CHIRAL PYRROLIDINYL-BIPHENYL PHOSPHINE LIGANDS IN GOLD(I) CATALYSIS

Giuseppe Zuccarello

UNIVERSITAT ROVIRA i VIRGILI

Chiral Pyrrolidinyl-Biphenyl Phosphine Ligands in Gold(I) Catalysis

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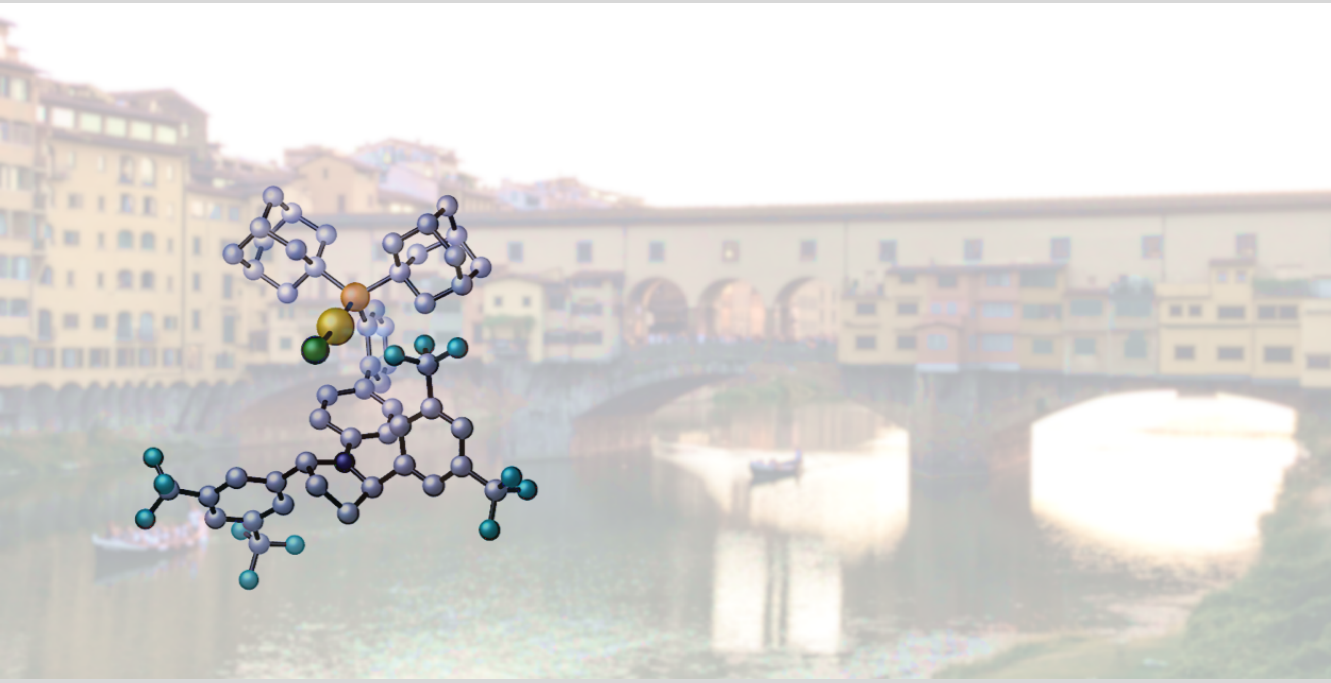

DOCTORAL THESIS
2020

Giuseppe Zuccarello

Chiral Pyrrolidinyl-Biphenyl Phosphine Ligands in Gold(I) Catalysis

DOCTORAL THESIS

Supervised by Prof. Antonio M. Echavarren

Institute of Chemical Research of Catalonia (ICIQ)

UNIVERSITAT ROVIRA i VIRGILI

ICIQ Institut Català d'Investigació Química

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UNIVERSITAT ROVIRA i VIRGILI

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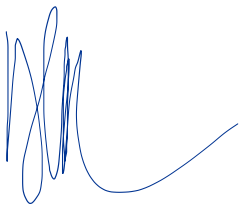
I STATE that the present study, entitled "Chiral Pyrrolidinyl-Biphenyl Phosphine Ligands in Gold(I) Catalysis", presented by Giuseppe Zuccarello for the award of the degree of Doctor, has been carried out under my supervision at the Institut Català d'Investigació Química (ICIQ).

Tarragona, May 18th, 2020

Doctoral Thesis Supervisor



Prof. Antonio M. Echavarren Pablo

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Prologue

This manuscript is divided in five main parts including a general introduction, three chapters describing the research results and a general conclusion. Each chapter contains five sections including a specific introduction in the topic, objectives, results and discussion, conclusion and an experimental section. The compounds and references are numbered continuously throughout the thesis.

The **General Introduction** gives an overview on the fundamentals of homogeneous gold(I) catalysis and summarizes the most successful and established approaches to enantioselective gold(I) catalysis.

Chapter 1. presents the design and synthesis of a new class of chiral mononuclear gold(I) complexes and their application in the cyclization of 1,6-arylenynes. The project was developed in collaboration with Joan G. Mayans, Dr. Dagmar Scharnagel, Dr. Mariia S. Kirillova, Alba H. Pérez-Jimeno, Dr. Pilar Calleja and Dr. Jordan R. Boothe. The discussed results have been published in *J. Am. Chem. Soc.* **2019**, *141*, 11858–11863 and reviewed in *Isr. J. Chem.* **2020**, *60*. DOI: 10.1002/ijch.201900179.

Chapter 2. discusses experimental and computational studies on the working mode of the new chiral gold(I) complexes. Additionally, a complete kinetic study sheds light on the rate-determining step of the formal [4+2] cycloaddition of 1,6-arylenynes and discusses possible pathways for the ligand exchange mechanism. The computational work has been entirely performed by Imma Escofet and for consistency, results obtained by Dr. Leonardo J. Nannini and Dr. Miguel Peña López have been included. Most of the presented results have been published in *J. Am. Chem. Soc.* **2019**, *141*, 11858–11863 and reviewed in *Isr. J. Chem.* **2020**, *60*. DOI: 10.1002/ijch.201900179.

Chapter 3. describes the synthesis of 1,2-dihydronaphthalenes from 7-aryl-cycloheptatrienes via a tandem retro-Buchner/C(sp^3)–H insertion/elimination process. The results were published in *Chem. Eur. J.* **2019**, *25*, 9485–9490.

A **General Conclusion** is provided at the end of this Doctoral Thesis.

List of Abbreviations and Acronyms

In this Doctoral Thesis, the abbreviations and acronyms most commonly used in organic and organometallic chemistry have been used following the recommendations from *"Guidelines for authors"* published in *Journal of Organic Chemistry*.
Additional abbreviations and acronyms are listed below:

APCI	Atmospheric Pressure Chemical Ionization
$BAr^F{}_4$	Tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
CyJohnPhos	(2-Biphenyl)dicyclohexylphosphine
ee	Enantiomeric excess
er	Enantiomeric ratio
ESI	Electrospray Ionization
HFIP	Hexafluoro-2-propanol
HRMS	High Resolution Mass Spectrometry
IMes	1,3-Bis(2,4,6-trimethylphenyl)imidazole-2-ylidene
IPr	1,3-Bis(2,6-diisopropylphenyl)imidazole-2-ylidene
JohnPhos	(2-Biphenyl)di-*tert*-butylphosphine
L-Selectride	Lithium tri-*sec*-butylborohydride
Men	Menthyl
Ms	Mesylate
Ns	2-nitrobenzene-1-sulfonyl
NTf_2	Bis(trifluoromethyl)imidate
OTf	Trifluoromethanesulfonate
*t*BuXPhos	2-Di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl
Ts	*p*-toluenesulfonyl

Abstract

Homogenous gold(I) catalysis has become a powerful synthetic tool for the rapid construction of complex molecular structures. Several gold(I)-catalyzed transformations have been applied in numerous total syntheses of natural products also due to the high chemoselectivity of gold(I) complexes towards the activation of alkynes. This research field experiences increasing interest which leads to its fast evolution and the development of numerous catalytic methods. Nevertheless, the enantioselective versions of this class of transformations are more difficult due to the linear dicoordination adopted by gold(I), which places the chiral information on the direct opposite site of the reactive center. The activation of alkynes, which are not prochiral, and the outer-sphere mechanism of gold(I)-mediated reactions provide additional difficulty for the development of efficient catalytic enantioselective transformations.

To address these limitations, we have taken advantage of the well-defined geometry of dialkylbiphenyl phosphine ligands and designed a new class of chiral ligands containing remote C_2-symmetric 2,5-disubstituted pyrrolidines. This particular ligand design places the chiral information next to the reactive center. We have disclosed a modular synthesis which gave access to a small family of the new pyrrolidinyl-biphenyl phosphine-supported gold(I) complexes. 5-*Exo*-dig and 6-*endo*-dig cyclizations of 1,6-arylenynes could be performed in good to excellent enantioselectivities.

Although mechanistically related, opposite enantioselectivities were found in the cyclizations of 1,6-enynes. We elucidated the mode of action and enantioinduction of our chiral catalysts experimentally and computationally. Attractive non-covalent interactions between stereodirecting moieties of the substrates and the ligand have been found to be crucial for high enantioselectivities. Additionally, a study on the specific role of each component of the ligand design was performed which culminated in the synthesis of a 2nd generation of chiral ligands. The gained knowledge on the working mode provided the basis for developing atroposelective transformations and improve enantioselective cascade cyclizations of 1-bromo-1,5-enynes. Kinetic investigations on the gold(I)-catalyzed formal [4+2] cycloaddition of 1,6-arylenynes established the effect of the pyrrolidine-containing ligands on the rate-determining step. While with conventional JohnPhos-supported gold(I) complexes the formation of the cyclopropyl gold(I) carbene is the rate-determining step, in the presence of pyrrolidinyl-biphenyl phosphine ligands the reaction rate is affected by two competing and temperature-dependent rate-limiting steps being the formation of the cyclopropyl gold(I) carbene and the ligand exchange. A highly positive entropy of activation $\Delta S^{\ddagger}$, determined by Eyring analysis, opens up to unprecedented pseudo-dissociative ligand exchange pathways in gold(I) catalysis.

Finally, we developed a new synthesis of substituted 1,2-dihydronaphthalenes from 7-aryl-cycloheptatrienes taking advantage of a gold(I)-catalyzed tandem retro-Buchner/C(sp^3)–H insertion/elimination process. The otherwise unfavored formation of 6- over 5-membered rings via C–H insertion was achieved targeting more reactive benzylic C–H bonds with an α-OMe group providing additional activation.

General Objectives

The objectives of this Doctoral Thesis include the development of a conceptually new ligand design for asymmetric gold(I) catalysis as well as non-asymmetric gold(I) catalyzed C(sp^3)–H insertion reactions. Precisely, our investigations focused on:

- The synthesis and design of a new class of gold(I) complexes supported by dialkylbiphenyl phosphine ligands featuring remote C_2-symmetric 2,5-disubstituted pyrrolidines and their application in catalysis.

- The systematic investigation of the mode of action and enantioinduction of the new chiral catalysts as well as their influence on the rate-determining step in the gold(I)-catalyzed formal [4+2] cycloaddition.

- The synthesis of 1,2-dihydronaphthalenes via a gold(I)-catalyzed tandem retro-Buchner/C(sp^3)–H insertion/elimination process.

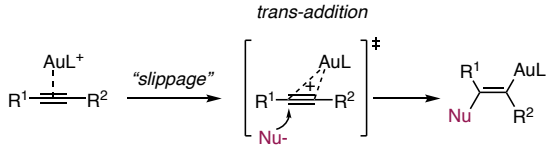
A more detailed description of the objectives can be found in the corresponding chapters.

General Introduction

Homogeneous Gold(I) Catalysis

The research field of homogeneous gold(I) catalysis is relatively young as it only blossomed in the last two decades. Prior to the reports by Ito and Hayashi[1] on the gold(I)-catalyzed synthesis of chiral oxazolines and later, on the hydroalkoxylation of alkynes presented by Tanaka[2] and Teles[3], gold was considered to be catalytically inactive despite few early examples.[4] Today, homogeneous gold(I) catalysis is recognized as a well-established tool for the mild and selective π-activation of multiple C–C bonds (alkynes, allenes and alkenes) for the atom economical construction of complex molecular settings otherwise difficult to access.[5] Numerous gold(I) catalyzed transformations have also been applied in the context of natural product total synthesis, testifying to the versatility of gold(I) catalysis.[6]

Upon π-activation, gold(I)-catalyzed transformations take place via outer-sphere mechanism in which the nucleophile adds *trans* to the gold atom. The nucleophilic attack induces a "slippage" of the metal fragment along the axis of the unsaturated C–C bond forming alkenyl-gold complexes (Scheme 1).[5f] Several nucleophiles have been added both intra- and intermolecularly spanning from water, alcohols, amines, thiols, imines, sulfoxides and *N*-oxides to carbon based nucleophiles such as alkenes and electron rich arenes.



Scheme 1. Outer-sphere *trans* nucleophilic addition to (η^2-alkyne)gold(I) complexes.

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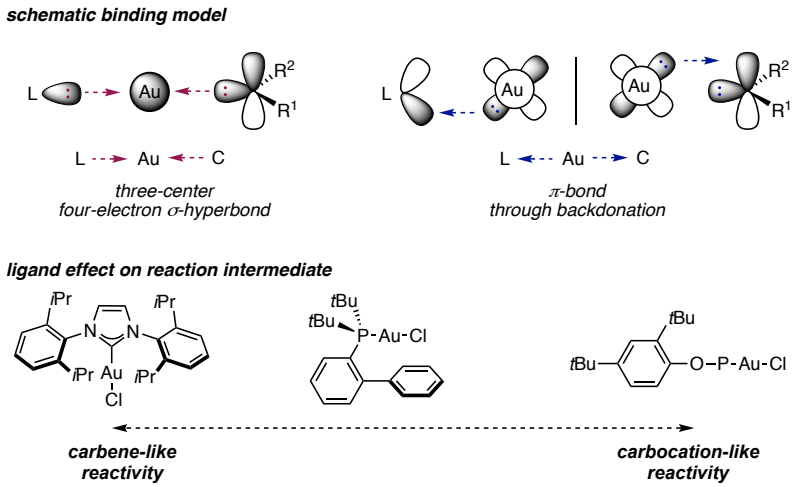
The pronounced π-acidity of gold complexes is ascribed to relativistic effects.[7] Electrons orbiting a heavy nucleus with a speed close to the speed of light experience an increase in mass leading to a contraction of the Bohr radius, and as a consequence, of the *s* and *p* orbitals with concomitant expansion of the *d* and *f* orbitals. Therefore, the 4*f* and 5*d* electrons experience a weaker nuclear attraction and less electron/electron repulsion which in turn, accounts for the preferential activation of "soft" electrophiles. These effects are more significant for elements with filled 5*d* and 4*f* orbitals whereby a maximum is achieved for gold.

The 6*s* orbital contraction leads to a stronger Au-L bond so that the electronic properties of the ancillary ligand directly affect reaction intermediates such as gold(I) carbenes, commonly invoked in a plethora of gold(I)-catalyzed transformation.[5] According to the binding model described by Toste[8] and Goddard, the ligand and the carbene carbon bind to gold(I) forming a linear three-center four-electron σ-hyperbond (Scheme 2). In addition, gold(I) is able to form two π-bonds via backdonation of its electrons in the filled 5*d* orbitals into the empty π orbitals of the carbene and the ligand.[9]



Scheme 2. Binding model and ligand effects.

Hence, σ-donating ligands such as *N*-heterocyclic carbenes (NHC) favor the formation of carbene-like intermediates with according reactivity. On the other hand, π-acidic

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phosphite ligands induce a stronger gold-to-ligand backdonation resulting in an elongation of the gold-carbene bond, which has a more carbocation-like character.

Catalytically active cationic gold(I) complexes are generated *in situ* from their neutral precursors either via protolysis of [LAuMe] or via chloride abstraction in [LAuCl] with AgX. However, the use of silver salts in gold(I) catalysis[10] has led to the formation of less active chloride-bridged digold complexes,[11] undesired side products,[12] and might have an effect on the selectivity of the reactions.[13]

Importantly, in addition to the high oxidation potential ($E^0(Au^{III/I}) = 1.41$ V), the linear coordination adopted by gold(I) also hampers elementary organometallic reactions such as oxidative addition and reductive elimination.[14] Thus, DFT studies have shown that the corresponding products of oxidative addition have reasonable energies but are kinetically inaccessible. Nonetheless, the employment of bidentate hemilabile (P,N) ligands[15] or bipyridines[16] that enhance backdonation from gold have recently given access to gold(I)/(III)-mediated cross coupling reactions, albeit under stochiometric conditions. Catalytic, gold(I)/(III)-mediated coupling reactions require strong external oxidants[17] or are performed in presence of a photocatalyst to promote the Au(I)/Au(III) turnover.[18]

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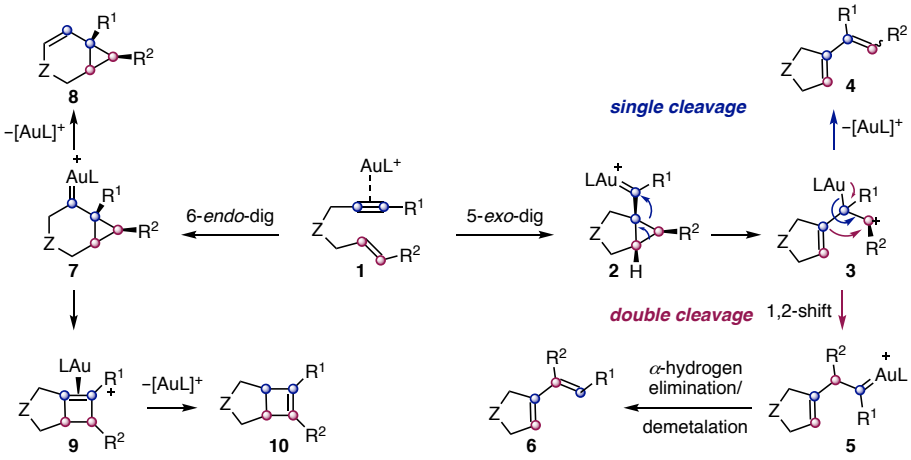
18. For reviews on this topic: (a) Hopkinson, M. N.; Tlahuext-Aca, A.; Glorius, F. *Acc. Chem. Res.* **2016**, *49*, 2261–2272. (b) Zhang, M.; Zhu, C.; Ye, L. W. *Synthesis.* **2017**, *49*, 1150–1157. Selected examples: (c) Xia, Z.; Corcé, V.; Zhao, F.; Przybylski, C.; Espagne, A.; Jullien, L.; Le Saux, T.; Gimbert, Y.; Dossmann, H.; Mouriès-Mansuy, V.; Ollivier, C.; Fensterbank, L. *Nat. Chem.* **2019**, *11*, 797–805. (d) Shu, X. Z.; Zhang, M.; He, Y.; Frei, H.; Toste, F. D. *J. Am. Chem. Soc.* **2014**, *136*, 5844–5847. (e) Sahoo, B.; Hopkinson, M. N.; Glorius, F. *J. Am. Chem. Soc.* **2013**, *135*, 5505–5508.

