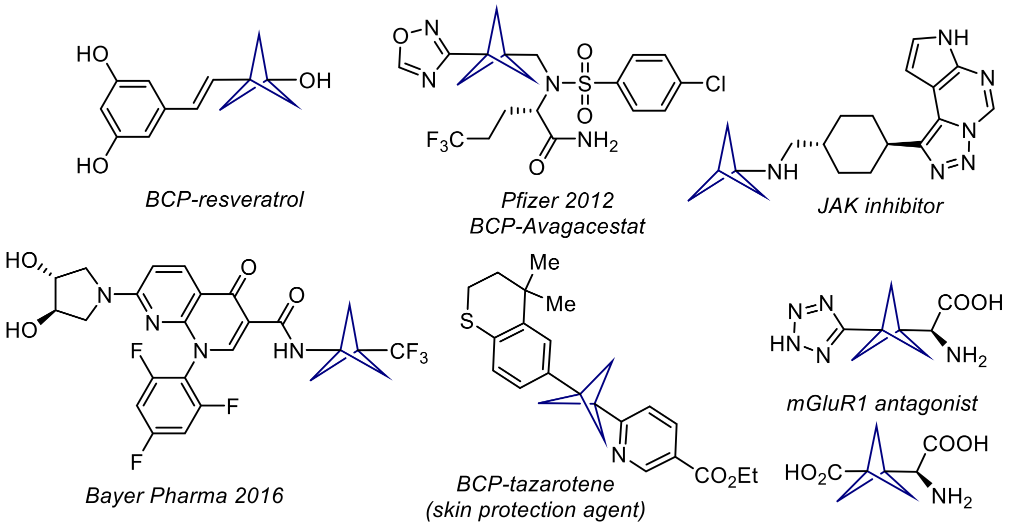
The results described in this chapter are based on the following submitted manuscript:

Q. Zeng, W. Shi, A. W. Kleij, *Expanding Chemical Space of Highly Functionalized Bicyclo[1.1.1]Pentanes by Radical Initiated Three-Component Stereoselective Allylation.*

4.1. Introduction

4.1.1. Bicyclo[1,1,1]pentanes

The presence of aryl rings in bioactive compounds and drug candidates can unfavorably cause sub-optimal pharmacological performance in terms of metabolic stability, lipid solubility and membrane permeability in clinical trials.[1] Therefore, replacing such aryl fragments by sp^3-hybridized bioisosteres has been an active area of research within the synthetic community providing suitable solutions to improve the aforementioned properties, and thus their effective bioactivity. In this regard, it is not surprising that sp^3-rich bicyclo[1,1,1]pentane (BCP) motifs have often been scrutinized in drug development (Scheme 4.1). Their presence, while replacing 2D internal alkyne and *para*-substituted arene units in promising pharma lead compounds,[2] has been successful as demonstrated by several examples known to improve the resultant medicinal activities.[3]



Scheme 4.1. Pharmaceutical compounds containing BCP motifs.

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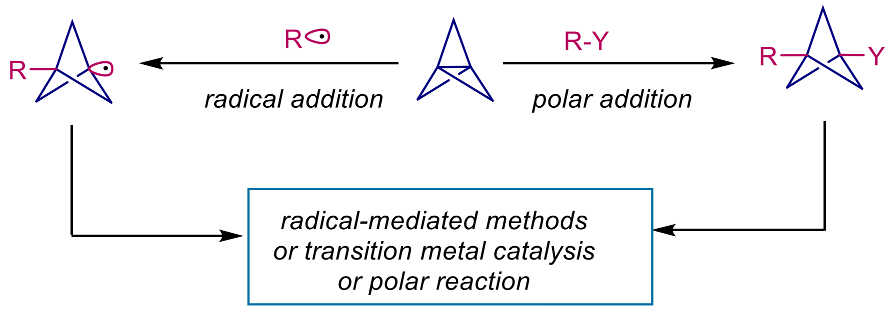
(1) a) A. Takahashi, Y. Kirio, M. Sodeoka, H. Sasai, M. Shibasaki, *J. Am. Chem. Soc.* **1989**, *111*, 643–647; b) L. Zaman, O. Arakawa, A. Shimosu, Y. Onoue, S. Nishio, Y. Shida, T. Noguchi, *Toxicon* **1997**, *35*, 205–212; c) R. A. Pilli, M. C. Oliveira, *Nat. Prod. Rep*. **2000**, *17*, 117–127; d) H. Yu, R. N. Richey, M. W. Carson, M. J. Coghlan, *Org. Lett.* **2006**, *8*, 1685–1688; e) A. S. A. S. Levenson, V. C. Jordan, *Eur. J. Cancer*. **1999**, *35*, 1974–1985.

(2) a) K. J. O'Sullivan, W. S. DiRico, A. Won. McDonald, P. H. Dorff, C. E. Nolan, S. L. Becker, L. R. Pustilnik, D. R. Riddell, G. W. Kauffman, B. L. Kormos, L. Zhang, Y. Lu, S. H. Capetta, M. E. Green, K. Karki, E. Sibley, K. P. Atchison, A. J. Hallgren, C. E. Oborski, A. E. Robshaw, B. Sneed, C. J. O'Donnell, *J. Med. Chem*. **2012**, *55*, 3414–3424; b) N. D. Measom, K. D. Down, D. J. Hirst, C. Jamieson, E. S. Manas, V. K. Patel, D. O. Somers, *ACS Med. Chem. Lett*. **2017**, *8*, 43–48.

(3) a) J. Kanazawa, M. Uchiyama, *Synlett* **2019**, *30*, 1–11; b) N. A. Meanwell, *Burger's Medicinal Chemistry and Drug Discovery*, Wiley, Hoboken, 2003, pp. 1–81; c) N. A. Meanwell, *J. Med. Chem.* **2011**, *54*, 2529–2591.

[1,1,1]-Propellanes have over the years been shown to be versatile intermediates for the synthesis of libraries functional BCPs derivatives. Commonly this is achieved via ring-opening of the inter-bridgehead C–C bond of the [1,1,1]-propellane enabled by strain release.[4] Since Wiberg and others investigated the properties of [1,1,1]-propellanes,[5] a wider range of approaches have been focusing on the functionalization of these propellanes through polar reactions,[6] transition metal (TM) catalysis[7] and radical-empowered methods (Scheme 4.2).[8]



Scheme 4.2. General functionalization pathways of [1,1,1]-propellanes involving radicals or anions.

4.1.2. Radical mediated formation of BCPs scaffolds

In the realm of radical based chemistry, the groups of MacMillan,[9] Molander[10] and Pan[11] separately reported on effective three-component (3C) radical approaches for the preparation of difunctionalized BCPs under (dual) photoredox catalysis (Scheme 4.3).

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(4) a) M. D. Levin, P. Kaszynski, J. Michl, *Chem. Rev*. **2000**, *100*, 169 – 234; b) S. Cuadros, J. Paut, E. Anselmi, G. Dagousset, E. Magnier, L. Dell'Amico, *Angew. Chem. Int. Ed*. **2024**, *63*, e202317333; c) J. M. Anderson, N. D. Measom, J. A. Murphy, Darren L. Poole, *Angew. Chem. Int. Ed*. **2021**, *60*, 24754-24769.

(5) a) K. B. Wiberg, D. S. Connor, *J. Am. Chem. Soc.* **1966**, *88*, 4437–4441; b) K. B. Wiberg, V. Z. Williams Jr, *J. Org. Chem.* **1970**, *35*, 369–373; c) K. B. Wiberg, S. T. Waddell, K. Laidig, *Tetrahedron Lett.* **1986**, *27*, 1553-1556; d) K. B. Wiberg, *Chem. Rev.* **1989**, *89*, 975–983; e) Kenneth B. Wiberg, S. T. Waddell, *J. Am. Chem. Soc.* **1990**, *112*, 2194–2216.

(6) a) Prieto, T. A. Brandt, M. R. Collins, G. M. Gallego, N. W. Sach, J. E. Spangler, H. Zhu, J. Zhu, P. S. Baran, *Science* **2016**, *351*, 241–246; b) B. R. Shire, E. A. Anderson, *JACS Au* **2023**, *3*, 1539–1553; c) I. S. Makarov, C. E. Brocklehurst, K. Karaghiosoff, G. Koch, P. Knochel, *Angew. Chem. Int. Ed.* **2017**, *56*, 12774–12777.

(7) a) M. Messner, S. I. Kozhushkov, A. de Meijere, *Eur. J. Org. Chem*. **2000**, 1137–1155; b) T. Yasukawa, K. S. Håheim, J. Cossy, *Org. Biomol. Chem*. **2023**, *21*, 7666–7680.

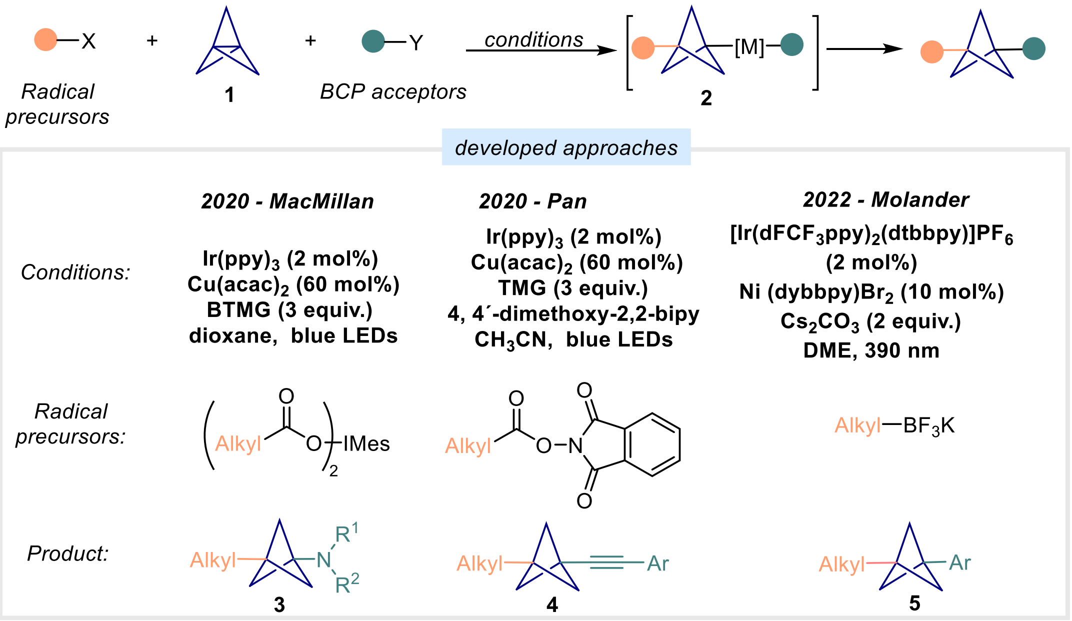
(8) a) D. F. Caputo, C. Arroniz, A. B. Dürr, J. J. Mousseau, A. F. Stepan, S. J. Mansfield, E. A. Anderson, *Chem. Sci*. **2018**, *9*, 5295–5300; b) S. Kim, H. Oh, W. Dong, J. Majhi, M. Sharique, B. Matsuo, S. Keess, G. A. Molander, *ACS Catal*. **2023**, *13*, 9542–9549.

(9) a) Y. Liang, X. Zhang, D. W. MacMillan, *Nature* **2018**, *559*, 83–88; b) X. Zhang, R. T. Smith, C. Le, S. J. McCarver, B. T. Shireman, N. I. Carruthers, D. W. MacMillan, *Nature* **2020**, *580*, 220–226.

(10) a) W. Huang, S. Keess, G. A. Molander, *Chem. Sci*. **2022**, *13*, 11936–11942; b) W. Huang, Y. Zheng, S. Keess, G. A. Molander, *J. Am. Chem. Soc*. **2022**, *144*, 12961–12969.

(11) Y. Mao, W. Zhao, S. Lu, L. Yu, Y. Wang, Y. Liang, S. Ni, Y. Pan, *Chem. Sci.* **2020**, *11*, 4939–4947.

These strategies involve a similar manifold that features a BCP-radical metal crossover process giving rise to a radical-metal adduct intermediate **2**, from which reductive elimination takes place to deliver the respective alkyl-amino, alkyl-alkynyl and alkyl-aryl disubstituted BCP product (i.e., **3**, **4** or **5**).



Scheme 4.3. Synthesis of difunctionalized BCPs enabled by dual photoredox/metal catalysis.

Furthermore, photoinduced and electron-donor/acceptor (EDA) complex mediated multi-component reactions are also effective towards difunctionalization of [1,1,1]-propellanes to yield a variety of functionalized BCPs.[12] For example, the Xu group reported on a visible light mediated three component arylation of BCP in the presence of glycine derivatives (Scheme 4.4).[12a] The process starts by formation of an EDA complex between *S*-phenyl dibenzothiophenium (DBT) salts and N-PMP glycinate (PMP = *p*-methoxyphenyl). Then, a single electron transfer (SET) from **7** to **6** occurs under visible light, rendering a phenyl DBT radical and glycine radical cation. The transient aryl radical **9**, generated after C–S bond cleavage, undergoes radical addition to [1,1,1]-propellane **1**, thereby rapidly producing tertiary radical species **11**. Simultaneously, an intermolecular HAT results into α-amino radical **10**, followed by radical crossing coupling with **11**, affording α-aminated aryl-BCPs product **8**. This practical protocol was successfully

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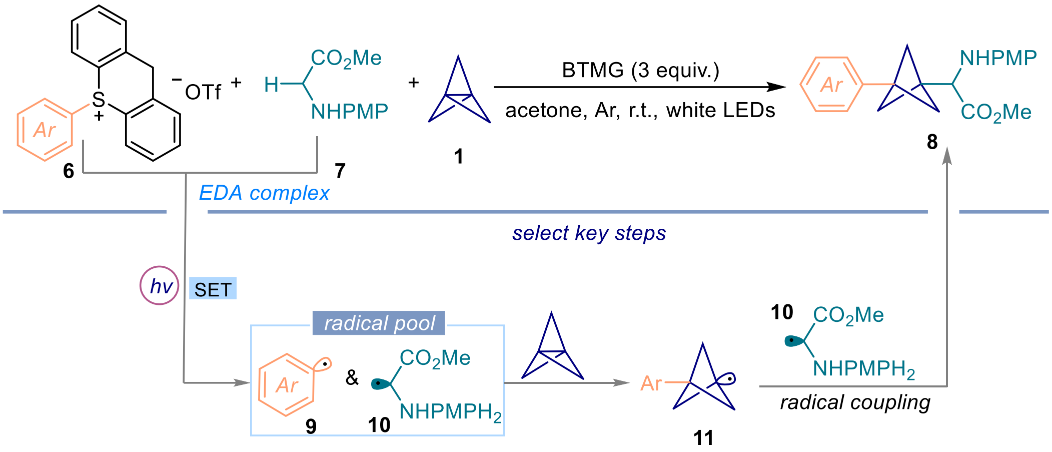
(12) a) X. Dang, Z. Li, J. Shang, C. Zhang, C. Wang, Z. Xu, *Angew. Chem. Int. Ed*. **2024**, *63*, e202400494; b) G. Zhang, Z. Luo, G. Mei, H. Wang, C. Ding, *Eur. J. Org. Chem*. **2024**, e202400386.

extended to a wider range of substrates including various aryl DBT salts and peptides, diversifying further the range of functional BCP derivatives.



Scheme 4.4. Photoinduced and EDA complex promoted difunctionalization of [1,1,1]-propellanes.

Anderson and coworkers developed a wide library of *α*-chiral and *α*-quaternary BCPs using a dual (organo)photoredox and hydrogen-atom transfer (HAT) catalytic approach (Scheme 4.5).[13] Here, the key radical species is generated by single electron transfer, then adds to the [1,1,1]-propellane to release the tertiary BCP radical **16** and **21**. Subsequently, the radical species (both **16** and **21)** abstract a H-atom from the thiol through a formal HAT process to afford the enantioenriched BCPs **13** and the *α*-quaternary products **18**, respectively. These two strategies involve both a photocatalytic and hydrogen-atom transfer based cycle towards chemoselective formation of the monosubstituted BCPs.

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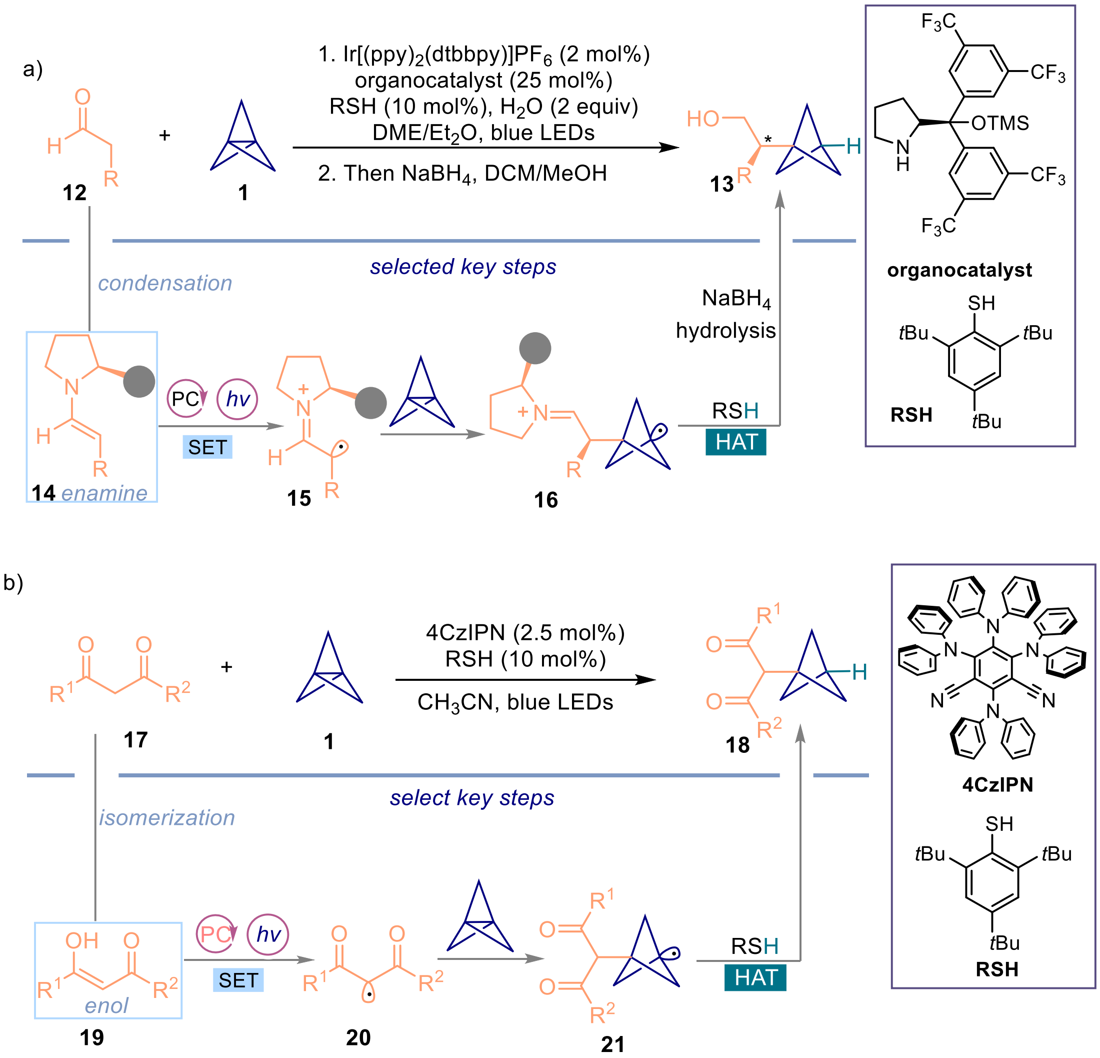
(13) a) M. L. Wong, A. J. Sterling, J. J. Mousseau, F. Duarte, E. A. Anderson, *Nat. Commun*. **2021**, *12*, 1644; b) J. Nugent, A. J. Sterling, N. Frank, J. J. Mousseau, E. A. Anderson, *Org. Lett*. **2021**, *23*, 8628–8633.



Scheme 4.5. (a) Synthesis of α-chiral BCPs, and (b) α-quaternary BCPs, both enabled by dual (organo)photoredox and hydrogen-atom transfer (HAT) catalysis.

4.1.3. Difunctionalized BCP derivatives via allylation

Chemoselective construction of allylated BCPs have also been achieved, for instance, via homolysis of the head-bridged carbon bond of [1,1,1]-propellane promoted by allylation using allyl sulfones affording difunctionalized BCPs, or via a stepwise approach enabled by a dual photo/HAT mediated transformation of iodinated and aminated BCPs in the presence of allyl sulfones.[14] Since organometallic reagents typically display a high reactivity due to a polar carbon-metal bond, various methods have been developed that involve the formation of Grignard-activated BCPs, which allow for easy introduction of

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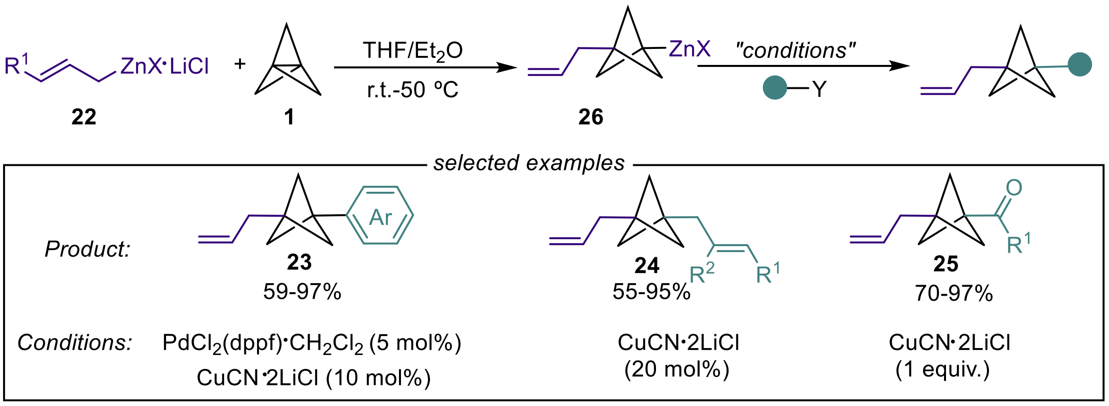
(14) a) Z. Wu, Y. Xu, H. Zhang, X. Wu, C. Zhu, *Chem. Commun.* **2021**, *57*, 6066-6069; b) H. D. Pickford, J. Nugent, B. Owen, J. J. Mousseau, R. C. Smith, E. A. Anderson, *J. Am. Chem. Soc.* **2021**, *143*, 9729−9736.

simple allyl fragments. For example, Knochel developed a highly regioselective functionalization of [1,1,1]-propellane **1** with various allylzinc reagents **22** and electrophiles to provide either aryl-allyl, bis-allyl and acyl-allyl derived BCPs (i.e., **23**, **24** or **25**, respectively; Scheme 4.6).[15] This protocol was amenable to the use of a wide series of allylic zinc reagents **22** including linear allylzinc bromide and cycloallyl zinc halides, as well as other allylzinc derivatives. The zincated BCPs **26** can be conveniently trapped by various electrophiles such as allylic halides, acid chlorides and aryl halides promoted by Cu and/or Pd catalysis.



Scheme 4.6. Polar addition of allyl zinc reagents to [1,1,1]-propellane **1** towards the formation of functionalized allylated BCPs.

Additionally, other (enantioselective) allylations utilizing Grignard-activated BCPs as intermediates have been reported under Ir- or *N*-heterocyclic carbene (NHC) catalysis. These methods represent practical and alternative strategies for the rapid access of α-chiral, allylated-BCP scaffolds.[16] Despite these known significant advancements for constructing 1,3-disubstituted BCPs scaffolds, a generic approach allowing for the simultaneous stereoselective introduction of advanced allylic fragments and pharma-relevant functional groups onto [1,1,1]-propellanes remains to be developed. Such an approach would undoubtedly rapidly increase the access to molecular BCP complexity, expanding chemical space of BCP-based libraries, and offer branching points to augment post-synthetic diversity.

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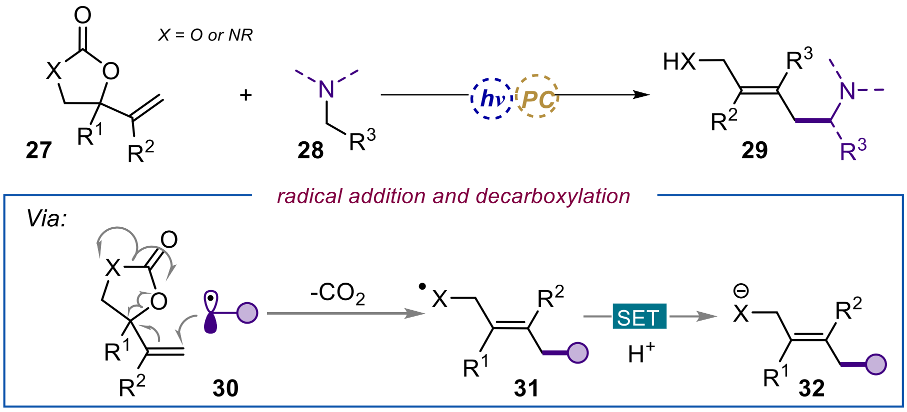
(15) K. Schwärzer, H. Zipse, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed*. **2020**, *59*, 20235-20241.

(16) a) S. Yu, C. Jing, A. Noble, V. K. Aggarwal, *Org. Lett.* **2020**, *22*, 5650−5655; b) S. Barbeira-Arán, I. Sánchez-Sordo, M. Fañanás-Mastral, *Org. Lett*. **2024**, *26*, 3784–3789.

4.1.4. Aim of the work in this chapter

At the onset of the work presented in this chapter, we were inspired by our previous and recent work on the two-component addition reaction between α-amino radicals **30** and vinyl cyclic carbonates (VCCs) **27** providing all-carbon based stereodefined olefins **29** (Scheme 4.7) via a photocatalyzed decarboxylative double bond relay pathway.[17] Expansion to 3CR approaches would not be necessarily straightforward for various reasons, including the high tendency of in situ formed transient radicals to add to the C=C bond of the VCC reagent in the absence of transition metal stabilized, α-allyl species.[18] Productive, radical-based 3CRs towards allyl-substituted BCP derivatives have thus far only been possible through stepwise approaches or using organometallic reagents.[14-16]



Scheme 4.7. Radical-based 2CR using VCCs enabled by visible light

Given the lack of direct, photocatalytic and stereoselective allylation of [1,1,1]-propellane **1** affording bifunctional BCPs that can substantially amplify the potential of such synthons in drug development,[4] we thus set out to bridge this current gap by harnessing the excellent radical scavenging nature of [1,1,1]-propellane **1** and using a transient, mono-substituted BCP radical to subsequently induce a formal and chemoselective 3CR in this chapter (Scheme 4.8). By carefully selecting pharma-relevant

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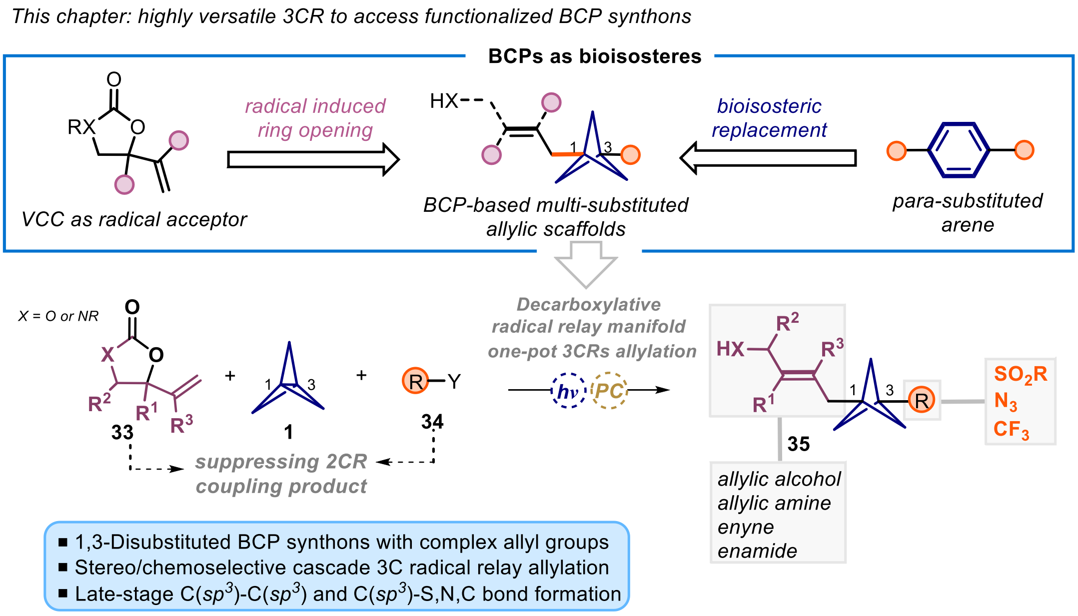
(17) Q. Zeng, N. Yamini, J. Benet-Buchholz, A. W. Kleij, *Angew. Chem. Int. Ed.* **2024**, *63*, e202403651.

(18) a) B. Giese, *Angew. Chem. Int. Ed*. **1983**, *22*, 753-764; b) H.-M. Huang, P. Bellotti, F. Glorius, *Chem. Soc. Rev*. **2020**, *49*, 6186−6197; c) H. Jiang, A. Studer, *Chem. Soc. Rev*. **2020**, *49*, 1790–1811; d) D. Leifert, A. Studer, *Angew. Chem. Int. Ed*. **2020**, 59, 74–108; e) Q. Zeng, F. Gao, J. Benet-Buchholz, A. W. Kleij, *ACS Catal*. **2023**, *13*, 7514−7522; f) S. Xue, À. Cristofol, B. Limburg, Q. Zeng, A. W. Kleij, *ACS Catal.* **2022**, *12*, 3651−3659.

radical precursors[19] and appropriate reaction conditions, we show in this chapter that highly functional libraries of novel types of 1,3-disubstituted BCPs **35** can be designed. Moreover, the developed process is able to bypass the unwanted 2CR coupling between the VCC **33** and the radical precursor **34**, allowing thus for a radical cascade under photocatalytic control. In addition, the process is amenable to a wide scope of reaction partners, and various post-synthetic modifications of the functionalized BCPs **35** increase the value of the reported building blocks.



Scheme 4.8. Radical-initiated three-component allylation towards difunctionalized BCPs of type **35**.

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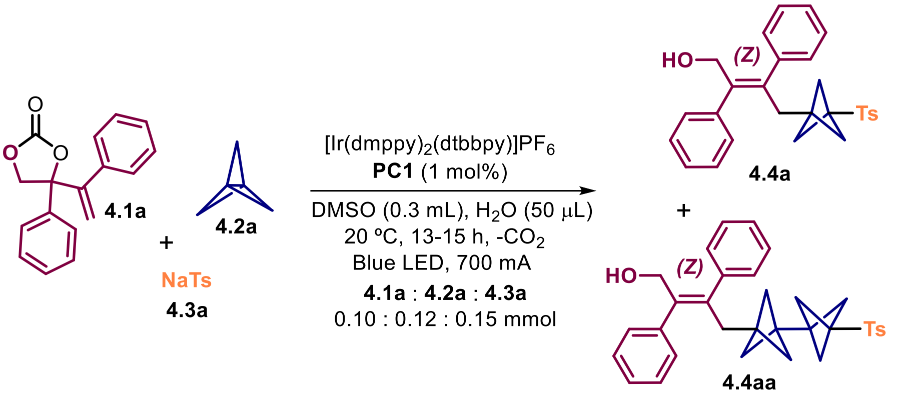
(19) a) G. Siemeister, U. Lucking, A. M. Wengner, P. Lienau, W. Steinke, C. Schatz, D. Mumberg, K. Ziegelbauer, *Mol. Cancer Ther*. **2012**, *11*, 2265–2273; b) N. A. Meanwell, *Chem. Res. Toxicol*. **2016**, *29*, 564–616; c) H. D. Pickford, V. Ripenko, R. E. McNamee, S. Holovchuk, A. L. Thompson, R. C. Smith, P. K. Mykhailiuk, E. A. Anderson, *Angew. Chem. Int. Ed*. **2023**, *62*, e202213508.

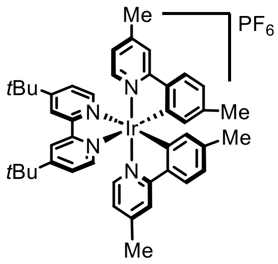
4.2. Results and Discussion

4.2.1. Optimization studies

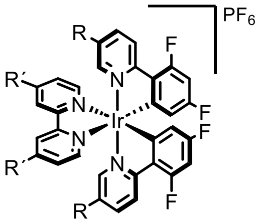
Process screening. At the onset of the screening stage (see Table 4.1), we selected VCC **4.1a**, [1,1,1]-propellane **4.2a** and sodium 4-methyl-benzenesulfinate (NaTs, **4.3a**) and tested several reaction conditions (solvent, photocatalyst) with the latter based on our previous experience in the 2CR coupling of **4.1a** and α-amino radicals.[17] Various photocatalysts (**PC1-4**, entries 1-4) were scrutinized in wet DMSO as a medium under ambient conditions affording two major products, *viz*. the target mono-BCP derivative **4.4a** and bis-BCP **4.4aa**. Interestingly, under these conditions we were not able to detect significant amounts of undesired coupling between **4.1a** and **4.3a** when **PC1** was used (entry 1; combined yield of **4.4a** and **4.4aa** is 87%) demonstrating high chemoselectivity for the three-component coupling process. Compared to the utilization of the other **PCs** (entries 2-4), the yield for **4.1a** (77% by NMR, 76% isolated) in the presence of **PC1** was the highest. Switching to other solvent systems (entries 5 and 6; CH_3CN and dioxane, see details in the Experimental Section) resulted in lower chemoselectivity towards **4.4a** (42-47%), and in the absence of a light source or the [Ir] photocatalyst **PC1**, no substrate conversion was observed (entries 7 and 8). The promoting effect of water is shown in entry 9, where a lower yield (66%) of **4.4a** is noted when performing the reaction in an anhydrous way.

Table 4.1. Screening of the 3CR involving VCC **4.1a**, [1,1,1]-propellane **4.2a** and NaTs **4.3a** under various conditions.[a]

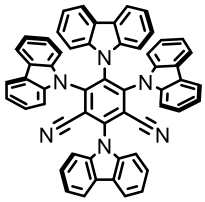




PC1: [Ir(dmppy)$_2$(dtbbpy)]PF$_6$



PC2: R = CF$_3$, R´ = H
PC3: R = CF$_3$, R´ = *t*Bu



PC4: 4CzIPN

Entry	Change to Std conditions	Conv. **4.1a** [%][b]	Yield **4.4a:4.4aa** [%][b]	*Z/E*-**4.4a**[b]
1	–	>99	77:10[c]	>99:1
2[d]	**PC2**	74	39:12	>99:1
3[d]	**PC3**	86	41:13	>99:1
4[d]	**PC4**	88	44:15	>99:1
5[e]	CH_3CN	>99	47:14	>99:1
6[e]	Dioxane	>99	42:15	>99:1
7	no light	<1	–	–
8	no [Ir]^{PC}	<1	–	–
9	no H_2O	>99	64:23	>99:1

[a] Optimized procedure in entry 1: **4.1a** (0.10 mmol), **4.2a** (0.12 mmol), **4.3a** (0.15 mmol), [Ir(dmppy)$_2$(dtbbpy)]PF$_6$, **PC1** (1.0 mol%), DMSO (0.30 mL), H_2O (50 µL), 700 mA blue LED, 20 ºC for 13-15 h. [b] Yields and *E/Z* values were determined by ^{1}H NMR ($CDCl_3$), 1,3,5-trimethyloxybenzene was used as internal standard. [c] The yield of isolated **4.4a** was 76%. [d] 0.15 equiv of **4.2a** and 0.2 equiv of **4.3a** were used, in 1.0 mL CH_3CN without adding H_2O. [e] 0.15 equiv of **4.2a** and 0.20 equiv of **4.3a** were used, and 1 mL solvent without adding H_2O.

4.2.2. Scope of products

With the conditions reported in entry 1 of Table 4.1 as a focal point, we first examined the scope of VCCs **4.1** (see Scheme 4.9). The great modularity of VCCs allows to vary the R^1-R^3 substituents giving access to BCPs incorporating substituted aryl and heteroaryl groups in good yields (**4.4a-4.4g**; up to 87%) and as single stereoisomers (*Z/E* >99:1). Other combinations, such as aryl/alkyl groups as illustrated by the isolation of compounds **4.4h** (53%) and **4.4i** (70%) are also feasible, while the use of a VCC featuring a 1,2,3-triazole group in its structure allowed to access 1,3-disubstituted BCP **4.4j** in 83% as a nearly equimolar mixture of *Z* and *E* stereoisomers. The loss of stereocontrol in this latter case is most likely because of undesired photo-isomerization or a result of energy-transfer events (cf., chromophores) involving the product which may be caused by a different degree of conjugation compared to the other BCP derivatives (**4.4a-i**).[17,20] Along these lines, products **4.4k-4.4p** were also isolated as mixtures of *E*+*Z* isomers in moderate to good yields (42-95%), showing that more complex organic fragments originating from VCCs can be introduced. The presence of relatively small alkyl groups (R^1 and R^3 in the VCCs in Scheme 4.9) was previously also shown to deliver mixtures of *E*+*Z* alkenes, and thus the stereo-outcomes for product **4.4k-m** and **4.4o** may be anticipated.[17] The assignment of the stereochemistry in **4.4c** was corroborated by X-ray analysis.[21]

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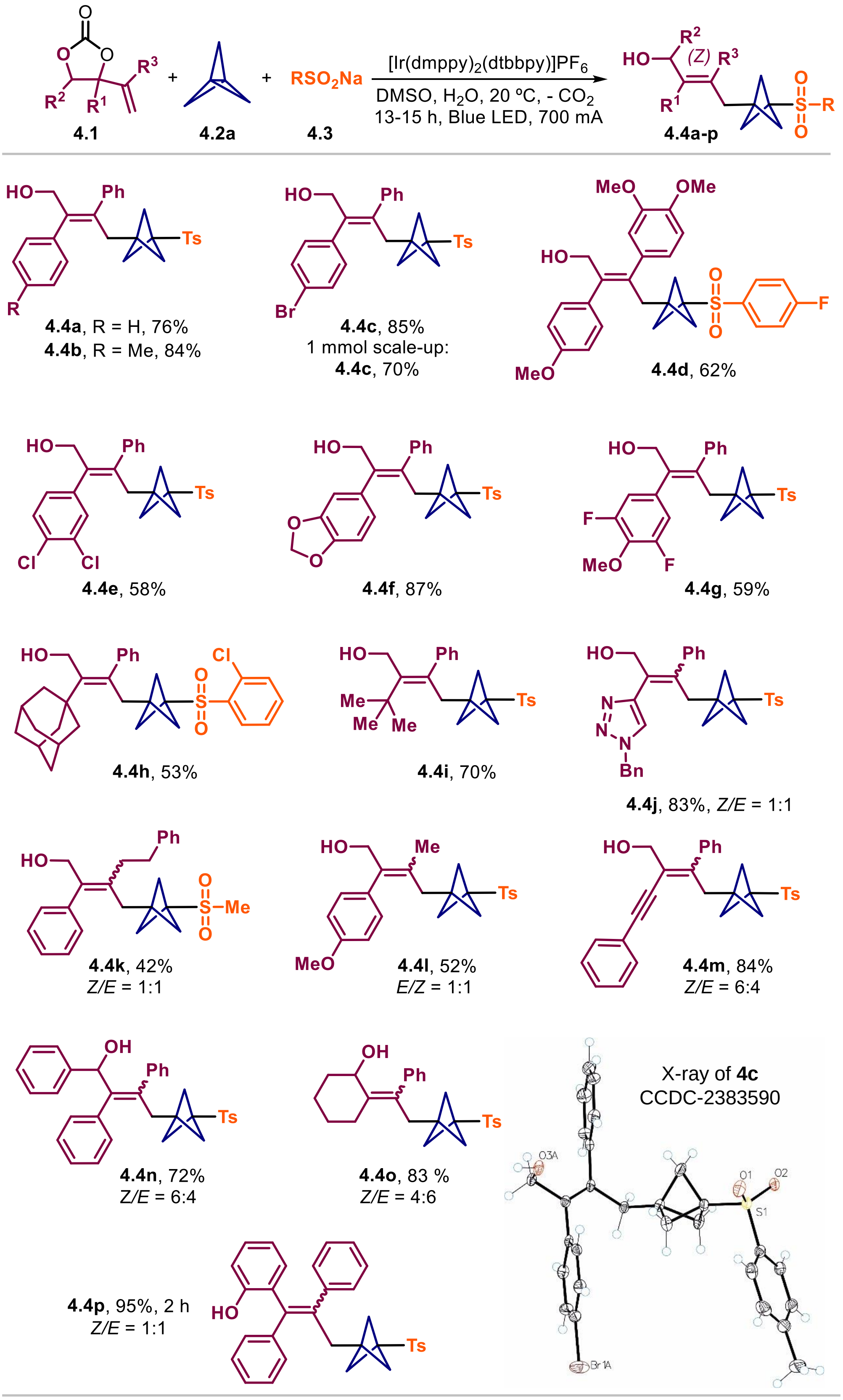
(20) a) F. Strieth-Kalthoff, F. Glorius, *Chem* **2020**, *6*, 1888–1903; b) T. Nevesely, M. Wienhold, J. J. Molloy, R. Gilmour, *Chem. Rev.* **2022**, *122*, 2650–2694; c) Y. Zhou, S. Maisonneuve, F. Maurel, J. Xie, R. Métivier, *Chem. Eur. J.* **2022**, *28*, e202202071.

(21) Deposition number 2383590 contains the supplementary crystallographic data for compound **4c**. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service, see: https://www.ccdc.cam.ac.uk/structures/.



Scheme 4.9. Scope of VCCs **4.1** in the 3CR leading to BCP derivatives **4.4a-4.4p.** Standard reaction conditions were used as reported in entry 1, Table 4.1. The insert at the bottom shows the X-ray molecular structure of **4.4c**.

Next, we varied the nature of the radical precursor **4.3** (Scheme 4.10) to diversify the scope of BCPs. We selected a few VCCs to extend the scope with BCPs now mostly diversified in the sulfone group. A wide range of sulfone-based BCPs[22] could be prepared using readily accessible sodium sulfinate reagents, allowing to introduce aryl-, heteroaryl- and various alkyl-derived sulfone groups in the BCP product. Sulfinate salts containing simple linear alkyl (**4.5a**, **4.5b**, **4.5d** and **4.5g**; 66-81%), cycloalkyl analogues (**4.5c**, **4.5e** and **4.5f**; 63-82%) and functionalized versions thereof such as those containing a CF_3, ester or terminal alkyne group (**4.5h-j**; 60-86%) were compatible in the 3CR with high levels of stereocontrol (*Z/E* >99:1). Apart from the aliphatic reagents, various heteroaryl-based sulfinates were also productive providing access to BCP products **4.5k-4.5o** in yields of up to 86% and as a single stereoisomer. The results in Scheme 4.10 underline the facile and valuable nature of rapidly accessing BCP sulfones of pharmaceutical importance.[22]

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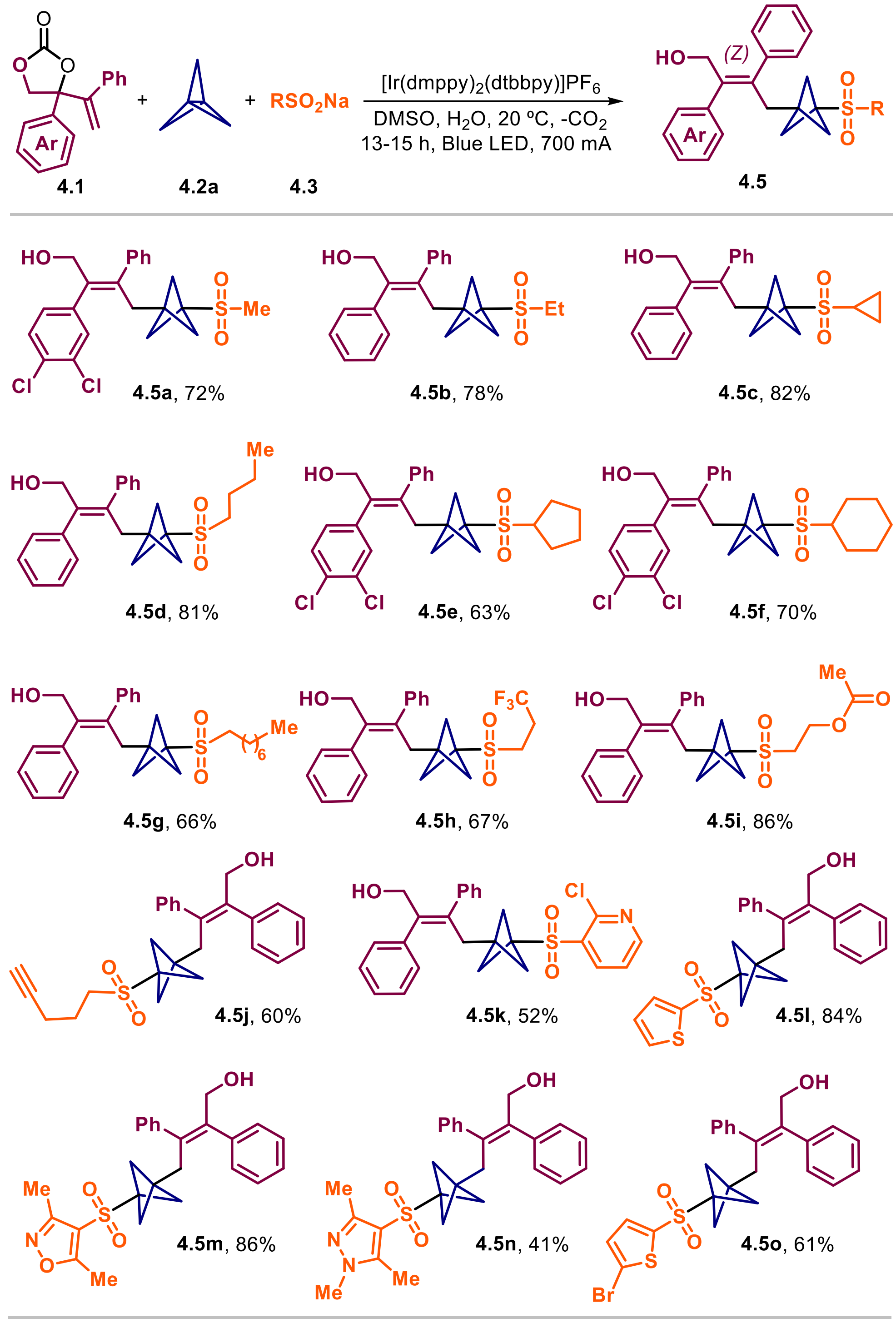
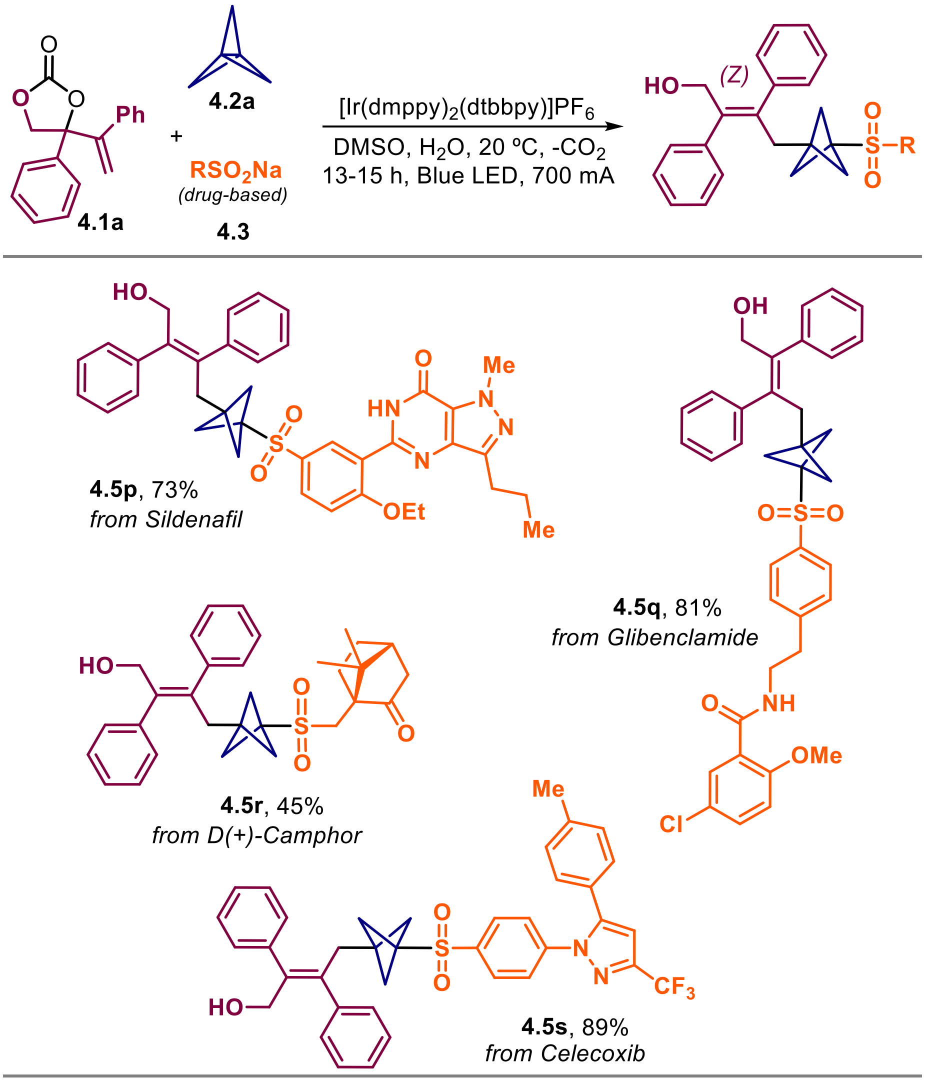
(22) Anderson reported on a convenient method for a range of pharma-relevant (hetero)arylsulfone-based BCPs using in situ prepared or pre-isolated sulfonyl halide reagents, see: H. D. Pickford, V. Ripenko, R. E. McNamee, S. Holovchuk, A. L. Thompson, R. C. Smith, P. K. Mykhailiuk, E. A. Anderson, *Angew. Chem. Int. Ed*. **2023**, *62*, e202213508.



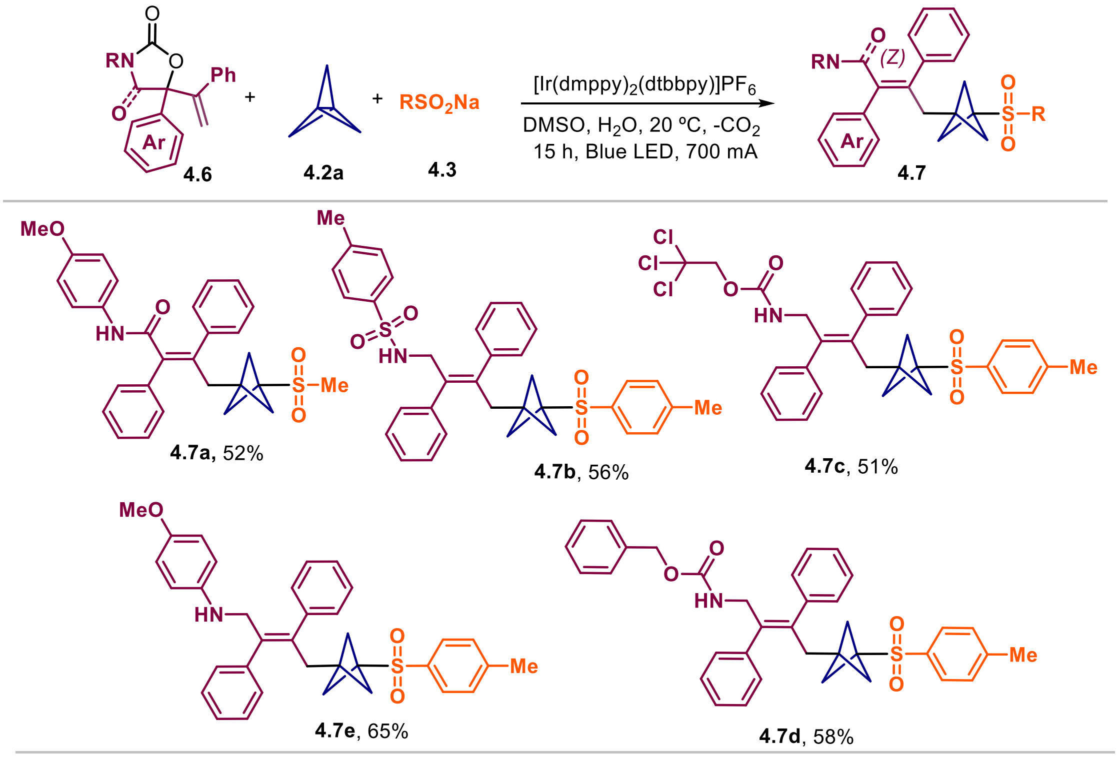
Scheme 4.10. Scope of sulfinyl radical precursors **4.3** in the 3CR leading to BCP derivatives **4.5a-4.5o**. Standard reaction conditions were used as reported in entry 1, Table 4.1. All *Z/E* ratios here are >99:1 as determined by ^{1}H NMR ($CDCl_3$).

To challenge the developed 3CR further, we selected several drug-based sulfones (of type **4.3**) and engaged them as precursors in the standard protocol (Scheme 4.11). Fortunately, several sulfone-based drug-like molecules including Sildenafil, Glibenclamide, *D*-(+)-Camphor and Celecoxib precursors participated productively as precursors towards the formation of structurally complex compounds **4.5p-4.5s** in yields of up to 89%. This simple access to drug-derived BCPs is a clear advantage in terms of extending chemical space within new drug discovery.



Scheme 4.11. 3CRs using sulfone-based drug molecules. Standard reaction conditions were used as reported in entry 1, Table 1; the solvent was 0.50 mL instead of 0.30 mL. All *Z/E* ratios here are >99:1 as determined by ^{1}H NMR ($CDCl_3$).