Cycloisomerization of 1,*n*-Enynes

The development of gold(I)-catalyzed cycloisomerizations of 1,*n*-enynes had a tremendous impact on the field. These reactions are particularly interesting because a significant increase in molecular complexity can be achieved in one single chemical transformation.[5e,h] Thus, several total syntheses have been completed taking advantage of this class of powerful reactions.[6] Depending on the substitution pattern at the alkene and the alkyne as well as on the ancillary ligand, gold(I)-catalyzed cycloisomerizations of 1,6-enynes can evolve following different reaction pathways (Scheme 3).[19] Usually, (η^2-alkyne)gold(I) complexes **1** undergo 5-*exo*-dig cyclization forming *anti*-cyclopropyl gold(I) carbenes **2**. In the absence of external nucleophiles, skeletal rearrangements deliver dienes **4** and **6** respectively via single and double cleavage mechanisms. Products of single cleavage **4** are formed via gold-stabilized carbocation **3** and subsequent demetallation. On the other hand, an additional 1,2-shift from **3** leads to gold carbene **5**, in which the external carbon of the original alkene is formally inserted into the alkyne carbons. Formal α-hydrogen elimination and demetallation from **5** gives products of double cleavage **6**.

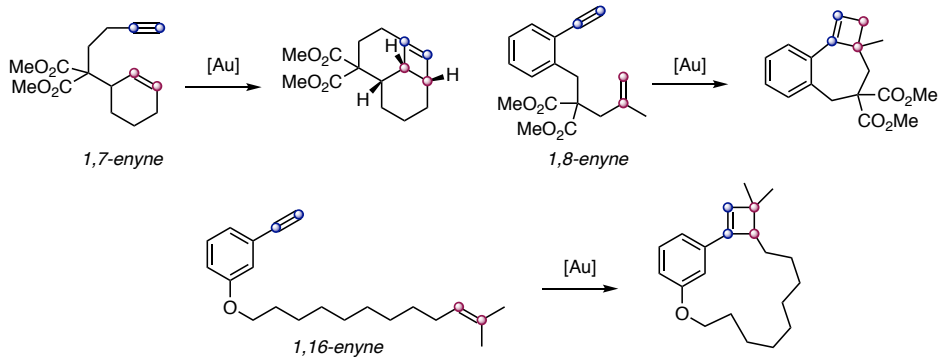


Scheme 3. Reaction pathways for cycloisomerizations of 1,6-enynes.

(η^2-Alkyne)gold(I) complexes of type **1** can also undergo 6-*endo*-dig cyclization forming cyclopropyl gold(I) carbene **7** which affords **8** upon α-proton elimination (Scheme

19. (a) Obradors, C.; Echavarren, A. M. *Acc. Chem. Res.* **2014**, *47*, 902–912. (b) Escribano-Cuesta, A.; Pérez-Galán, P.; Herrero-Gómez, E.; Sekine, M.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *Org. Biomol. Chem.* **2012**, *10*, 6105–6111. (c) Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Cárdenas, D. J.; Buñuel, E.; Nevado, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6146–6148.

3).[20] Alternatively, carbene **7** undergoes ring expansion to **9** followed by double bond isomerization to give **10**. The proposed cyclopropyl gold carbene intermediates are highly distorted species that can be seen as gold-stabilized homoallylic carbocations.[21] Higher 1,*n*-enynes (n>6) undergo formal [2+2] cycloadditions[19b,c] which proved useful for the construction of macrocycles (Scheme 4).[22]



Scheme 4. Cyclization of higher 1,*n*-enynes (n>6).

Asymmetric Gold(I) Catalysis

Owing to the synthetic power of gold(I)-catalyzed reactions, the development of asymmetric versions would provide additional preparative potential. However, in contrast to the non-asymmetric transformations, efficient enantioselective transformations experienced a much slower development.[23] The associated difficulties are mainly attributed to the preferred linear diccoordination adopted by gold(I) (Scheme 5). This particular coordination motif places the reaction center (substrate) on the direct opposite side of the the chiral information resulting in poor enantioinduction. Additional limitation arises from the outer-sphere mechanism of gold(I)-catalyzed transformations which further extends the distance between the chiral source and the reactive center. Furthermore, substrate fixation in a chiral environment is difficult as both the L*–Au and Au–substrate bonds can easily

20. Young, T. L.; Youn, K. K.; Young, K. C. *J. Org. Chem.* **2009**, *74*, 7922–7934.
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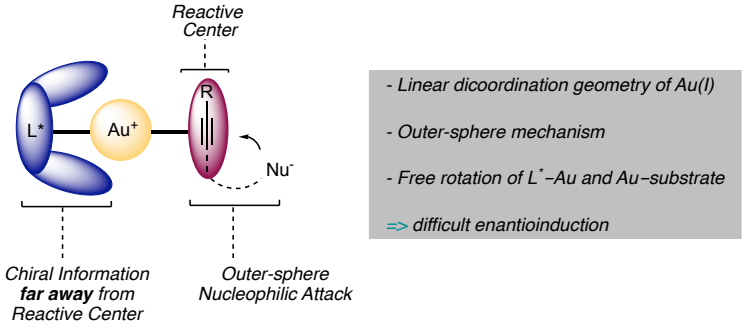
23. (a) Li, Y.; Li, W.; Zhang, J. *Chem. Eur. J.* **2017**, *23*, 467–512. (b) Zi, W.; Dean Toste, F. *Chem. Soc. Rev.* **2016**, *45*, 4567–4589. (c) Wang, Y. M.; Lackner, A. D.; Toste, F. D. *Acc. Chem. Res.* **2014**, *47*, 889–901. (d) Pradal, A.; Toullec, P. Y.; Michelet, V. *Synthesis* **2011**, 10, 1501–1514. (e) Sengupta, S.; Shi, X. *ChemCatChem* **2010**, *2*, 609–619. (f) Widenhoefer, R. A. *Chem. Eur. J.* **2008**, *14*, 5382–5391.

rotate. Thus, the implementation of new concepts for asymmetric gold(I) catalysis remains a challenging task.



Scheme 5. Limitations associated with enantioselective gold(I) catalysis.

The first enantioselective gold(I)-catalyzed transformation was reported by Ito and Hayashi[1] in 1986 on the synthesis of chiral oxazolines via aldol-type addition of isocyanates to benzylic aldehydes. Only 20 years later our group reported the second example of gold(I)-catalyzed enantioselective transformation describing the alkoxycyclization of 1,6-enynes using dinuclear gold complexes with atropisomeric bisphosphines. Although the enantioselectivities were strongly substrate-dependent,[24] this report represents a milestone in the field of enantioselective gold(I) catalysis, which was followed by many efforts on the development of catalytic enantioselective systems.[23]

Three main solutions have been implemented in the field. The first approach relies on the use of axially-chiral digold complexes suppoted either by bisphosphines or by acyclic diaminocarbenes (Figure 1).[25] Axially-chiral bisphosphine-supported dinuclear complexes represent the most studied system, employed in numerous inter- and intramolecular transformations including cyclopropanations,[26] cycloisomerizations of 1,*n*-enynes[24,27]

24. Paz Muñoz, M.; Adrio, J.; Carretero, J. C.; Echavarren, A. M. *Organometallics* **2005**, *24*, 1293–1300.
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hydrofunctionalizations of alkenes[28] and allenes[29] and other annulation reactions.[30] Digold complexes supported by spirocyclic bisphosphines have also been used.[31] While it remains unclear wheather aurophilic interactions are important for high enantioinduction in digold complexes, it has been experimentally established in several cases that the second phosphine-gold center is crucial for a successful reaction outcome.

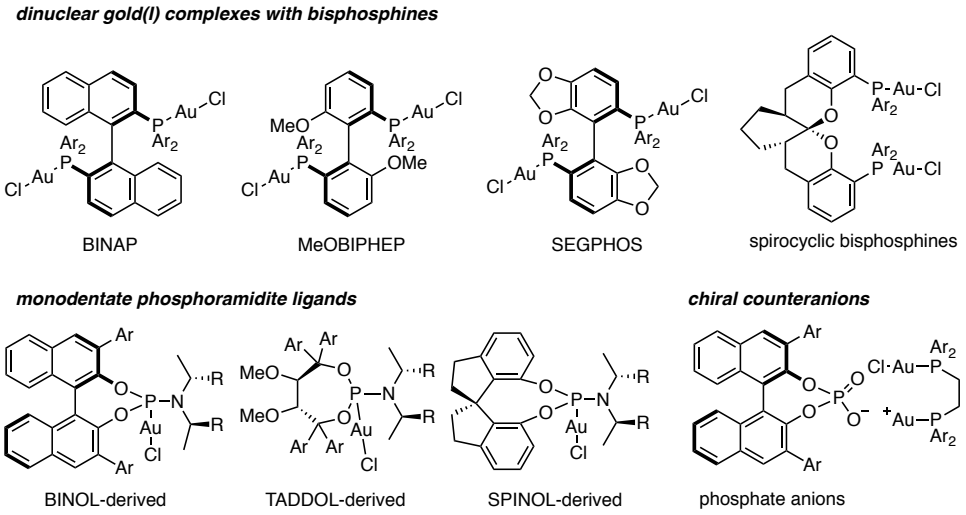

Figure 1. Three main designs for enantioselective gold(I) catalysis.

The second approach involves the use of one-point binding phosphoramidite ligands containing BINOL, TADDOL or SPINOL backbones which together with the substituents on the amine moiety effectively construct chiral "walls" around the reactive center. The

28. (a) Lee, S. Du; Timmerman, J. C.; Widenhoefer, R. A. *Adv. Synth. Catal.* **2014**, *356*, 3187–3192. (b) Fang, W.; Presset, M.; Guérinot, A.; Bour, C.; Bezzenine-Lafollée, S.; Gandon, V. *Org. Chem. Front.* **2014**, *1*, 608–613. (c) Bandini, M.; Bottoni, A.; Chiarucci, M.; Cera, G.; Miscione, G. Pietro.. *J. Am. Chem. Soc.* **2012**, *134*, 20690–20700. (d) Mukherjee, P.; Widenhoefer, R. A. Gold(I)-Catalyzed *Angew. Chem. Int. Ed.* **2012**, *51*, 1405–1407. (e) Zhang, Z.; Lee, S. Du; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2009**, *131*, 5372–5373.
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31. Cao, Z. Y.; Wang, X.; Tan, C.; Zhao, X. L.; Zhou, J.; Ding, K. *J. Am. Chem. Soc.* **2013**, *135*, 8197–8200.

groups of Fürstner,[32] Mascareñas[33] and Toste[23c] have contributed to the development of this type of ligands, which are readily available, highly modular and have been especially effective in several cycloadditions of allenes.[34] Adapting the same concept, the group of Alcarazo has recently introduced TADDOL-derived cationic phosphonite ligands which were found to be suitable for synthesizing chiral helicenes[35] and axially-chiral compounds[36] via gold(I)-mediated hydroarylations. Furthermore, our group has used chiral monodentate phosphite ligands for the enantioselective formal [4+2] cycloaddition of 1,6-arylenynes.[37]

Equally successful has been the synergistic use of chiral counteranions with both chiral and nonchiral cationic gold(I) complexes.[38] This third approach has been introduced by Toste[39] in the context of intramolecular hydroaminations and hydrocarboxylations of allenes using binaphthol-derived phosphate anions. The chiral information is kept next to the reactive center via ion pair interactions overcoming the limitations posed by the linear coordination motif of gold(I) and by the general outer-sphere reaction mechanisms. However, this concept cannot be extended to the asymmetric activation of terminal alkynes,[40] since chiral phosphates are basic enough to deprotonate the alkynyl proton and favor the formation of catalytically inactive gold(I) acetylides.[41] Very recently, the group of Marinetti has covalently linked the chiral phosphoric acid to a nonchiral phosphine ligand resulting in a cooperative bifunctional system.[42]

The approaches to enantioselective gold(I) catalysis presented above are well established and have proven efficient for several processes, although none of these systems show sufficient broad scope. Hence, other concepts have been recently emerging. The

32. Teller, H.; Corbet, M.; Mantilli, L.; Gopakumar, G.; Goddard, R.; Thiel, W.; Fürstner, A. *J. Am. Chem. Soc.* **2012**, *134*, 15331−15342.
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35. (a) Hartung, T.; Machleid, R.; Simon, M.; Golz, C.; Alcarazo, M. *Angew. Chem. Int. Ed.* **2020**. Doi:10.1002/anie.201915870. (b) Nicholls, L. D. M.; Marx, M.; Hartung, T.; González-Fernández, E.; Golz, C.; Alcarazo, M. *ACS Catal.* **2018**, *8*, 6079–6085.
36. Zhang, J.; Simon, M.; Golz, C.; Alcarazo, M. *Angew. Chem. Int. Ed.* **2020**. Doi: 10.1002/anie.201915456.
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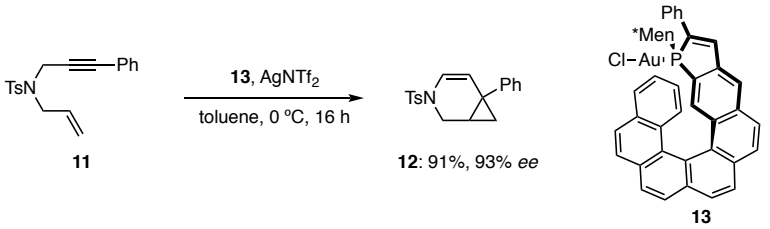
41. Ferrer, S.; Echavarren, A. M. *Organometallics* **2018**, *37*, 781−786.
42. Zhang, Z.; Smal, V.; Retailleau, P.; Voituriez, A.; Frison, G.; Marinetti, A.; Guinchard, X. *J. Am. Chem. Soc.* **2020**, 142, 3797–3808.

group of Marinetti and Voituriez[43] have introduced the use of gold(I) complexes of type **13** supported by monodentate helically chiral ligands with embedded *meta*-fused phospholes. These complexes were found to catalyze the cyclization of nitrogen-tethered 1,6-enynes such as **11** to give the corresponding aza-bicyclo[4.1.0]heptanes **12** (Scheme 6).



Scheme 6. Application of helically chiral gold(I) complexes.

Recent ligand designs have relied on bifunctional monophosphines that provide substrate fixation and preorientation via non-covalent interactions. Although this approach is not widely diffused yet, it has proven to be efficient in various enantioselective trasformations. Junliang Zhang and his coworkers have contributed to the development of this type of systems incorporating chiral sulfinamides in phosphine ligands such as **14** also known as Ming-Phos and Xiang-Phos (Scheme 7). Their mode of action relies on non-covalent H-bonding with the substrates and has led to efficient enantioselective inter- and intramolecular cycloadditions.[44] For the intramolecular cyclization of *N*-allenamides **16** giving chiral tetrahydrocarbolines **17** this group designed a similar phosphine ligand **15** merging the properties of **14** with the Xant-Phos backbone.[45] This allowed to broaden the space between the coordinating phosphine and the chiral source, moving it closer to the reactive center and thus adapting the ligand to the linear structure of gold(I) complexes. Interestingly, in this transformation the fine-tuning of the sulfonamide in **16** resulted crucial as it interacts with the ligand via H-bonding.

43. (a) Aillard, P.; Voituriez, A.; Dova, D.; Cauteruccio, S.; Licandro, E.; Marinetti, A. *Chem. Eur. J.* **2014**, *20*, 12373–12376. (b) Yavari, K.; Aillard, P.; Zhang, Y.; Nuter, F.; Retailleau, P.; Voituriez, A.; Marinetti, A. *Angew. Chem. Int. Ed.* **2014**, *53*, 861–865. (c) Aillard, P.; Retailleau, P.; Voituriez, A.; Marinetti, A. *Chem. Eur. J.* **2015**, *21*, 11989–11993.
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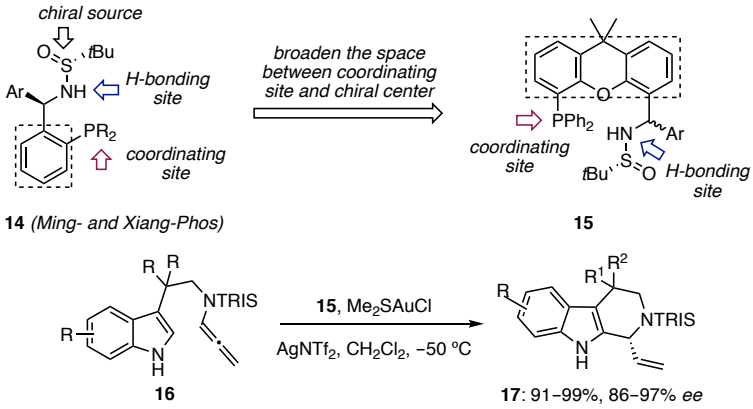
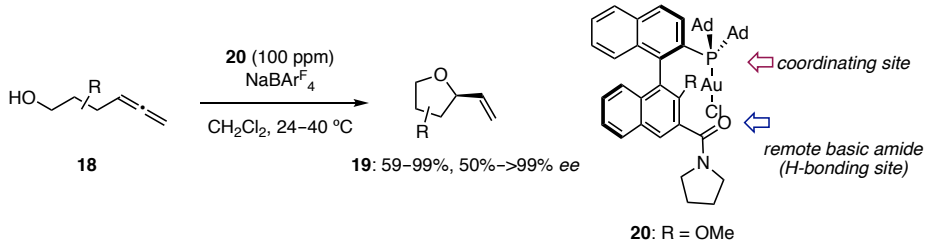
45. Wang, Y.; Zhang, P.; Di, X.; Dai, Q.; Zhang, Z. M.; Zhang, J. *Angew. Chem. Int. Ed.* **2017**, *56*, 15905–15909.



Scheme 7. Chiral sulfinamide monophosphine ligands in gold(I) catalysis.

A similar approach has been used by the group of Liming Zhang relying on axially-chiral binaphthyl phosphine-supported gold(I) complex **20** featuring a remote basic amide group (Scheme 8).[46] Cyclization of 4-allene-1-ols **18** giving 2-vinyltetrahydrofuranes **19** were performed in high enantioselectivities due to the ligand-assisted preorientation of the substrate via non-covalent H-bonding. This metal-ligand cooperative catalysis resulted in dramatic rate accelerations as the remote basic functionality acts as a general base catalyst enhancing the nucleophilicity of the alcohol. Because of this effect, catalyst loadings as low as 100 ppm could be used. The same group used this strategy also for the tandem asymmetric alkyne-alkene isomerization/cyclization of propargylic alcohols affording enantioenriched 2,5-dihydrofurans.[47]



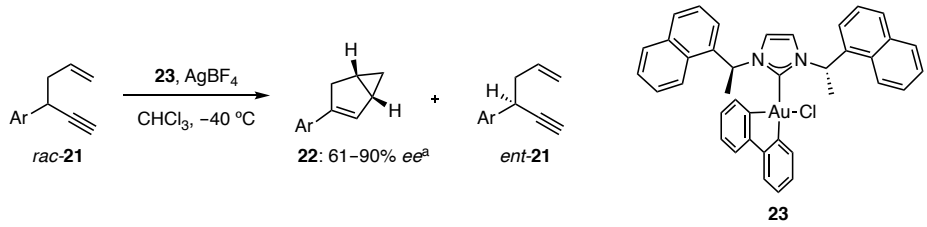
Scheme 8. Accelerative asymmetric gold(I)-catalyzed allenol cyclization.