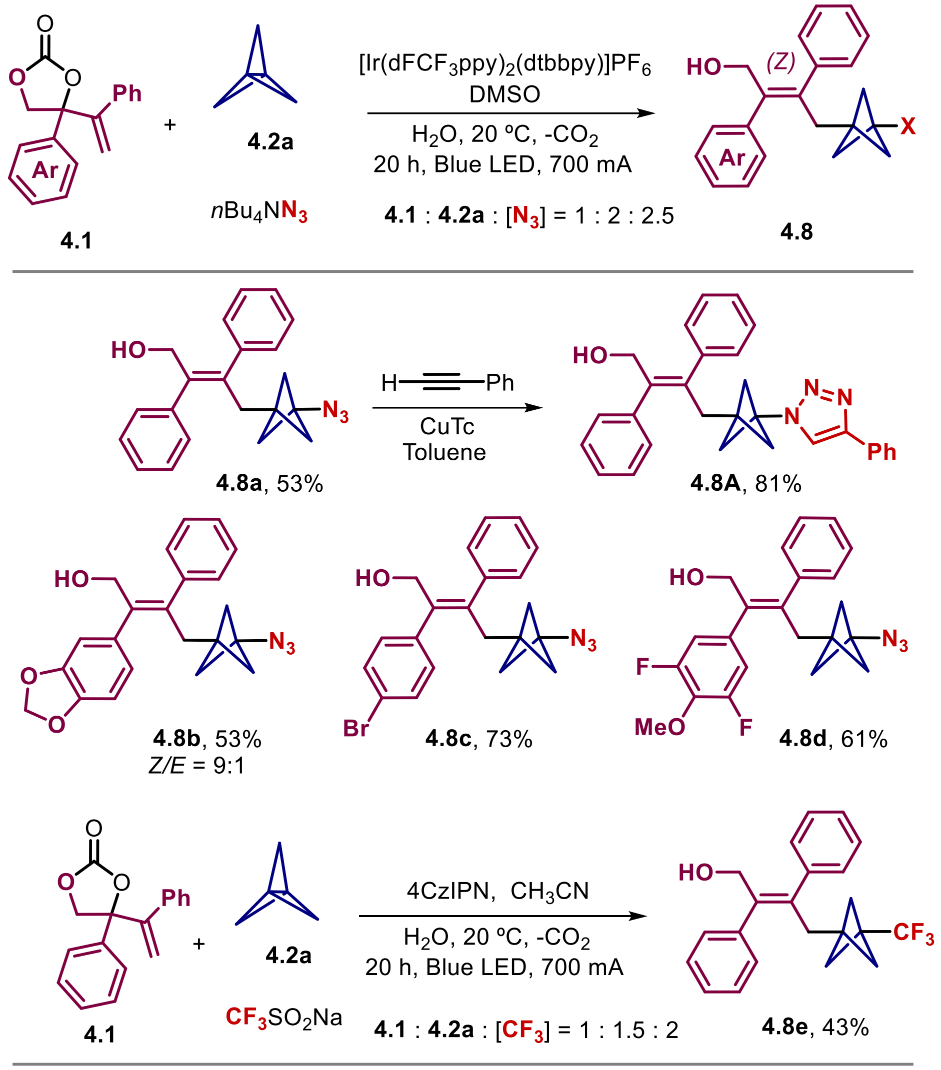
In order to demonstrate that other potential BCP-type libraries can also be designed, we used related vinyl-substituted heterocycles **4.6** akin of VCCs (Scheme 4.12), *i.e.* cyclic carbamates and oxazolidine-2,4-diones. The utilization of both types of these alternative vinyl-derived heterocycles created another useful embodiment of sulfone-based BCPs allowing to introduce allylic amide (**4.7a**, 52%), allylic sulfonamide (**4.7b**, 56%), allylic carbamate (**4.7c**: 51% and **4.7d**: 58%) and allylic amine groups (**4.7e**, 65%). These latter results clearly demonstrate the high adaptive nature of the developed 3CR protocol in the creation of functionalized BCP building blocks.



Scheme 4.12. 3CR examples using other types of heterocyclic precursors. Standard reaction conditions were used as reported in entry 1, Table 4.1. All *Z/E* ratios here are >99:1 as determined by ^{1}H NMR ($CDCl_3$).

Apart from pharma-relevant BCPs, other types of radical precursors can also be used to cover additional chemical space (Scheme 4.13). For instance, we first used *n*Bu_4NN_3 as a radical source providing access to azide-appended BCP synthons **4.8a-4.8d**, with the azide-based BCP **4.8a** undergoing a facile Cu-mediated "click" reaction with phenyl acetylene producing 1,2,3-triazole derivative **4.8A** in 81% yield. When sodium trifluoromethanesulfinate (CF_3SO_2Na) is the radical source, CF_3-substituted BCPs **4.8e**

(43%) can be forged being of relevance towards new drug design as illustrated by Scheme 4.1 (Bayer Pharma 2016). In these preparations, 4CzIPN (2 mol%, **PC4**) instead of **PC1** was used as photocatalyst.

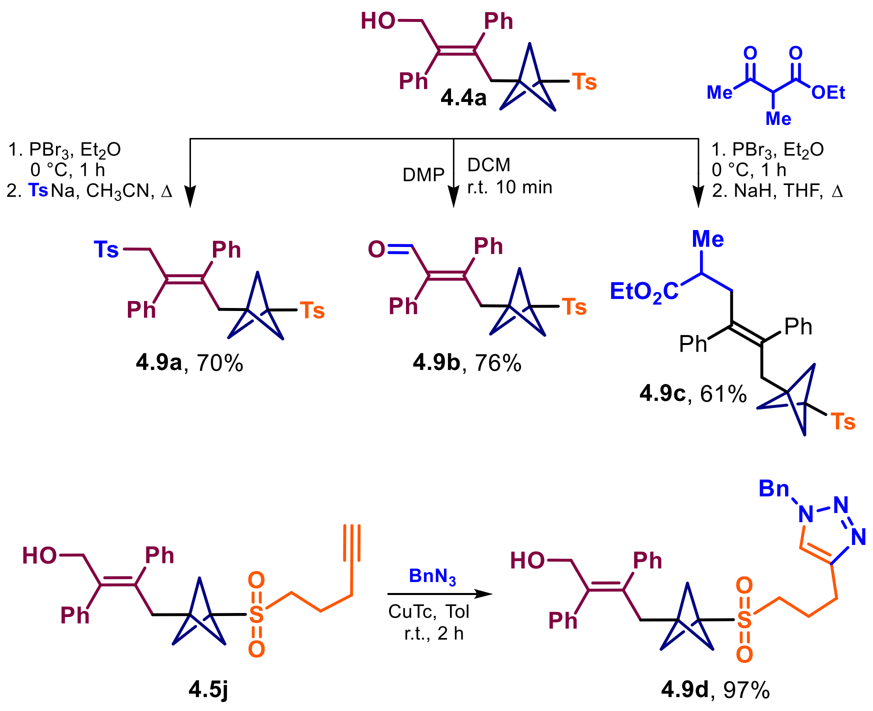


Scheme 4.13. 3CR based protocol using different radical precursors leading to azide and trifluoromethyl BCP products **4.8a-4.8e**. The isolated yield (81%) of **4.8A** is based on **4.8a** at a 0.10 mmol scale.

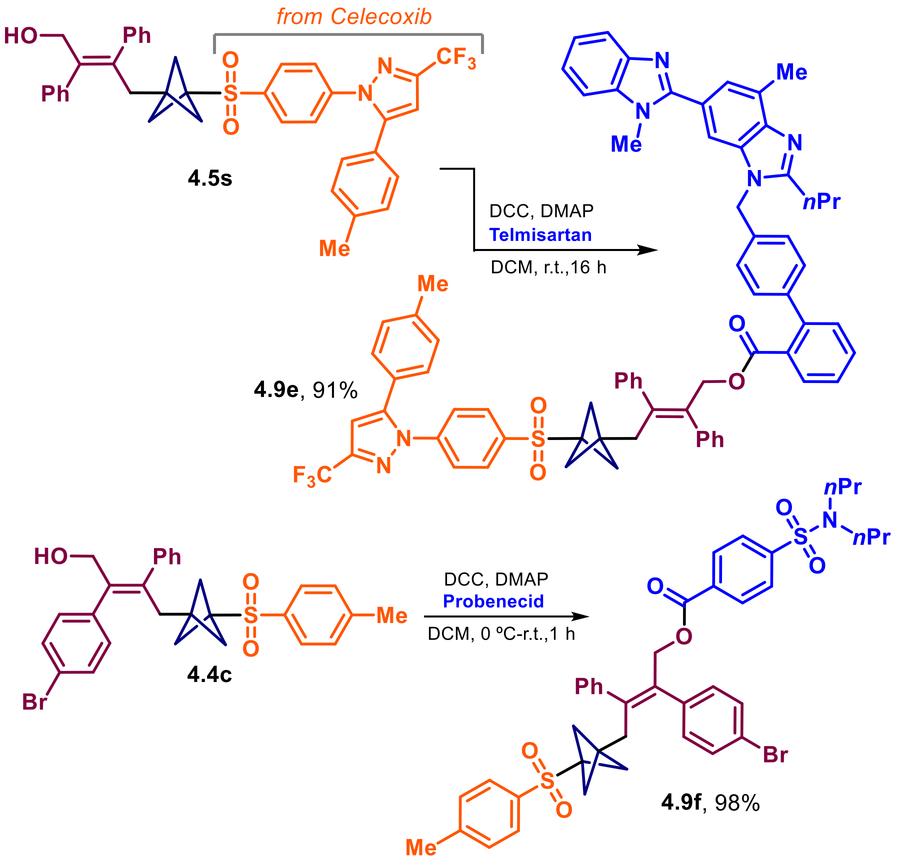
4.2.3. Post-synthetic use of allylated BCP products

Subsequently, we set out to demonstrate the synthetic value and stability of the stereodefined allylic alcohol groups in the 1,3-difunctionalized BCPs (Scheme 4.14, Part A). Treatment of **4.4a** with PBr_3 followed by addition of sodium sulfinate afforded bis-sulfone functionalized **4.9a** in 70% yield. The latter scenario shows that BCPs can be easily equipped with either one (on either side of the BCP) or two sulfones depending on the starting materials. Compound **4.4a** was further oxidized by DMP providing access to α,β-unsaturated aldehyde **4.9b** (76%), while converting the allylic alcohol in the presence of a carbon-based pronucleophile allowed to prepare ester derivative **4.9c** in 61% yield. Terminal alkyne-based BCP **4.5j** undergoes smooth coupling with benzyl azide under suitable Cu-catalysis to give the 1,2,3-triazole product **4.9d** in nearly quantitative yield (97%).

One further type of transformation was probed, and known Steglich type esterification of **4.5s** in the presence of Telmisartan (Scheme 4.14, Part B: a drug used to treat high blood pressure, heart failure, and diabetic kidney disease) delivers the hybrid drug-based molecule **4.9e** in high yield (91%). A similar procedure that involves **4.4c** furnishes Probenecid-derived **4.9f** in 98% yield, with Probenecid being a medication that increases uric acid excretion in the urine. The latter processes describe a potentially useful entry towards drug “conjugation” based on allylic alcohol functionalized BCPs.



Scheme 4.14. Part A of post-synthetic transformations of allyl alcohol-functionalized BCPs.

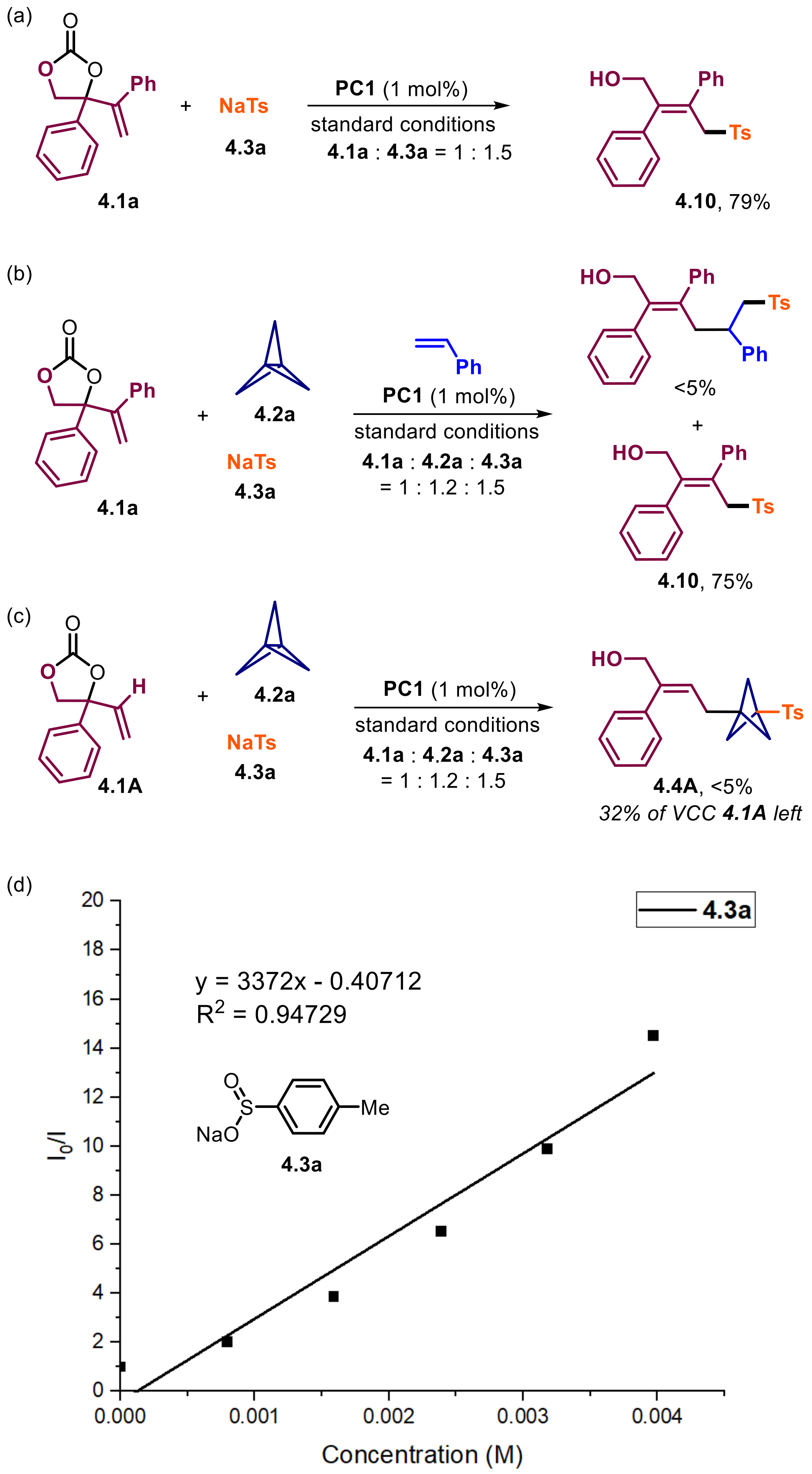


Scheme 4.14. Part B of post-synthetic transformations of allyl alcohol-functionalized BCPs.

4.2.4. Mechanistic control experiments

We finally performed some control experiments and Stern-Volmer quenching studies (Scheme 4.15). As mentioned before, in the absence of [1,1,1]-propellane **4.2a**, a 2CR occurs between **4.1a** and **4.3a** under the optimized conditions (entry 1, Table 4.1; see Scheme 4.15a) giving the anticipated product **4.10** in 79% yield. This result shows the facile nature of direct radical addition to the C=C bond of the VCC substrate. If we replace [1,1,1]-propellane **4.2a** by another radical acceptor (i.e., styrene: Scheme 4.15b), predominant formation of 2CR product **4.10** in 75% yield occurs with only <5% of a 3CR product. This highlights the essential nature of the [1,1,1]-propellane to create a chemoselective 3CR coupling between a VCC, **4.2a** and a radical precursor. Finally, when the VCC is devoid of a substituent on the C=C bond (Scheme 4.15c, **4.1A**), only very low amounts of the desired BCP-derived product (**4.4A**, <5%) can be observed, and 32% of the starting VCC remained in the reaction mixture. These combined experiments

(Scheme 4.15a-c) help to establish that the nature of the VCC (and related heterocyclic substrates, Scheme 4.12) and the presence of [1,1,1]-propellane **4.2a** benefit a high chemoselectivity towards the target 3CR product **4.10**. Various Stern-Volmer quenching experiments were then performed (Scheme 4.15d, and the Experimental Section) showing that sodium sulfinate **4.3a** is an efficient photo-quencher, whereas both VCC **4.1a** and [1,1,1]-propellane **4.2a** are not under the experimental conditions. Thus, it is reasonable to assume that the excited photocatalyst (PC1) is quenched by **4.3a** and then adds to **4.2a** following a second radical addition to VCC **4.1a** thereby inducing a decarboxylative double bond relay and protonation sequence such as depicted in Scheme 4.7.



Scheme 4.15. (a-c) Control experiments and (d) Stern-Volmer quenching studies.

4.3. Conclusions

In summary, we here report a highly versatile 3CR approach towards the formation of functionalized BCPs that incorporate a stereodefined allylic alcohol fragment with a synthetically useful branching point for follow-up chemistry. Apart from the presence of a tetrasubstituted C=C bond, simultaneous introduction of pharma-interesting (hetero)aryl and alkyl sulfone, azide or CF_3 groups can be realized using appropriate radical sources. The scope of this new 3CR transformation is easily extended to other types of heterocycles as well, with potentially access to a plethora of new libraries of various allylic derivatives, drug-derived synthons and drug conjugates. We believe that our methodology unfolds new chemical space for structurally diverse and versatile synthons with value within pharmaceutical discovery and development.

4.4. Experimental section

4.4.1. General information

Air- and water-sensitive reactions were carried out in heat-gun-dried glassware under an Ar or N_2 atmosphere using standard Schlenk techniques. Reactions were monitored by TLC and/or ^{1}H NMR. TLC was carried out on 0.25 mm Merck aluminum backed sheets coated with 60 F_{254} silica gel. Visualization of the silica plates was achieved using a UV lamp (λ = 254 nm) and/or by using the stain solutions of a $KMnO_4$ or ceric ammonium molybdate. Flash chromatography was carried out on Sigma-Aldrich silica gel 60 (70-230 mesh) using the indicated eluent system.

Commercially available reagents and solvents were purchased from Sigma-Aldrich, TCI, Fluorochem, Strem Chemicals, ABCR GmbH, Acros Organics or Alfa Aesar, and were used without further purification. Starting materials were synthesized by following procedures as stated, $[Ir(dmppy)_2(dtbbpy)]PF_6$ was synthesized according to a previously reported procedure.[23] Solvents were dried using an Innovative Technology PURE SOLV solvent purification system.

^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded at room temperature on a Bruker AV-300, AV-400 or AV-500 spectrometer and referenced to their residual deuterated solvent signals. Coupling constants (*J*) are reported in Hertz with the following splitting abbreviations: s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiples. All reported NMR values are given in parts per million (ppm). Mass spectrometric and X-ray analysis were performed by the Research Support Group at ICIQ. Fluorescence measurements were carried out on a Fluorolog Horiba Jobin Yvon spectrofluorimeter equipped with a photomultiplier detector, a double monochromator, and a 350W xenon light source.

Photoreactions were performed in a parallel photoreactor with 8 spots using flat-bottom 10-mL vial (see chapter 2, experimental section 2.3). The reactions were thermostated using a Heidolph rotacool. OSRAM Oslon SSL 80 royal-blue LEDs mounting on a star PCB were used and cooled passively by a common heatsink. The LEDs were powered in series using a current limited power supply (RS Pro RS-3005D).

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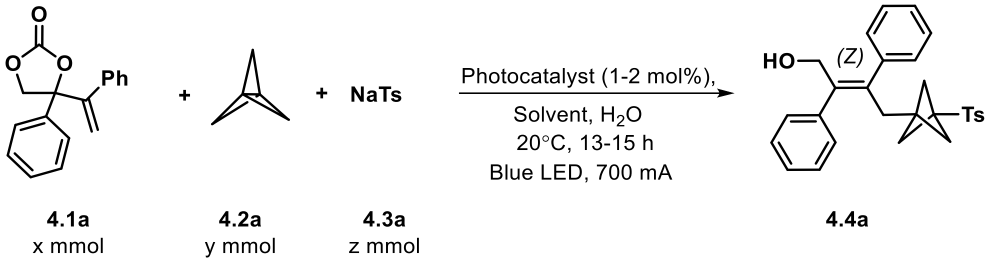
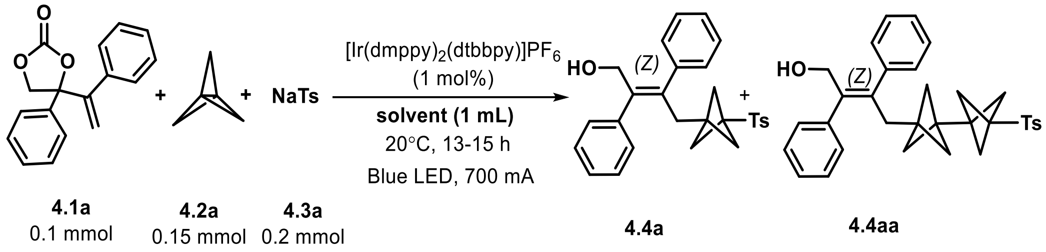
(23) J. A. Terrett, M. D. Clift, D. W. C. MacMillan, *J. Am. Chem. Soc*. **2014**, *136*, 6858–6861.

4.4.2. Process optimization studies using VCC 4.1a



The photocatalyst (**PC**, 1-2 mol%), VCC **4.1a** (*x* mmol) and NaTs **4.3a** (*y* mmol) were weighed in a 10 mL screw-cap vial. The reaction vial was sealed with a cap containing a silicone septum, evacuated, and three times filled with Ar. The degassed solvent, H_2O and [1,1,1]-propellane **4.2a** (*y* mmol) were added affording a light-yellow solution under Ar atmosphere. The reaction system was further sealed with Parafilm® and irradiated for 13-15 h at 20 °C using a single high-power blue LED (λ_{em} = 445 nm, 700 mA) from the bottom. After completion, to the mixture was directly added 1,3,5-trimethyloxybenzene as internal standard, followed by extraction with EtOAc (3 × 20 mL). The organic phrase was collected and evaporated to dryness, and then the residue was dissolved in $CDCl_3$ and analyzed by ^{1}H NMR ($CDCl_3$).

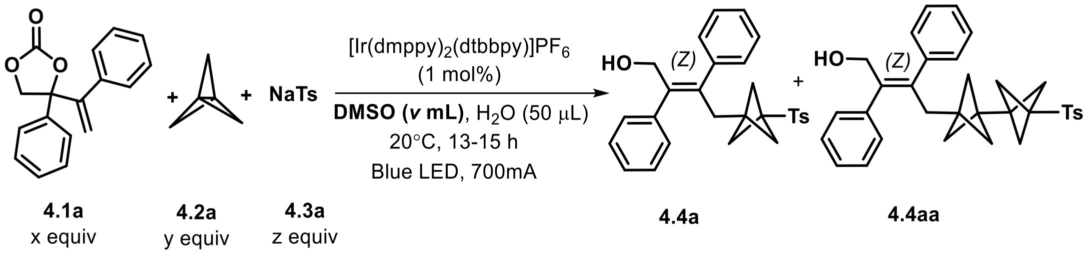
Table 4.2. Variation of solvents in the 3CR allylic substitution process.[a]



Entry	Solvent	Conv. **4.1a** (%)	Yield **4.3a** (%)[b]	Yield **4.3aa** (%)[b]	*Z/E*-**4.3a** [b]
1	CH_3CN	>99	47	14	>99:1
2	THF	>99	32	10	>99:1
3	Dioxane	>99	42	15	>99:1
4	Acetone	>99	40	11	>99:1
5	DMSO	>99	50	20	>99:1
6	**DMSO+50 µL H_2O**	**>99**	**57**	**24**	**>99:1**
7	DMSO+100 µL H_2O	>99	41	35	>99:1

[a] General procedure: **4.1a** (0.1 mmol), **4.2a** (0.15 mmol) in 0.408 M pentane solution, **4.3a** (0.2 mmol), $[Ir(dmppy)_2(dtbbpy)]PF_6$ (1 mol%), solvent (1 mL), 700 mA blue LED, 20 ºC for 13-15 h. [b] Yields were determined by ^{1}H NMR using 1,3,5-trimethyloxybenzene as internal standard.

Table 4.3. Variation of the reaction stoichiometry in the 3CR allylic substitution process.[a]



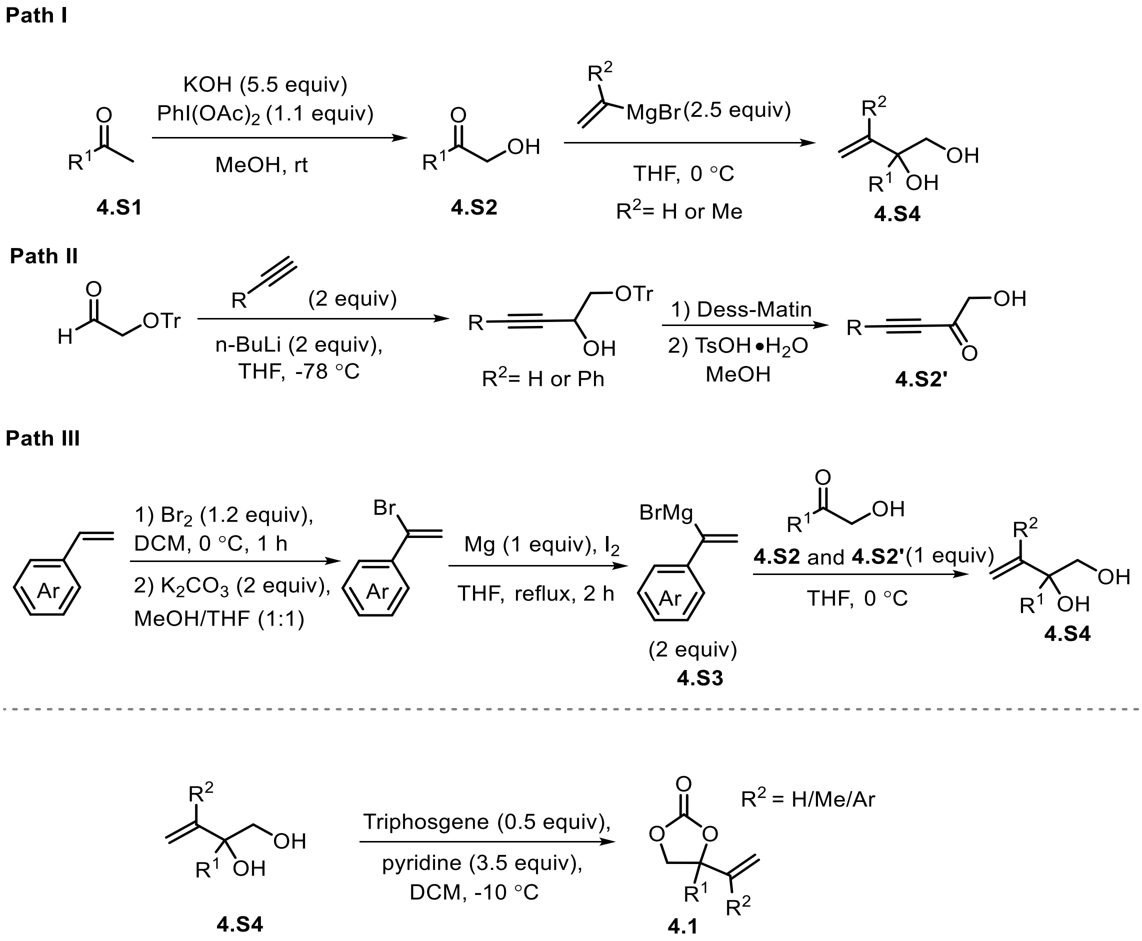
Entry	*x* (equiv) VCC	*y* (equiv) **4.2a**	*z* (equiv) NaTs	Solvent (mL)	Yield **4.4a** (%)[b]	Yield **4.4aa** (%)[b]
1	1	1.5	2	1.0	57	24
2	1	1.5	2.5	1.0	53	29
3	**1**	**1.5**	**1.5**	**1.0**	**54**	**25**
4	1	2.5	1.5	1.0	37	38
5	1.5	1	2.5	1.0	50	14
6	1	1.5	2.5	2.0	50	26
7	1	1.5	1.5	0.50	53	26
8	1	1.2	1.5	0.50	60	19
9	1	1.2[c]	1.5	0.50	65	20
10	1	1.2[d]	1.5	0.50	69	15
11	1	1.2[d]	1.5	0.30	77(76)[f]	10
12	1	1.2[e]	1.5	0.50	64	15

[a] General procedure A: **4.1a** (*x* mmol), **4.2a** (*y* mmol) in 0.408 M pentane solution, **4.3a** (*z* mmol), [Ir(dmppy)$_2$(dtbbpy)]PF$_6$ (1 mol%), DMSO (*v* mL) and H_2O (50 µL), 700 mA blue LED, 20 ºC for 13-15 h. [b] Yields were determined by ^{1}H NMR using 1,3,5-trimethyloxybenzene as internal standard, the Z/*E* isomer ratios were > 99:1 and conversions were typically >99%. [c] **4.2a** was diluted by 0.50 mL pentane, [**4.2a**] was 0.24 M in pentane. [d] **2a** was diluted by 1.0 mL pentane, [**4.2a**] was 0.12 M in pentane. [e] **4.2a** was diluted by 1.5 mL pentane, [**4.2a**] was 0.08 M in pentane. [f] The isolated yield for **4.4a** is reported in brackets.