A rather innovative approach to asymmetric gold(I) catalysis was introduced by the groups of Sollogoup and Fensterbank in which the metal is encapsulated in NHC-capped

46. Wang, Z.; Nicolini, C.; Hervieu, C.; Wong, Y. F.; Zanoni, G.; Zhang, L. *J. Am. Chem. Soc.* **2017**, *139*, 16064–16067.
47. Cheng, X.; Wang, Z.; Quintanilla, C. D.; Zhang, L. *J. Am. Chem. Soc.* **2019**, *141*, 3787–3791.

cyclodextrin cavitants.[48] However, only moderate enantioselecitiviteis were obtained in cycloisomerizations of 1,6-enynes.

Finally, an important contribution on the first enantioselective transformation catalyzed by a well-defined cationic gold(III) catalyst was presented by Toste (Scheme 9).[49] The square-planar geometry of gold(III) complex **23** places the active site closer to the chiral NHC-ligand, leading to efficient chiral induction. Complex **23** is an efficient catalyst in the kinetic resolution of racemic 1,5-enynes *rac*-**21** giving bicyclo[3.1.0]hexene **22** and *ent*-**21**.



Scheme 9. Gold(III)-catalyzed kinetic resolution. [a]*ee* Values determined at different conversions.

48. Guitet, M.; Zhang, P.; Marcelo, F.; Tugny, C.; Jiménez-Barbero, J.; Buriez, O.; Amatore, C.; Mouriès-Mansuy, V.; Goddard, J. P.; Fensterbank, L.; Zhang, Y.; Roland, S.; Ménand, M.; Sollogoub, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 7213–7218. Zhang, P.; Tugny, C.; Meijide Suárez, J.; Guitet, M.; Derat, E.; Vanthuyne, N.; Zhang, Y.; Bistri, O.; Mouriès-Mansuy, V.; Ménand, M.; Roland, S.; Fensterbank, L.; Sollogoub, M. *Chem* **2017**, *3*, 174–191.
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Chapter 1.

Design and Synthesis of Chiral Mononuclear Gold(I) Complexes and their Application in Catalysis

Introduction

Dialkylbiaryl Phosphine Ligands in Gold(I) Catalysis

In 1998,[50] Buchwald introduced bulky dialkylbiaryl phosphine ligands in the context of Pd-catalyzed Suzuki-Miyaura cross-coupling reactions, amination of unactivated aryl chlorides and synthesis of diaryl ethers.[51] This class of ligands proved particularly efficient due to their bulkiness and high electron density that enhance the rate of oxidative addition and reductive elimination. Numerous dialkylbiaryl phosphine-assisted Pd-catalyzed C–C[52] and C–X[53] (X = N, O, F) bond-forming reactions have been reported taking advantage of the stability of this phosphine ligands with respect to oxidation[54] and their straightforward synthetic accessibility.[55] Furthermore, other transition metals such as Ag,[56] Rh,[57] Ru,[58] and Cu[59] have also been used in combination with this privileged class of ligands. The first application of dialkylbiaryl phosphine ligands in the field of homogeneous gold(I) catalysis was reported by our group in 2005.[60] A family of highly electrophilic gold(I) complexes **1.1a-d** was introduced, which were found to be catalytically active in diverse transformations upon chloride abstraction. Importantly, cationic complexes **1.1e-g** are easily prepared from their gold chloride precursors and $AgSbF_6$ in the presence of MeCN and are bench-stable white solids that can be directly used in catalysis without pre-activation (Figure 1.1).

50. (a) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722–9723. (b) Wolfe, J. P.; Buchwald, S. L. A. *Angew. Chem. Int. Ed.* **1999**, *38*, 2413–2416
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54. Barder, T. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 5096–5101.
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56. Porcel, S.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 2672-2676.
57. (a) Dhondi, P. K.; Carberry, P.; Choi, L. B.; Chisholm, J. D. *J. Org. Chem.* **2007**, *72*, 9590–9596. (b) Dhondi, P. K.; Chisholm, J. D.. *Org. Lett.* **2006**, *8*, 67–69.
58. Faller, J. W.; D'Alliessi, D. G. *Organometallics* **2003**, *22*, 2749–2757.
59. Haider, J.; Kunz, K.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 717–722.
60. Nieto-Oberhuber, C.; López, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178–6179.

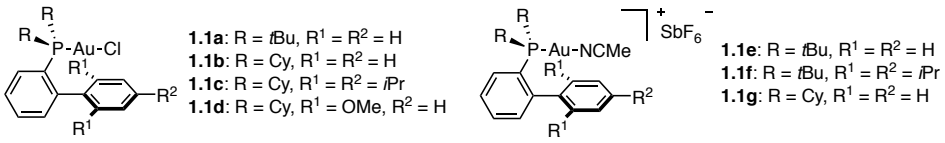
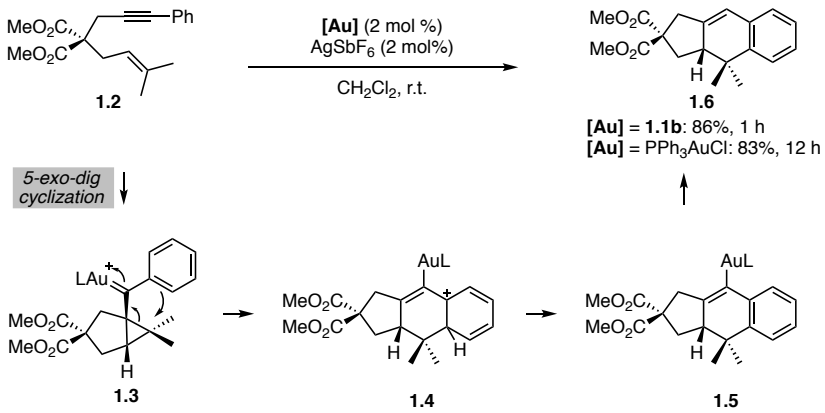


Figure 1.1. Dialkyl biaryl phosphine-supported gold(I) complexes.

As discussed in the general introduction, the gold(I)-catalyzed cyclization of 1,*n*-enynes can proceed following different reaction pathways depending on the substitution pattern at the alkene and the alkyne. However, 1,*n*-enynes containing internal alkynes, especially arylalkynes, are particularly reluctant to undergo cycloisomerization.[60] Gold(I) complexes supported by dialkylbiaryl phosphine ligands provided an improved reactivity for the intramolecular formal [4+2] cycloaddition of 1,6-arylenynes **1.2** giving cyclopenta[*b*]naphthalenes **1.6** in excellent yields and reduced reaction times compared to the use of Ph_3PAuCl (Scheme 1.1). Experimental and theoretical studies suggested that the broad scope formation of compounds **1.6** occurs *via* 5-*exo*-dig formation of *anti*-cyclopropyl gold(I) carbene **1.3** followed by Friedel-Crafts-type reaction to form Wheland intermediate **1.4** and sequential proton loss and final protodeauration from **1.5**.[61]

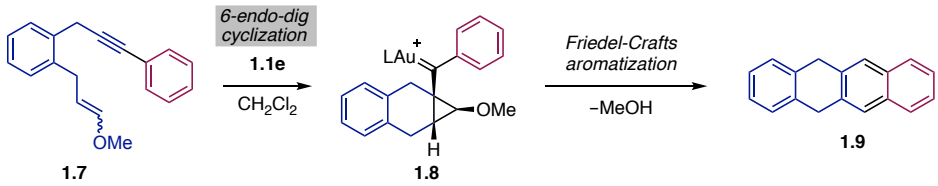


Scheme 1.1. Formal [4+2] cycloaddition of 1,6-arylenynes.

Later, our group extended the formal [4+2] cycloaddition to 1,7-enynes **1.7** in which the alkene is replaced by an enol ether, affording dihydrotetracenes **1.9** (Scheme 1.2).[62] This reaction proceeds similarly via 6-*endo*-dig cyclization forming gold(I) carbene **1.8**

61. Nieto-Oberhuber, C.; Pérez-Galán, P.; Herrero-Gómez, E.; Lauterbach, T.; Rodríguez, C.; López, S.; Bour, C.; Rosellón, A.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2008**, *130*, 269–279.
62. Dorel, R.; McGonigal, P. R.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2016**, *55*, 11120–11123.

followed by aromatization with concomitant loss of one molecule of methanol. JohnPhos-supported cationic catalyst **1.1e** outcompeted NHC- and phosphite-supported gold(I) catalysts for this process. Interestingly, dihydroacenes are partially saturated precursor of acenes, a class of polycyclic hydrocarbons that display important semiconducting properties,[63] which were generated *in situ* via dehydrogenation on metal surfaces.[64]



Scheme 1.2. Preparation of dihydroacenes via gold(I)-catalyzed 1,7-enyne cyclization.

The use of dialkylbiaryl phosphine ligands in homogeneous gold(I) catalysis has significantly marked the development of the research field over the past 15 years. In addition to being robust and highly active, complexes **1.1a-g** lead to different regio- and chemoselectivities otherwise not accessible under the action of other gold(I) catalysts. The success of electron-donating bulky biaryl phosphine ligands is mainly attributed to the ability of stabilizing carbene- and/or carbocation-like intermediates.[65]

The reaction outcome of the gold(I)-catalyzed intramolecular hydroarylation of alkynyl-indoles **1.10**[66] was found to be catalyst dependent (Scheme 1.3). Azepino[4,5-*b*]indole **1.12** was selectively formed using cationic complex **1.1e** whereas the employment of $AuCl_3$ or AuCl salts led exclusively to indoloazocine **1.14**. Both products are formed following a stepwise mechanism including 6-e*xo*-dig and 7-*endo*-dig electrophilic aromatic substitution at the more nucleophilic C-3 carbon to give spirofused intermediates **1.11** and **1.13** respectively, followed by ring expansion via 1,2-migration.[67] Recently, our group has applied the gold-catalyzed formation of indoloazocines **1.14** in the total synthesis of *Kopsia*

63. Anthony, J. E. *Chem. Rev.* **2006**, *106*, 5028–5048.
64. (a) R. Zuzak, R. Dorel, M. Krawiec, B. Such, M. Kolmer, M. Szymonski, A. M. Echavarren, S. Godlewski, *ACS Nano* **2017**, *11*, 9321–9329. (b) R. Zuzak, R. Dorel, M. Kolmer, M. Szymonski, S. Godlewski, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2018**, *57*, 10500–10505.
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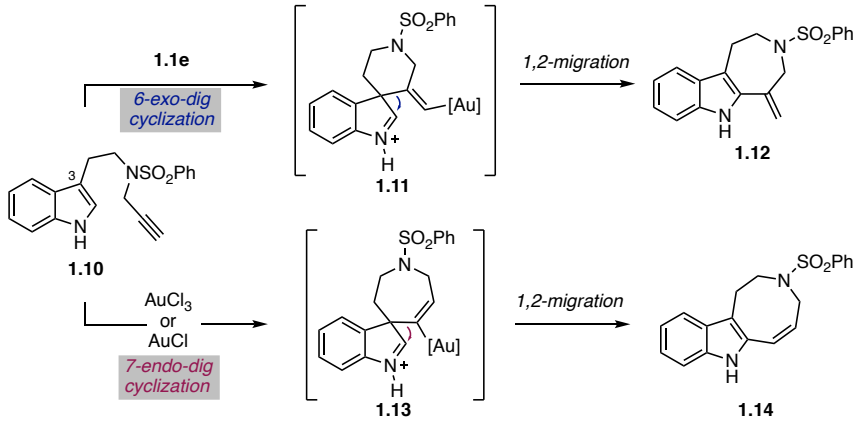
66. (a) Zhang, L.; Chang, L.; Hu, H.; Wang, H.; Yao, Z. J.; Wang, S. *Chem. Eur. J.* **2014**, *20*, 2925–2932. (b) Ferrer, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 1105–1109. (c) Ferrer, C.; Amijs, C. H. M.; Echavarren, A. M. *Chem. Eur. J.* **2007**, *13*, 1358–1373.
67. (a) Damm, W.; Dickhaut, J.; Wetterich, F.; Giese, B. *Tetrahedron Lett.* **1993**, *34*, 431–434. (b) Jackson, A. H.; Smith, P. *Tetrahedron* **1968**, *24*, 2227–2239.

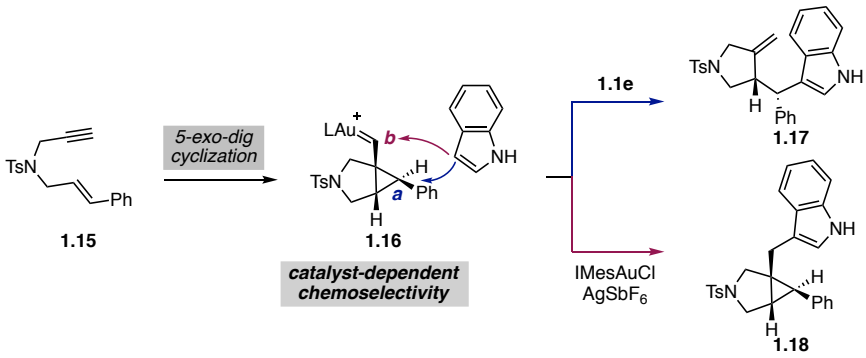
alkaloids[68] such as (–)-lundurines A-C[69] and seven members of the lapidilectine/grandilodine family.[70]



Scheme 1.3. Gold(I)-catalyzed hydroarylation of alkynyl-indoles.

Analogously, *N*-tethered 1,6-enyne **1.15** undergoes 5-*exo*-dig cyclization to form *anti*-cyclopropyl gold(I) carbene **1.16** (Scheme 1.4). In the presence of complex **1.1e** and an external nucleophile, such as indole or electron-rich arenes, carbene **1.16** reacts preferentially at the cyclopropyl carbon ***a*** giving rise to a 4:1 mixture of **1.17** and **1.18**. This selectivity arises from the stabilization of carbocation-like intermediates. However, using σ-donating NHC-supported complexes such as IMesAuCl leads to the stabilization of carbene-like intermediates and in turn, to an inversion in chemoselectivity slightly favoring the formation of **1.18** (1:0.8). Hence, nucleophilic attack occurs at carbene carbon ***b***.[71]

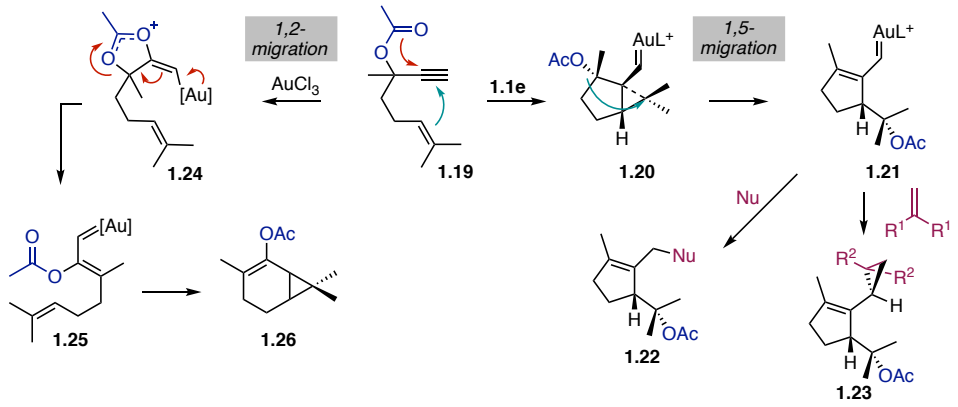
68. Kirillova, M. S.; Miloserdov, F. M.; Echavarren, A. M. *Org. Chem. Front.* **2018**, *5*, 273–287
69. Kirillova, M. S.; Muratore, M. E.; Dorel, R.; Echavarren, A. M. *J. Am. Chem. Soc.* **2016**, *138*, 3671–3674.
70. Miloserdov, F. M.; Kirillova, M. S.; Muratore, M. E.; Echavarren, A. M. *J. Am. Chem. Soc.* **2018**, *140*, 5393–5400.
71. Amijs, C. H. M.; Ferrer, C.; Echavarren, A. M. *Chem. Commun.* **2007**, 698–700.



Scheme 1.4. Catalyst-dependent chemoselectivity of **1.16**.

Dialkylbiaryl phosphine-supported gold(I) complexes have also led to the discovery of novel reactivities. Catalyst **1.1e** promotes 5-*exo*-dig formation of cyclopropyl gold(I) carbene **1.20** from enyne **1.19**, followed by 1,5-migration[72] of the acetate group giving gold(I) carbene **1.21** (Scheme 1.5). Reaction with external nucleophiles such as 1,3-diketones or electron rich alkenes affords products of α-alkylation **1.22** and cyclopropanation **1.23**, respectively. Electron rich heterocycles such as indoles[72a] and furans[73] have also been employed as nucleophiles in this transformation. In contrast, $AuCl_3$ triggers the formation of bicyclo[4.1.0]hept-2-ene **1.26** from 1,6-enynes **1.19** following a reaction mechanism reminiscent to the Rautenstrauch rearrangement.[74] Alternatively, 1,2-Migration of the acetate group gives allylic gold carbene **1.25** through intermediate **1.24** and subsequent intramolecular cyclopropanation affords **1.26**.

72. Jiménez-Núñez, E.; Raducan, M.; Lauterbach, T.; Malawi, K.; Solorio, C. R.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2009**, *48*, 6152–6155. (b) Calleja, P.; Pablo, Ó.; Ranieri, B.; Gaydou, M. Pitaval, A.; Moreno, M.; Raducan, M.; Echavarren, A. M. *Chem. Eur. J.* **2016**, *22*, 13613–13618.
73. Lebœuf, D.; Gaydou, M.; Wang, Y.; Echavarren, A. M. *Org. Chem. Front.* **2014**, *1*, 759–764.
74. Nieto Faza, O.; Silva López, C.; Álvarez, R.; De Lera, A. R. *J. Am. Chem. Soc.* **2006**, *128*, 2434–2437.

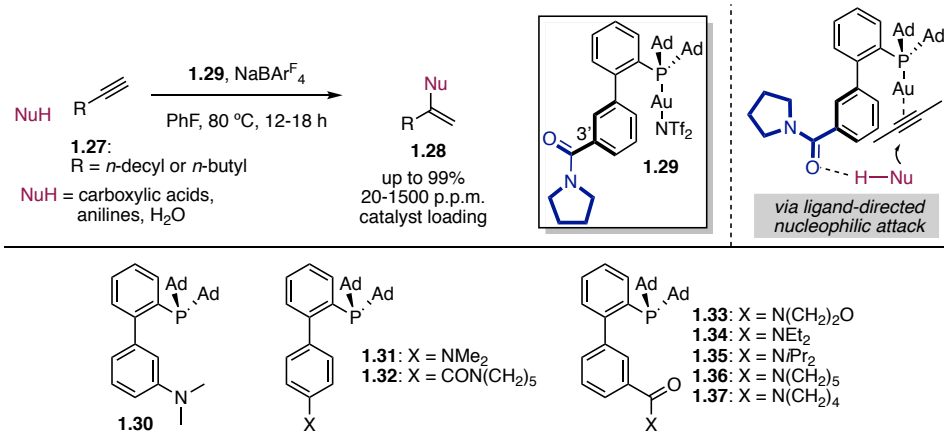


Scheme 1.5. Catalyst-dependent reactivities of propargylic acetate-containing 1,6-enyne **1.19**.