4.4.3. General procedure for the preparation of starting materials

Substituted vinyl cyclic carbonates **4.1** and carbamates **4.6** were prepared according to a previously reported procedure.[24]

General procedure A for synthesis of the vinyl cyclic carbonates 4.1:



There are two pathways to prepare compound 4.S4, which are described below.

Path I

Step 1: To a cold solution of the ketone **4.S1** (15 mmol, 1 equiv) in MeOH was added the KOH (4.63 g, 82.5 mmol, 5.5 equiv) in portions, and then $PhI(OAc)_2$ (diacetoxy iodobenzene) (5.31 g, 16.5 mmol, 1.1 equiv) was added slowly. After stirring the mixture at 0 ^{o}C-to-room temperature for 2-3 hours, it was concentrated under reduced pressure

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(24) a) W. Guo, L. Martínez-Rodríguez, R. Kuniyil, E. Martin, E. C. Escudero-Adán, F. Maseras, A. W. Kleij, *J. Am. Chem. Soc.* **2016**, *138*, 11970–11978; b) A. Roblin, N. Casaretto, A. Archambeau, *Org. Lett.* **2023**, *25*, 6453–6458; c) L. Shi, Y. He, Y. Chang, N. Zheng, Z. Yang, J. Gong, *Org. Lett.* **2019**, *21*, 3077–3080.

and the residue was washed with H_2O (30 mL) and extracted with Et_2O (30 mL). The organic phase was separated, dried over Na_2SO_4 and filtered. After concentration, the obtained residue was dissolved in MeOH (30 ml), 2 N HCl (30 mL) added, and the mixture then stirred for 16 h at room temperature. Next, a saturated aqueous solution of $NaHCO_3$ was added until pH 7 and diluted with DCM (30 mL). The organic phase was separated and dried with anhydrous Na_2SO_4, and the filtrate was concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (hexanes/EtOAc = 30:1 to 20:1) to yield **4.S2** (*Note: this compound was made several times, the yield was typically 60-70%; the same applies to the other procedures below where typical yield ranges are mentioned*).

Step 2: An oven-dried Schlenk tube (containing a magnetic stirring bar) was charged with **4.S2** (10 mmol, 1 equiv) before evacuating and back-filling with N_2, and then THF (20 mL) and the respective Grignard reagent (1.0 M in THF, 25 mL, 2.5 equiv) were added by a syringe at 0 °C. After being stirred at room temperature for 4-5 hours, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate (3 × 15 mL). The combined organic phases were dried over Na_2SO_4, concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (hexanes/EtOAc = 10:1 to 5:1) to afford the pure product **4.S4** (typically in 50-70% yield).

Path II

Step 1:[25] An oven-dried Schlenk tube containing a magnetic stirring bar was charged with the alkyne (2.79 mL, 20 mmol, 2 equiv) before evacuating and back-filling with N_2, and then THF (20 mL) and *n*-BuLi (8 mL, 2.5 M in THF, 2 equiv) were added by a syringe at -78 ºC. After stirring for 0.5 h, a solution of the respective aldehyde derivative (3.02 g, 10 mmol, 1 equiv) in 5 mL of THF was added to the reaction mixture, which was stirred for 1 h at -78 ºC and then allowed to reach room temperature. The mixture was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate (3 × 15 mL). The combined organic phases were dried over Na_2SO_4, concentrated under reduced pressure. Then the obtained residue was purified by column chromatography on silica gel (hexanes/EtOAc = 10:1 to 5:1) to afford the pure product (typically in 95% yield).

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(25) K. Guo, Q. Zeng, A. Villar-Yanez, C. Bo, A. W. Kleij, *Org. Lett.* **2022**, *24*, 637−641.

Step 2 and 3: An oven-dried Schlenk tube containing a magnetic stirring bar charged with the alcohol derivative (10 mmol, 1 equiv) and the Dess-Martin reagent (4.57 g, 10.8 mmol, 1.05 equiv) and DCM (20 mL) at room temperature. After stirring for 0.5 h, the mixture was concentrated under reduced pressure, and then the obtained residue was purified by column chromatography on silica gel (hexanes/EtOAc = 10:1 to 5:1) to afford the pure product. Next, the freshly prepared ketone compound and *p*-TsOH·H_2O (475 mg, 2.5 mmol, 0.25 equiv) were dissolved in MeOH (30 mL), and product generation monitored by TLC. After stirring at room temperature for 2 h, the mixture was concentrated under reduced pressure, and then the obtained residue was purified by column chromatography on silica gel (hexanes/EtOAc = 10:1 to 2:1) to afford the product **4.S2’** in 90% yield.

Path III

Step 1: To a 100 mL, dried round flask, the respective styrene derivative (40 mmol) and DCM (80 mL, 0.5 M) were added. After cooling to 0 °C, Br_2 was added dropwise and the reaction mixture was stirred at 0 °C-r.t. for 1 h. After the styrene reagent had been consumed as monitored by thin layer chromatography (TLC), the solution was quenched with the aqueous $Na_2S_2O_3$ and filtered through Celite. The mixture was extracted with DCM and the organic phase was collected. Then, the solution was concentrated under the reduced pressure and residue was directly used in the next step without any further purification. To a solution of this crude in THF/MeOH (80 mL: 80 mL, 0.25 M) was added K_2CO_3 (1.10 g, 80 mmol, 2 equiv) at room temperature. After being stirred for 16 h, the reaction mixture was quenched with water and the organic solvent was removed by a rotary evaporator. The reaction residue was extracted with Et_2O (40 mL) and washed with water 40 (mL). The organic phase was collected and dried over Na_2SO_4 and filtered. After concentration under reduced pressure, the residue was purified by silica gel chromatography (hexanes/EtOAc = 100:1) to provide the pure α-brominated alkene (typically in 50-70% yield).

Step 2:[26] Mg chips (243 mg, 2 equiv), one granule I_2 and THF (30 mL) were added into a dry two-necked round flask under N_2. After the reaction temperature was increased to 80 °C (refluxing conditions), the above α-brominated styrene was added dropwise (1 drop every 2 seconds) and the reaction monitored by the color change (typically from brown to colorless) at the same time. After the mixture had become fully colorless, the rest of the styrene was added into the reaction system and "refluxing" was continued for 2 hours. The Mg chips had been consumed at this time, and the mixture was cooled down to 0 °C, following the addition of **4.S2** or **4.S2'** (5 mmol dissolved in 10 mL THF, 1 equiv) to the Grignard reagent **4.S3** (about 2 equiv). After being stirred at 0 °C-r.t. for 16 h, the reaction mixture was extracted with EtOAc (3 × 30 mL) and washed with H_2O (3 × 30 mL). The organic phase was separated and dried on anhydrous Na_2SO_4. Then the filtrate was concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (hexanes/EtOAc = 10:1 to 5:1) to yield **4.S4** (typically in70-90% yield).

Synthesis of 4.1: An oven-dried Schlenk tube containing a magnetic stirring bar was charged with diol **4.S4** (3.5 mmol, 1 equiv) before evacuating and back-filling it with N_2. Then sequentially pyridine (969 mg, 12.2 mmol, 3.5 equiv) and a solution of triphosgene (518 g, 1.75 mmol, 0.5 equiv) in 10 mL DCM were added by a syringe at −10 °C. After being stirred at -10 °C to room temperature for 1-2 hours, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and diluted with DCM (30 mL). The organic phase was washed with 1 N HCl (3 × 20 mL), $NaHCO_3$ (3 × 20 mL) and brine (3 × 20 mL). The combined organic phases were dried over Na_2SO_4, concentrated under reduced pressure. Then the residue was purified by column chromatography on silica gel (hexanes/EtOAc = 15:1 to 10:1) to afford the pure product as a light-yellow oil (typically in 70-90% yield).

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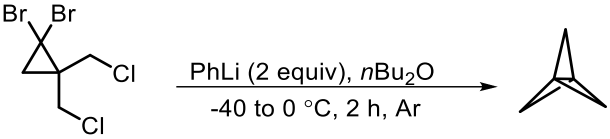
(26) L. Dai, W. Liu, Y. Q. Zhou, Z. Zeng, X. Y. Hu, W. D. Cao, X. M. Feng, *Angew. Chem. Int. Ed.* **2021**, *60*, 26599–26603.

General procedure B for synthesis of BCPs:



Synthesis of 4.2a:[27] A 250 mL-round flask containing a magnetic stirring bar was charged with 1,1-dibromo-2,2-bis(chloromethyl)cyclopropane (8.9 g, 30 mmol, 1 equiv) before evacuating and back-filling it with Ar. Then dry $n\mathrm{Bu_2O}$ (8 mL) and PhLi (1.9M in $n\mathrm{Bu_2O}$, 2 equiv) were slowly added by a syringe. After being stirring at -40 ºC (using a dry ice/acetonitrile bath) for 15 min, the reaction mixture was allowed to reach 0 ºC and stirred for 2 hours. To the mixture was then added pentane (30 mL) and connected to vacuum-distilled. A vacuum was slowly applied to the system while collecting the distillate. Approximately 30-40 mL of distillate was collected (50% yield), which was stored at -20 ºC for a few months.

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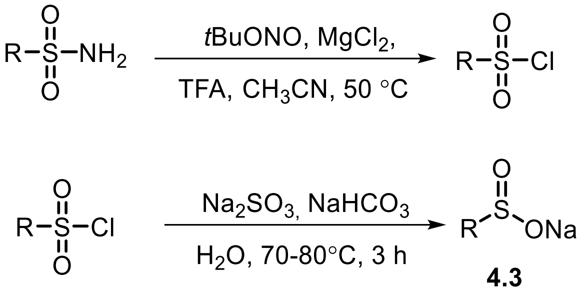
(27) a) X. Zhang, R. Smith, C. Le, S. J. McCarver, B. T. Shireman, N. I. Carruthers, D. W. C. MacMillan, *Nature* **2020**, *580*, 220–226; b) J. Kanazawa, K. Maeda, M. Uchiyama, *J. Am. Chem. Soc.* **2017**, *139*, 17791–17794.

General procedure C for the synthesis of radical precursors 4.3:



Synthesis of sulfonyl chloride derivatives: [28] A 100 mL-round flask containing a magnetic stirring bar was charged with $MgCl_2$ (476 mg, 5 mmol, 1 equiv) and sulfonamide (5 mmol, 1.0 equiv) before adding CH_3CN (25 mL) following a three-time evacuation/fill (N_2) procedure. Then TFA (383 µL, 5 mmol, 1 equiv) and *t*BuONO (1.78 mL, 15 mmol, 3 equiv) were added by a syringe under N_2. After being stirred at 50 ºC for 7 h, the reaction mixture was filtered and extracted with EtOAc. The combined organics were concentrated under reduced pressure. Then the obtained residue was purified by column chromatography on silica gel to afford the pure sulfonyl chloride (typically in 80-90% yield).

Synthesis of sodium sulfinate derivatives 4.3: [29] Sodium sulfinates were prepared according to a previous report. A 50 mL-round flask containing a magnetic stirring bar was charged with sodium sulfite (1.26 g, 10 mmol, 2 equiv), sodium bicarbonate (840 mg, 10 mmol, 2 equiv) and the corresponding sulfonyl chloride (5 mmol, 1 equiv) before adding 5 mL of H_2O. After stirring at 70 ºC for 2-4 h, the water was removed by a rotary evaporator. The remaining residue was washed with hot ethanol (or with methanol if the product had low solubility) to provide the product as a white solid (typically in 60-80% yield).

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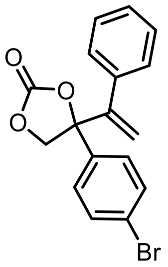
(28) J.-S. Li, J. Liu, Y.-T. Wang, J.-Y. Dai, Z.-W. Li, W.-W. Luo, Y.-F. Zhang, H.-W. Liu, W.-D. Liu, *Org. Lett.* **2023**, *25*, 8263−8268.

(29) a) C. Tran, B. Flamme, A. Chagnes, M. Haddad, P. Phansavath, V. Ratovelomanana-Vidal, *Synlett* **2018**, 1622-1626; b) A. D. Hudwekar, G. L. Reddy, P. K. Verma, S. Gupta, R. A. Vishwakarma, S. D. Sawant, *ChemistrySelect* **2017**, *2*, 4963–4968; c) H. D. Pickford, V. Ripenko, R. E. McNamee, S. Holovchuk, A. L. Thompson, R. C. Smith, P. K. Mykhailiuk, E. A. Anderson, *Angew. Chem. Int. Ed.* **2023**, *62*, e202213508.

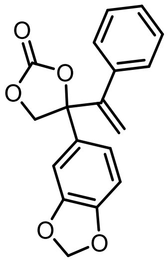
Data for the newly reported substrates:

4-(4-Bromophenyl)-4-(1-phenylvinyl)-1,3-dioxolan-2-one (4.1c)



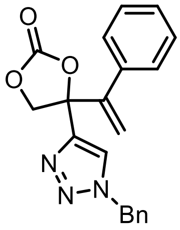
Yellowish oil (General Procedure A, 1.173g, 85%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.58 – 7.52 (m, 2H), 7.30 – 7.24 (m, 5H), 7.08 – 7.02 (m, 2H), 5.61 (s, 1H), 5.57 (s, 1H), 4.76 – 4.64 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.2, 137.7, 137.2, 132.3, 128.61, 128.59, 128.4, 127.7, 123.6, 118.3, 87.0, 73.4; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd for. $C_{17}H_{13}BrNaO_3^+$ 366.9940; found 366.9941.

4-(Benzo[d][1,3]dioxol-5-yl)-4-(1-phenylvinyl)-1,3-dioxolan-2-one (4.1f)



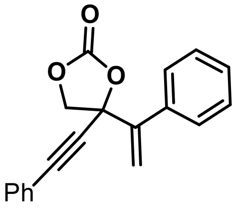
Yellowish oil (General Procedure A, 868 mg, 80%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30 – 7.22 (m, 3H), 7.13 – 7.03 (m, 2H), 6.98 – 6.86 (m, 2H), 6.82 (d, *J* = 8.1 Hz, 1H), 6.01 (s, 2H), 5.64 (s, 1H), 5.59 (s, 1H), 4.74 – 4.60 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.8, 148.6, 148.5, 147.4, 137.4, 132.1, 128.54, 128.47, 128.3, 120.0, 117.7, 108.5, 106.9, 101.8, 87.4, 73.5; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd for. $C_{18}H_{14}NaO_5^+$ 333.0733; found 333.0731.

4-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-4-(1-phenylvinyl)-1,3-dioxolan-2-one (4.1j)



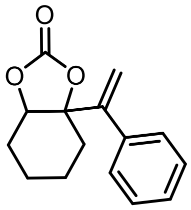
Yellowish oil (General Procedure A, 313 mg, 90%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.41 – 7.34 (m, 3H), 7.31 – 7.26 (m, 3H), 7.25 – 7.19 (m, 2H), 7.13 – 7.04 (m, 2H), 5.67 (s, 1H), 5.60 (s, 1H), 5.54 (d, *J* = 2.4 Hz, 2H), 5.47 (d, *J* = 8.5 Hz, 1H), 4.55 (d, *J* = 8.6 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.7, 146.4, 136.5, 134.0, 129.4, 129.2, 128.8, 128.7, 128.1, 127.8, 123.8, 117.6, 82.0, 72.0, 54.7; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd for. $C_{20}H_{17}N_3NaO_3^+$ 370.1162; found 370.1171.

4-(Phenylethynyl)-4-(1-phenylvinyl)-1,3-dioxolan-2-one (4.1m)



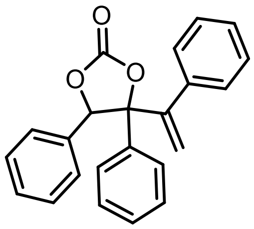
Yellowish oil (General Procedure A, 999 mg, 86%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50 – 7.44 (m, 4H), 7.43 – 7.33 (m, 6H), 5.97 (s, 1H), 5.55 (s, 1H), 4.64 (d, *J* = 8.4 Hz, 1H), 4.43 (d, *J* = 8.4 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.6, 144.8, 136.5, 132.0, 129.8, 128.9, 128.8, 128.7, 128.6, 120.9, 119.0, 90.4, 84.7, 79.8, 74.4; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd for. $C_{19}H_{14}NaO_3^+$ 313.0835; found 313.0831.

3a-(1-Phenylvinyl)hexahydrobenzo[d][1,3]dioxol-2-one (4.1o)



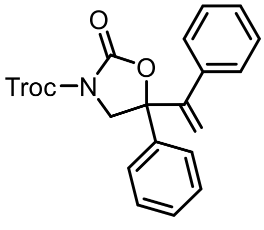
Yellowish oil (General Procedure A, 590 mg, 70% yield); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37 – 7.33 (m, 3H), 7.32 – 7.27 (m, 2H), 5.56 (s, 1H), 5.39 (s, 1H), 4.73 (t, *J* = 4.2 Hz, 1H), 2.19 – 2.11 (m, 1H), 2.04 – 1.97 (m, 1H), 1.92 – 1.86 (m, 1H), 1.78 – 1.70 (m, 1H), 1.69 – 1.60 (m, 2H), 1.55 – 1.48 (m, 1H), 1.45 – 1.36 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.5, 147.5, 138.7, 129.0, 128.5, 128.2, 118.5, 85.2, 78.5, 31.6, 26.1, 19.7, 18.3; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd for. $C_{15}H_{16}NaO_3^+$ 267.0992; found 267.0995.

4,5-Diphenyl-4-(1-phenylvinyl)-1,3-dioxolan-2-one (4.1n)



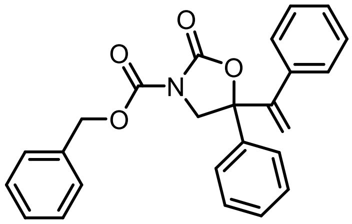
Yellowish oil (General Procedure A, 838 mg, 70% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.28 – 7.24 (m, 3H), 7.22 – 7.16 (m, 3H), 7.15 – 7.07 (m, 5H), 7.03 – 6.98 (m, 2H), 6.92 – 6.87 (m, 2H), 6.16 (s, 1H), 5.79 (s, 1H), 5.68 (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.9, 148.8, 138.8, 135.3, 133.4, 129.3, 128.8, 128.32, 128.25, 128.2, 127.9, 127.4, 126.8, 119.6, 91.6, 85.5; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd for. $C_{23}H_{18}NaO_3^+$ 365.1148; found 365.1159.

2,2,2-Trichloroethyl 2-oxo-5-phenyl-5-(1-phenylvinyl)oxazolidine-3-carboxylate (4.6c)



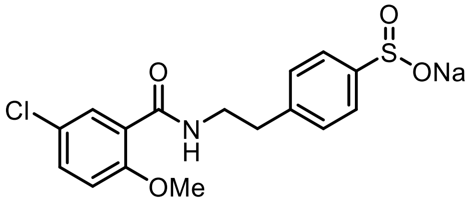
Yellowish oil (General Procedure A and report literature [23c], 397 mg, 90%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 – 7.38 (m, 4H), 7.30 – 7.21 (m, 4H), 7.06 – 7.01 (m, 2H), 5.57 (s, 1H), 5.46 (s, 1H), 4.89 – 4.79 (m, 2H), 4.50 – 4.32 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.2, 149.1, 148.6, 138.9, 137.8, 129.2, 129.0, 128.8, 128.43, 128.35, 126.1, 118.4, 84.3, 75.5; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd for. $C_{20}H_{16}Cl_3NNaO_4^+$ 462.0037; found 462.0048.

Benzyl-2-oxo-5-phenyl-5-(1-phenylvinyl)oxazolidine-3-carboxylate (4.6d)



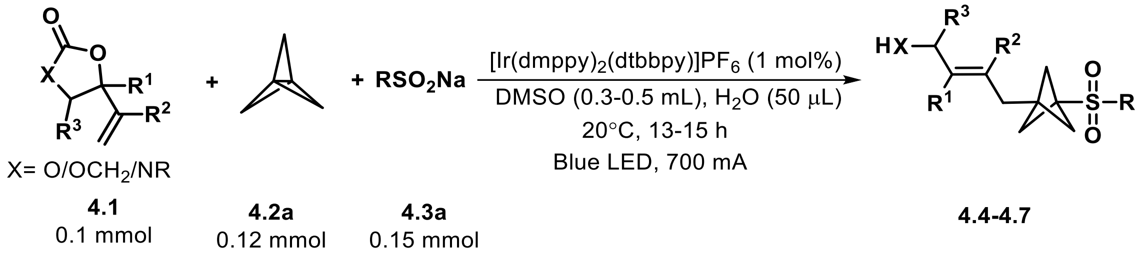
Yellowish oil (General Procedure A and report literature [23c], 347 mg, 87%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.42 – 7.34 (m, 10H), 7.25 – 7.17 (m, 3H), 7.04 – 6.99 (m, 2H), 5.56 (s, 1H), 5.45 (s, 1H), 5.26 (s, 2H), 4.39 – 4.27 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 150.8, 150.6, 148.7, 139.3, 137.9, 134.9, 129.0, 128.9, 128.8, 128.74, 128.68, 128.4, 128.3, 128.2, 126.1, 118.0, 83.9, 68.9, 53.3; **HRMS** (ESI/TOF) *m/z*: [M + Na]$^+$ Calcd for. $C_{25}H_{21}NNaO_4^+$ 422.1363; found 422.1365.

Sodium 4-(2-(5-chloro-2-methoxybenzamido)ethyl)benzenesulfinate (4.3q)

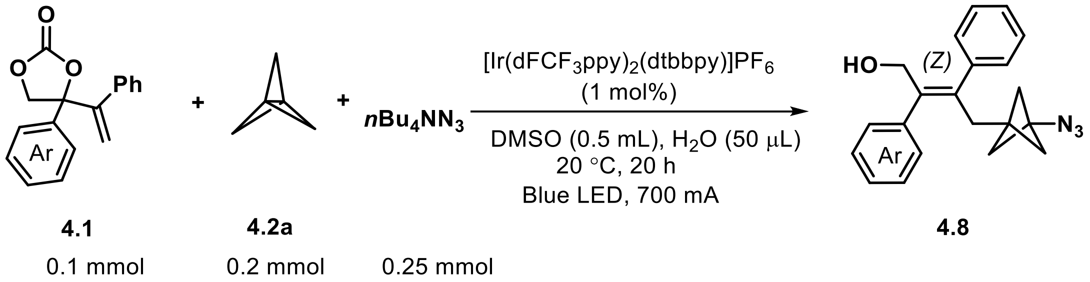


White solid (General Procedure C, 1.27 g, 75%); ^{1}**H NMR** 400 MHz, CD_3OD) δ 7.84 (d, *J* = 2.8 Hz, 1H), 7.68 – 7.59 (m, 2H), 7.49 – 7.40 (m, 1H), 7.40 – 7.30 (m, 2H), 7.10 (d, *J* = 8.9 Hz, 1H), 3.84 (s, 3H), 3.67 (t, *J* = 7.0 Hz, 2H), 2.95 (t, *J* = 6.9 Hz, 2H); ^{13}**C NMR** (101 MHz, CD_3OD) δ 166.5, 157.7, 155.5, 142.1, 133.5, 131.5, 130.0, 126.0, 125.5, 124.5, 114.7, 57.0, 42.2, 36.0; **HRMS** (ESI/TOF) *m/z*: [M + H]$^+$ Calcd for. $C_{16}H_{16}ClNNaO_4S^+$ 376.0381; found 376.0381.

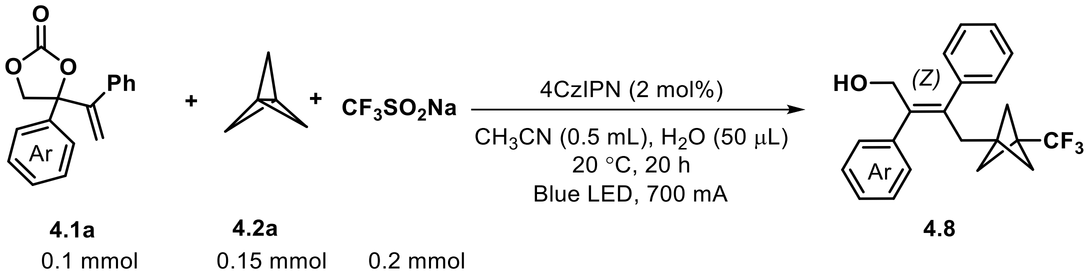
4.4.4. General procedure for the synthesis of allylated BCPs



Method A: [Ir(dmppy)$_2$(dtbbpy)]PF$_6$ (1.0 mg, 1 mol%), the respective VCC (0.1 mmol) and sodium sulfinite (26.7 mg, 0.15 mmol) were weighed into a 10 mL screw-cap vial. The reaction vial was sealed with a cap containing a silicone septum, evacuated, and filled with Ar three times. Then degassed DMSO (0.3 mL-0.5 mL), H_2O (50 µL) and [1,1,1]-propellane **4.2a** (1 mL, 0.12 M in pentane, 0.12 mmol) were added affording a light-yellow solution under an Ar atmosphere. The reaction system was further sealed with Parafilm® and irradiated for 13-15 h at 20 ºC using a single high-power blue LED (λ_{em} = 445 nm, 700 mA) from the bottom. After completion, the mixture was directly extracted with EtOAc (20 mL). The organic phase was collected and evaporated to dryness, and then the residue was purified by column chromatography (SiO_2, hexanes/EtOAc) to afford products **4.4**-**4.7**.



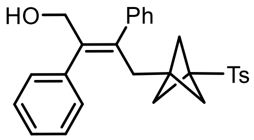
Method B: [Ir(dFCF$_3$ppy)$_2$(dtbbpy)]PF$_6$ (1.1 mg, 1 mol%), the respective VCC (0.1 mmol) and *n*Bu$_4$NN$_3$ (71.1 mg, 0.25 mmol) were weighed into a 10 mL screw-cap vial. The reaction vial was sealed with a cap containing a silicone septum, evacuated, and filled with Ar three times. Then degassed DMSO (0.5 mL), H_2O (50 µL) and [1,1,1]-propellane **4.2a** (770 µL, 0.26 M in Et_2O, 0.2 mmol) were added affording a light-yellow solution under an Ar atmosphere. The reaction system was further sealed with Parafilm® and irradiated for 20 h at 20 ºC using a single high-power blue LED (λ_{em} = 445 nm, 700 mA) from the bottom. After completion, the mixture was directly extracted with EtOAc (20 mL). The organic phase was collected and evaporated to dryness, after which the residue was purified by column chromatography (SiO_2, hexanes/EtOAc) to afford products **4.8**.



Method C: 4CzIPN (1.6 mg, 2 mol%), the respective VCC (0.1 mmol) and CF_3SO_2Na (31.2 mg, 0.2 mmol) were weighed into a 10 mL screw-cap vial. The reaction vial was sealed with a cap containing a silicone septum, evacuated, and filled with Ar three times. Then degassed CH_3CN (0.5 mL), H_2O (50 µL) and [1,1,1]-propellane **4.2a** (580 µL, 0.26 M in Et_2O, 0.15 mmol) were added affording a light-yellow solution under an Ar atmosphere. The reaction system was further sealed with Parafilm® and irradiated for 20 h at 20 ºC using a single high-power blue LED (λ_{em} = 445 nm, 700 mA) from the bottom. After completion, the mixture was directly evaporated to dryness, after which the residue was purified by column chromatography (SiO_2, hexanes/EtOAc) to afford products **4.8**.

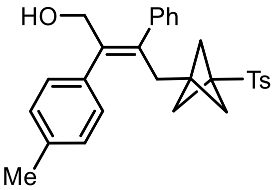
4.4.5. Characterization data for all new compounds

(*Z*)-2,3-Diphenyl-4-(3-tosylbicyclo[1.1.1]pentan-1-yl)but-2-en-1-ol (4.4a)



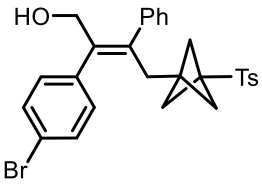
Yellowish solid (Method A, 33.7 mg, 76% yield); **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.63 – 7.57 (m, 2H), 7.40 – 7.27 (m, 8H), 7.26 – 7.22 (m, 2H), 7.20 – 7.16 (m, 2H), 4.20 (s, 2H), 2.52 (s, 2H), 2.42 (s, 3H), 1.57 (s, 6H); **^{13}C NMR** (101 MHz, CDCl$_3$) δ 144.5, 140.4, 140.1, 139.4, 137.8, 134.1, 129.8, 129.1, 128.8, 128.7, 128.6, 128.5, 127.7, 127.5, 64.4, 51.9, 51.3, 38.3, 36.7, 21.8; **HRMS** (ESI/TOF) *m/z*: [M + Na]$^+$ Calcd for. $C_{28}H_{28}NaO_3S^+$ 467.1651; found 467.1652.

(*Z*)-3-Phenyl-2-(p-tolyl)-4-(3-tosylbicyclo[1.1.1]pentan-1-yl)but-2-en-1-ol (4.4b)



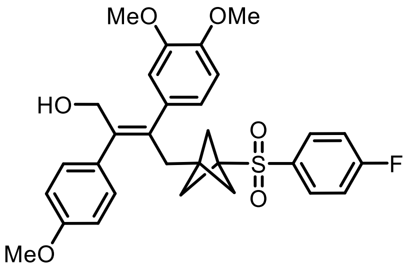
Yellowish solid (Method A, 38.5 mg, 84% yield); **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.60 (d, *J* = 8.2 Hz, 2H), 7.36 – 7.26 (m, 5H), 7.25 – 7.21 (m, 2H), 7.19 – 7.15 (m, 2H), 7.09 – 7.04 (m, 2H), 4.18 (s, 2H), 2.53 (s, 2H), 2.41 (s, 3H), 2.36 (s, 3H), 1.57 (s, 6H); **^{13}C NMR** (101 MHz, CDCl$_3$) δ 144.4, 140.5, 139.2, 137.4, 137.0, 136.7, 134.0, 129.7, 129.3, 128.9, 128.8, 128.6, 128.4, 127.5, 64.3, 51.8, 51.2, 38.3, 36.6, 21.7, 21.3; **HRMS** (ESI/TOF) *m/z*: [M + Na]$^+$ Calcd for. $C_{29}H_{30}NaO_3S^+$ 481.1808; found 481.1822.

(*Z*)-2-(4-Bromophenyl)-3-phenyl-4-(3-tosylbicyclo[1.1.1]pentan-1-yl)but-2-en-1-ol (4.4c)



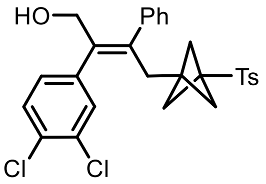
Yellowish solid (Method A, 44.5 mg, 85% yield); **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.62 – 7.56 (m, 2H), 7.52 – 7.47 (m, 2H), 7.35 – 7.27 (m, 5H), 7.24 – 7.20 (m, 2H), 7.09 – 7.04 (m, 2H), 4.17 (s, 2H), 2.50 (s, 2H), 2.42 (s, 3H), 1.56 (s, 6H); **^{13}C NMR** (101 MHz, CDCl$_3$) δ 144.6, 140.1, 139.2, 138.5, 138.2, 134.0, 131.8, 130.8, 129.8, 128.7, 128.6, 128.5, 127.8, 121.4, 64.1, 51.9, 51.2, 38.1, 36.7, 21.7; **HRMS** (ESI/TOF) *m/z*: [M + Na]$^+$ Calcd for. $C_{28}H_{27}BrNaO_3S^+$ 545.0756; found 545.0748.

(*Z*)-3-(3,4-Dimethoxyphenyl)-4-(3-((4-fluorophenyl)sulfonyl)bicyclo[1.1.1]pentan-1-yl)-2-(4-methoxyphenyl)but-2-en-1-ol (4.4d)



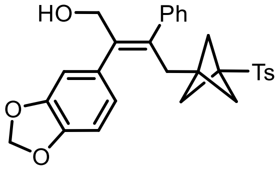
Yellowish oil (Method A, 33.5 mg, 62% yield); **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.78 – 7.71 (m, 2H), 7.22 – 7.15 (m, 2H), 7.13 – 7.07 (m, 2H), 6.95 – 6.88 (m, 2H), 6.85 – 6.75 (m, 3H), 4.21 (s, 2H), 3.90 (s, 3H), 3.86 (s, 3H), 3.82 (s, 3H), 2.52 (s, 2H), 1.61 (s, 6H); **^{13}C NMR** (101 MHz, CDCl$_3$) δ 165.9 (d, *J* = 255.9 Hz), 158.9, 148.8, 148.5, 138.7, 137.4, 133.1 (d, *J* = 2.9 Hz), 133.1, 132.2, 131.4 (d, *J* = 9.6 Hz), 130.1, 121.3, 116.48 (d, *J* = 22.5 Hz), 114.1, 112.0, 111.0, 64.6, 56.1, 56.0, 55.4, 51.9, 51.3, 38.6, 36.4; **^{19}F NMR** (376 MHz, CDCl$_3$) δ -104.0; **HRMS** (ESI/TOF) *m/z*: [M + Na]$^+$ Calcd. for C$_{30}$H$_{31}$FNaO$_6$S$^+$ 561.1718; found 561.1707.

(*Z*)-2-(3,4-Dichlorophenyl)-3-phenyl-4-(3-tosylbicyclo[1.1.1]pentan-1-yl)but-2-en-1-ol (4.4e)



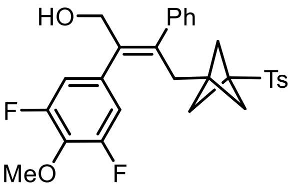
Yellowish oil (Method A, 29.7 mg, 58% yield); **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.66 – 7.57 (m, 2H), 7.45 (d, *J* = 8.2 Hz, 1H), 7.38 – 7.27 (m, 6H), 7.24 – 7.20 (m, 2H), 7.08 – 7.02 (m, 1H), 4.18 (d, *J* = 4.7 Hz, 2H), 2.52 (s, 2H), 2.42 (s, 3H), 1.58 (s, 6H); **^{13}C NMR** (101 MHz, CDCl$_3$) δ 144.6, 140.4, 139.8, 139.4, 137.2, 134.0, 132.8, 131.6, 131.1, 130.6, 129.8, 128.7, 128.64, 128.63, 128.5, 128.0, 64.1, 51.9, 51.3, 38.1, 36.8, 21.8; **HRMS** (ESI/TOF) *m/z*: [M + H]$^+$ Calcd. for C$_{28}$H$_{27}$Cl$_2$O$_3$S$^+$ 513.1052; found 513.1065.

(*Z*)-2-(Benzo[d][1,3]dioxol-5-yl)-3-phenyl-4-(3-tosylbicyclo[1.1.1]pentan-1-yl)but-2-en-1-ol (4.4f)



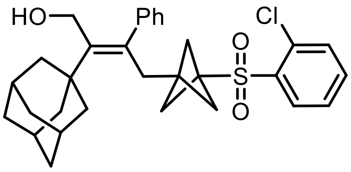
Yellowish oil (Method A, 42.3 mg, 87% yield); **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.59 (d, *J* = 8.2 Hz, 2H), 7.35 – 7.26 (m, 5H), 7.23 – 7.17 (m, 2H), 6.80 (d, *J* = 7.9 Hz, 1H), 6.67 (d, *J* = 1.6 Hz, 1H), 6.65 – 6.61 (m, 1H), 5.96 (s, 2H), 4.15 (s, 2H), 2.55 (s, 2H), 2.41 (s, 3H), 1.57 (s, 6H); **^{13}C NMR** (101 MHz, CDCl$_3$) δ 147.9, 146.9, 144.5, 140.4, 138.8, 137.9, 134.0, 133.6, 129.7, 128.7, 128.6, 128.4, 127.6, 122.2, 109.4, 108.5, 101.2, 64.3, 51.8, 51.2, 38.2, 36.6, 21.7; **HRMS** (ESI/TOF) *m/z*: [M + Na]$^+$ Calcd. for C$_{29}$H$_{28}$NaO$_5$S$^+$ 511.1550; found 511.1552.

(*Z*)-2-(3,5-Difluoro-4-methoxyphenyl)-3-phenyl-4-(3-tosylbicyclo[1.1.1]pentan-1-yl)but-2-en-1-ol (4.4g)



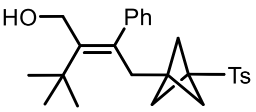
Yellowish oil (Method A, 30.3 mg, 59% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.63 – 7.57 (m, 2H), 7.37 – 7.27 (m, 5H), 7.23 – 7.18 (m, 2H), 6.80 – 6.70 (m, 2H), 4.15 (s, 2H), 4.01 (s, 3H), 2.54 (s, 2H), 2.42 (s, 3H), 1.58 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.6 (dd, *J* = 249.5, 6.4 Hz), 144.6, 139.8, 139.3, 137.1 (dd, *J* = 1.5, 1.5 Hz), 135.6 (dd, *J* = 14.0, 14.0 Hz), 135.3 (dd, *J* = 8.7, 8.7 Hz), 134.0, 129.8, 128.7, 128.62, 128.59, 128.0, 113.0 (dd, *J* = 7.1, 17.2 Hz), 64.0, 62.0 (dd, *J* = 3.3, 3.3 Hz), 51.9, 51.2, 38.1, 36.8, 21.7; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -128.3; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{29}H_{28}F_2NaO_4S^+$ 533.1569; found 533.1572.

(*Z*)-2-((1s,3s)-Adamantan-1-yl)-4-(3-((2-chlorophenyl)sulfonyl)bicyclo[1.1.1]pentan-1-yl)-3-phenylbut-2-en-1-ol (4.4h)



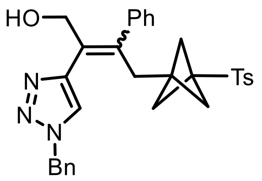
Yellowish oil (Method A, 27.6 mg, 53% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.55 – 7.47 (m, 2H), 7.43 – 7.37 (m, 1H), 7.30 – 7.27 (m, 1H), 7.26 – 7.22 (m, 2H), 7.11 – 7.04 (m, 2H), 3.92 (s, 2H), 3.01 (s, 2H), 2.02 (s, 9H), 1.76 (s, 6H), 1.73 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.2, 144.2, 140.1, 135.5, 134.7, 133.7, 132.5, 132.1, 128.9, 128.4, 127.4, 127.1, 62.0, 52.6, 52.5, 42.2, 37.81, 37.75, 37.03, 36.98, 29.25; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{31}H_{35}ClNaO_3S^+$ 545.1888; found 545.1882.

(*Z*)-2-(*tert*-Butyl)-3-phenyl-4-(3-tosylbicyclo[1.1.1]pentan-1-yl)but-2-en-1-ol (4.4i)



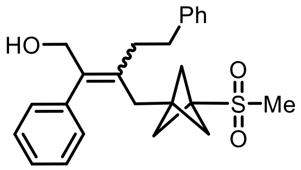
Yellowish oil (Method A, 29.8 mg, 70% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.64 – 7.56 (m, 2H), 7.31 – 7.23 (m, 5H), 7.11 – 7.03 (m, 2H), 3.91 (s, 2H), 2.91 (s, 2H), 2.42 (s, 3H), 1.61 (s, 6H), 1.29 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.9, 144.5, 143.7, 139.8, 134.1, 129.7, 128.9, 128.6, 128.3, 127.1, 62.9, 52.0, 51.5, 38.1, 37.1, 35.1, 31.8, 21.7; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{26}H_{32}NaO_3S^+$ 447.1964; found 447.1976.

2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-3-phenyl-4-(3-tosylbicyclo[1.1.1]pentan-1-yl)but-2-en-1-ol (4.4j)



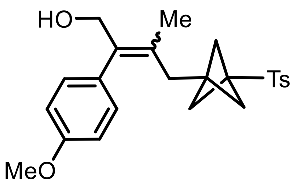
Yellowish oil (Method A, 43.8 mg, 83% yield, *Z/E* = 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) **(*Z*-isomer)** δ 7.59 (d, *J* = 8.2 Hz, 2H), 7.50 (s, 1H), 7.38 – 7.34 (m, 3H), 7.33 – 7.26 (m, 7H), 7.18 – 7.14 (m, 2H), 5.52 (s, 2H), 4.22 (s, 2H), 2.91 (s, 2H), 2.42 (s, 3H), 1.60 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.7, 144.5, 141.1, 140.9, 134.6, 134.0, 129.8, 129.3, 129.0, 128.6, 128.6, 128.5, 128.2, 127.8, 127.6, 122.5, 63.3, 54.3, 51.9, 51.4, 38.2, 36.9, 21.7; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{31}H_{32}N_3O_3S^+$ 526.2159; found 526.2158; **^{1}H NMR** (400 MHz, $CDCl_3$) **(*E*-isomer)** δ 7.66 (d, *J* = 8.2 Hz, 2H), 7.33 – 7.28 (m, 5H), 7.26 (s, 1H), 7.18 – 7.15 (m, 3H), 7.00 – 6.94 (m, 4H), 5.84 (s, 1H), 5.22 (s, 2H), 4.60 (d, *J* = 6.1 Hz, 2H), 2.85 (s, 2H), 2.43 (s, 3H), 1.84 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.9, 144.7, 142.8, 138.5, 134.3, 134.0, 129.9, 129.1, 129.0, 128.78, 128.75, 128.7, 128.3, 128.1, 127.7, 123.0, 61.2, 54.0, 52.0, 51.4, 38.3, 36.9, 21.8; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{31}H_{32}N_3O_3S^+$ 526.2159; found 526.2157.

3-((3-(Methylsulfonyl)bicyclo[1.1.1]pentan-1-yl)methyl)-2,5-diphenylpent-2-en-1-ol (4.4k)



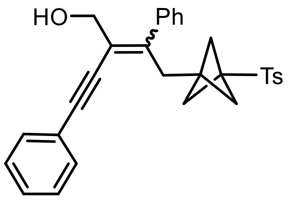
Yellowish oil (Method A, 16.7 mg, 42% yield, *Z/E* = 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) **(*E*-isomer)** δ 7.37 – 7.31 (m, 4H), 7.29 – 7.26 (m, 1H), 7.25 – 7.20 (m, 3H), 7.05 – 7.01 (m, 2H), 4.13 (s, 2H), 2.81 (t, *J* = 7.4 Hz, 2H), 2.77 (s, 3H), 2.50 (t, *J* = 7.5 Hz, 2H), 2.25 (s, 2H), 1.97 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.5, 140.1, 139.1, 134.8, 129.1, 128.7, 128.5, 128.3, 127.3, 126.1, 63.1, 51.4, 51.0, 38.3, 37.6, 36.4, 35.0, 32.5; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{24}H_{28}NaO_3S^+$ 419.1651; found 419.1663; **^{1}H NMR** (400 MHz, $CDCl_3$) **(*Z*-isomer)** δ 7.39 – 7.29 (m, 3H), 7.22 – 7.12 (m, 3H), 7.08 – 7.02 (m, 2H), 6.92 – 6.86 (m, 2H), 4.29 (s, 2H), 2.83 (s, 3H), 2.60 (s, 2H), 2.59 – 2.53 (m, 2H), 2.17 (s, 6H), 2.13 – 2.06 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.3, 140.5, 139.6, 134.3, 129.2, 128.9, 128.7, 128.6, 127.2, 126.5, 63.1, 51.6, 50.9, 37.8, 37.5, 35.3, 33.9, 33.5; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{24}H_{28}NaO_3S^+$ 419.1651; found 419.1654.

2-(4-Methoxyphenyl)-3-methyl-4-(3-tosylbicyclo[1.1.1]pentan-1-yl)but-2-en-1-ol (4.4l)



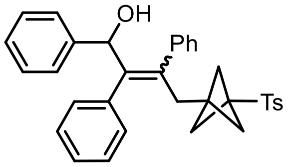
Yellowish oil (Method A, 21.6 mg, 52% yield, *Z/E* = 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) **(*Z*+*E*-isomers)** δ 7.76 – 7.67 (m, 4H), 7.39 – 7.30 (m, 4H), 7.07 – 7.01 (m, 2H), 6.98 – 6.92 (m, 2H), 6.92 – 6.82 (m, 4H), 4.31 (s, 2H), 4.23 (s, 2H), 3.80 (s, 3H), 3.80 (s, 3H), 2.49 – 2.40 (m, 8H), 2.15 (s, 2H), 1.96 (s, 6H), 1.82 (s, 6H), 1.78 (s, 3H), 1.64 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) **(*Z*+*E*-isomers)** δ 158.64, 158.60, 144.71, 144.65, 137.2, 136.9, 134.11, 134.08, 132.6, 132.5, 131.6, 131.5, 130.3, 129.90, 129.86, 128.8, 128.7, 114.01, 113.95, 63.4, 62.9, 55.38, 55.35, 51.7, 51.4, 51.2, 38.6, 38.3, 37.2, 35.7, 21.78, 21.77, 21.74, 18.6; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{24}H_{28}NaO_4S^+$ 435.1601; found 435.1608.

3-Phenyl-2-(phenylethynyl)-4-(3-tosylbicyclo[1.1.1]pentan-1-yl)but-2-en-1-ol (4.4m)



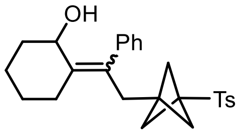
Yellowish oil (Method A, 39.4 mg, *Z/E* = 6:4, 84% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) **(*Z* -isomer)** δ 7.67 – 7.62 (m, 2H), 7.46 – 7.40 (m, 2H), 7.36 – 7.27 (m, 8H), 7.17 – 7.12 (m, 2H), 4.15 (d, *J* = 6.1 Hz, 2H), 3.06 (s, 2H), 2.42 (s, 3H), 1.80 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.7, 144.6, 139.3, 134.1, 131.6, 129.8, 128.69, 128.67, 128.6, 128.5, 128.4, 128.2, 123.0, 121.9, 95.4, 87.7, 62.5, 51.9, 51.5, 39.1, 38.6, 21.8; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{30}H_{28}NaO_3S^+$ 491.1651; found 491.1656; **^{1}H NMR** (400 MHz, $CDCl_3$) **(*E*-isomers)** δ 7.66 – 7.62 (m, 2H), 7.44 – 7.40 (m, 2H), 7.36 – 7.27 (m, 6H), 7.24 – 7.21 (m, 2H), 7.20 – 7.16 (m, 2H), 4.31 (s, 2H), 2.88 (s, 2H), 2.42 (s, 3H), 1.76 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.8, 144.6, 141.2, 134.0, 131.4, 129.8, 128.7, 128.4, 128.3, 128.1, 128.0, 123.1, 121.1, 93.5, 88.7, 62.0, 51.9, 51.2, 38.3, 35.1, 21.7; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{30}H_{28}NaO_3S^+$ 491.1651; found 491.1653.

1,2,3-Triphenyl-4-(3-tosylbicyclo[1.1.1]pentan-1-yl)but-2-en-1-ol (4.4n)



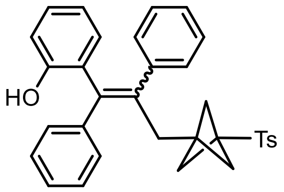
Yellowish oil (Method A, 37.7 mg, *Z/E* = 6:4, 72% yield); **^{1}H NMR** (500 MHz, $CDCl_3$) **(*Z*+*E*-isomers)** δ 7.68 – 7.63 (m, 2H), 7.63 – 7.60 (m, 1H), 7.42 – 7.37 (m, 3H), 7.35 – 7.26 (m, 9H), 7.25 – 7.14 (m, 6H), 7.05 – 6.89 (m, 10H), 6.80 – 6.71 (m, 3H), 5.91 (d, *J* = 7.2 Hz, 1H), 5.73 (d, *J* = 5.6 Hz, 1H), 3.12 – 2.97 (m, 2H), 2.43 (s, 3H), 2.42 (s, 3H), 1.94 (d, *J* = 7.4 Hz, 1H), 1.84 (d, *J* = 6.6 Hz, 1H), 1.81 – 1.76 (m, 6H), 1.65 – 1.54 (m, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) **(*Z*+*E*-isomers)** δ 144.6, 144.5, 142.5, 142.4, 141.9, 141.5, 141.2, 140.7, 137.9, 137.8, 136.7, 134.1, 131.3, 130.5, 129.80, 129.76, 129.4, 129.1, 128.8, 128.7, 128.6, 128.4, 127.9, 127.82, 127.78, 127.7, 127.6, 127.4, 127.3, 127.1, 126.7, 126.6, 126.0, 125.8, 73.1, 73.1, 52.0, 51.9, 51.4, 51.3, 38.4, 38.1, 37.4, 35.6, 21.77, 21.75; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{34}H_{32}NaO_3S^+$ 543.1964; found 543.1982.

2-(1-Phenyl-2-(3-tosylbicyclo[1.1.1]pentan-1-yl)ethylidene)cyclohexan-1-ol (4.4o)



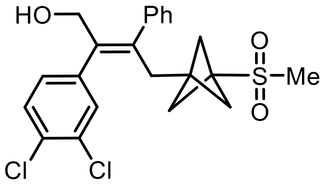
Yellowish oil (Method A, 35.0 mg, *Z/E* = 4:6, 83% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) **(*Z* -isomer)** δ 7.66 (d, *J* = 8.2 Hz, 2H), 7.33 – 7.26 (m, 4H), 7.24 – 7.18 (m, 1H), 7.10 – 7.01 (m, 2H), 4.37 (s, 1H), 2.64 (s, 2H), 2.43 (s, 3H), 2.40 – 2.25 (m, 2H), 1.89 – 1.79 (m, 3H), 1.76 (s, 6H), 1.60 – 1.39 (m, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.6, 142.3, 139.1, 134.1, 131.8, 129.8, 128.9, 128.7, 128.3, 126.9, 67.7, 61.0, 51.2, 38.6, 35.9, 34.5, 27.9, 25.7, 21.8, 20.1; $[M + Na]^+$ Calcd. for $C_{26}H_{30}NaO_3S^+$ 445.1808; found 445.1809; **^{1}H NMR** (400 MHz, $CDCl_3$) **(*E* -isomer)** δ 7.65 (d, *J* = 8.3 Hz, 2H), 7.32 – 7.27 (m, 3H), 7.26 – 7.25 (m, 1H), 7.23 – 7.18 (m, 1H), 7.06 – 7.01 (m, 2H), 4.70 (s, 1H), 2.86 – 2.78 (m, 1H), 2.63 – 2.55 (m, 1H), 2.42 (s, 3H), 2.24 – 2.16 (m, 1H), 2.12 – 1.98 (m, 2H), 1.83 – 1.77 (m, 1H), 1.74 (s, 6H), 1.70 (s, 1H), 1.63 – 1.49 (m, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.6, 142.6, 138.8, 134.1, 131.8, 129.8, 128.9, 128.7, 128.3, 126.8, 66.8, 51.9, 51.1, 38.7, 35.4, 34.8, 28.1, 26.6, 21.8, 20.1; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{26}H_{30}NaO_3S^+$ 445.1808; found 445.1805.

2-(1,2-Diphenyl-3-(3-tosylbicyclo[1.1.1]pentan-1-yl)prop-1-en-1-yl)phenol (4.4p)



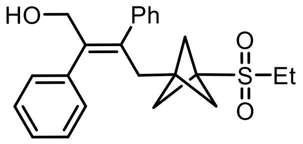
Yellowish solid (Method A, the reaction time was 2 h, 48.2 mg, *Z/E* = 1:1, 95% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) ***(Z+E*-isomers)** δ 7.67 – 7.58 (m, 4H), 7.32 – 7.27 (m, 6H), 7.21 – 7.17 (m, 3H), 7.16 – 7.02 (m, 16H), 6.96 – 6.92 (m, 3H), 6.90 – 6.86 (m, 2H), 6.69 – 6.60 (m, 2H), 5.17 – 5.05 (m, 2H), 2.85 (s, 2H), 2.72 (s, 2H), 2.43 (s, 3H), 2.42 (s, 3H), 1.72 (s, 6H), 1.64 (d, *J* = 9.9 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) ***(Z+E*-isomers)** δ 152.8, 152.1, 144.6, 144.5, 141.7, 140.8, 140.7, 140.4, 140.3, 139.1, 136.9, 135.6, 133.99, 133.97, 131.7, 130.6, 130.3, 129.79, 129.75, 129.6, 129.3, 129.20, 129.15, 128.9, 128.8, 128.7, 128.62, 128.61, 128.59, 128.3, 128.2, 128.1, 127.54, 127.50, 127.3, 126.9, 120.5, 120.3, 116.2, 115.8, 51.9, 51.8, 51.5, 51.4, 38.6, 38.4, 37.4, 36.1, 21.73, 21.71; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{33}H_{30}NaO_3S^+$ 529.1808; found 529.1813.

(*Z*)-2-(3,4-Dichlorophenyl)-4-(3-(methylsulfonyl)bicyclo[1.1.1]pentan-1-yl)-3-phenylbut-2-en-1-ol (4.5a)



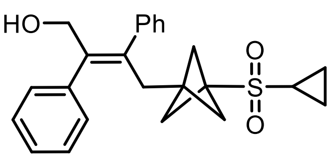
Yellowish oil (Method A, 31.4 mg, 72% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.4 Hz, 1H), 7.41 – 7.31 (m, 4H), 7.29 – 7.26 (m, 2H), 7.13 – 7.06 (m, 1H), 4.20 (s, 2H), 2.67 (s, 3H), 2.60 (s, 2H), 1.75 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.4, 139.8, 139.2, 137.4, 132.7, 131.6, 131.1, 130.6, 128.70, 128.65, 128.5, 128.1, 64.0, 51.4, 51.1, 37.6, 37.4, 36.6; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{22}H_{22}Cl_2NaO_3S^+$ 459.0559; found 459.0580.

(*Z*)-4-(3-(Ethylsulfonyl)bicyclo[1.1.1]pentan-1-yl)-2,3-diphenylbut-2-en-1-ol (4.5b)



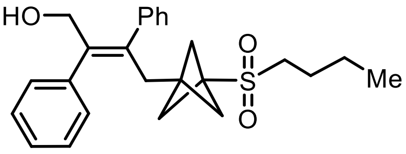
Yellowish oil (Method A, 29.8 mg, 78% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 – 7.27 (m, 8H), 7.25 – 7.20 (m, 2H), 4.24 (s, 2H), 2.80 (q, *J* = 7.5 Hz, 2H), 2.59 (s, 2H), 1.75 (d, *J* = 1.2 Hz, 6H), 1.27 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.4, 140.1, 139.5, 137.6, 129.0, 128.9, 128.7, 128.5, 127.7, 127.5, 64.4, 51.8, 50.4, 44.5, 38.2, 36.5, 6.1; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{23}H_{26}NaO_3S^+$ 405.1495; found 405.1508.