Functionalized Biaryl Phosphine Ligands in Gold(I) Catalysis

The well-defined geometry of bulky biaryl phosphine ligands has inspired chemists to develop modifications of this privileged ligand scaffold that allowed for the uncovering of new reactivities and for improving existing transformations. In this regard, the group of Liming Zhang has reported pioneering work in the context of homogeneous gold(I) catalysis. Knowing that gold(I)-catalyzed transformations follow an outer-sphere reaction mechanism, this group identified the rigid biphenyl scaffold as the optimal platform to strategically place a distal functional group that would direct, and therefore facilitate, nucleophilic attack. This concept culminated in the development of a gold(I)-catalyzed ligand-directed anti-nucleophilic addition of carboxylic acids, anilines and water to alkynes **1.27** giving compounds of type **1.28** (Scheme 1.6).[75] In their ligand design, the bottom phenyl ring is functionalized at the 3'-position with a hydrogen-bond acceptor such as amines and amides (**1.30**-**1.37**). The remote amide in **1.29** pre-orients the incoming nucleophile and converts the intermolecular transformation into a partially intramolecular process. Importantly, the distal functional group acts firstly as a general base ("soft deprotonation" according to the authors) and, in a second step, as a general acid promoting a rapid intramolecular protodeauration. This results in enhanced reaction rates and overall reaction efficiency giving the target compounds in excellent results with ppm levels of catalyst loading. Other bifunctional ligands bearing a remote basic site have been developed and outclassed more conventional ligands such as JohnPhos and NHC ligands in this particular transformation.

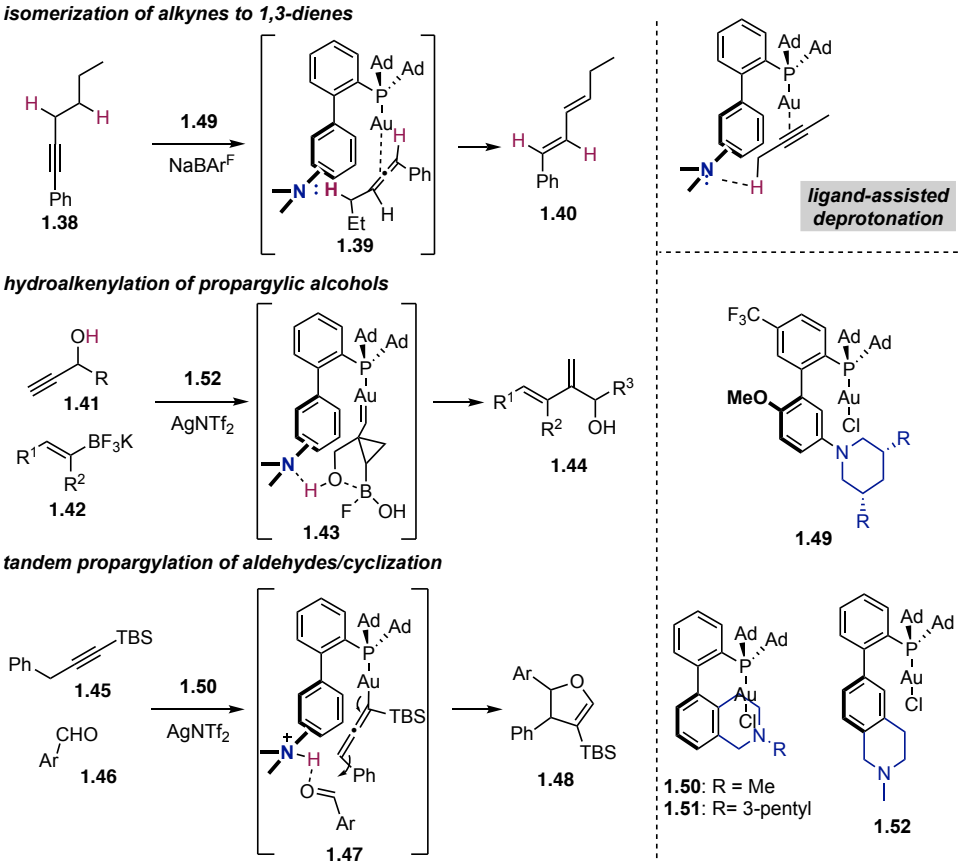
75. Wang, Y.; Wang, Z.; Li, Y.; Wu, G.; Cao, Z.; Zhang, L. *Nat. Commun.* **2014**, *5*, 3470.



Scheme 1.6. Bifunctional biaryl phosphine ligands in directed additions to alkynes.

The group of Liming Zhang reported numerous transformations based on this concept of "soft deprotonation". Access to *trans*-dienes such as **1.40** could be obtained from alkyne **1.38** under this strategy (Scheme 1.7). The isomerization process occurs through allenyl gold(I) intermediate **1.39** in which the strategically positioned Brønsted base in **1.49** acts as a proton shuttle.[76] Similarly, the isomerizations of ynamides and allenamides,[77] propargylic esters[78] and allyl ynoates[79] have been achieved. Intermolecular transformations were also developed. Thus, propargylic alcohols **1.41** and alkenyltrifluoroborates **1.42** undergo formal hydroalkenylation affording dienol **1.44**.[80] Theorethical studies have shown that the basic site in **1.52** and the propargylic alcohol interact via H-bonding increasing the nucleophilicity of the oxygen, which in turn reacts with the boronate and facilitates the formation of cyclopropyl gold(I) carbene **1.43**. Finally, alkynyl silanes **1.45** undergo ligand-assisted isomerization and generate σ-allenylgold intermediate **1.47**, which is stabilized by a β-silicon effect preventing fast protodeauration to occur.[81] Thus, this indermediate can react with electrophiles such as aldehydes **1.46** via 1,2-addition, followed by cyclization with concomitant 1,2-silyl migration, affording silylated dihydrofuranes **1.48**.[82]

76. Wang, Z.; Wang, Y.; Zhang, L. *J. Am. Chem. Soc.* **2014**, *136*, 8887–8890.
77. Li, X.; Wang, Z.; Ma, X. Liu, P. N.; Zhang, L. *Org. Lett.* **2017**, *19*, 5744–5747.
78. Z. Wang, A. Ying, Z. Fan, C. Hervieu, L. Zhang, *ACS Catal.* **2017**, *7*, 3676–3680.
79. H. Wang, T. Li, Z. Zheng, L. Zhang, *ACS Catal.* **2019**, *9*, 10339–10342.
80. Liao, S.; Porta, A.; Cheng, X.; Ma, X.; Zanoni, G.; Zhang, L. *Angew. Chem. Int. Ed.* **2018**, *57*, 8250–8254.
81. Li, T.; Yang, Y.; Li, B.; Bao, X.; Zhang, L. *Org. Lett.* **2019**, *21*, 7791–7794.
82. Li, T.; Zhang, L. *J. Am. Chem. Soc.* **2018**, *140*, 17439–17443.



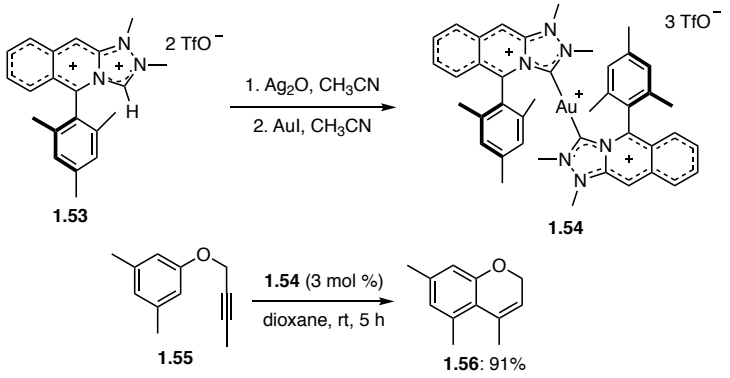
Scheme 1.7. Application of biaryl phosphine ligands with remote cooperativity.

Electronically Tuned Biaryl Scaffolds

Due to the importance of biaryl phosphine ligands in homogeneous gold(I) catalysis efforts on modifying the electronic properties of the biaryl motif have been reported. The groups of Fernández and Lassaletta have recently merged the biaryl scaffold and a triazoquinoline core to develop cationic NHC ligands that increase the π-acidity of the corresponding metal complexes (Scheme 1.8).[83] Dicationic azolium salt **1.53** was used as the carbene precursor to access tricationic gold(I) complex **1.54**, which was found to be a good catalyst for the intramolecular hydroarylation of **1.55**. Other gold(I) complexes

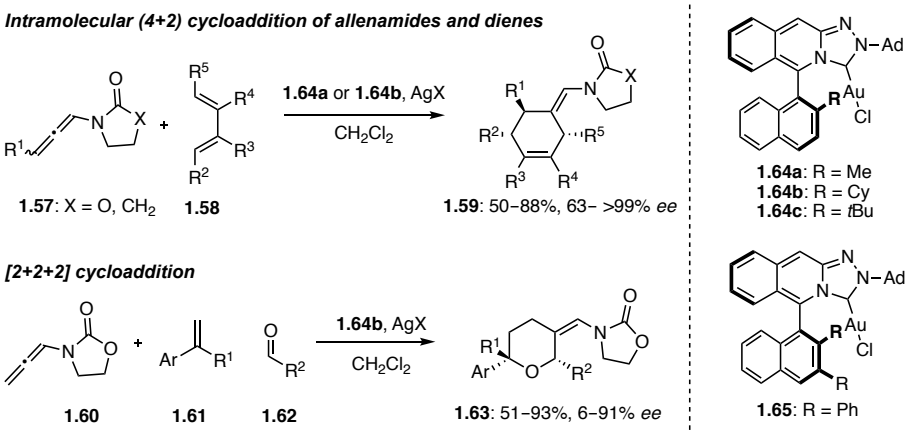
83. Iglesias-Sigüenza, J.; Izquierdo, C.; Díez, E.; Fernández, R.; Lassaletta, J. M. *Dalton Trans.* **2018**, *47*, 5196–5206.

supported by more traditional NHC ligands such as [IMes(NCMe)]SbF_6 and [IPrAu(NCMe)]SbF_6 gave chromene **1.56** in poorer result.[84]



Scheme 1.8. Cationic triazoquinoline ligands in gold(I) catalysis.

Fernández and Lassaletta also reported neutral axially-chiral NHC-gold(I) complexes **1.64a-c** and **1.65** containing a similar triazoquinoline-modified biaryl core for enantioselective transformations (Scheme 1.9). In particular the enantioselective intermolecular (4+2) cycloaddition of allenamides **1.57** and dienes **1.58** afforded enantioenriched cyclohexenes **1.59**.[85]



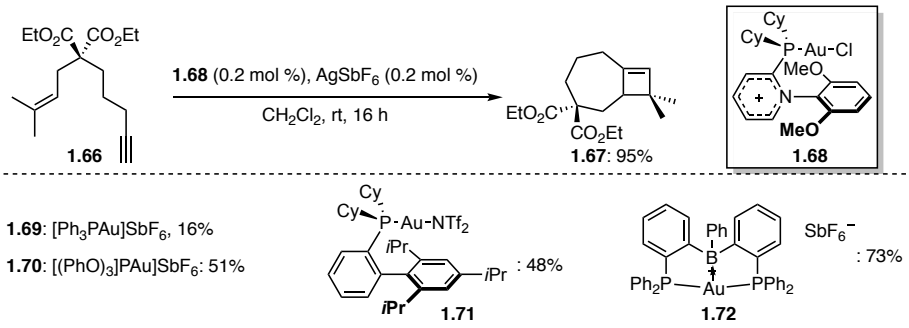
Scheme 1.9. Axially-chiral triazoquinoline-biaryl-based ligands and their application in catalysis.

84. Lau, V. M.; Pfalzgraff, W. C.; Markland, T. E.; Kanan, M. W. *J. Am. Chem. Soc.* **2017**, *139*, 4035–4041.

85. Francos, J.; Grande-Carmona, F.; Faustino, H.; Iglesias-Sigüenza, J.; Díez, E.; Alonso, I.; Fernández, R.; Lassaletta, J. M.; López, F.; Mascareñas, J. L. *J. Am. Chem. Soc.* **2012**, *134*, 14322–14325.

Similarly, allenamides **1.60**, styrenes **1.61** and aldehydes **1.62** engage in a [2+2+2] cycloaddition to give chiral pyranes **1.63**.[86] Related chiral ligands in which the biaryl scaffold is incorporated into an imidazole core were also reported.[87]

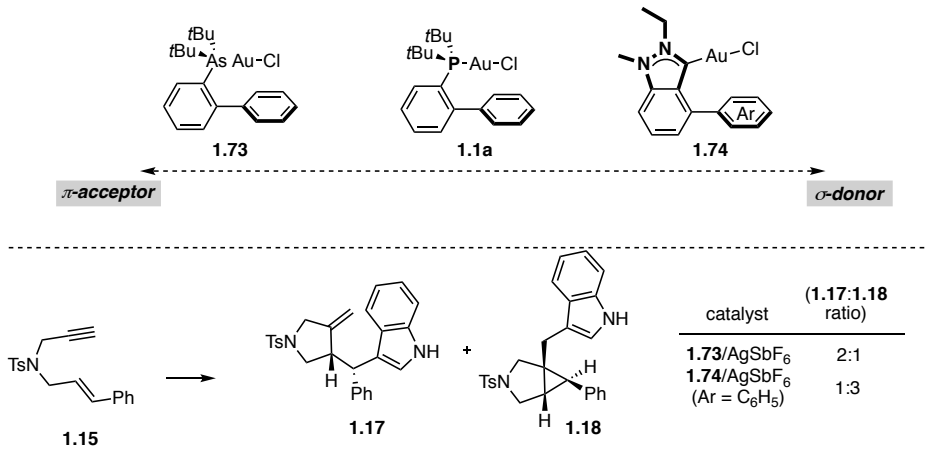
A series of gold(I) complexes of type **1.68** supported by cationic *N*-arylpyridinophosphines have been reported by Alcarazo (Scheme 1.10). In this ligand design, the strong π-acceptor property of pyridinophosphines[88] and the robustness of biaryl phosphine ligands is combined. The cationic nature of the ligand allows for the activation of poorly reactive substrates and the bottom aryl ring provides stabilization preventing the catalyst from decomposition. This class of modified dialkylbiaryl phosphine ligands performed well in the gold(I)-catalyzed intramolecular [2+2] reaction of 1,8-enyne **1.66** giving bicyclo[5.2.0]non-7-ene **1.67** in 95% yield. In comparison, other catalysts including **1.69-1.72** gave **1.67** in modest to moderate yields.



Scheme 1.10. Performance of **1.68** in catalysis.

Our group also contributed to the synthesis of electronically tuned JohnPhos-type ligands with both π-acceptor and σ-donor properties.[89] The arsine analogue of JohnPhos featuring more π-acceptor character and the corresponding gold(I) complex **1.73** was synthesized (Scheme 1.11). To study the other side of the electronic spectrum, a family of gold(I) complexes **1.74** supported by 4-arylindazole-incorporated biaryl ligands with σ-donating properties was also introduced.

86. Varela, I.; Faustino, H.; Díez, E.; Iglesias-Sigüenza, J.; Grande-Carmona, F.; Fernández, R.; Lassaletta, J. M.; Mascareñas, J. L.; López, F. *ACS Catal.* **2017**, *7*, 2397–2402.
87. (a) M. Espina, I. Rivilla, A. Conde, M. M. Díaz-Requejo, P. J. Pérez, E. Álvarez, R. Fernández, J. M. Lassaletta, *Organometallics* **2015**, *34*, 1328–1338. (b) F. Grande-Carmona, J. Iglesias-Sigüenza, E. Álvarez, E. Díez, R. Fernández, J. M. Lassaletta, *Organometallics* **2015**, *34*, 5073–5080.
88. (a) Tinnermann, H.; Wille, C.; Alcarazo, M. *Angew. Chem. Int. Ed.* **2014**, *53*, 8732–8736. (b) Alcarazo, M. *Acc. Chem. Res.* **2016**, *49*, 1797–1805.
89. Carreras, J.; Pereira, A.; Zanini, M.; Echavarren, A. M. *Organometallics* **2018**, *37*, 3588–3597.

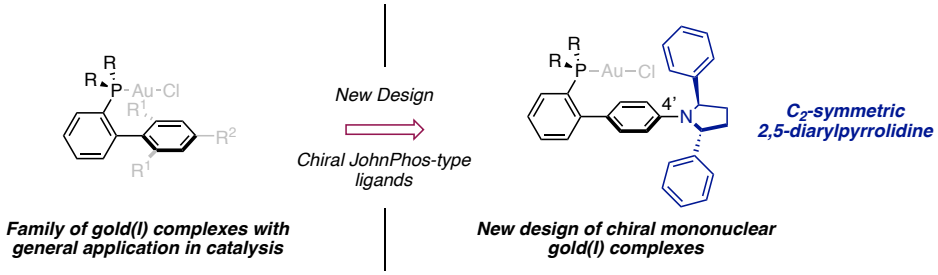


Scheme 1.11. Electronic variation of JohnPhos and their performance in catalysis.

The reaction of enyne **1.15** with indole as external nucleophile was chosen to evaluate the catalytic performance of the new complexes and, as expected,[8] **1.73** favors the formation of **1.17** while **1.18** is preferentially formed in presence of **1.74** supported by σ-donating arylindazole ligand.

Objectives

In view of the general applicability and importance of biaryl phosphine ligands in homogeneous gold(I) catalysis, as well as their relatively straight forward synthesis, we envisioned to base a chiral ligand design on this privileged scaffold. As presented in the introduction of this chapter, the group of Liming Zhang showcased how the particular geometry of the biphenyl scaffold could be exploited for the discovery of new reactivities upon judicious functionalization. Hence, we sought to functionalize the lower phenyl ring of a JohnPhos-type ligand at the 4' position with C_2-symmetric 2,5-diarylpyrrolidines as the chiral element (Scheme 1.12). Importantly, in this ligand design the chiral information is appropriately positioned next to the reactive center taking into consideration the outer-sphere mechanism of gold(I)-catalyzed transformations.



Scheme 1.12. New design of chiral mononuclear gold(I) catalyst.

To render this class of pyrrolidinyl-biphenyl phosphine ligands synthetically accessible we planned to develop a modular synthesis.

The asymmetric activation of non-prochiral alkynes by Au(I) catalysis is considered to be highly challenging. Hence, we decided to study the performance of this new complexes in three different cyclizations of 1,6-enynes.

Results and Discussion

Key Properties of the Catalyst Design

We envisioned that the well-defined geometry of bulky dialkylbiaryl phosphine ligands such as JohnPhos would represent the optimal platform to address the difficulties in asymmetric gold(I) catalysis arising from the linear dicoordination adopted by the metal. The design of chiral JonPhos-type ligands was guided by the ultimate challenge of placing chiral information around the reactive center (hence, the substrate). Thus, functionalizing the lower phenyl ring at position 4' with C_2-symmetric *trans*-2,5-diarylpyrrolidines would result in a ligand design that meets the required geometrical properties and considers the outer-sphere mechanism of gold(I)-catalyzed transformations (Figure 1.2). This type of chiral pyrrolidines has been employed as organocatalysts,[90] chiral auxiliaries[91] and in the backbone of chiral ligands.[92] In addition, the chiral 2,5-diarylpyrrolidine represents an unambiguous source of chirality as it acts as a local C_2-axis, preventing formation of rotamers.

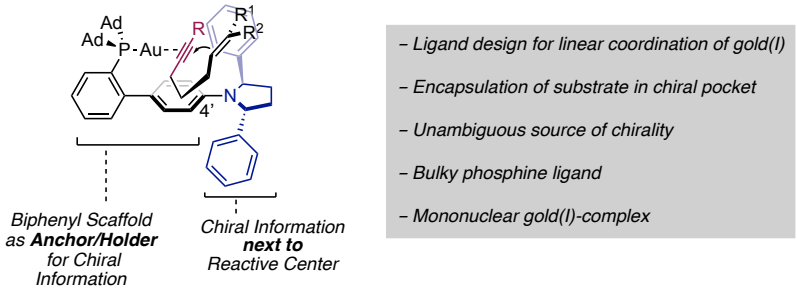


Figure 1.2. New catalyst design with key properties.