(*Z*)-4-(3-(Cyclopropylsulfonyl)bicyclo[1.1.1]pentan-1-yl)-2,3-diphenylbut-2-en-1-ol (4.5c)



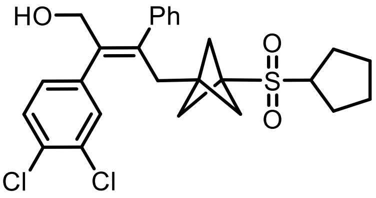
Yellowish oil (Method A, 32.3 mg, 82% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 – 7.28 (m, 8H), 7.25 – 7.20 (m, 2H), 4.24 (d, *J* = 4.7 Hz, 2H), 2.60 (s, 2H), 2.22 – 2.05 (m, 1H), 1.76 (s, 6H), 1.10 – 1.03 (m, 2H), 0.93 – 0.87 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.5, 140.1, 139.4, 137.7, 129.0, 128.9, 128.7, 128.5, 127.7, 127.4, 64.4, 51.7, 50.7, 38.4, 36.6, 26.3, 3.9; **HRMS** (ESI/TOF) *m/z*: [M + Na]$^+$ Calcd. for $C_{24}H_{26}NaO_3S^+$ 417.1495; found 417.1504.

(*Z*)-4-(3-(Butylsulfonyl)bicyclo[1.1.1]pentan-1-yl)-2,3-diphenylbut-2-en-1-ol (4.5d)



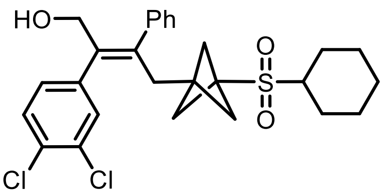
Yellowish oil (Method A, 33.4 mg, 81% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 – 7.42 (m, 1H), 7.41 – 7.35 (m, 4H), 7.33 – 7.29 (m, 3H), 7.25 – 7.20 (m, 2H), 4.24 (s, 2H), 2.80 – 2.71 (m, 2H), 2.59 (s, 2H), 1.74 (s, 6H), 1.73 – 1.66 (m, 2H), 1.43 – 1.35 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.4, 140.1, 139.5, 137.6, 129.0, 128.9, 128.7, 128.5, 127.7, 127.5, 64.4, 51.7, 50.7, 49.7, 38.1, 36.5, 23.3, 22.0, 13.6; **HRMS** (ESI/TOF) *m/z*: [M + Na]$^+$ Calcd. for $C_{25}H_{30}NaO_3S^+$ 433.1808; found 433.1821.

(*Z*)-4-(3-(Cyclopentylsulfonyl)bicyclo[1.1.1]pentan-1-yl)-2-(3,4-dichlorophenyl)-3-phenylbut-2-en-1-ol (4.5e)



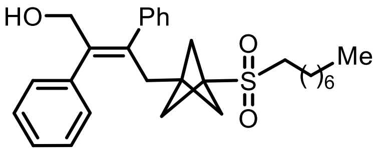
Yellowish oil (Method A, 31.0 mg, 63% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.2 Hz, 1H), 7.41 – 7.31 (m, 4H), 7.31 – 7.26 (m, 2H), 7.12 – 7.05 (m, 1H), 4.21 (s, 2H), 3.34 – 3.14 (m, 1H), 2.58 (s, 2H), 2.02 – 1.93 (m, 2H), 1.90 – 1.81 (m, 2H), 1.76 (s, 6H), 1.71 – 1.49 (m, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.5, 139.8, 139.4, 137.3, 132.8, 131.6, 131.1, 130.6, 128.72, 128.65, 128.6, 128.1, 64.0, 58.9, 52.1, 50.3, 38.4, 36.8, 26.9, 26.2; **HRMS** (ESI/TOF) *m/z*: [M + H]$^+$ Calcd. for $C_{26}H_{29}Cl_2O_3S^+$ 491.1209; found 491.1207.

(*Z*)-4-(3-(Cyclohexylsulfonyl)bicyclo[1.1.1]pentan-1-yl)-2-(3,4-dichlorophenyl)-3-phenylbut-2-en-1-ol (4.5f)



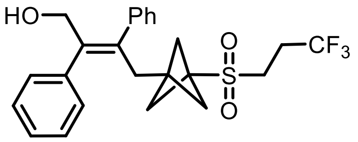
Yellowish oil (Method A, 35.5 mg, 70% yield); **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.48 (d, *J* = 8.2 Hz, 1H), 7.40 – 7.32 (m, 4H), 7.30 – 7.26 (m, 2H), 7.11 – 7.05 (m, 1H), 4.20 (s, 2H), 2.82 – 2.70 (m, 1H), 2.58 (s, 2H), 2.07 – 1.99 (m, 2H), 1.90 – 1.82 (m, 2H), 1.79 (s, 6H), 1.71 – 1.60 (m, 2H), 1.48 – 1.38 (m, 2H), 1.24 – 1.18 (m, 2H); **^{13}C NMR** (101 MHz, CDCl$_3$) δ 140.5, 139.8, 139.3, 137.3, 132.7, 131.6, 131.1, 130.6, 128.7, 128.64, 128.56, 128.1, 64.0, 59.8, 52.5, 50.2, 38.6, 36.8, 25.4, 25.2; **HRMS** (ESI/TOF) *m/z*: [M + H]$^+$ Calcd. for $C_{27}H_{31}Cl_2O_3S^+$ 505.1365; found 505.1373.

(*Z*)-4-(3-(Octylsulfonyl)bicyclo[1.1.1]pentan-1-yl)-2,3-diphenylbut-2-en-1-ol (4.5g)



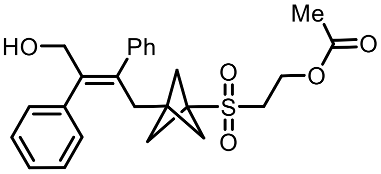
Yellowish oil (Method A, 31.0 mg, 66% yield); **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.44 – 7.29 (m, 8H), 7.25 – 7.20 (m, 2H), 4.24 (s, 2H), 2.79 – 2.70 (m, 2H), 2.60 (s, 2H), 1.75 (s, 6H), 1.73 – 1.67 (m, 2H), 1.33 – 1.25 (m, 10H), 0.88 (s, 3H); **^{13}C NMR** (101 MHz, CDCl$_3$) δ 140.4, 140.1, 139.5, 137.6, 129.1, 128.9, 128.7, 128.5, 127.7, 127.5, 64.4, 51.7, 50.6, 50.0, 38.1, 36.5, 31.8, 29.1, 29.0, 28.7, 22.7, 21.3, 14.2; **HRMS** (ESI/TOF) *m/z*: [M + Na]$^+$ Calcd. for $C_{29}H_{38}NaO_3S^+$ 489.2434; found 489.2443.

(*Z*)-2,3-Diphenyl-4-(3-((3,3,3-trifluoropropyl)sulfonyl)bicyclo[1.1.1]pentan-1-yl)but-2-en-1-ol (4.5h)



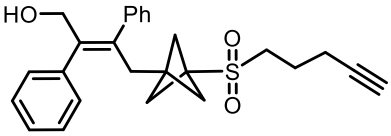
Yellowish oil (Method A, 30.3 mg, 67% yield); **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.45 – 7.29 (m, 8H), 7.25 – 7.21 (m, 2H), 4.26 (s, 2H), 3.03 – 2.92 (m, 2H), 2.62 (s, 2H), 2.60 – 2.47 (m, 2H), 1.78 (s, 6H); **^{13}C NMR** (101 MHz, CDCl$_3$) δ 140.3, 140.0, 139.7, 137.4, 129.0, 128.9, 128.8, 128.6, 127.9, 127.6, 125.6 (q, *J* = 276.3 Hz), 64.4, 51.8, 50.8, 42.9 (q, *J* = 2.9 Hz), 38.4, 36.4, 26.7 (q, *J* = 31.5 Hz); **HRMS** (ESI/TOF) *m/z*: [M + Na]$^+$ Calcd. for $C_{24}H_{25}F_3NaO_3S^+$ 473.1369; found 473.1379.

(*Z*)-2-((3-(4-Hydroxy-2,3-diphenylbut-2-en-1-yl)bicyclo[1.1.1]pentan-1-yl)sulfonyl)-ethyl acetate (4.5i)



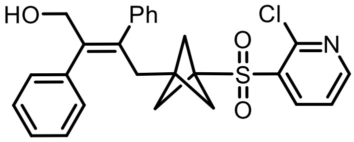
Yellowish oil (Method A, 38.1 mg, 86% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 – 7.35 (m, 5H), 7.34 – 7.29 (m, 3H), 7.25 – 7.20 (m, 2H), 4.37 (t, *J* = 6.5 Hz, 2H), 4.25 (s, 2H), 3.12 (t, *J* = 6.5 Hz, 2H), 2.61 (s, 2H), 2.02 (s, 3H), 1.77 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.5, 140.4, 140.1, 139.6, 137.5, 129.0, 128.9, 128.8, 128.6, 127.8, 127.5, 64.4, 57.0, 51.6, 51.1, 49.2, 38.1, 36.5, 20.9; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{25}H_{28}NaO_5S^+$ 463.1550; found 463.1562.

(*Z*)-4-(3-(Pent-4-yn-1-ylsulfonyl)bicyclo[1.1.1]pentan-1-yl)-2,3-diphenylbut-2-en-1-ol (4.5j)



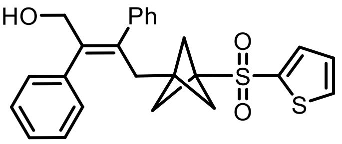
Yellowish oil (Method A, 25.2 mg, 60% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 – 7.35 (m, 5H), 7.33 – 7.29 (m, 3H), 7.25 – 7.20 (m, 2H), 4.24 (s, 2H), 2.95 – 2.86 (m, 2H), 2.60 (s, 2H), 2.36 – 2.28 (m, 2H), 1.99 (t, *J* = 2.6 Hz, 1H), 1.98 – 1.90 (m, 2H), 1.77 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.4, 140.1, 139.5, 137.6, 129.04, 128.9, 128.7, 128.6, 127.8, 127.5, 82.1, 70.3, 64.4, 51.7, 50.8, 48.7, 38.2, 36.5, 20.6, 17.6; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{26}H_{28}NaO_3S^+$ 443.1651; found 443.1648.

(*Z*)-4-(3-((2-Chloropyridin-3-yl)sulfonyl)bicyclo[1.1.1]pentan-1-yl)-2,3-diphenylbut-2-en-1-ol (4.5k)



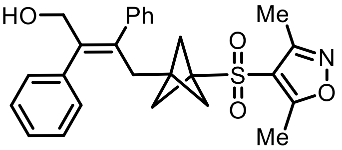
Yellowish oil (Method A, 24.1 mg, 52% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.59 – 8.54 (m, 1H), 8.32 – 8.26 (m, 1H), 7.44 – 7.26 (m, 9H), 7.22 – 7.16 (m, 2H), 4.23 (s, 2H), 2.57 (s, 2H), 1.75 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.6, 149.9, 141.6, 140.3, 140.0, 139.6, 137.5, 133.3, 129.0, 128.80, 128.75, 128.6, 127.8, 127.5, 122.9, 64.4, 52.5, 52.4, 38.1, 36.4; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{26}H_{25}ClNO_3S^+$ 466.1238; found 466.1240.

(*Z*)-2,3-Diphenyl-4-(3-(thiophen-2-ylsulfonyl)bicyclo[1.1.1]pentan-1-yl)but-2-en-1-ol (4.5l)



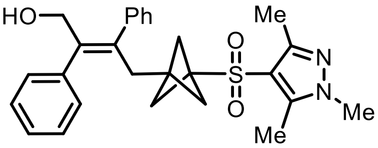
Yellowish oil (Method A, 36.6 mg, 84% yield); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.52 (dd, *J* = 3.8, 1.3 Hz, 1H), 7.41 – 7.29 (m, 6H), 7.27 – 7.24 (m, 2H), 7.21 – 7.17 (m, 2H), 7.13 – 7.09 (m, 1H), 4.21 (s, 2H), 2.55 (s, 2H), 1.63 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 140.4, 140.0, 139.4, 137.9, 137.6, 134.3, 134.2, 129.0, 128.8, 128.7, 128.5, 128.0, 127.7, 127.4, 64.4, 52.6, 51.4, 37.7, 36.5; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{25}H_{24}NaO_3S_2^+$ 459.1059; found 459.1063.

(*Z*)-4-(3-((3,5-Dimethylisoxazol-4-yl)sulfonyl)bicyclo[1.1.1]pentan-1-yl)-2,3-diphenylbut-2-en-1-ol (4.5m)



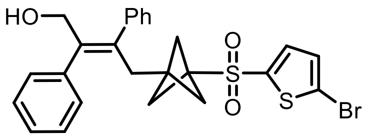
Yellowish oil (Method A, 38.5 mg, 86% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 – 7.27 (m, 8H), 7.22 – 7.16 (m, 2H), 4.22 (s, 2H), 2.58 (s, 2H), 2.51 (s, 3H), 2.27 (s, 3H), 1.63 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.1, 158.5, 140.3, 140.0, 139.6, 137.4, 129.0, 128.8, 128.7, 128.6, 127.8, 127.5, 113.3, 64.3, 52.8, 50.9, 38.3, 36.4, 12.6, 11.0; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{26}H_{28}NO_4S^+$ 450.1734; found 450.1731.

(*Z*)-2,3-Diphenyl-4-(3-((1,3,5-trimethyl-1*H*-pyrazol-4-yl)sulfonyl)bicyclo[1.1.1]-pentan-1-yl)but-2-en-1-ol (4.5n)



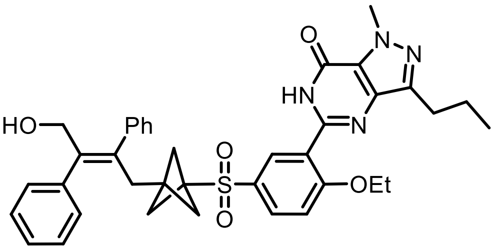
Yellowish oil (Method A, 18.8 mg, 41% yield); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.42 – 7.26 (m, 8H), 7.23 – 7.19 (m, 2H), 4.24 (s, 2H), 3.71 (s, 3H), 2.56 (s, 2H), 2.33 (s, 3H), 2.25 (s, 3H), 1.59 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 149.2, 143.3, 140.5, 140.1, 139.3, 137.8, 129.1, 128.8, 128.7, 128.5, 127.7, 127.5, 112.7, 64.5, 52.9, 50.8, 38.0, 36.7, 36.4, 13.1, 10.6; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{27}H_{30}N_2NaO_3S^+$ 485.1869; found 485.1877.

(*Z*)-4-(3-((5-Bromothiophen-2-yl)sulfonyl)bicyclo[1.1.1]pentan-1-yl)-2,3-diphenylbut-2-en-1-ol (4.5o)



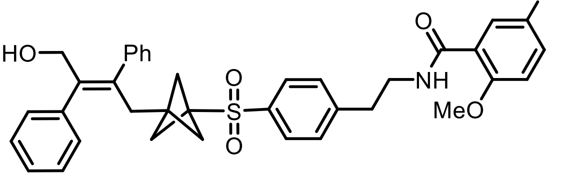
Yellowish oil (Method A, 31.3 mg, 61% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 – 7.31 (m, 6H), 7.28 – 7.25 (m, 3H), 7.22 – 7.18 (m, 2H), 7.10 – 7.07 (m, 1H), 4.23 (d, *J* = 5.3 Hz, 2H), 2.57 (s, 2H), 1.64 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.3, 140.0, 139.5, 138.8, 137.5, 134.6, 131.1, 129.0, 128.8, 128.7, 128.5, 127.8, 127.5, 122.2, 64.4, 52.5, 51.4, 37.8, 36.5; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{25}H_{23}BrNaO_3S_2^+$ 537.0164; found 537.0162.

(*Z*)-5-(2-Ethoxy-5-((3-(4-hydroxy-2,3-diphenylbut-2-en-1-yl)bicyclo[1.1.1]pentan-1-yl)sulfonyl)-phenyl)-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-d]pyrimidin-7-one (4.5p)



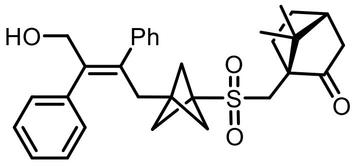
Yellowish solid (Method A, 48.8 mg, 73% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.80 (s, 1H), 8.72 (s, 1H), 7.76 (ddd, *J* = 8.8, 2.4, 1.4 Hz, 1H), 7.37 – 7.27 (m, 5H), 7.26 – 7.21 (m, 3H), 7.20 – 7.14 (m, 2H), 7.08 (d, *J* = 8.7 Hz, 1H), 4.33 (q, *J* = 6.9 Hz, 2H), 4.23 (s, 3H), 4.19 (s, 2H), 2.90 (t, *J* = 7.5 Hz, 2H), 2.53 (s, 2H), 1.83 (q, *J* = 7.5 Hz, 2H), 1.63 (s, 6H), 1.60 (d, *J* = 7.0 Hz, 3H), 1.00 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.9, 153.7, 147.1, 146.5, 140.4, 140.1, 139.5, 138.4, 137.5, 132.3, 132.0, 130.2, 129.0, 128.8, 128.6, 128.4, 127.6, 127.3, 124.5, 121.3, 113.1, 66.2, 64.3, 51.9, 51.3, 38.4, 38.3, 36.6, 27.7, 22.3, 14.6, 14.1; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{38}H_{41}N_4O_5S^+$ 665.2792; found 665.2777.

(*Z*)-5-Chloro-*N*-(4-((3-(4-hydroxy-2,3-diphenylbut-2-en-1-yl)bicyclo[1.1.1]pentan-1-yl)sulfonyl)-phenethyl)-2-methoxybenzamide (4.5q)



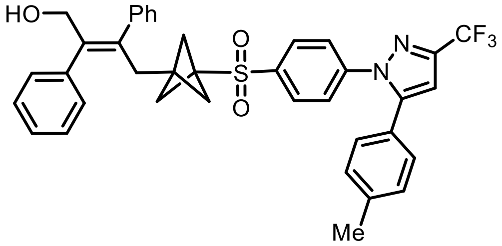
Yellowish solid (Method A, 52.1 mg, 81% yield); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 2.7 Hz, 1H), 7.65 (d, *J* = 8.3 Hz, 2H), 7.37 – 7.33 (m, 6H), 7.32 – 7.27 (m, 3H), 7.24 (d, *J* = 6.7 Hz, 2H), 7.19 – 7.17 (m, 2H), 6.85 (d, *J* = 8.8 Hz, 1H), 4.20 (d, *J* = 4.5 Hz, 2H), 3.74 (s, 3H), 3.72 – 3.68 (m, 2H), 2.98 (t, *J* = 6.9 Hz, 2H), 2.52 (s, 2H), 1.57 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 164.1, 156.0, 145.7, 140.4, 140.1, 139.4, 137.5, 135.2, 132.5, 131.9, 129.6, 129.0, 128.79, 128.78, 128.6, 128.4, 127.6, 127.4, 126.8, 122.7, 113.0, 64.3, 56.3, 51.8, 51.2, 40.7, 38.3, 36.5, 35.6; **HRMS** (ESI/TOF) *m/z*: [M + Na]$^+$ Calcd. for $C_{37}H_{36}ClNNaO_5S^+$ 664.1895; found 664.1894.

(1*S*,4*R*)-1-(((3-((*Z*)-4-Hydroxy-2,3-diphenylbut-2-en-1-yl)bicyclo[1.1.1]pentan-1-yl)sulfonyl)-methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one (4.5r)



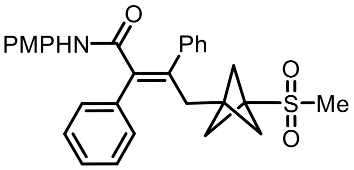
Yellowish oil (Method A, 22.5 mg, 45% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 – 7.29 (m, 8H), 7.26 – 7.22 (m, 2H), 4.26 (s, 2H), 3.25 (d, *J* = 14.5 Hz, 1H), 2.61 (s, 2H), 2.57 – 2.51 (m, 1H), 2.41 – 2.28 (m, 1H), 2.09 – 2.04 (m, 1H), 2.03 – 1.97 (m, 1H), 1.79 (s, 6H), 1.60 – 1.53 (m, 3H), 1.41 – 1.35 (m, 1H), 1.10 (s, 3H), 0.84 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 215.1, 140.5, 140.1, 139.5, 137.8, 129.1, 128.9, 128.8, 128.6, 127.8, 127.5, 64.5, 58.7, 52.1, 51.7, 48.0, 45.4, 42.8, 42.7, 37.7, 36.6, 27.0, 24.8, 20.3, 19.9; **HRMS** (ESI/TOF) *m/z*: [M + Na]$^+$ Calcd. for $C_{31}H_{36}NaO_4S^+$ 527.2227; found 527.2227.

(*Z*)-2,3-Diphenyl-4-(3-((4-(5-(*p*-tolyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)-sulfonyl)-bicyclo-[1.1.1]pentan-1-yl)but-2-en-1-ol (4.5s)



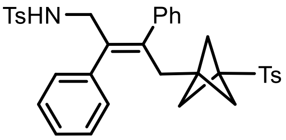
Yellowish oil (Method A, 58.6 mg, 89% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76 – 7.66 (m, 2H), 7.48 – 7.43 (m, 2H), 7.40 – 7.28 (m, 6H), 7.26 – 7.24 (m, 2H), 7.20 – 7.11 (m, 4H), 7.09 – 7.03 (m, 2H), 6.75 (s, 1H), 4.20 (s, 2H), 2.54 (s, 2H), 2.37 (s, 3H), 1.57 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.5, 144.3 (q, *J* = 38.6 Hz), 143.3, 140.3, 140.0, 139.9, 139.5, 137.4, 136.5, 129.8, 129.6, 128.9, 128.7, 128.6, 128.5, 127.7, 127.4, 125.61, 125.56, 121.1 (q, *J* = 269.2 Hz), 106.4 (q, *J* = 1.9 Hz), 64.3, 51.7, 51.3, 38.5, 36.5, 21.4; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.5; **HRMS** (ESI/TOF) *m/z*: [M + Na]$^+$ Calcd. for $C_{38}H_{33}F_3N_2NaO_3S^+$ 677.2056; found 677.2066.

(*Z*)-*N*-(4-Methoxyphenyl)-4-(3-(methylsulfonyl)bicyclo[1.1.1]pentan-1-yl)-2,3-diphenylbut-2-enamide (4.7a)



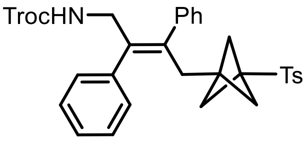
Yellowish oil (Method A, 25.5 mg, 52% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 – 7.40 (m, 4H), 7.39 – 7.32 (m, 6H), 6.90 (d, *J* = 9.0 Hz, 2H), 6.75 (s, 1H), 6.69 (d, *J* = 9.0 Hz, 2H), 3.71 (s, 3H), 2.79 (s, 2H), 2.69 (s, 3H), 1.80 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.2, 156.7, 140.3, 140.1, 139.0, 137.2, 130.4, 129.2, 129.1, 128.8, 128.7, 128.2, 127.9, 122.1, 114.0, 55.5, 51.6, 51.1, 37.5, 37.5, 35.6; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{29}H_{29}NNaO_4S^+$ 510.1710; found 510.1725.

(*Z*)-*N*-(2,3-diphenyl-4-(3-tosylbicyclo[1.1.1]pentan-1-yl)but-2-en-1-yl)-4-methylbenzenesulfonamide (4.7b)



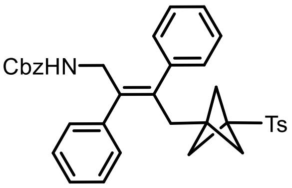
Yellowish oil (Method A, 33.6 mg, 56% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61 – 7.57 (m, 2H), 7.38 (d, *J* = 8.3 Hz, 2H), 7.33 – 7.26 (m, 8H), 7.16 – 7.13 (m, 2H), 7.10 – 7.06 (m, 2H), 7.01 – 6.97 (m, 2H), 4.17 (t, *J* = 6.0 Hz, 1H), 3.71 (d, *J* = 6.0 Hz, 2H), 2.45 (s, 2H), 2.41 (d, *J* = 5.8 Hz, 6H), 1.53 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.6, 143.3, 139.9, 139.2, 138.9, 136.4, 134.6, 134.0, 129.8, 129.6, 128.88, 128.86, 128.7, 128.6, 128.5, 127.8, 127.7, 127.2, 51.9, 51.2, 46.6, 38.1, 36.8, 21.8, 21.6; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{35}H_{35}NNaO_4S_2^+$ 620.1900; found 620.1905.

2,2,2-Trichloroethyl (*Z*)-(2,3-diphenyl-4-(3-tosylbicyclo[1.1.1]pentan-1-yl)but-2-en-1-yl)carba-mate (4.7c)



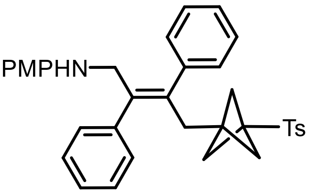
Yellowish oil (Method A, 31.6 mg, 51% yield); **^{1}H NMR** (500 MHz, $CDCl_3$) (major) δ 7.60 (d, *J* = 8.3 Hz, 2H), 7.37 – 7.34 (m, 4H), 7.32 – 7.27 (m, 4H), 7.23 – 7.20 (m, 2H), 7.17 – 7.11 (m, 2H), 4.57 (s, 2H), 4.04 (d, *J* = 6.0 Hz, 2H), 2.51 (s, 2H), 2.42 (s, 3H), 1.57 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.1, 144.5, 140.3, 139.3, 138.3, 136.1, 134.1, 129.8, 129.0, 128.8, 128.72, 128.68, 128.6, 127.8, 127.6, 74.5, 51.9, 51.2, 44.7, 38.2, 37.0, 21.8; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{31}H_{30}Cl_3NNaO_4S^+$ 640.0853; found 640.0880.

Benzyl-(*Z*)-(2,3-diphenyl-4-(3-tosylbicyclo[1.1.1]pentan-1-yl)but-2-en-1-yl)-carbamate (4.7d)



Yellowish oil (Method A, 33.3 mg, 58% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.3 Hz, 2H), 7.38 – 7.27 (m, 12H), 7.22 (d, *J* = 7.1 Hz, 3H), 7.11 (d, *J* = 7.3 Hz, 2H), 4.95 (s, 2H), 4.48 (s, 1H), 4.01 (d, *J* = 5.9 Hz, 2H), 2.50 (s, 2H), 2.42 (s, 3H), 1.57 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.9, 144.5, 140.4, 139.6, 137.8, 136.5, 134.1, 129.8, 128.9, 128.71, 128.67, 128.61, 128.56, 128.2, 128.1, 127.7, 127.5, 66.6, 51.9, 51.2, 44.6, 38.2, 36.9, 21.7; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{36}H_{35}NNaO_4S^+$ 600.2179; found 600.2181.

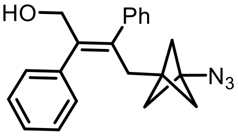
(*Z*)-*N*-(2,3-Diphenyl-4-(3-tosylbicyclo[1.1.1]pentan-1-yl)but-2-en-1-yl)-4-methoxyaniline (4.7e)



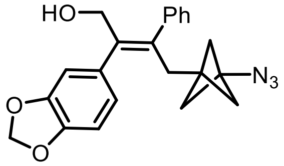
Yellowish oil (Method A, 36.0 mg, 65% yield); **^{1}H NMR** (500 MHz, $CDCl_3$) (major) δ 7.60 (d, *J* = 8.3 Hz, 2H), 7.40 – 7.26 (m, 9H), 7.26 – 7.24 (m, 1H), 7.10 – 7.06 (m, 2H), 6.64 (d, *J* = 8.9 Hz, 2H), 6.22 (d, *J* = 9.0 Hz, 2H), 3.87 (s, 2H), 3.70 (s, 3H), 2.49 (s, 2H), 2.42 (s, 3H), 1.56 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 152.2, 144.5, 141.9, 140.7, 140.3, 137.6, 137.5, 134.1, 129.7, 128.94, 128.92, 128.62, 128.57, 128.5, 127.6, 127.3, 114.8, 114.7, 55.9, 51.9, 51.2, 48.2, 38.3, 36.8, 21.7; **HRMS** (MALDI/TOF) *m/z*: $[M-C_{12}H_{13}O_2S + Na]^+$ Calcd. for $C_{23}H_{23}NNaO^+$ 352.1672; found 352.1688; Note that here molecular fragments were found as this product easily decomposes and cannot be kept for a long time.

(*Z*)-4-(3-Azidobicyclo[1.1.1]pentan-1-yl)-2,3-diphenylbut-2-en-1-ol (4.8a)

Yellowish oil (Method B, 17.5 mg, 53% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 – 7.29 (m, 8H), 7.26 – 7.23 (m, 2H), 4.25 (s, 2H), 2.61 (s, 2H), 1.53 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.7, 140.2, 138.8, 130.1, 129.2, 128.9, 128.7, 128.4, 127.5, 127.4, 64.6, 53.2, 50.3, 35.5, 34.1; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{21}H_{21}N_3NaO^+$ 354.1577; found 354.1570.

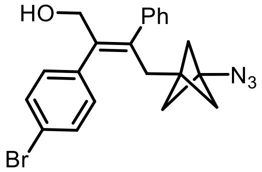


(*Z*)-4-(3-Azidobicyclo[1.1.1]pentan-1-yl)-2-(benzo[*d*][1,3]dioxol-5-yl)-3-phenylbut-2-en-1-ol (4.8b)



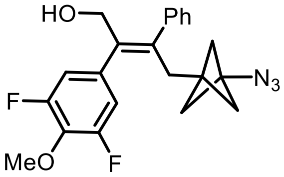
Yellowish oil (Method B, 20.0 mg, 53% yield, *Z/E* = 9:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.26 (m, 5H), 6.85 (d, *J* = 7.8 Hz, 1H), 6.75 – 6.67 (m, 2H), 6.00 (s, 2H), 4.20 (s, 2H), 2.64 (s, 2H), 1.53 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.0, 146.9, 140.7, 139.1, 138.3, 133.8, 128.9, 128.4, 127.5, 122.4, 109.6, 108.5, 101.2, 64.5, 53.2, 51.3, 35.5, 34.1; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{22}H_{21}N_3NaO_3^+$ 398.1475; found 398.1472.

(*Z*)-4-(3-Azidobicyclo[1.1.1]pentan-1-yl)-2-(4-bromophenyl)-3-phenylbut-2-en-1-ol (4.8c)



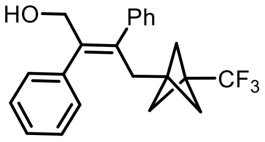
Yellowish oil (Method B, 30.0 mg, 73% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 – 7.51 (m, 2H), 7.40 – 7.27 (m, 5H), 7.16 – 7.11 (m, 2H), 4.22 (s, 2H), 2.59 (s, 2H), 1.52 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.4, 139.6, 139.3, 137.7, 131.8, 130.9, 128.8, 128.5, 127.7, 121.5, 64.3, 53.2, 51.3, 35.5, 34.0; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{21}H_{20}BrN_3NaO^+$ 432.0682; found 432.0678.

(*Z*)-4-(3-Azidobicyclo[1.1.1]pentan-1-yl)-2-(3,5-difluoro-4-methoxyphenyl)-3-phenylbut-2-en-1-ol (4.8d)



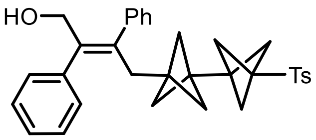
Yellowish oil (Method B, 24.1 mg, 61% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 – 7.30 (m, 3H), 7.28 – 7.27 (m, 1H), 7.25 (t, *J* = 1.5 Hz, 1H), 6.86 – 6.78 (m, 2H), 4.19 (s, 2H), 4.04 (s, 3H), 2.62 (s, 2H), 1.54 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.7 (dd, *J* = 249.3, 6.5 Hz), 140.4, 140.1, 136.6 (dd, *J* = 1.5, 1.5 Hz), 135.6 (dd, *J* = 7.9, 7.9 Hz), 135.5 (dd, *J* = 8.8, 8.8 Hz), 128.8, 128.5, 127.9, 113.1 (dd, *J* = 7.1, 16.2 Hz), 64.2, 62.0 (dd, *J* = 3.3, 3.3 Hz), 53.2, 51.3, 35.6, 34.0; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -128.5; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{22}H_{21}F_2N_3NaO_2^+$ 420.1494; found 420.1476.

(*Z*)-2,3-Diphenyl-4-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)but-2-en-1-ol (4.8e)



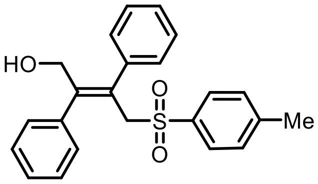
Yellowish oil (Method C, 15.4 mg, 43% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 – 7.28 (m, 8H), 7.26 – 7.23 (m, 2H), 4.26 (s, 2H), 2.55 (s, 2H), 1.51 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.8, 140.2, 139.0, 138.4, 128.9, 128.7, 128.4, 127.6, 127.4, 122.7 (q, *J* = 276.7 Hz), 64.6, 49.4 (q, *J* = 2.0 Hz), 38.5 (q, *J* = 1.8 Hz), 37.4 (q, *J* = 37.6 Hz), 36.8, 29.9; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -73.4; **HRMS** (APCI/TOF) *m/z*: [M - OH] Calcd. for $C_{22}H_{20}F_3$· 341.1517; found 341.1513.

(*Z*)-2,3-Diphenyl-4-(3'-tosyl-[1,1'-bi(bicyclo[1.1.1]pentan)]-3-yl)but-2-en-1-ol (4.4aa)



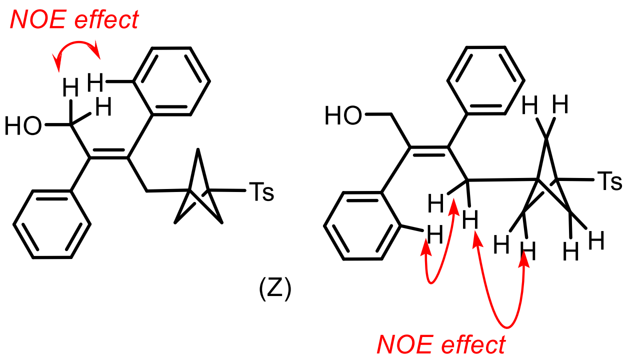
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.2 Hz, 2H), 7.41 – 7.26 (m, 10H), 7.25 – 7.21 (m, 2H), 4.22 (s, 2H), 2.45 (s, 2H), 2.42 (s, 3H), 1.72 (s, 6H), 1.14 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.5, 141.2, 140.5, 139.3, 138.3, 134.1, 129.8, 129.2, 129.0, 128.7, 128.5, 128.2, 127.3, 127.2, 64.6, 51.0, 50.1, 49.6, 38.6, 38.5, 37.9, 37.5, 21.7; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{33}H_{34}NaO_3S^+$ 533.2121; found 533.2129.

(*E*)-2,3-Diphenyl-4-tosylbut-2-en-1-ol (4.10)



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.35 (m, 4H), 7.31 – 7.26 (m, 4H), 7.24 – 7.20 (m, 2H), 7.13 – 7.09 (m, 2H), 4.23 (s, 2H), 4.16 (s, 2H), 2.37 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.1, 144.2, 138.3, 138.0, 137.3, 129.6, 129.2, 129.1, 129.0, 128.8, 128.4, 128.00, 127.96, 127.9, 64.1, 62.5, 21.6; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{23}H_{22}NaO_3S^+$ 401.1182; found 401.1180.

GOESY analysis of product 4.4a:



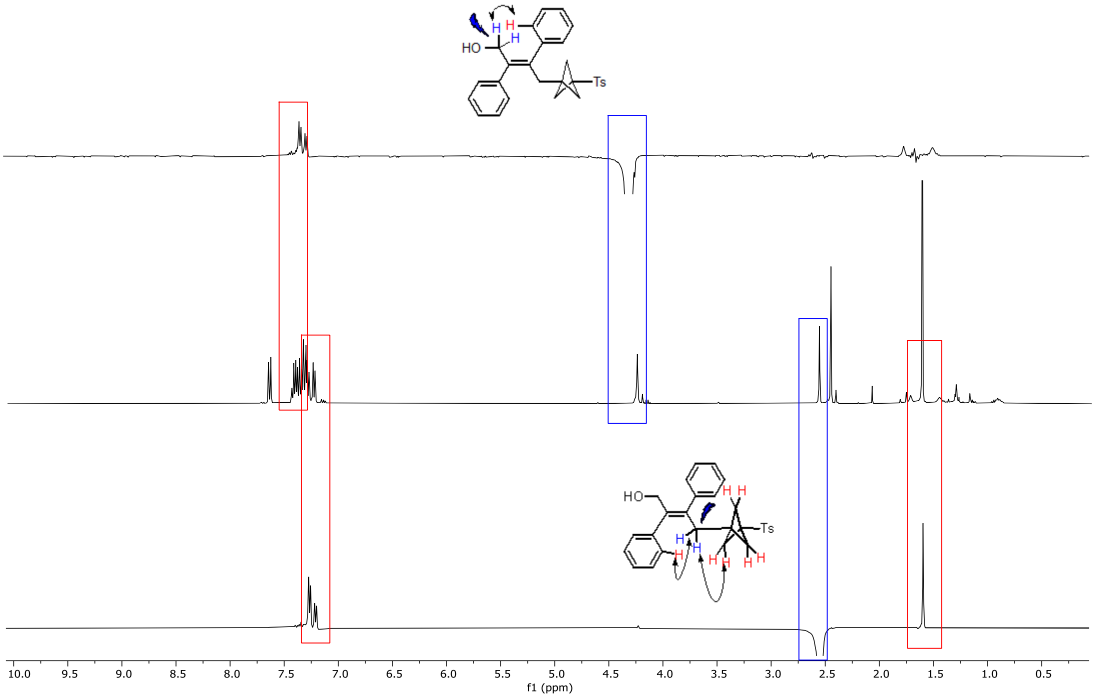
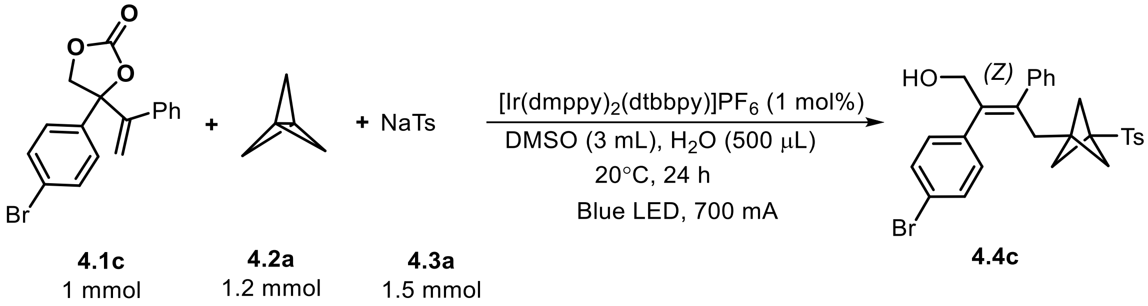


Figure S4.1. ^1H-^1H GOESY NMR spectrum of **4.4a**.

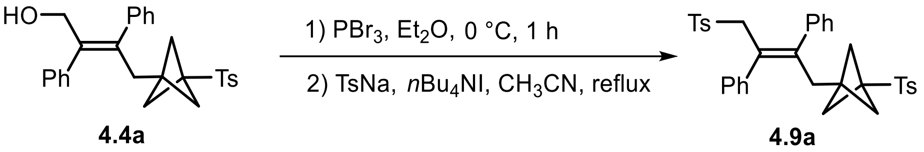
4.4.6. Scale up of the synthesis of 4.4c



Method A: [Ir(dmppy)$_2$(dtbbpy)]PF$_6$ (9.0 mg, 1 mol%), VCC **4.1c** (345 mg, 1 mmol) and NaTs (267 mg, 1.5 mmol) were weighed into a 10 mL screw-cap vial. The reaction vial was sealed with a cap containing a silicone septum, evacuated, and filled with Ar three times. Then degassed DMSO (3 mL), H_2O (500 µL) and [1,1,1]-propellane **4.2a** (8 mL, 0.15 M in pentane, 1.2 mmol) were added affording a light-yellow solution under an Ar atmosphere. The reaction system was further sealed with Parafilm® and irradiated for 24 h at 20 °C using a single high-power blue LED (λ_{em} = 445 nm, 700 mA) from the bottom. After completion, the mixture was directly extracted with EtOAc (20 mL). The organic phrase was collected and evaporated to dryness, after which the residue was purified by acid-neutralized column chromatography (SiO_2, hexanes/EtOAc) to afford product **4.4c** in 70% (366 mg).

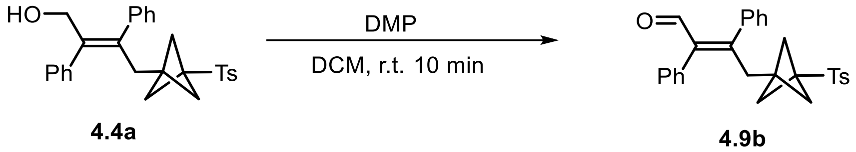
4.4.7. Post-synthetic transformations

***(Z)*-1-(2,3-Diphenyl-4-tosylbut-2-en-1-yl)-3-tosylbicyclo[1.1.1]pentane (4.9a)**



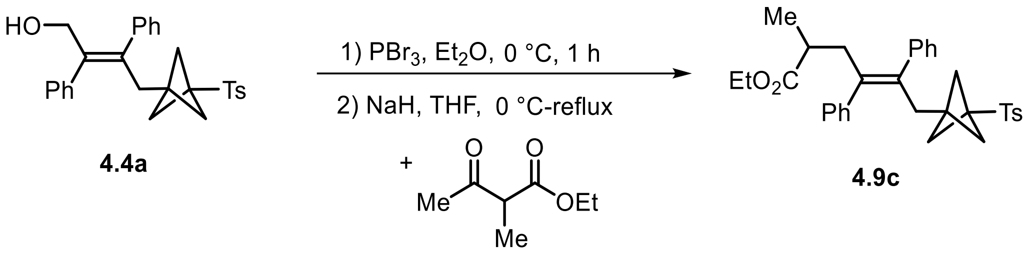
To a solution of allylic alcohol product **4.4a** (133.5 mg, 0.3 mmol, 1.0 equiv) in Et_2O (9 mL) was added PBr_3 (142.5 µL, 1.5 mmol, 1.5 equiv) dropwise at 0 ºC. The mixture was stirred at the same temperature for 1 h and then quenched by a saturated NH_4Cl aqueous solution (10 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and evaporated. The crude mixture was purified by flash column chromatography (hexane/EtOAc). The freshly prepared allylic bromide (50.7 mg, 0.1 mmol, 1.0 equiv), sodium *p*-toluenesulfinate (21.4 mg, 0.12 mmol, 1.2 equiv) and tetrabutylammonium iodide (7.4 mg, 0.02 mmol, 0.2 equiv) were dissolved into 1 mL of CH_3CN. The mixture was refluxed for 12 h and concentrated to dryness. The residue was purified by flash column chromatography (hexane/EtOAc) to afford the pure product **4.9a** (40.6 mg, 70% yield); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.64 – 7.59 (m, 2H), 7.41 – 7.35 (m, 2H), 7.34 – 7.27 (m, 6H), 7.26 – 7.20 (m, 4H), 7.15 – 7.07 (m, 4H), 4.14 (s, 2H), 2.56 (s, 2H), 2.43 (s, 3H), 2.36 (s, 3H), 1.62 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.6, 144.14, 144.07, 140.0, 139.2, 137.7, 134.0, 129.8, 129.6, 129.14, 128.73, 128.67, 128.6, 128.5, 128.3, 128.0, 127.8, 127.6, 62.9, 51.9, 51.3, 38.1, 37.3, 21.8, 21.6; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{35}H_{34}NaO_4S_2^+$ 605.1791; found 605.1785.

(*Z*)-2,3-Diphenyl-4-(3-tosylbicyclo[1.1.1]pentan-1-yl)but-2-enal (4.9b)



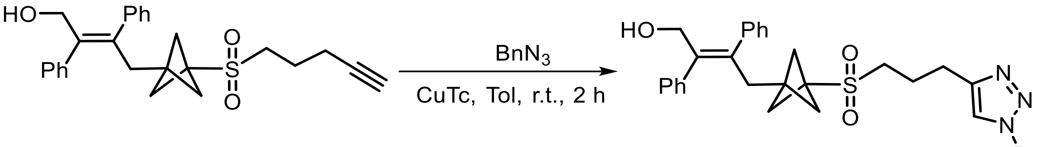
To a solution of allylic alcohol product **4.4a** (44.5 mg, 0.1 mmol, 1.0 equiv) in DCM (1 mL) was added DMP (46.7 mg, 0.11 mmol, 1.1 equiv). The mixture was stirred for 10 min and was then concentrated to dryness. The residue was purified by flash column chromatography (hexane/EtOAc) to afford the pure product **4.9b** (33.7 mg, 76% yield) as a colorless oil; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.64 (s, 1H), 7.63 – 7.58 (m, 2H), 7.44 – 7.38 (m, 5H), 7.35 – 7.28 (m, 5H), 7.08 – 7.05 (m, 2H), 2.80 (s, 2H), 2.42 (s, 3H), 1.61 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 192.8, 158.2, 144.7, 141.7, 137.4, 135.0, 133.9, 129.83, 129.79, 129.74, 129.72, 128.8, 128.6, 128.5, 128.1, 51.9, 51.4, 38.1, 37.8, 21.8; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{28}H_{26}NaO_3S^+$ 465.1495; found 465.1481.

Ethyl-(*E*)-2-methyl-4,5-diphenyl-6-(3-tosylbicyclo[1.1.1]pentan-1-yl)hex-4-enoate (4.9c)



Ethyl-2-methyl-3-oxobutanoate (17.3 mg, 0.12 mmol, 1.2 equiv) was dissolved into 1 mL of THF, and then NaH (60%, 6.0 mg, 0.15 mmol, 1.5 equiv) was added. The mixture was stirred for 30 min at 0 ºC before the freshly prepared allylic bromide (50.7 mg, 0.1 mmol, 1.0 equiv) was added. The mixture was then "refluxed" for 48 h and cooled to room temperature. Water was added and the mixture was extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated. The residue was purified by flash column chromatography (hexane/EtOAc) to afford product **4.9c** (32.0 mg, 61% yield) as light yellow oil; **^{1}H NMR** (300 MHz, $CDCl_3$) (major) δ 7.62 – 7.58 (m, 2H), 7.38 – 7.26 (m, 7H), 7.25 – 7.22 (m, 1H), 7.19 – 7.09 (m, 4H), 3.94 – 3.85 (m, 2H), 2.72 – 2.63 (m, 1H), 2.48 (d, *J* = 4.6 Hz, 2H), 2.41 (s, 3H), 2.41 – 2.36 (m, 1H), 2.22 – 2.14 (m, 1H), 1.56 (s, 6H), 1.13 – 1.09 (m, 3H), 0.94 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 176.1, 144.5, 141.5, 141.1, 138.0, 136.4, 134.1, 129.7, 129.1, 128.9, 128.6, 128.40, 128.37, 127.03, 126.98, 60.2, 51.9, 51.2, 38.42, 38.39, 37.9, 37.2, 21.7, 16.8, 14.2; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{33}H_{36}NaO_4S^+$ 551.2227; found 551.2241.

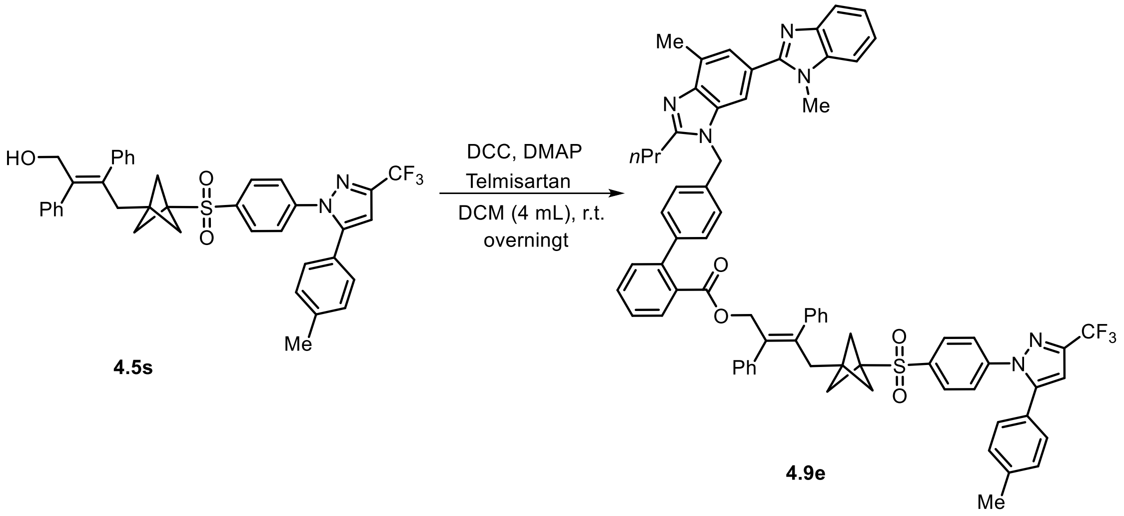
(*Z*)-4-(3-((3-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propyl)sulfonyl)bicyclo[1.1.1]pentan-1-yl)-2,3-diphe-nylbut-2-en-1-ol (4.9d)



4.5j **4.9d**

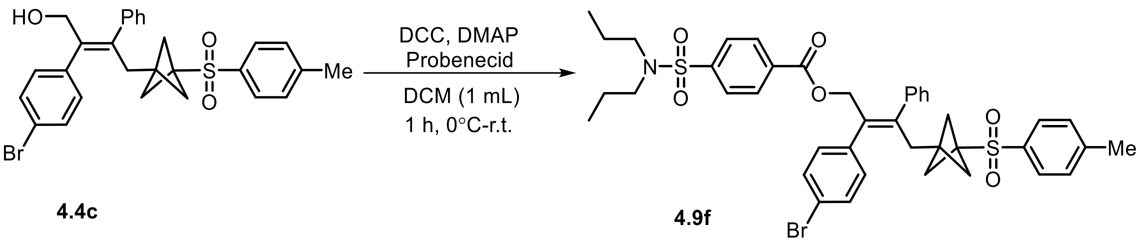
To a solution of allylic alcohol product **4.5j** (44.5 mg, 0.1 mmol, 1.0 equiv) and CuTc (1.9 mg, 10%) in toluene (1 mL) was added a 1 mL toluene solution of BnN_3 (17.3 mg, 0.13 mmol, 1.3 equiv). The mixture was stirred for 2 hours and then concentrated to dryness. The residue was purified by flash column chromatography (hexane/EtOAc) to afford the pure product **4.9d** (53.7 mg, 97% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 – 7.28 (m, 12H), 7.25 – 7.21 (m, 4H), 5.48 (s, 2H), 4.25 (s, 2H), 2.88 – 2.74 (m, 4H), 2.59 (s, 2H), 2.18 – 2.06 (m, 2H), 1.73 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.5, 140.4, 140.1, 139.5, 137.6, 134.8, 129.2, 129.0, 128.8, 128.7, 128.5, 128.1, 127.7, 127.4, 121.3, 64.4, 54.2, 51.6, 50.7, 48.9, 38.1, 36.5, 24.3, 21.2; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{33}H_{35}N_3NaO_3S^+$ 576.2291; found 576.2292.

(*Z*)-2,3-Diphenyl-4-(3-((4-(5-(*p*-tolyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)-sulfonyl)bicyclo-[1.1.1]pentan-1-yl)but-2-en-1-yl-4'-((1,7'-dimethyl-2'-propyl-1*H*,3'*H*-[2,5'-bibenzo[d]imidazol]-3'-yl)methyl)-[1,1'-biphenyl]-2-carboxylate (4.9e)



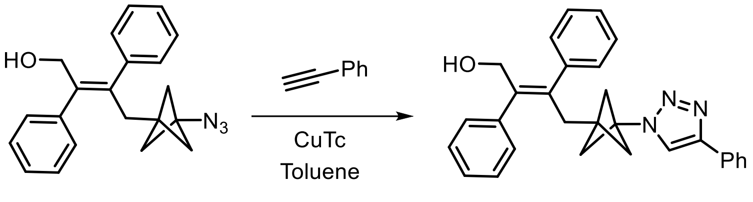
To a solution of **4.5s** (0.1 mmol, 1 equiv), Telmisartan (62 mg, 0.12 mmol, 1.2 equiv), DMAP (2.4 mg, 0.02 mmol, 20 mol%) in DCM (4 mL) was added DCC (24.8 mg, 0.12 mmol, 1.2 equiv) at room temperature. After stirring the mixture for 16 h at room temperature, it was filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (hexanes/EtOAc) to afford the pure product **4.9e** (104.8 mg, 91% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 – 7.78 (m, 1H), 7.70 (d, *J* = 8.6 Hz, 2H), 7.49 – 7.40 (m, 6H), 7.35 – 7.26 (m, 8H), 7.25 – 7.16 (m, 5H), 7.15 – 7.08 (m, 4H), 7.07 – 7.01 (m, 4H), 6.94 (d, *J* = 8.3 Hz, 2H), 6.74 (s, 1H), 5.38 (s, 2H), 4.73 (s, 2H), 3.72 (s, 3H), 2.93 – 2.87 (m, 2H), 2.78 (s, 3H), 2.54 (s, 2H), 2.36 (s, 3H), 1.89 – 1.82 (m, 2H), 1.56 (s, 6H), 1.04 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.4, 156.6, 154.8, 145.5, 144.34 (d, *J* = 38.1 Hz), 143.4, 143.3, 143.1, 141.8, 140.8, 140.6, 140.0, 139.9, 139.7, 136.8, 136.5, 135.1, 135.0, 134.7, 131.3, 130.9, 130.7, 129.9, 129.7, 129.6, 129.1, 128.9, 128.8, 128.64, 128.61, 128.5, 128.0, 127.40, 127.36, 126.0, 125.6, 124.04, 123.99, 122.6, 122.4, 121.0 (q, *J* = 272.0 Hz) 119.7, 109.6, 109.1, 106.4 (q, *J* = 1.6 Hz), 66.5, 51.8, 51.3, 47.2, 38.4, 36.6, 31.9, 29.9, 22.0, 21.4, 17.0, 14.2; **^{19}F NMR** (471 MHz, $CDCl_3$) δ -62.4; **HRMS** (ESI/TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{71}H_{62}F_3N_6O_4S^+$ 1151.4500; found 1151.4508.