The rigid biphenyl scaffold serves as an anchor/holder to connect the chiral 2,5-diarylpyrroldine and the coordinating phosphine enclosing the gold(I) nucleus in a chiral pocket. Bulky substituents on the phosphines are essential to prevent rotation around the

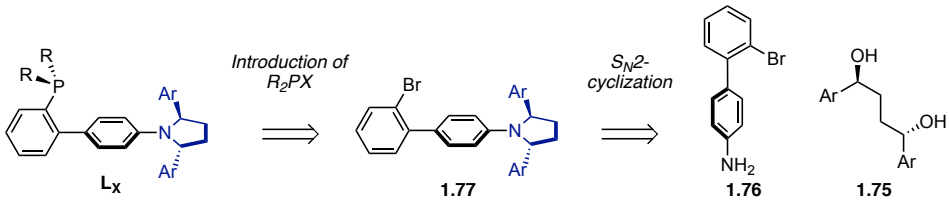
90. (a) Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 4790–4791. (b) Fadeyi, O. O.; Schulte, M. L.; Lindsley, C. W. *Org. Lett.* **2010**, *12*, 3276–3278. (c) Zhang, X.; Song, X.; Li, H.; Zhang, S.; Chen, X.; Yu, X.; Wang, W. *Angew. Chem. Int. Ed.* **2012**, *51*, 7282–7286. (d) Kemppainen, E. K.; Sahoo, G.; Piisola, A.; Hamza, A.; Kõtai, B.; Pápai, I.; Pihko, P. M. *Chem. Eur. J.* **2014**, *20*, 5983–5993.
91. Liu, Z.; Qu, H.; Gu, X.; Min, B. J.; Nyberg, J.; Hruby, V. J. *Org. Lett.* **2008**, *10*, 4105–4108.
92. (a) Chen, H.; Sweet, J. A.; Lam, K. C.; Rheingold, A. L.; McGrath, D. V. *Tetrahedron: Asymmetry* **2009**, *20*, 1672–1682. (b) Choi, Y. H.; Choi, J. Y.; Yang, H. Y.; Kim, Y. H. *Tetrahedron: Asymmetry* **2002**, *13*, 801–804. (c) Denmark, S. E.; Chang, W. T. T.; Houk, K. N.; Liu, P. *J. Org. Chem.* **2015**, *80*, 313–366.

C_{aryl}–P bond and force the P–Au–Cl axis to be parallel to the biphenyl axis and point towards the chiral information. Finally, the design is based on a mononuclear, rather than on a dinuclear gold(I) complex, which facilitates mechanistic investigations and studies on their mode of action.

Synthesis of Pyrrolidinyl-biaryl Phosphine Ligands

First Synthetic Approaches

Encouraged by the reports of Yamada[93] and Rao[94] on the synthesis of C_2-symmetric pyrrolidines, our retrosynthesis of ligands **L**x was based on the late-stage introduction of the bulky phosphines from precursor **1.77** (Scheme 1.13). The chiral pyrrolidine moiety in **1.77** would be constructed via S_N2 reaction from biphenyl amine **1.76** and the bis-mesylate derivative of 1,4-diarylbutane-1,4-diol **1.75**, formed *in situ*. Additionally, amine **1.76** was prepared adapting a modified literature procedure (See Experimental section).[95]

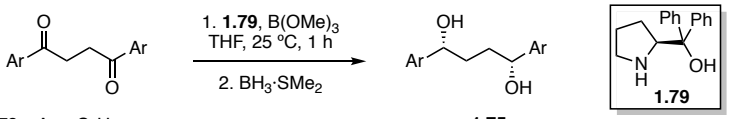


Scheme 1.13. Retrosynthetic analysis of ligands **L**x.

In our first approach, chiral 1,4-diols **1.75a-c** were synthesized by Corey-Bakshi-Shibata reduction of the corresponding 1,4-diones **1.78a-c**[90b,96] following a procedure adapted from the literature.[92a 97] Despite the robustness of this method, 1,4-diols **1.75a,b** were obtained in excellent yields and enantiomeric ratios, albeit as a 6:1 and 4:1 mixture of diastereomers, respectively (Table 1.1, entries 1 and 2). Thus, the subsequently planned stereospecific cyclization would lead to substantial amounts of *meso*-**1.77**.

93. Sato, M.; Gunji, Y.; Ikeno, T.; Yamada, T. *Synthesis* **2004**, 1434–1438.
94. Periasamy, M.; Seenivasaperumal, M.; Rao, V. D. *Synthesis* **2003**, 2507–2510.
95. Lemenovskii, D. A.; Makarov, M. V.; Dyadchenko, V. P.; Bruce, A. E.; Bruce, M. R. M.; Larkin, S. A.; Averkiev, B. B.; Starikova, Z. A.; Antipin, M. Y. *Russ. Chem. Bull.* **2003**, *52*, 607–615.
96. Le, N. N.; Rodriguez, A. M.; Alleyn, J. R.; Gesinski, M. R. *Synlett* **2018**, *29*, 2195–2198.
97. Kemppainen, E. K.; Sahoo, G.; Valkonen, A.; Pihko, P. M. *Org. Lett.* **2012**, *14*, 1086−1089.

Table 1.1. Corey-Bakshi-Shibata reduction of 1,4-diones **1.78a-c**.



1.78a: Ar = C_6H_5
1.78b: Ar = 4-$MeOC_6H_4$
1.78c: Ar = 3,5-(tBu)$_2C_6H_3$

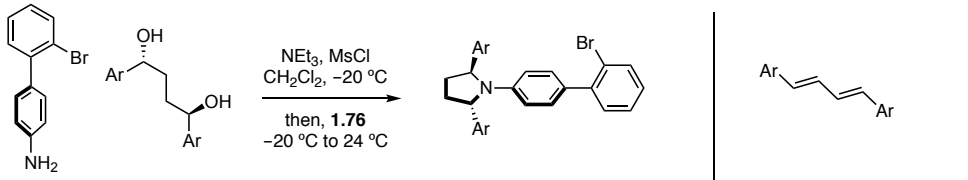
1.75a-c

entry	Ar	yield (%)[a]	*er*[b]	dr*(trans/meso)*[c]
1	C_6H_5	95	>99:1	6:1
2	4-$MeOC_6H_4$	96	>99:1	4:1
3	3,5-(tBu)$_2C_6H_3$	95	55:45	1:1

[a]Isolated yields. [b]*er* determined by chiral HPLC. [c]*dr* determined by crude ^{1}H NMR.

Furthermore, the reduction turned out to be sensitive to sterical hindrance. Thus, reduction of 1,4-dione **1.78c** led to 1,4-diol **1.75c** with a very low *er* (55:45) and as a 1:1 mixture of diastereomers (Table 1.1, entry 3).[98]

We continued the ligand synthesis by *in situ* mesylation of 1,4-diols **1.75a,b** followed by S_N2 reaction with aniline **1.76** to give **1.77a,b** (Scheme 1.14). Compound **1.77a** was isolated in good yields as a 6:1 mixture of *trans*/*meso* isomers, which were separated by recrystallization.



1.75a: Ar = C_6H_5
1.75b: Ar = 4-$MeOC_6H_4$

1.77a: Ar = C_6H_5 (52%, 6:1 *dr*)
177b: Ar = 4-$MeOC_6H_4$ (24%, 1:1 *dr*)

1.80: Ar = 4-$MeOC_6H_4$ (20%)

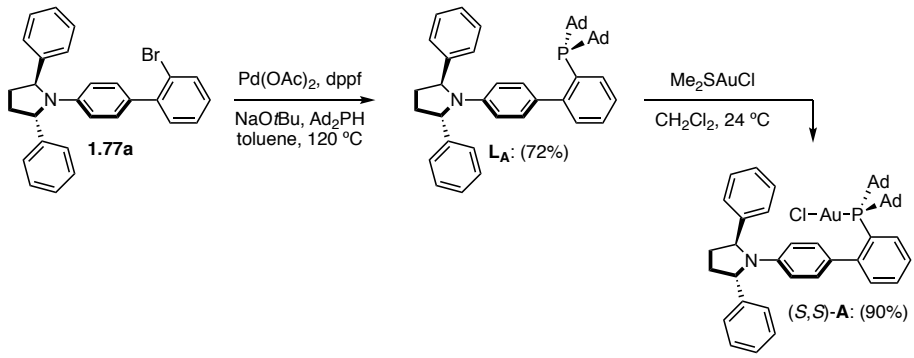
Scheme 1.14. Synthesis of pyrrolidinylbiphenyl bromides **1.77a,b**.

In contrast, intermediate **1.77b** was obtained from benzylic 1,4-diol **1.75b** in a moderate 24% yield as a 1:1 mixture of diastereomers along with a substantial amount of the elimination product **1.80**. The formation of diene **1.80** indicates that a competing E1 pathway takes place whereby the electron donating methoxy substituent at the aromatic rings favors the formation of a benzylic carbocation. More importantly, the chiral information was lost during the construction of the pyrrolidine ring, since **1.77b** was

98. Kündig, E. P.; Botuha, C.; Lemercier, G.; Romanens, P.; Saudan, L.; Thibault, S. *Helv. Chim. Acta* **2004**, *87*, 561–579.

isolated as a racemic mixture, suggesting the formation of **1.77b** to proceed through a S_N1 mechanism. Thus, the developed synthetic route was limited to benzylic 1,4-diols with electron deficient aryl rings

Precursor **1.77a** was subjected to Pd-catalyzed cross-coupling conditions to introduce the bulky adamantyl-phosphine moiety and ligand $\mathbf{L_A}$ was isolated in 72% yield.[99] Complexation of $\mathbf{L_A}$ with [Me_2SAuCl] proceeded smoothly and afforded (*S*,*S*)-**A** in 90% yield (Scheme **1.15**).

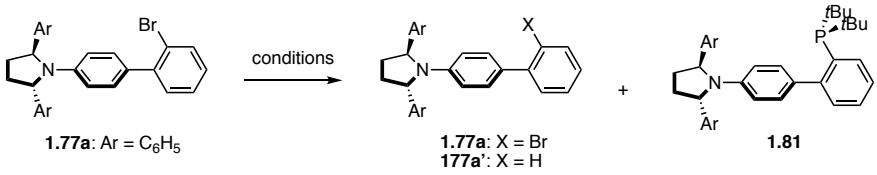


Scheme 1.15. Endgame of the synthesis of complex (*S*,*S*)-**A**.

Importantly, other methods for the introduction of the phosphine were unsuccessful (Table 1.2). Adapting the procedure reported by Buchwald[100] employing metallic magnesium and tBu$_2$PCl gave only traces of di-*tert*-butylphosphine **1.81** along with a significant amount of non-reacted starting material **1.77a** and reduced **1.77a'** (Table 1.2, entry 1). Bromine-magnesium exchange using iPrMgCl or bimetallic iPrMgCl·Li complex[101] followed by addition of tBu$_2$PCl (Table 1.2 entry 2) gave traces of reduced **1.77a'**, whereas halogen-lithium exchange and reaction with Ph_2PCl only lead to decomposition of **1.77a** (Table 1.2, entry 3).

99. Zuccarello, G.; Mayans, J. G.; Escofet, I.; Scharnagel, D.; Kirillova, M. S.; Pérez-Jimeno, A. H.; Calleja, P.; Boothe, J. R.; Echavarren, A. M. *J. Am. Chem. Soc.* **2019**, *141*, 11858–11863.
100. (a) Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4369–4378. (b) (8) Tomori, H.; Fox, J. M.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 5334–5341.
101. (a) Krasovskiy, A.; Knochel, P. *Angew. Chem Int. Ed.* **2004**, *43*, 3333–3336. (b) Ziegler, D. S.; Wei, B.; Knochel, P. *Chem. Eur. J.* **2019**, *25*, 2695–2703. (c) Kunz, T.; Knochel, P. *Angew. Chem. Int. Ed.* **2012**, *51*, 1958–1961.

Table 1.2. Introduction of bulky phosphines.



1.77a: Ar = C_6H_5 | **1.77a**: X = Br, **177a'**: X = H | **1.81**

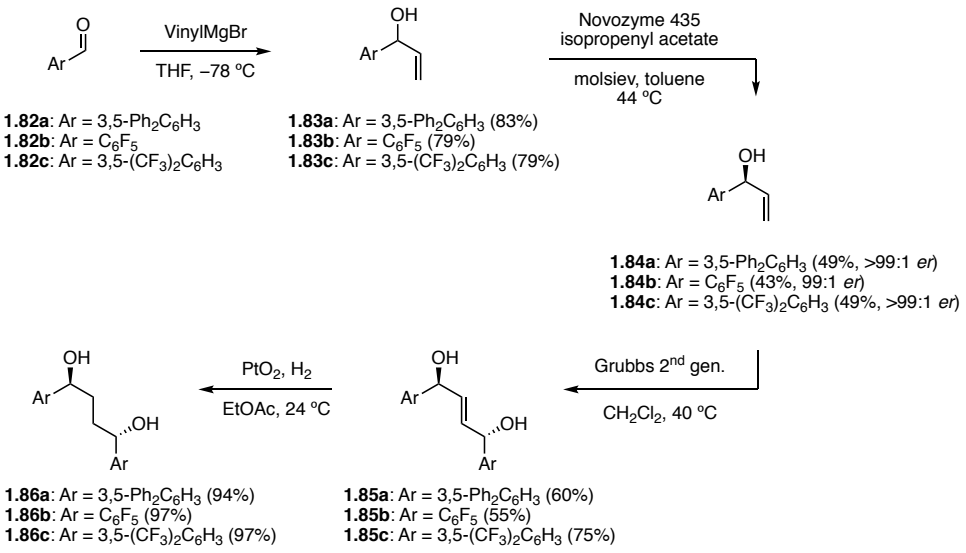
		ratios[a]		
entry	**conditions**	**1.77a**	**1.77a'**	**1.81**
1	Mg, THF, 66 ºC, 2 h; then CuCl, *t*Bu$_2$PCl	2	1	traces
2	*i*PrMgCl *or* *i*PrMgCl·LiCl, toluene/THF (8:1) 20 ºC, 2 h; then CuCl, *t*Bu$_2$PCl	-[b]	traces	-
3	*n*BuLi, THF/Et$_2$O (1:2), –20 to 0 ºC: then Ph$_2$PCl	-[b]	-	-

[a]Ratios determined by ^{1}H NMR in crude reaction mixtures. [b]Decomposition.

Uniform Synthetic Route

The aforementioned limitations to access chiral 1,4-diarylbutane-1,4-diols of type **1.75** via Corey-Bakshi-Shibata reduction made the synthetic strategy rather unattractive. Thus, our general interest in synthesizing a small family of pyrrolidinyl-biphenyl phosphine ligands called for an improved and reliable synthetic plan. We developed a more general synthetic route to access substituted benzylic 1,4-diols **1.86a-c** based on alkene methatesis. Starting from the corresponding benzaldehydes **1.82a-c**, vinylmagnesium bromide addition afforded allylic alcohols **1.83a-c** in good yields (79-83%) (Scheme 1.16). Essentially enantiopure allylic alcohols **1.84a-c** were obtained in excellent yields (43-49%) by enzymatic kinetic resolution using Novozyme 435 and isopropenyl acetate.[102] Alkene metathesis using Grubbs 2nd generation catalyst[103] afforded allylic 1,4-diols **1.85a-f** in moderate to good yields. Enantiopure benzylic (*S*,*S*)-1,4-diols **1.86a-c** were obtained in quantitative yield by hydrogenation in presence of catalytic amounts of Adams' precatalyst.[104]

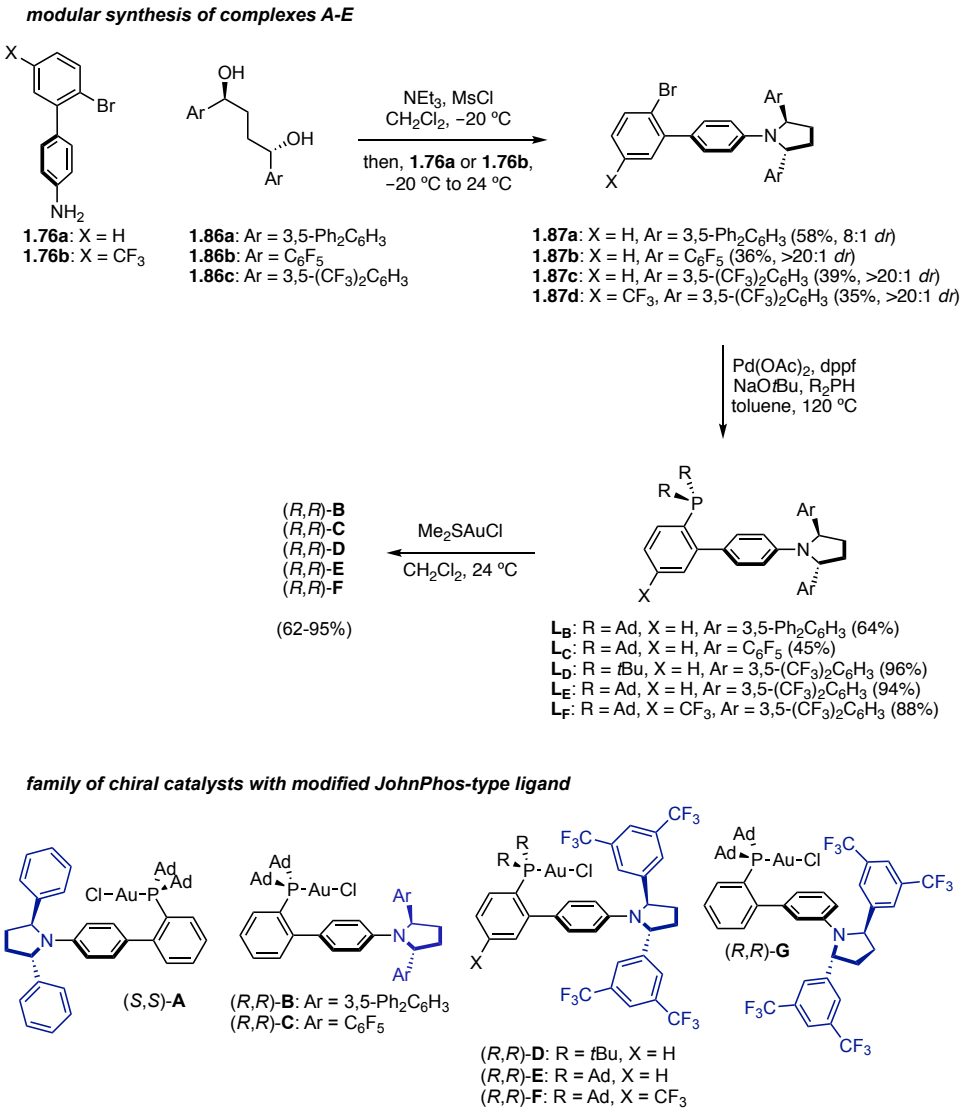
102. (a) Štambaský, J.; Malkov, A. V.; Kočovský, P. *J. Org. Chem.* **2008**, *73*, 9148–9150. (b) Kirillova, M. S.; Muratore, M. E.; Dorel, R.; Echavarren, A. M. *J. Am. Chem. Soc.* **2016**, *138*, 3671–3674.
103. (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956. (b) Carbenes, C. M. N.; Carbenes, C. B. N.; N, S. R. **2010**, *110*, 1746–1787.
104. Voorhees, V.; Adams, R. *J. Am. Chem. Soc.* **1922**, *44* (6), 1397–1405.



Scheme 1.16. Synthesis of enantiopure (*S*,*S*)-1,4-diaryl-1,4-diols **1.86a-c**.

With enantiopure (*S*,*S*)-1,4-diarylbutane-1,4-diols **1.86a-c** in hand, we synthesized complexes (*R*,*R*)-**B**-**F** (Scheme 1.17a). As previously described for the synthesis of complex (*S*,*S*)-**A**, *in situ* mesylation of diols **1.86a-c** and sequential reaction with anilines **1.76a,b** through a double S_N2 reaction with inversion of configuration led to pyrrolidinyl-biphenyl bromide precursors **1.87a-d** in good yields (35 to 58%) and excellent diastereomeric ratios (8:1 to >20:1 *dr*). The bulky phosphines were introduced by means of Pd-catalyzed coupling reaction[99] giving ligands $\mathbf{L_B}$-$\mathbf{L_F}$ in good to excellent yields (45-96%). Further complexation with [Me_2SAuCl] gave complexes (*R*,*R*)-**B**-**F**. Complex (*R*,*R*)-**G** bearing chiral 2,5-bis(3,5-bis(trifluoromethyl)phenyl)pyrrolidine at position 3' was synthesized analogously from 2′-bromo-(1,1′-biphenyl)-3-amine and diol **1.86c** and was obtained as a 5:1 mixture of rotamers.[105] The structures of complexes (*S*,*S*)-**A** and **D**-**G** were confirmed by single-crystal X-ray diffraction.

105. The synthesis of (*R*,*R*)-**G** was performed in collaboration with Alba H. Pérez-Jimeno.



Scheme 1.17. Synthetic route and family of JohnPhos-type ligands-supported complexes **A-G**.

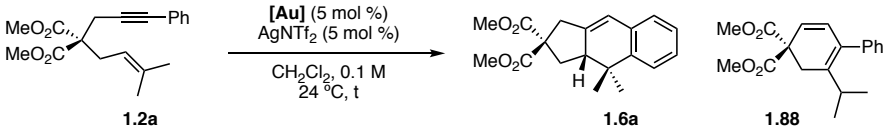
Application of Complexes A-G in Catalysis

Formal [4+2] Cycloaddition

We studied the performance of the novel pyrrolidinyl-biphenyl phosphine-supported gold(I) complexes **A-G** in the formal [4+2] cycloaddition of 1,6-arylenyne **1.2a**. In the

presence of complexes **A**-**G** and $AgNTf_2$ in CH_2Cl_2, 1,6-arylenyne **1.2a** was converted into cyclopenta[*b*]naphthalene **1.6a** (Table 1.3.).

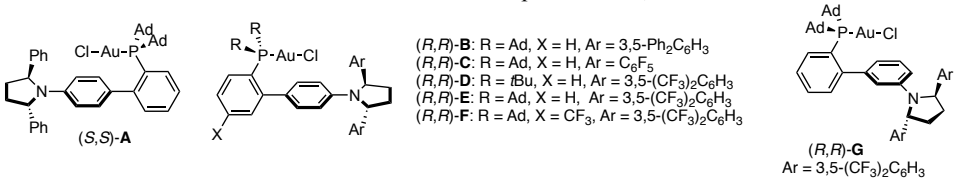
Table 1.3: Screening of chiral gold(I) complexes.[a]



1.2a **1.6a** **1.88**

entry	[Au]	T (*h*)	yield (%)[b]	*er*[c]
1	(*S*,*S*)-**A**	40	75	20:80
2	(*R*,*R*)-**B**	40	61	84:16
3	(*R*,*R*)-**C**	40	93	85:15
4	(*R*,*R*)-**D**	43	39[d]	86:14
5	(*R*,*R*)-**E**	43	56[e]	90:10
6	(*R*,*R*)-**F**	40	57[f]	92:8
7	(*R*,*R*)-**G**	46	74	24:76

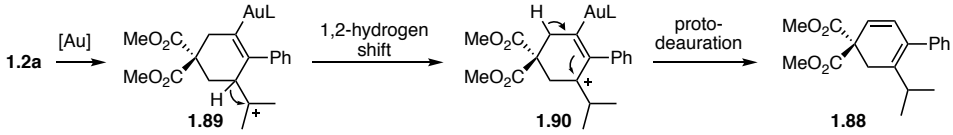
[a]**1.2a** = 0.1 mmol scale. [b]Yields determined by 1H NMR using 1,3,5-tribromobenzene as internal standard. [c]*er* determined by chiral HPLC. [d]58% conversion. [e]68% conversion. [f]6% of side product **1.88**; 82% conversion.



To our delight, complex (*S*,*S*)-**A** gave **1.6a** in 75% yield and promising 20:80 *er* (Table 1.3, entry 1). Interestignly, complex (*R*,*R*)-**C** bearing 2,5-bis(perfluorophenyl)pyrrolidine in the ligand backbone afforded **1.6a** in excellent 93% yield and slightly higher 85:15 *er* compared to complex (*R*,*R*)-**B** (61%, 84:16 *er*) with significantly bulkier 2,5-di([1,1':3',1"-terphenyl]-5'-yl)pyrrolidine (Table 1.3, entries 2 and 3). This observation suggests that the electronic properties of the substituents at the chiral pyrrolidine predominate over steric factors in achieving improved enantiomeric ratios. In contrast, the steric bulk arising from the di-adamantyl-phospine moieties in complexes (*R*,*R*)-**E** and (*R*,*R*)-**F** proved to be beneficial for a higher *er* giving **1.6a** in 56-57% yield and 90:10 and 92:8 *er*, respectively (Table 1.3, entries 5 and 6). In comparison, complex (*R*,*R*)-**D** with di-*tert*-butylphosphine afforded product **1.6a** in lower yield and enantiomeric ratio (39%, 86:16 *er*) (Table 1.3, entry 4). Despite the absolute configuration at the chiral pyrrolidines in complexes **B**-**F** and

G being identical, (*R*,*R*)-**G** favors the formation of the opposite enantiomer *ent*-**1.6a** in good yield and moderate *er* (Table 1.3, entry 7).

The reaction with complex (*R*,*R*)-**F** gave significant amounts of cyclohexadiene **1.88** as a side product, whose isolation was not possible by preparative TLC nor by preparative HPLC (Scheme 1.18). Its structure was proposed by ^{1}H NMR based on characteristic signals and is in accordance with side products previously observed by our group in similar transformations.[61]

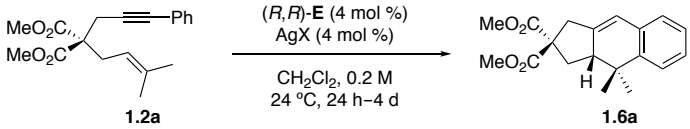


Scheme 1.18. Proposed mechanism for the formation of **1.88**.

A possible mechanism for the formation of **1.88** includes 6-*endo*-dig cyclization forming gold(I)-stabilized carbocation **1.89** followed by 1,2-hydrogen shift and protodeauration from **1.90** (Scheme 1.18). With the remaining complexes, diene **1.88** was only observed in very small amounts.

Further reaction optimization was carried out using complex (*R*,*R*)-**E**. The addition of 1 equiv of TFA with respect to the catalyst loading as well as using (*R*,*R*)-**E**/$AgNTf_2$ in a 1:2 ratio led to a decrease in *er* (Table 1.4, entries 1 and 2). Presumably, in presence of a Brønsted or Lewis acid the geometry of the pyrrolidine is modified upon protonation or coordination of the nitrogen to the Lewis acid. Furthermore, among the screened chloride scavengers, $AgPF_6$ performed best giving **1.6a** in 78% and slightly improved 91:9 *er* (Table 1.4, entry 5). In absence of (*R*,*R*)-**E**, only starting 1,6-enyne **1.2** was recovered.

Table 1.4. Screening of chloride scavengers and additives.



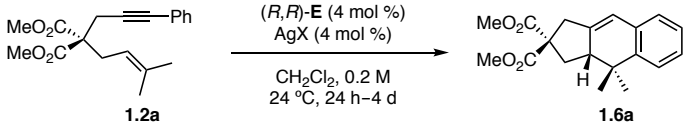
entry	AgX	additives	yield (%)[a]	*er*
1	$AgNTf_2$	TFA	75	88:12
2	$AgNTf_2$[b]	-	67	86:14
3	$NaBAr^F{}_4$	-	[c]	87:13
4	$AgSbF_6$	-	88	87:13
5	$AgPF_6$	-	78	91:9
6	AgOTf	-	-	-

7	$AgBF_4$	-	60	82:18
8	AgOBn	-	-	-
9	AgAc	-	-	-
10	AgTFA	-	36	85:15
11	AgF	-	-	-
12	$[Ag(MeCN)_2]SbF_6$	-	42[e]	82:18

[a]Yields determined by ^{1}H NMR using 1,3,5-tribromobenzene as internal standard. [b]2 equiv of $AgNTf_2$ per gold complex. [c]After 60 h reaction time the SM/product ratio, was estimated by ^{1}H NMR to be 5:1. [d]Reaction run at -5 ºC for 4 d, 90% conversion. [e]After 60 h reaction time 42% conversion.

Turning our attention to solvent effects, performing the reaction in 1,2-dichloroethane improved both yield and *er* slightly (83%, 92:8 *er*) (Table 1.5, entry 1). Using a 3:1 mixture of 1,2-dichloroethane/HFIP resulted in a minor decrease in yield and *er* (78%, 90:10 *er*) probably due to interactions between HFIP and the chiral pyrrolidine through H-bonding (Table 1.5, entry 6).[106] Decreasing the reaction temperature to –5 ºC gave **1.6a** with 93:7 *er* albeit in modest 21% yield and long reaction times (4 days) were required (Table 1.5, entry 7).

Table 1.5. Screening of solvents.



1.2a **1.6a**

entry	**solvent**	**yield (%)**[a]	***er***
1	1,2-dichloroethane	83	92:8
2	PhCl	-	-
3	benzene	-	-
4	EtOAc	19	87:13
5	THF	-	-
6	$ClCH_2CH_2Cl$/HFIP 3:1	78	90:10
7[b]	1,2-dichloroethane	21	93:7
8	α,α,α-trifluorotoluene	65	91:9
9	1,3-α,α,α-bis(trifluoromethyl)benzene	21	85:15
10	anisole	-	-
11	$CHCl_3$	-	-

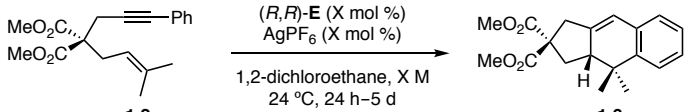
106. Berkessel, A.; Adrio, J. A.; Hüttenhain, D.; Neudörfl, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 8421–8426.

12	1,1,2-trichloroethane	-	-
13	1,1,2,2-tetrachloroethane	-	-

[a]Yields determined by ^{1}H NMR using 1,3,5-tribromobenzene as internal standard.
[b]Run at –5 ºC, t = 4 d, 90% conversion.

Finally, maintaining 4 mol % of catalyst loading and lowering the reaction concentration to 0.05 M afforded compound **1.6a** in 83% yield and 93:7 *er* (Table 1.6, entry 3).

Table 1.6. Screening of catalyst loading and molarity.



1.2a **1.6a**

entry	(*R*,*R*)-D (mol %)	concentration (M	yield (%)[a]	*er*
1	4	0.5	73	92:8
2	4	0.1	76	92:8
3	4	0.05	83(64)[b]	93:7
4	4	0.01	-	-
5	2	0.05	[c]	91:9
6	1	0.05	-[d]	-

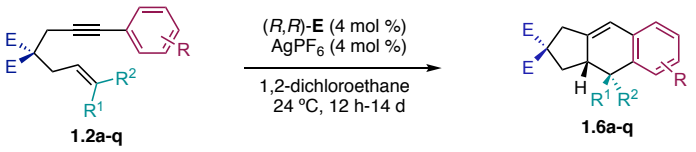
[a]Yields determined by ^{1}H NMR using 1,3,5-tribromobenzene as internal standard.
[b]Isolated yield. [c]After 16 h reaction time the SM/product ratio, was estimated by ^{1}H NMR to be 3:1. [d]No reaction after 16 h.

Scope of the Enantioselective Formal [4+2] Cyclization

With the optimized reaction conditions in hand we investigated the reaction scope (Table 1.7). In general, fused tricyclic compounds **1.6a-q** were obtained from the corresponding 1,6-arylenynes **1.2a-q**. 1,6-Enynes **1.2b,c** with Me- and MOM-protected diols in the tether gave **1.6b,c** in good yields and selectivities (94:6 and 93:7 *er*). On the contrary, diacetate **1.6d** was obtained with lower enantioselectivities (79:21 *er*). Electron donating (**1.6e**,**1.6l** and **1.6n**) and electron withdrawing substituents (**1.6f** and **1.6i**) as well as aliphatic substituents (**1.6g** and **1.6k**) on the aromatic ring were well tolerated giving consistently good results (90:10 to 96:4 *er*). Compounds **1.6h**, **1.6m** and **1.6o** were also isolated in excellent yields (91-98%) and enantiomeric ratios (93:7 to 95:5 *er*). The cyclization of 1,6-enynes **1.2p,q**, which led to **1.6p,q** as single diastereomers required long reaction times (7 and 14 days, respectively), whereby **1.6p** was isolated in 77% yield and

93:7 *er* and **1.6q** in 61% yield and 81:19 *er*. Replacing the Me-protected diols in enynes **1.2p,q** by dimethylmalonate resulted in no formation of the corresponding product.

Table 1.7. Scope of formal [4+2] cycloaddition.



1.2a-q → **1.6a-q**

1.6a: E = CO_2Me (64%, 93:7 *er*)
1.6b: E = CH_2OMe (92%, 94:6 *er*)
1.6c: E = CH_2OMOM (91%, 93:7 *er*)
1.6d: E = CH_2OAc (94%, 79:21 *er*)

1.6e: R = OMe (97%, 96:4 *er*)
1.6f: R = NO_2 (94%, 90:10 *er*)
1.6g: R = *t*Bu (99%, 91:9 *er*)
1.6h: R = Cl (97%, 94:6 *er*)
1.6i: R = CF_3 (97%, 91:9 *er*)

1.6j: R = F (88%, 93:7 *er*)
1.6k: R = Me (85%, 95:5 *er*)

1.6l: (90%, 93:7 *er*)

1.6m: (91%, 95:5 *er*)

1.6n: (85%, 96:4 *er*)

1.6o: (98%, 93:7 *er*)

1.6p: (77%, 93:7 *er*)

1.6q: (61%, 81:19 *er*)

The absolute configuration of **1.6o** was assigned by single-crystal X-ray diffraction[107] to be (*R*), and those of the remaining cycloadducts were correlated by circular dichroism.[108] The CD-spectra have been measured from 0.025–0.05 M solutions in MeCN of the corresponding compounds and display a positive Cotton effect around 250–280 nm (Figure 1.3).

107. Escudero-Adán, E. C.; Benet-Buchholz, J.; Ballester, P. *Acta Crystallogr., Sect. B: Struct. Sci., Cryst. Eng. Mater.* **2014**, *70*, 660−668.
108. Klyagina, A. P.; Golovaneva, I. F.; Sadikov, G. G.; Levin, A. A. *Russ. Chem. Bull.* **1990**, *39*, 1615–1617.

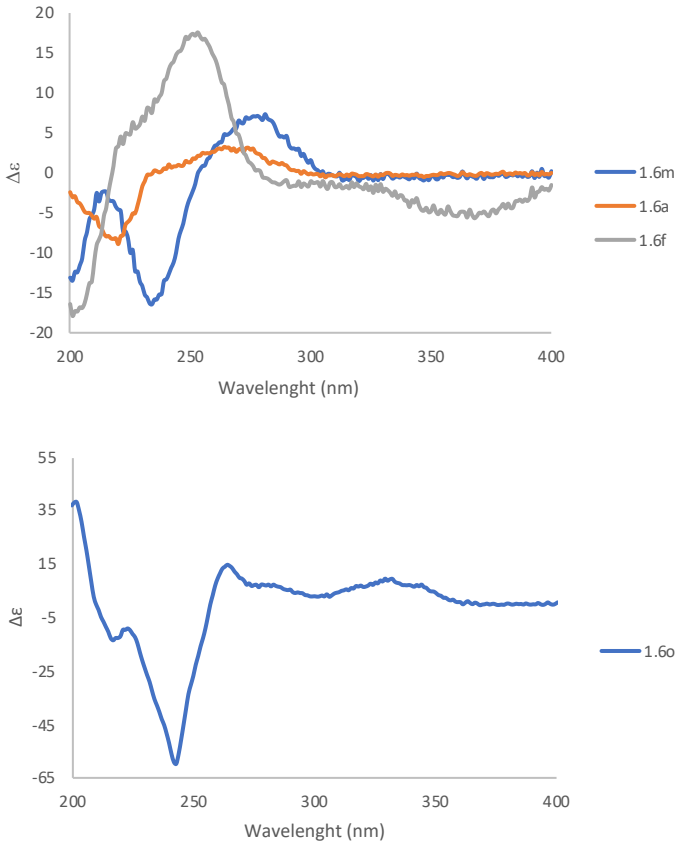


Figure 1.3. CD-spectra of compounds **1.6a**, **1.6f**, **1.6m** and **1.6o**.

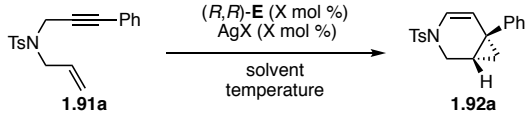
Synthesis of Azabicyclo[4.1.0]hept-4-enes

To further study the generality of our designed complexes we investigated the cyclization of nitrogen-tethered 1,6-arylenyne **1.91a** which under gold(I) and $PtCl_2$-catalyzed[109] reaction conditions gives azabicyclic compound **1.92a** via a 6-*endo*-dig cyclization pathway. Under the optimized reaction conditions previously found for the formal [4+2] cyclization of **1.2a**, **1.92a** was obtained with promising 87:13 *er*. However, a considerable amount of starting 1,6-enyne **1.91a** was recovered after 43 h reaction time (Table 1.8. entry 1). Replacing $AgPF_6$ by $AgBF_4$ was beneficial for the conversion of **1.91a** but formed **1.92a** with slightly lower *er* (Table 1.8, entry 2). Aromatic solvents had an important impact on the enantiomeric ratios giving **1.92a** with 93:7-95:5 *er* (Table 1.8,

109. (a) Fürstner, A.; Szillat, H.; Stelzer, F. *J. Am. Chem. Soc.* **2000**, *122*, 6785–6786. (b) Fürstner, A.; Stelzer, F.; Szillat, H. *J. Am. Chem. Soc.* **2001**, *123*, 11863–11869.

entries 3-5). Performing the reaction at 40 ºC gave **1.92a** in moderate 35% yield and good 95:5 *er*, whereas doubling the catalyst loading lead to a marginal decrease in *er* (Table 1.8, entry 3 and 4).

Table 1.8. Reaction optimization.