(*Z*)-2-(4-bromophenyl)-3-phenyl-4-(3-tosylbicyclo[1.1.1]pentan-1-yl)but-2-en-1-yl-4-(*N*,*N*-dipro-pylsulfamoyl)benzoate (4.9f)



To a solution of product **4.4c** (0.1 mmol, 1 equiv), Probenecid (34.2 mg, 0.12 mmol, 1.2 equiv) and DMAP (2.4 mg, 0.02 mmol, 20 mol%) in DCM (2 mL) was added DCC (24.8 mg, 0.12 mmol, 1.2 equiv) at 0 ºC. After stirring the mixture for an additional 1 hour at room temperature, it was filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (hexanes/EtOAc) to afford the pure product **4.9f** (77.4 mg, 98% yield); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.96 – 7.90 (m, 2H), 7.84 – 7.79 (m, 2H), 7.61 – 7.57 (m, 2H), 7.50 – 7.44 (m, 2H), 7.37 – 7.26 (m, 5H), 7.25 – 7.20 (m, 2H), 7.12 – 7.05 (m, 2H), 4.91 (s, 2H), 3.12 – 3.00 (m, 4H), 2.56 (s, 2H), 2.39 (s, 3H), 1.59 (s, 6H), 1.57 – 1.47 (m, 4H), 0.85 (t, *J* = 7.4 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.7, 144.6, 144.3, 141.8, 139.5, 138.5, 133.8, 133.3, 133.2, 131.7, 130.6, 130.1, 129.7, 128.6, 128.49, 128.47, 128.1, 127.0, 121.5, 66.7, 51.8, 51.1, 50.0, 37.9, 36.8, 22.0, 21.7, 11.2; **HRMS** (ESI/TOF) *m/z*: [M + Na]$^+$ Calcd. for $C_{41}H_{44}BrNNaO_6S_2^+$ 812.1686; found 812.1655.

(*Z*)-2,3-Diphenyl-4-(3-(4-phenyl-1*H*-1,2,3-triazol-1-yl)bicyclo[1.1.1]pentan-1-yl)-but-2-en-1-ol (4.8A)



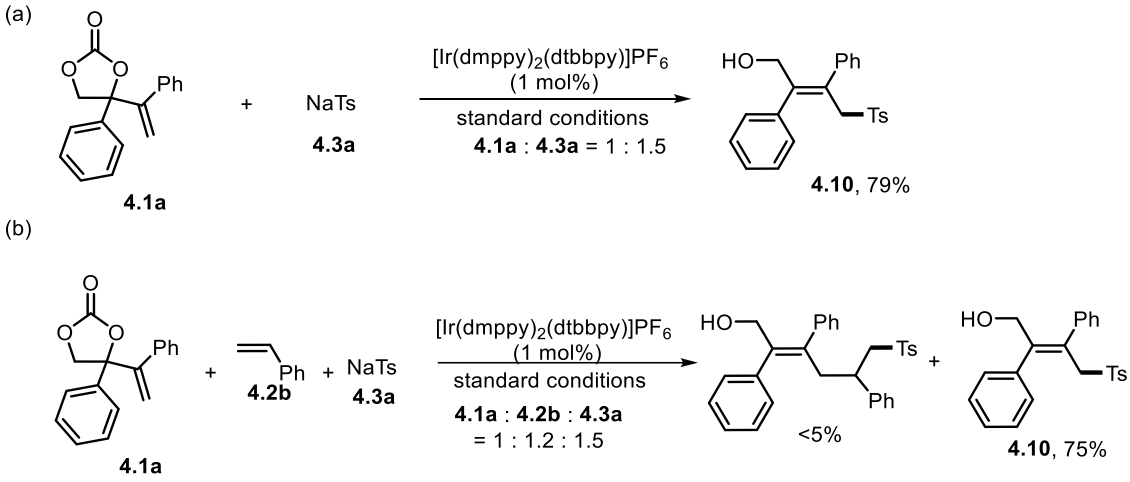
4.8a **4.8A**

To a solution of allylic alcohol product **4.8a** (33.1 mg, 0.1 mmol) and CuTc (1.9 mg, 10%) in toluene (1 mL) was added a 1 mL toluene solution of ethynyl benzene (13.2 µL, 0.12 mmol). The mixture was stirred for 2 h and then concentrated to dryness. The residue was purified by flash column chromatography (hexane/EtOAc) to afford the pure product **4.8A** (35.1 mg, 81% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 – 7.73 (m, 2H), 7.59 – 7.57 (m, 1H), 7.45 – 7.27 (m, 13H), 4.28 (s, 2H), 2.72 (s, 2H), 1.95 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.4, 140.6, 140.2, 139.2, 138.3, 130.6, 129.1, 128.93, 128.85, 128.7, 128.5, 128.1, 127.6, 127.4, 125.8, 118.1, 64.4, 54.1, 49.9, 35.3, 35.2; **HRMS** (ESI/TOF) *m/z*: $[M + Na]^+$ Calcd. for $C_{29}H_{27}N_3NaO^+$ 456.2046; found 456.2057.

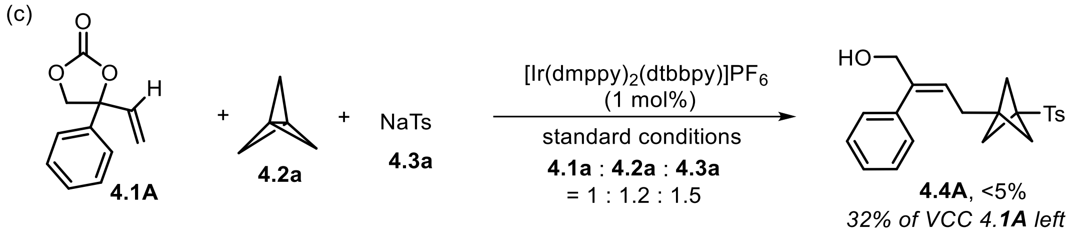
4.4.8. Mechanistic studies

4.4.8.1. Confirming a radical-based chemoselective process

Experiment 1: [1,1,1]-propellane **4.2a** is a crucial factor for a chemoselective 3CR.



Experiment 2: Substitution on the double bond of the VCC is a crucial factor for an efficient 3CR



__Procedure:__ [Ir(dmppy)$_2$(dtbbpy)]PF$_6$ (1.0 mg, 1 mol%), the respective VCC (0.1 mmol) and NaTs (26.7 mg, 0.15 mmol) were weighed into a 10 mL screw-cap vial. The reaction vial was sealed with a cap containing a silicone septum, evacuated, and filled with Ar three times. Then degassed DMSO (0.3 mL), H_2O (50 µL) and styrene **4.2b** (0.12 mmol) or [1,1,1]-propellane **4.2a** (1 mL, 0.12 M in pentane, 0.12 mmol) were added affording a light-yellow solution under an Ar atmosphere. The reaction system was further sealed with Parafilm® and irradiated for 13 h at 20 ºC using a single high-power blue LED (λ_{em} = 445 nm, 700 mA) from the bottom. After completion, the mixture was directly extracted with EtOAc (20 mL). The organic phase was collected and evaporated to dryness and the residue was purified by column chromatography (SiO_2, hexanes/EtOAc) to afford product **4.10** as a white solid in 79% (29.9 mg) and 75% (28.4mg), respectively *under **a** and **b***.

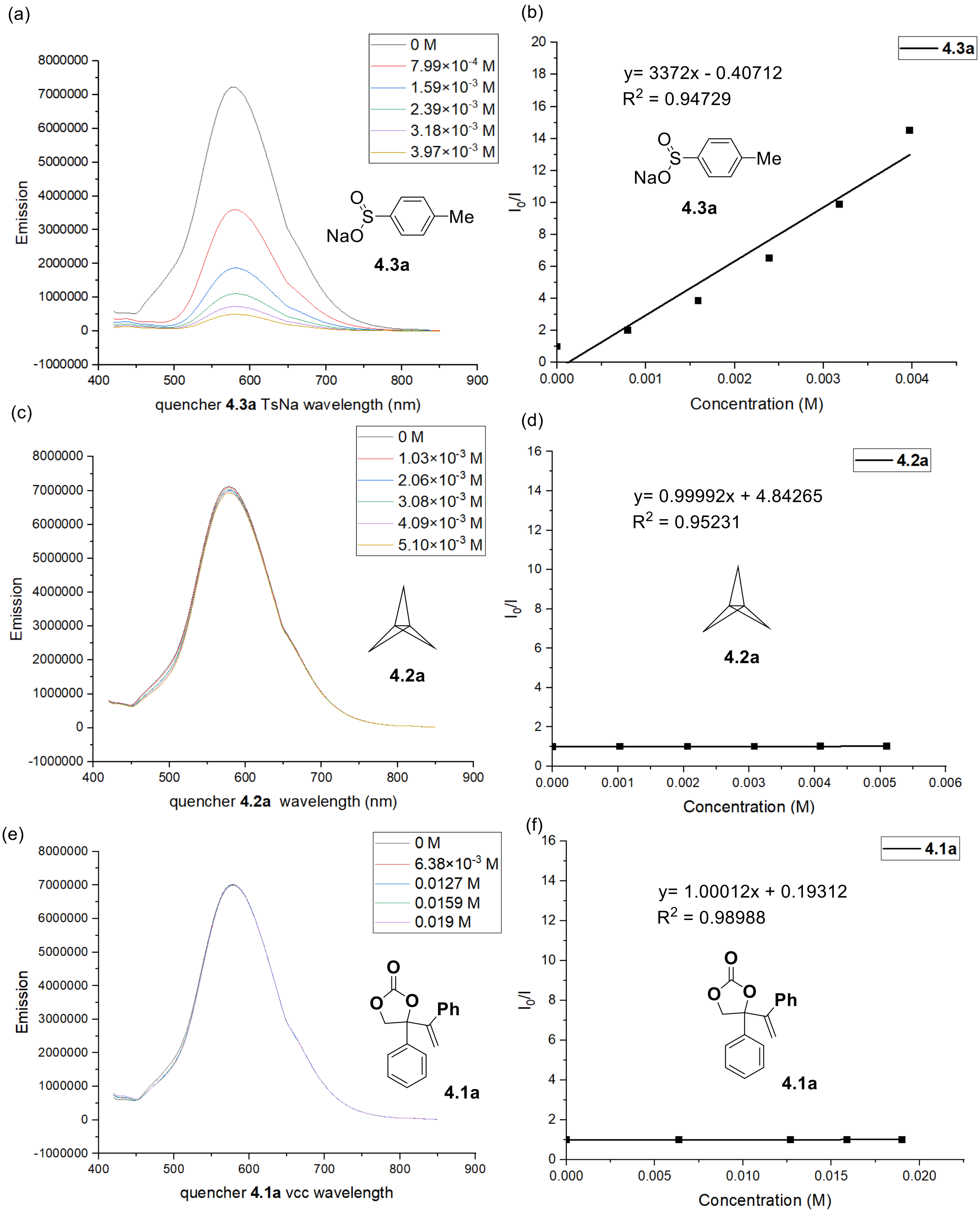
After completion, to the mixture was directly added 1,3,5-trimethyloxybenzene as an internal standard, followed by extraction with EtOAc (3 × 20 mL). The organic phase was collected and evaporated to dryness, and then the residue was dissolved in $CDCl_3$ and analyzed by ^{1}H NMR *under **c***.

4.4.8.2. Stern-Volmer quenching studies

The Stern-Volmer plot for emission quenching of [Ir(dmppy)$_2$(dtbbpy)]PF$_6$ by **4.1a, 4.2a** and **4.3a** is shown in DMSO in **Figure S2**. The emission spectra were recorded in a Fluorolog Horiba Jobin Yvon spectrofluorimeter equipped with a photomultiplier detector, a double monochromator, and a 350 W xenon light source. Samples containing a solution of [Ir(dmppy)$_2$(dtbbpy)]PF$_6$ (1 mg photocatalyst in 50 mL degassed DMSO to obtain a concentration of 2×10^{-5} M) in a total volume of 2.5 mL of DMSO were deoxygenated through purging of argon in a 10 × 10 mm light path quartz fluorescence cuvette equipped with a silicone/PTFE 3.2 mm septum under an argon atmosphere. Then, 8 μL of a 2.0 M solution of **4.1a** in DMSO was added to the solution of [Ir(dmppy)$_2$(dtbbpy)]PF$_6$ to give a final concentration of **4.1a**. Alternatively, 10 μL of a 0.26 M solution of **4.2a** in DMSO was added to the solution of [Ir(dmppy)$_2$(dtbbpy)]PF$_6$ to give a final concentration of **4.2a**. Or alternatively, 4 μL of a 0.5 M solution of **4.3a** in DMSO was added to the solution of [Ir(dmppy)$_2$(dtbbpy)]PF$_6$ to give a final concentration of **4.3a**. The addition of the **4.1a**, **4.2a** and **4.3a** solutions was repeated five consecutive times. The emission light was acquired from 350 nm to 650 nm. The results shown in **Figure S2** indicate that the components quench the excited state of [Ir(dmppy)$_2$(dtbbpy)]PF$_6$ and its emission. A small change in the emission spectra of the solution was observed upon the first addition (λ_{max} = 578 nm to 581 nm).

The maximum emission intensity at 581 nm without quencher divided by the emission intensity with quencher (i.e., I_0/I) was then plotted as a function of the concentration of quencher to obtain the Stern-Volmer plot according to the following equation:

$$\frac{I_0}{I} = 1 + I_0 k_q [Q]$$



For ***4.3a*** *as a quencher, we calculated a Stern-Volmer quenching constant of 3372 M^{-1}.*

For ***4.2a*** *as a quencher, we calculated a Stern-Volmer quenching constant of 0.99992 M^{-1}.*

For ***4.1a*** *as a quencher, we calculated a Stern-Volmer quenching constant of 1.00012 M^{-1}.*

Figure S2. Quenching experiments using **4.1a**, **4.2a** or **4.3a** (a, c, e), and Stern-Volmer quenching plots based on the utilization of **4.1a, 4.2a** or **4.3a** as a quencher (b, d, f).

From these Stern-Volmer quenching experiments, **4.3a** can be as an efficient quencher. There is no significant quenching when using VCC **4.1a** or **4.2a**.

4.4.9. Crystallographic details for 4.4c

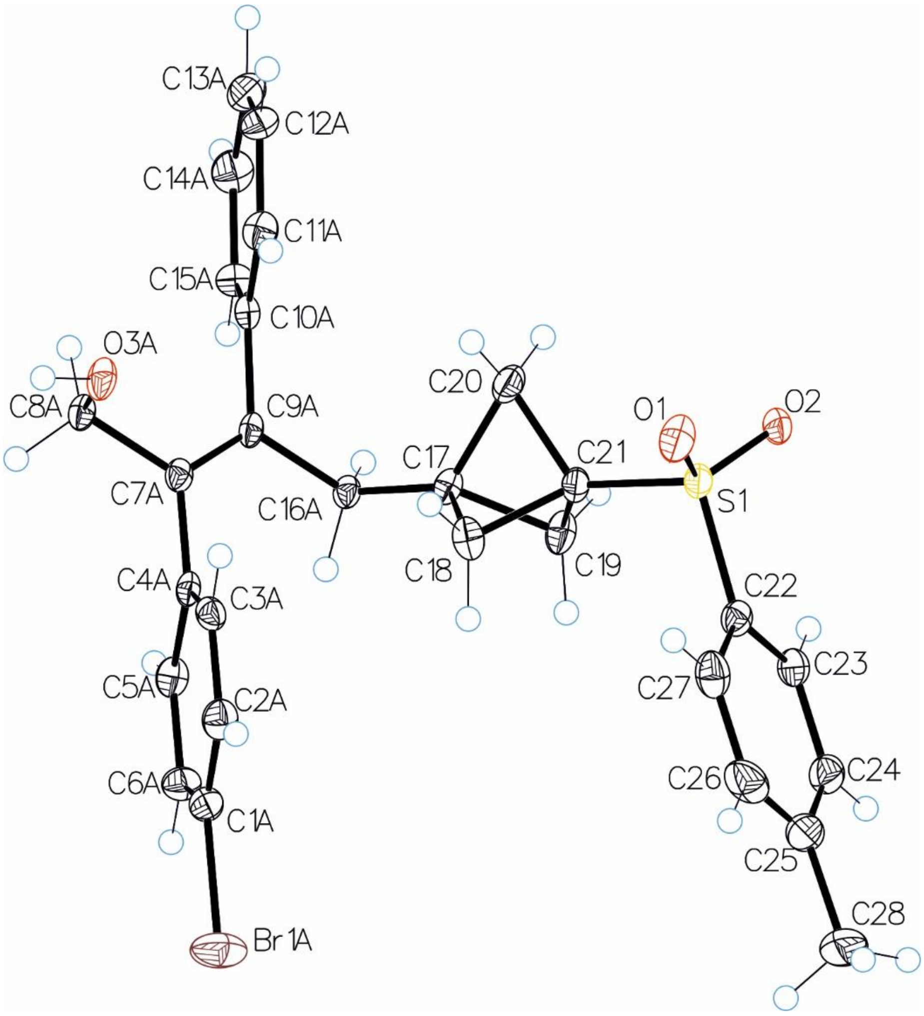


Figure S4.2. Molecular structure (ORTEP) for compound **4.4c** (*no disorder shown*).

Deposition number 2383590 contains the supplementary crystallographic data for compound **4.4c**, see also the main text in this chapter.

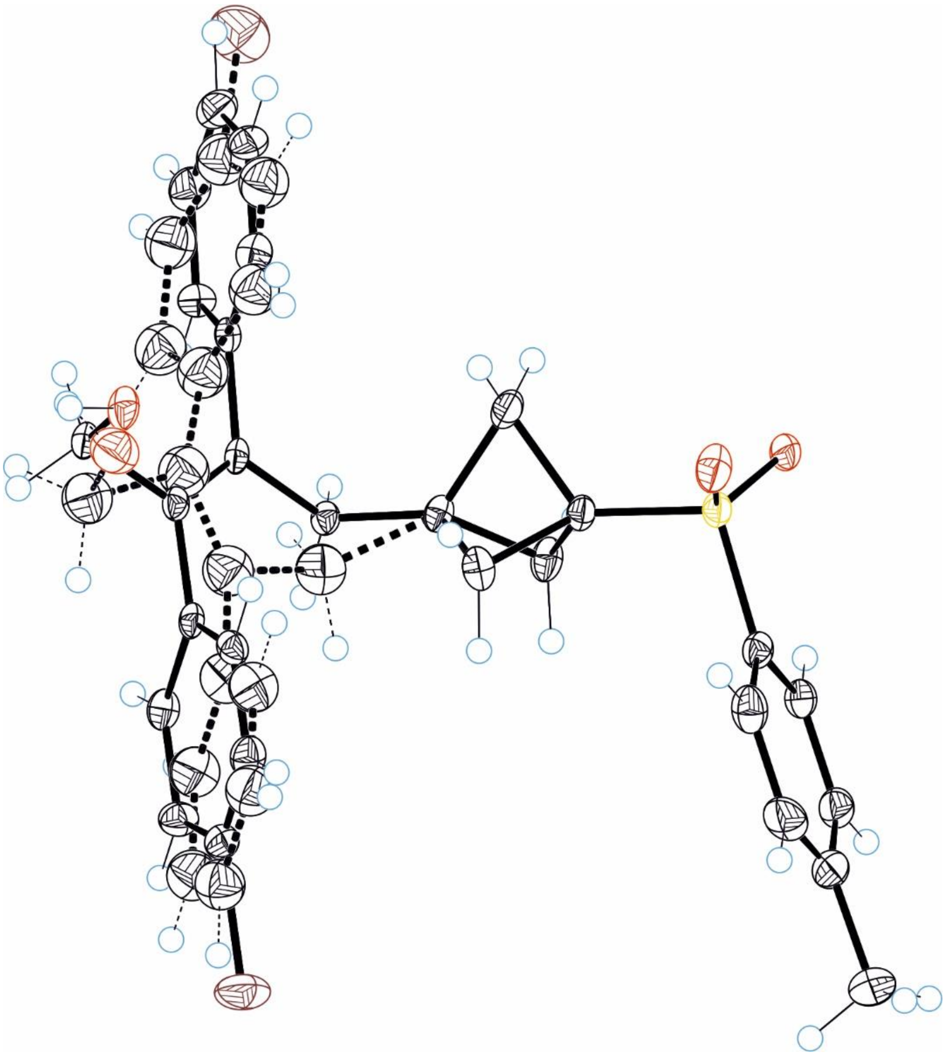


Figure S4.3. Molecular structure (ORTEP) for **4.4c** (*with positional disorder*).

Crystallographic data for 4.4c

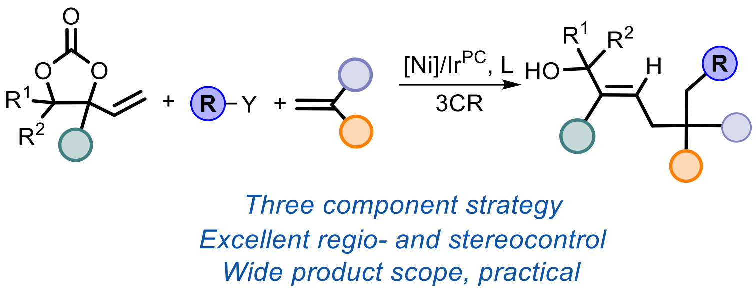
Empirical formula	$C_{28}H_{27}BrO_3S$	
Formula weight	523.46	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 6.0405(13)Å	α = 90°.
	b = 19.139(6)Å	β = 101.195(14)°.
	c = 10.659(3)Å	γ = 90°.
Volume	1208.8(6) Å^3	
Z	2	
Density (calculated)	1.438 Mg/m^3	
Absorption coefficient	1.815 mm^{-1}	
F(000)	540	
Crystal size	0.20 × 0.20 × 0.10 mm^3	
Theta range for data collection	3.896 to 27.58°.	
Index ranges	-7<=h<=5,-24<=k<=24,-13<=l<=13	
Reflections collected	9818	
Independent reflections	5203 [*R*(int) = 0.0398]	
Completeness to theta =55.15°	93%	
Data / restraints / parameters	5203/ 278 / 439	
Goodness-of-fit on F^2	1.055	
Final R indices [I>2sigma(I)]	R_1 = 0.0372, wR_2 = 0.0861	
R indices (all data)	R_1 = 0.0427, wR_2 = 0.0884	
Flack parameter	x = 0.115(6)	
Largest diff. peak and hole	0.34 and -0.25 e·Å^{-3}	

Chapter 5.

Summary and General Conclusions

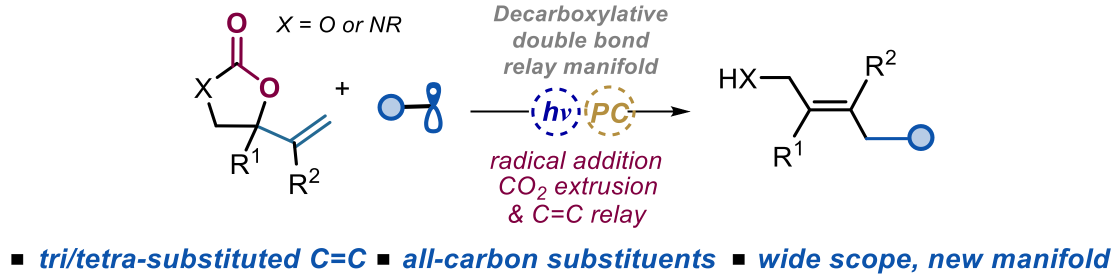
Functionalized allylic structures are valuable motifs playing a significant role in bioactive and pharmaceuticals. Great efforts have thus been devoted to the formation of allylic scaffolds, and conventional methods based on transition metal catalysts that can stabilize and fine-tune the reactivity of π- and/or σ-allyl intermediates have proven to be of high synthetic value. More recently, metal and/or photoredox catalysis promoted allylations have been developed providing alternative approaches to allyl complexity, though these manifolds are usually depending one SET steps thereby expanding the opportunities that exist for allylation chemistry. Nonetheless, multi-component strategies empowered by radical intermediates remain so far underdeveloped despite their potential to rapidly expand the chemical space for advanced allylic synthons. Our main objective in this doctoral thesis was to develop novel, stereo- and regioselective transformations by combing diverse allylic precursors with radical coupling partners, facilitating the fabrication of mostly C–C and C–S bonds via dual metal/photoredox catalyzed allylation and radical-induced cascade ring-opening/allylation approaches.

In *Chapter 2*, we introduced a dual Ni/photoredox catalytic 3CR type allylation procedure by using versatile allylic precursors, alkenes and various radical precursors as coupling partners (Scheme 5.1). The developed process illustrates that radical-based allylation is not restricted to two-component reactions, but multi-components approaches under high regio- and stereoselective control can also be designed. The products, highly substituted allylic alcohols featuring a congested quaternary carbon center, can be regarded as advanced synthetic building blocks with a high degree of functionality. Mechanistic controls in combination with spectroscopic analysis give support for the hypothesis that allyl radicals can be involved in this manifold possibly enabling some degree of radical cross-coupling with the in situ prepared radicals.



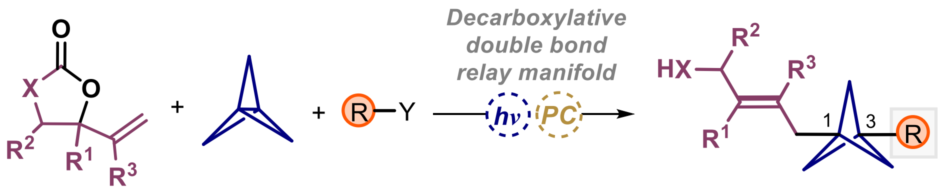
Scheme 5.1. Ni/photoredox dual catalyzed 3CR allylation for the synthesis multifunctionalized allylic scaffolds.

In *Chapter 3*, we describe the development of a radical-induced decarboxylative ring-opening/allylation sequence under photocatalysis for the synthesis of stereodefined multi-substituted allylic compounds (Scheme 5.2). This protocol is highly effective for both polarity-mismatched and -matched substrate combinations, and there is a wide scope of allylic precursors and radical sources while the procedure can be extended to drug-based molecules. Mechanistic studies were performed that support the view that decarboxylation is a crucial driving force towards the generation of product, whereas competition experiments indicate that polarity matching is indeed an important process design feature as more electrophilic alkene based substrates undergo radical addition more facilely with a better stabilization of the intermediate.



Scheme 5.2. Radical-initiated decarboxylative formation of stereodefined olefins.

In *Chapter 4*, we report the exploration of a 3CR cascade difunctionalization of [1,1,1]-propellane in a chemo- and stereo-selective manner (Scheme 5.3). Compared to the work described in Chapter 3, we expanded the radical multicomponent approach to allyl-substituted BCPs using various vinyl-equipped heterocycles and sulfinate salts. Further amplification of radical precursors to other pharma-important functional groups such as azide and CF_3 radical precursors is also easily achieved. This protocol demonstrates that 3CR process initiated by a selective light-promoted radical addition to [1,1,1]-propellane followed by coupling with vinyl-substituted heterocycles can be conveniently designed. The entire process can be regarded as a radical-induced decarboxylation/radical relay/protonation sequence.



Exquisite library of complex 1,3-disubstituted pharma synthons
Stereo/chemoselective 3C radical relay cascade process
Late-stage C(sp^3)-C(sp^3) and C(sp^3)-S/N/C bond formation

Scheme 5.3. A radical cascade 3CR leading to highly functionalized BCPs.

Based on the content of this thesis, we believe that it exemplifies the potential value of multi-component radical-based strategies in synthetic methodology to rapidly build up molecular complexity allowing to prepare advanced, complex allylic synthons. We thus expect that multicomponent cascade strategies will be of future value in academic and commercial laboratories thereby aiding drug discovery and development. The already widespread incorporation and use of photocatalytic strategies in the synthetic communities and the highly versatile nature of vinyl cyclic carbonates and related heterocycles to deliver new types of reactivity patterns hold promise for the creation of new radical processes whose selectivity can be controlled through a proper design. On the other hand, we foresee an even wider scope of (larger) heterocyclic substrates becoming available, thereby setting the stage to cover a larger area of chemical space upon their transformation via photo-induced radical chemistry.

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