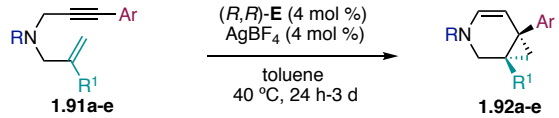
1.91a **1.92a**

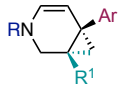
entry	(*R*,*R*)-E (mol %)	AgX (mol %)	solvent	T (ºC)	yield (%)[a]	*er*
1	4	$AgPF_6$ (4)	1,2-dichloroethane	24	-[b]	87:13
2	4	$AgBF_4$ (4)	1,2-dichloroethane	24	-[c]	85:15
3	4	$AgBF_4$ (4)	toluene	40	35 (49 brsm)	95:5
4	8	$AgBF_4$ (8)	toluene	24	51[d]	94:6
5	4	$AgBF_4$ (4)	chlorobenzene	24	21[e]	93:7
6	4	$AgBF_4$ (4)	$PhCF_3$	24	-[f]	-

[a]Isolated yields. [b]After 43 h reaction time the SM/product ratio, was estimated by ^{1}H NMR to be 3.6:1. [c]After 43 h reaction time the SM/product ratio, was estimated by ^{1}H NMR to be 1:1.2. [d]66% conversion. [e]34% conversion. [f]No conversion of starting material.

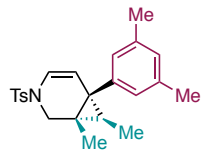
Nitrogen-tethered 1,6-enynes **1.91a-e** were converted into azabicyclo[4.1.0]hept-4-enes **1.92a-e** in good yields (35-89%) and enantiomeric ratios (90:10 to 95:5 *er*) (Table 1.9). However, mesyl-substituted **1.92d** was obtained with 74:26 *er*. 1,6-Enyne **1.91f** bearing a higher substituted alkene as well as **1.91g** containing a cyclopentene ring were converted into the desired compounds **1.92f** and **1.92g** in excellent yields (94-97%) and *er* (96:4-97:3). The absolute configurations were assigned by comparison with the literature.[32]

Table 1.9. Synthesis of Azabicyclo[4.1.0]hept-4-enes **1.92a-g**.

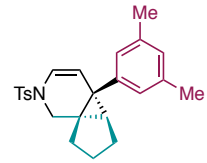




1.92a: R = Ts, R^1 = H, Ar = Ph (35%, 95:5 *er*)
1.92b: R = Ts, R^1 = Me, Ar = Ph (89%, 90:10 *er*)
1.92c: R = Ts, R^1 = H, Ar = *p*-$MeOC_6H_4$ (74%, 94:6 *er*)
1.92d: R = Ms, R^1 = Me, Ar = Ph (88%, 74:26 *er*)
1.92e: R = Cbz, R^1 = H, Ar = Ph (56%, 91:9 *er*)



1.92f: (97%, 97:3 *er*, 10:1 dr)



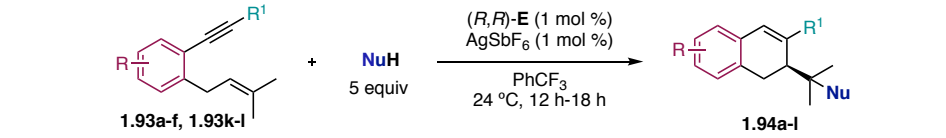
1.92g: (94%, 96:4 *er*)

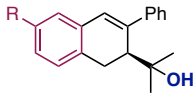
Synthesis of Substituted 1,2-Dihydronaphthalenes and Application in Total Synthesis

Guided by our ultimate goal to expand the scope of asymmetric cyclizations and encouraged by the excellent results obtained, we tested our catalysts on the 6-*endo*-dig cyclization of aryl-tethered 1,6-enynes **1.93** (Table 1.10). In presence of water and other external nucleophiles enynes **1.93** are converted into 2,3-substituted 1,2-dihydronaphthalenes **1.94**.[110] The reaction optimization was performed with enyne **1.93k**.[111] Before testing the pyrrolidinyl-biphenyl posphine-supported catalysts **A-G** we screened *ca.* 80 chiral ligands from different ligand families including axially-chiral bisphosphines, phosphoramidites and Josiphos-type ligands. The latter ligand class performed better, as already found for the enantioselective intermolecular [2+2] cycloaddition of alkynes with alkenes reported by our group,[112] giving **1.94k** with 80:20 *er*. Remarkably, complex (*R*,*R*)-**E** proved superior and gave hydroxycyclization product **1.94k** in 60% yield and outstanding 99:1 *er*.

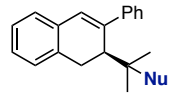
110. Sanjuán, A. M.; Martínez, A.; García-García, P.; Fernández-Rodríguez, M. A.; Sanz, R. *Beilstein J. Org. Chem.* **2013**, *9*, 2242–2249.
111. The reaction optimization has been performed by Joan G. Mayans, Pilar Calleja and Jordan R. Boothe.
112. García-Morales, C.; Ranieri, B.; Escofet, I.; López-Suarez, L.; Obradors, C.; Konovalov, A. I.; Echavarren, A. M. *J. Am. Chem. Soc.* **2017**, *139*, 13628−13631.

Table 1.10. Asymmetric synthesis of 1,2-dihydronaphthalenes **1.94a-l**.

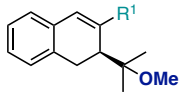




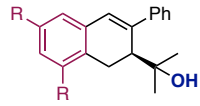
1.94a: R = H (68%, 97:3 *er*)
1.94b: R = CF_3, R^2 = H (69%, 94:6 *er*)
1.94c: R = Cl, R^2 = H (43%, 95:5 *er*)
1.94d: R = OMe, R^2 = H (60%, 97:3 *er*)



1.94e: NuH = allylalcohol (63%, 95:5 *er*)
1.94f: NuH = BnOH (75%, 95:5 *er*)
1.94g: NuH = AcOH (41%, 90:10 *er*)
1.94h: Nu = "F^-" (40%, 96:4 *er*)



1.94i: R^1 = *p*-ClC_6H_4 (50%, 96:4 *er*)
1.94j: R^1 = *p*-$MeOC_6H_4$ (52%, 96:4 *er*)



1.94k: R = OMe (60%, 99:1 *er*)
1.94l: R = OBn (68%, 98:2 *er*)

Dihydronaphthalenes **1.94a-g** and **1.94i-l** were obtained in presence of water, alcohols and acetic acid in good yields (41 to 75%) and excellent *er* (90:10 to 98:2 *er*). Interestingly, the fluorination with HF·pyridine proceeded smoothly giving **1.94h** in 40% yield and 96:4 *er*. The absolute configuration of **1.94k** was unambiguously assigned as (*S*) by single-crystal X-ray diffraction and the remaining ones were correlated by circular dichroism. The CD-spectra have been measured from 0.025 M solutions in MeCN of the corresponding chiral dihydronaphthalenes. The CD-spectra show a negative Cotton effect around 240 nm (Figure 1.4).

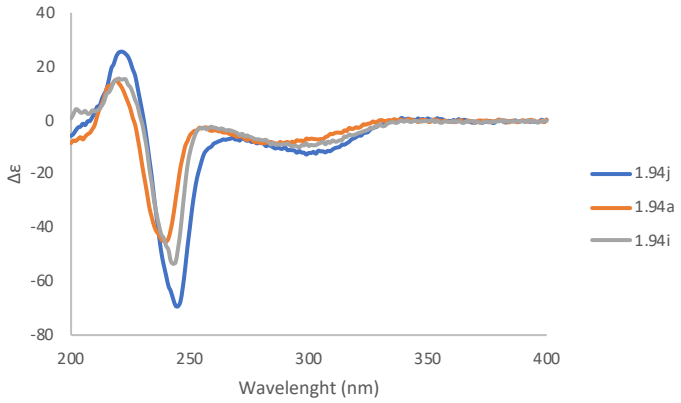
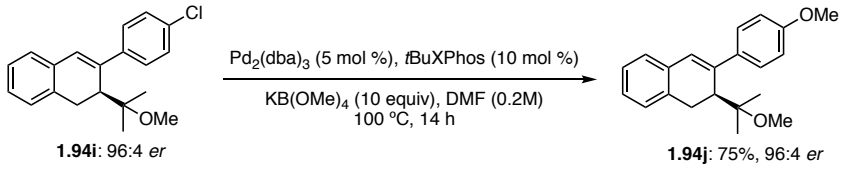


Figure 1.4. Superimposed CD-spectra of compounds **1.94a**, **1.94i** and **1.94j**

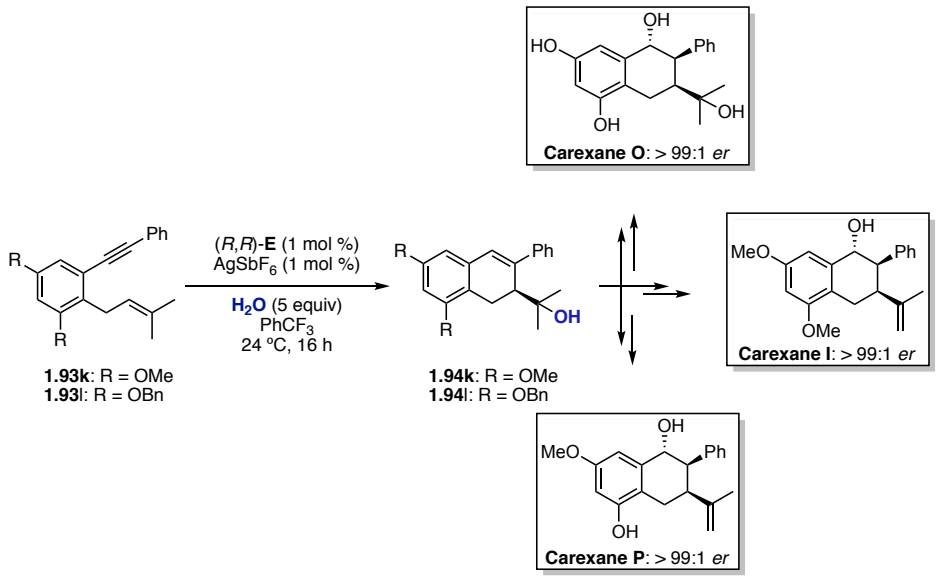
Additional correlation of the absolute configuration was performed interconverting dihydronaphthalene **1.94i** into **1.94j** adapting a procedure from the literature (Scheme 1.19).[113]



Scheme 1.19. Pd-catalyzed interconversionof **1.94i** into **1.94j**.

The synthetic power of this transformation was demonstrated by our group in the context of the first enantioselective total syntheses of three members of the carexane family of natural products, carexanes O, I and P (Scheme 1.20).[114] These natural products have been isolated from the leaves of *Carex distachya* and display antimicrobial activity.[115]

113. Tolonai, G. L.; Petho B.; Králl, P.; Novák, Z. *Adv. Synth. Catal.* **2014**, *356*, 125−129.
114. The total syntheses of carexane O, I and P were completed by Joan G. Mayans and will not be further discussed in this Doctoral Thesis.
115. (a) D'Abrosca, B.; Fiorentino, A.; Golino, A.; Monaco, P.; Oriano, P.; Pacifico, S. *Tetrahedron Lett.* **2005**, *46*, 5269−5272. (b) Fiorentino, A.; D'Abrosca, B.; Izzo, A.; Pacifico, S.; Monaco, P. *Tetrahedron* **2006**, *62*, 3259−3265. (c) Fiorentino, A.; D'Abrosca, B.; Pacifico, S.; Iacovino, R.; Izzo, A.; Uzzo, P.; Russo, A.; Di Blasio, B.; Monaco, P. *Tetrahedron* **2008**, *64*, 7782−7786.



Scheme 1.20. Enantioselective total synthesis of carexane O, I and P.

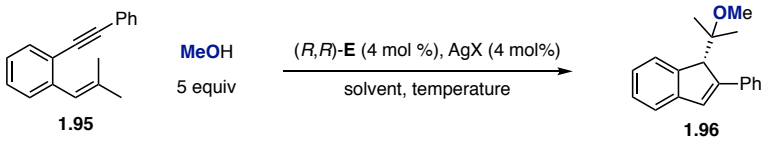
Unsuccessful Transformations

5-Endo-dig Cyclization of 1,5-Arylenyne 1.95

We tested the performance of catalyst (*R*,*R*)-**E** in several other transformations. First, we turned our attention to the analogous cyclization of 1,5-arylenyne **1.95** in presence of an external nucleophile. However, despite the structural similarity, 5-*endo*-dig cyclization of 1,5-arylenyne **1.95**[116] was more difficult than the 6-*endo*-dig cyclization of related 1,6-enynes **1.93** discussed above. At room temperature, no product formation was observed (Table 1.11, entries 1 and 2), whereas at higher temperatures desired 1*H*-indene **1.96** was isolated in 53% yield, however as a racemic mixture (Table 1.11, entry 3).

116. (a) Sanjuán, A. M.; Rashid, M. A.; García-García, P.; Martínez-Cuezva, A.; Fernández-Rodríguez, M. A.; Rodríguez, F.; Sanz, R. *Chem. Eur. J.* **2015**, *21*, 3042–3052. (b) Martínez, A.; García-García, P.; Fernández-Rodríguez, M. A.; Rodríguez, F.; Sanz, R. *Angew. Chem. Int. Ed.* **2010**, *49*, 4633–4637.

Table 1.11. 5-*Endo*-dig cyclization of 1,5-arylenyne **1.95**.



1.95 **1.96**

entrçy	AgX	solvent	T (ºC)	yield (%)[a]	*er*
1	$AgPF_6$	CH_2Cl_2	24	n.d.[b]	-
2	$AgSbF_6$	CH_2Cl_2	24	n.d.[b]	-
3[b]	$AgBF_4$	toluene	40	53	51:49

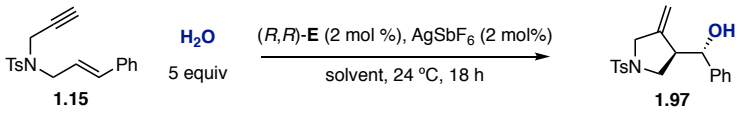
[a]Isolated yields. [b]n.d. = not detected. [c]30 h reaction time.

Hydroxycyclization of 1,6-Enyne 1.15

In view of the good results obtained for the synthesis of azabicyclo[4.1.0]hept-4-enes **1.92** we tested complex (*R*,*R*)-**E** in the hydroxycyclization of 1,6-enyne **1.15** (Table 1.12). *N*-Tethered 1,6-enynes with a terminal alkyne react in presence of a gold catalyst through 5-*exo*-dig formation of an anti-cyclopropyl gold(I) carbene, which is trapped by the external nucleophile (See scheme 1.4).[117] The asymmetric versions of this type of transformation have been extensively studied by the group of Michelet employing digold complexes supported by axially-chiral bisphosphine ligands.[118a] However, good enantioselectivities were only obtained in the presence of carbon nucleophiles.[118b] In our preliminary investigations compound **1.97** was isolated in excellent yields but with only moderate enantioselectivities (74:26 *er*) (Table 1.12, entry 1). Interestingly, we found important solvent effects on the enantioselectivity. Performing the reaction in toluene gave **1.97** in poor 18% yield and only slightly improved 75:25 *er*. However, using α,α,α-trifluorotoluene afforded preferentially the opposite enantiomer,[119] albeit in poor 10% yield (Table 1.12, entries 2 and 3).

117. Amijs, C. H. M.; López-Carrillo, V.; Raducan, M.; Pérez-Galán, P.; Ferrer, C.; Echavarren, A. M. *J. Org. Chem.* **2008**, *73*, 7721–7730.
118. (a) Chao, C. M.; Genin, E.; Toullec, P. Y.; Genêt, J. P.; Michelet, V. *J. Organomet. Chem.* **2009**, *694*, 538–545. (b) Pradal, A.; Chao, C. M.; Vitale, M. R.; Toullec, P. Y.; Michelet, V. *Tetrahedron* **2011**, *67*, 4371–4377.
119. For selected publication on the inversion of enantioselectivity induced by solvent effects: (a) Bartók, M. *Chem. Rev.* **2010**, *110*, 1663–1705. (b) Flores-Ferrándiz, J.; Fiser, B.; Gómez-Bengoa, E.; Chinchilla, R. *Eur. J. Org. Chem.* **2015**, *2015*, 1218–1225. (c) Seerden, J. G.; Kuypers, M. M. M.; Scheeren, H. W. *Tetrahedron: Asymmetry* **1995**, *6*, 1441–1450.

Table 1.12. Hydroxycyclization of 1,6-enyne **1.15**.



entry	solvent	yield (%)[a]	*er*
1	1,2-dichloroethane	91	74:26
2	toluene	18	75:25
3	$PhCF_3$	10	38:62

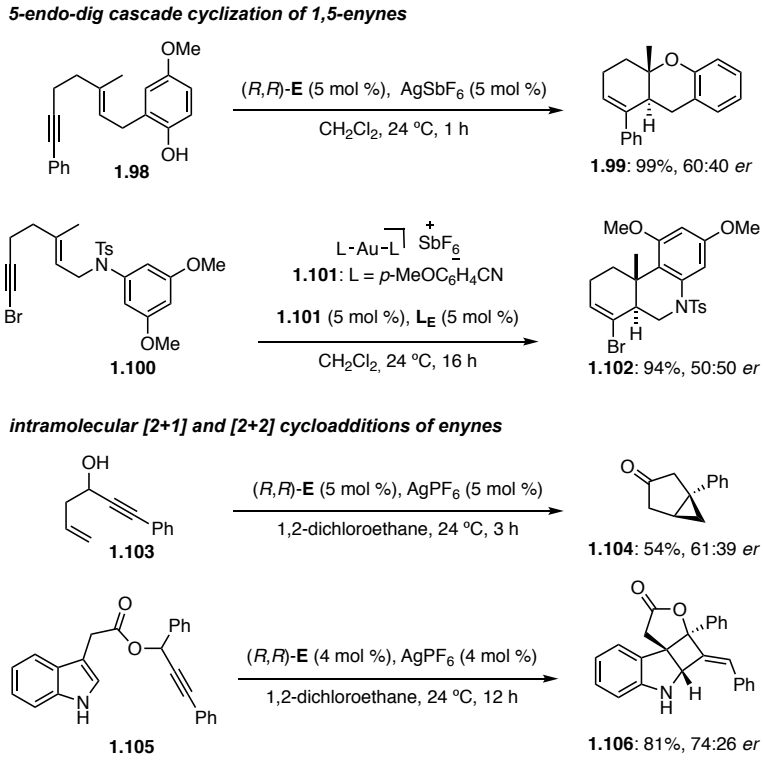
[a]Isolated yields.

Gold(I)-Catalyzed Cascade Cyclizations

5-*Endo*-dig cascade cyclizations of 1,5-enynes **1.98** and **1.100** containing an internal nucleophile (phenol in **1.98** and aromatic ring in **1.100**) gave fused tricyclic compounds **1.99**[120] and **1.102**,[121] respectively with poor 60:40 *er* or as a racemic mixture (Scheme 1.21). For the formation of **1.102** cationic complex **1.101**[122] was used together with ligand **L**$_{\mathbf{E}}$. Complexes of type **1.101** were developed in our group as precatalysts for the time-efficient screening of various ligands in gold(I) catalysis.[123] Additionally, the use of **1.101** allows to circumvent the use of silver salts to generate the catalytically active cationic gold complex. Similary, 1,5-enyne **1.103** with a propargylic OH-group[124] afforded bicyclo[3.1.0]hexan-3-one **1.104** in modest results (54%, 61:39 *er*).

The tandem rearrangement/cyclization[125] reaction of **1.105** where the reacting alkene is part of an indole afforded compound **1.106** in 81% yield and promising 74:26 *er*. However, no further optimization was performed. The group of Sigman and Toste reported a complete study on this transformation using a digold(I) complex supported by an axially-chiral acyclic diaminocarbene ligand.[25a]

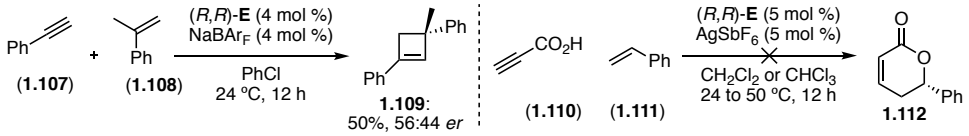
120. Toullec, P. Y.; Blarre, T.; Michelet, V. *Org. Lett.* **2009**, *11*, 2888–2891.
121. Rong, Z.; Echavarren, A. M. *Org. Biomol. Chem.* **2017**, *15*, 2163–2167.
122. The synthesis of complex **[Au1]** was performed by Dr. Jean-Simon Suppo.
123. Raducan, M.; Rodríguez-Escrich, C.; Cambeiro, X. C.; Escudero-Adán, E. C.; Pericàs, M. A.; Echavarren, A. M. *Chem. Commun.* **2011**, *47*, 4893–4895.
124. Mamane, V.; Gress, T.; Krause, H.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654–8655.
125. Zhang, L. *J. Am. Chem. Soc.* **2005**, *127*, 16804–16805.



Scheme 1.21. Unsuccessful transformations.

Intermolecular Transformations

Intermolecular transformations were also briefly investigated (Scheme 1.22). The formal [2+2] cycloaddition[126] of phenylacetylene (**1.107**) and α-methylstyrene (**1.108**) gave cyclobutene **1.109** with poor 56:44 *er* and no formation of dihydropyranone **1.112** via formal [4+2] annulation from propiolic acid (**1.110**) and styrene (**1.111**) was observed.[127]



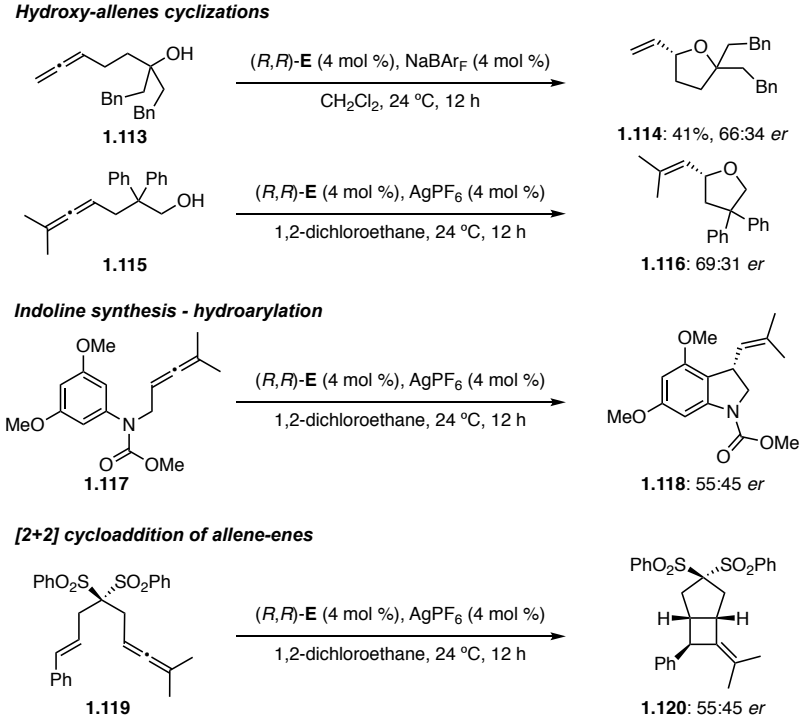
Scheme 1.22. Unsuccessful intermolecular cycloadditions.

126. (a) López-Carrillo, V.; Echavarren, A. M. *J. Am. Chem. Soc.* **2010**, *132*, 9292–9294. (b) De Orbe, M. E.; Amenós, L.; Kirillova, M. S.; Wang, Y.; López-Carrillo, V.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2017**, *139*, 10302–10311.

127. (a) Yeom, H. S.; Koo, J.; Park, H. S.; Wang, Y.; Liang, Y.; Yu, Z. X.; Shin, S. *J. Am. Chem. Soc.* **2012**, *134*, 208–211. (b) Kim, H.; Choi, S. Y.; Shin, S. *Angew. Chem. Int. Ed.* **2018**, *57*, 13130–13134.

Asymmetric Activation of Allenes

The asymmetric activation of allenes with (*R*,*R*)-**E** proved particularly challenging as the corresponding products were either obtained in poor yields (Scheme 1.23).



Scheme 1.23. Asymmetric activation of allenes.

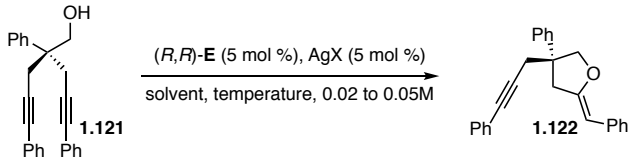
Allenols **1.113**[46] and **1.115**[128] were converted to the corresponding substituted tetrahydrofuranes **1.114** and **1.116** in moderate yield and enantioselectivity. Similarly, indoline **1.118**, formed via intramolecular hydroarylation from **1.117** was only obtained with poor enantioselectivity. Finally, unsatisfactory results were also obtained in the intramolecular [2+2] cycloaddition of allene-ene **1.119**[32] to give bicyclo[3.2.0]heptane **1.120**.

128. Ilg, M. K.; Wolf, L. M.; Mantilli, L.; Farès, C.; Thiel, W.; Fürstner, A. *Chem. Eur. J.* **2015**, *21*, 12279–12284.

Desymmetrization of Diynyl Alcohol 1.121

Owing to the power of enantioselective desymmetrization to construct all-carbon quaternary stereocenters,[129] and inspired by the reports of Sasai[130] and Hennecke,[131] we attempted the synthesis of highly substituted furan **1.122** via desymmetrization of diynyl alcohol **1.121**. Performing the reaction at 24 ºC gave a complex mixture of products whereas at –60 ºC **1.122** was formed with 58:42 *er* (Table 1.13, entries 1 and 2). As found for the synthesis of azabicyclo[4.1.0]hept-4-enes, the use of aromatic solvents such as toluene and α,α,α-trifluorotoluene showed a positive influence on the enantiomeric ratio giving **1.122** with promising enantioselectivities (68:32 to 70:30 *er*) (Table 1.13, entries 3 and 4). Only traces of furan **1.122** were observed when the reaction was carried out at –90 ºC mainly due to the precipitation of **1.121** (Table 1.13, entries 5). In view of the obtained results, future efforts will focus on additional reaction optimization and on modification of the substrate.

Table 1.13. Desymmetrization of diynyl alcohol **1.120**.



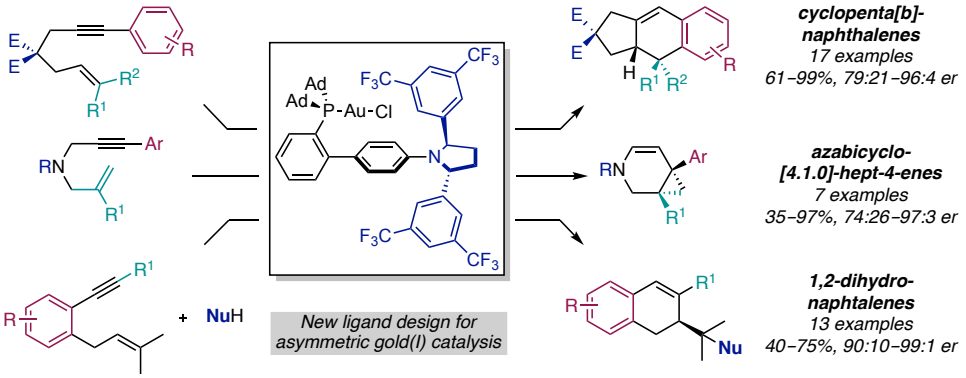
entry	AgX	solvent	T (ºC)	Time (*h*)	conv. (%)[a]	*er*
1	$AgPF_6$	1,2-dichloroethane	24	1	100	-[b]
2	$AgPF_6$	1,2-dichloroethane	–60	16	100	58:42
3	$AgBF_4$	toluene	–60	18	10	70:30
4	$AgSbF_6$	$PhCF_3$	–25	4	100	68:32
5	$AgBF_4$	toluene	–90	40	traces	-

[a]Conversions determined by ^1H NMR using 1,3,5-tribromobenzene as internal standard. [b]Formation of complex mixture.

129. (a) Zeng, X. P.; Cao, Z. Y.; Wang, Y. H.; Zhou, F.; Zhou, J. *Chem. Rev.* **2016**, *116*, 7330–7396. (b)Willis, M. C. *J. Chem. Soc. - Perkin Trans. 1* **1999**, 1765–1784.
130. Sridharan, V.; Fan, L.; Takizawa, S.; Suzuki, T.; Sasai, H. *Org. Biomol. Chem.* **2013**, *11*, 5936–5943.
131. Wilking, M.; Mück-Lichtenfeld, C.; Daniliuc, C. G.; Hennecke, U. *J. Am. Chem. Soc.* **2013**, *135*, 8133–8136.

Conclusions

We have designed a new family of chiral mononuclear gold(I) catalysts supported by modified JohnPhos-type ligands bearing remote C_2-symmetric *trans*-2,5-diarylpyrrolidines. The chiral information was strategically positioned to overcome the limitations in enantioselective gold(I) catalysis originating from the preferred linear coordination of the metal. The catalysts were applied in three different enantioselective cyclizations of 1,6-arylenynes giving the corresponding products of formal [4+2] cyloaddition, azabicyclo[4.1.0]hept-4-enes and 1,2-dihydronaphthalenes in good yields and enantioselectivities. The enantioselective synthesis of 1,2-dihydronaphthalenes has been applied in the synthesis of three members of the carexane family of natural products.



Scheme 1.24. Application of pyrrolidinyl-biaryl phosphine-supported gold(I) complex in catalysis.

Experimental Section

General Information

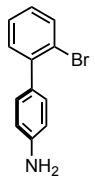
Unless otherwise stated, all the reactions were performed under an inert atmosphere of argon. All solvents and other chemicals were used as received. All the reactions were run in dry solvents (passed through an activated alumina column on a PureSolv^{TM} solvent purification system). Reactions were followed using a GC-MS apparatus, by TLC (thin layer chromatography) or by NMR analysis. Analytical thin layer chromatography was carried out using TLC aluminum sheets coated with 0.2 mm of silica gel (Merck 60 F254) using UV light as the visualizing agent and an acidic solution of vanillin in ethanol or basic solution of KMnO4 in water as stain. Chromatographic purifications were carried out using flash grade silica gel (PanReac Silica Gel 60, 40-63 μm) or automated flash column chromatographer CombiFlash Companion. Preparative thin layer chromatography was performed on TLC plates (Analtec Silica Gel GF UV254, 20×20 cm, 1000 μm). Melting points were determined using a Mettler Toledo MP70 melting point apparatus. NMR spectra were recorded at 298 K on BrukerAvance Ultrashield NMR spectrometers (300 MHz, 400 MHz, 500 MHz and 500 MHz with CryoProbe). Chemical shifts (δ) are reported in parts per million (ppm) and referenced to residual solvent (For ^{1}H NMR: $CDCl_3$ at 7.26 ppm, CD_2Cl_2 at 5.31 ppm, C_6D_6 at 7.16 ppm, CD_3OD at 3.31 ppm, for $^{13}C\{^{1}H\}$ NMR: $CDCl_3$ at 77.16 ppm, CD_2Cl_2 at 54.00 ppm, C_6D_6 at 128.06 ppm, CD_3OD at 49.00 ppm). The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, br s = broad singlet. Coupling constants (*J*) are reported in Hertz (Hz). Infrared spectra were recorded neat on a Bruker ALPHA FTIR-ATR TR0 spectrometer. The peaks are reported as absorption maxima (n, cm^{-1}). Mass spectra were recorded on MicroTOF Focus or Maxis Impact spectrometers (both from Bruker Daltonics). Elemental analyses were performed on a LECO CHNS 932 micro-analyzer at the Universidad Complutense de Madrid. Specific optical rotation measurements were carried out on a Jasco P-1030 model polarimeter equipped with a PMT detector using the sodium line at 589 nm, and 1 mL (10 mm pathlength) or 2 mL (100 mm pathlength) cells. Chiral HPLC analyses were performed on an Agilent Technologies 1200 series, a Waters ACQUITY UPC2 System with diode array detector and by Chiral Technologies Europe analytical service. X-ray diffraction data were collected at 100 K on a Rigaku MicroMax-007HF, Mo *Kα* rotating anode, equipped with a Pilatus 200 K detector or on a Bruker APEX DUO, Mo *Kα* Microfocus source E025 IuS anode, equipped with an

APEX DUO detector using omega scans. Circular dichroism spectra measurements were carried out on an Applied Photophysics Chirascan Circular Dichroism spectrometer equipped with a photomultiplier detector, dual polarizing prism design monochromator, photo-elastic modulator (PEM) and 150W Xenon light source.

Synthetic Procedures and Characterization of Compounds

Synthesis of Complexes

2'-Bromo-[1,1'-biphenyl]-4-amine

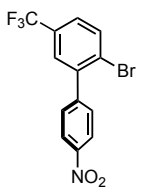


A two-necked round bottom flask equipped with condenser and stirring bar was charged with 1-bromo-4-nitrobenzene (12.5 g, 61.9 mmol, 1.0 equiv), (2-bromophenyl)boronic acid (13.1 g, 65.0 mmol, 1.05 equiv), Na_2CO_3 (26.2 g, 248 mmol, 4.0 equiv), methyltrioctylammonium chloride (2.5 g, 6.1 mmol, 0.1 equiv), $Pd(PPh_3)_4$ (358 mg, 0.31 mmol, 0.5 mol %) and toluene (248 mL) and water (124 mL) were added. The reaction mixture was stirred at 70 ºC for 2 h. The reaction was monitored by TLC (cyclohexane/Et_2O 10:1) and GC-MS analysis. After full conversion of the starting material the reaction was diluted with EtOAc. The phases were separated, the organic phase was washed with water (2x 200 mL), dried over Na_2SO_4, filtered and concentrated. The crude product was taken into the next step without further purification.

A solution of tin(II) chloride dihydrate (73.0 g, 324 mmol, 4.5 equiv) in conc. HCl (81 mL, 4 M) was added to a solution of 2-bromo-4'-nitro-1,1'-biphenyl (20 g, 71.9 mmol, 1.0 equiv) in EtOH (160 mL). The reaction mixture was stirred at 80 ºC for 2.5 h. Then, the reaction mixture was cooled to 24 ºC and diluted with water (20 mL). The precipitate was filtered off and a solution of KOH (66 g) in water (100 mL) was added. The reaction mixture was stirred overnight at 24 ºC. Et_2O was added to the reaction, the aqueous phase was extracted with Et_2O (2x), dried over Na_2SO_4, filtered and concentrated. The crude was purified by flash column chromatography (cyclohexane/CH_2Cl_2 1:1) to afford the title compound (10.3 g, 41.5 mmol, 58%) as a pale brown viscous oil over two steps.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 – 7.63 (m, 1H), 7.34 – 7.30 (m, 2H), 7.25 – 7.22 (m, 2H), 7.15 (ddd, J = 8.0, 5.5, 3.6 Hz, 1H), 6.77 – 6.71 (m, 2H), 3.75 (br s, 2H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 146.1, 142.7, 133.2, 131.51, 131.47, 130.6, 128.2, 127.5, 123.1, 114.6. **HRMS** (ESI+) calculated for $[C_{12}H_{11}BrN]^+$ 248.0069 *m/z*; found $[M + H]^+$ 248.0069 *m/z*.

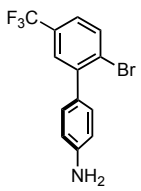
2-Bromo-4'-nitro-5-(trifluoromethyl)-1,1'-biphenyl



A Schlenk flask equipped with a stirring bar was charged with (4-nitrophenyl)boronic acid (1.00 g, 6.00 mmol, 1.2 equiv), 1-bromo-2-iodo-4-(trifluoromethyl)benzene (1.76 g, 5.00 mmol, 1.0 equiv), K_2CO_3 (1.38 g, 10.0 mmol, 2.0 equiv), $Pd(OAc)_2$ (112 mg, 0.500 mmol, 0.1 equiv), PPh_3 (262 mg, 1.00 mmol, 0.2 equiv) and toluene (6 mL) and water (6 mL) were added. The reaction mixture was stirred at 80 °C for 4 d and monitored by TLC (cyclohexane/CH_2Cl_2 9:1). The reaction mixture was diluted with EtOAc (20 mL) and the phases were separated. The organic phase was washed with water (2x 10 mL), dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography (cyclohexane/CH_2Cl_2 9:1) to give the coupling product (1.14 g, 3.29 mmol, 66%) as an off-white solid.

M.p. = 98 – 101 °C (cyclohexane/CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.33 (d, J = 8.8 Hz, 2H), 7.86 (d, J = 8.3 Hz, 1H), 7.64 – 7.51 (m, 4H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 147.9, 146.1, 141.4, 134.3, 130.6, 130.3 (q, J = 52.2 Hz), 127.7 (q, J = 3.6 Hz), 126.7 (q, J = 3.5 Hz), 126.3, 123.71, 123.67 (q, J = 125.0 Hz). **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) δ –62.8. **HRMS** (APCI+) calculated for $[C_{13}H_7BrF_3NO_2]^+$ 344.9607 *m/z*; found $[M]^+$ 344.9601.

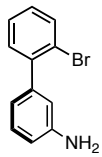
2'-Bromo-5'-(trifluoromethyl)-[1,1'-biphenyl]-4-amine



2-Bromo-4'-nitro-5-(trifluoromethyl)-1,1'-biphenyl (1.13 g, 3.26 mmol, 1.0 equiv) was dissolved in acetic acid (7 mL) and water (2.3 mL) at 80 °C and iron (1.82 g, 32.6 mmol, 10 equiv) was added in portions. The mixture was stirred for 1 h at 80 °C and the solvent was removed under vacuum. The residue was suspended in CH_2Cl_2 (30 mL) and H_2O (20 mL) and basified with NaOH (3M, 30 mL). The aqueous phase was extracted with CH_2Cl_2 (2x 50 mL) and the combined organic phases were washed with H_2O (30 mL), dried over Na_2SO_4 and concentrated to give the title compound (914 mg, 2.89 mmol, 89%) as a yellowish oil which solidified upon standing.

M.p. = 57 – 59 °C (CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.3 Hz, 1H), 7.58 (d, J = 1.9 Hz, 1H), 7.40 (dd, J = 8.3, 1.9 Hz, 1H), 7.24 (d, J = 8.5 Hz, 2H), 6.76 (d, J = 8.5 Hz, 2H), 3.81 (br s, 2H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 146.6, 143.5, 133.8, 130.5, 129.99, 129.98 (q, J = 33.0 Hz), 128.1 (q, J = 3.5 Hz), 126.9, 124.7 (q, J = 3.5 Hz), 124.0 (q, J = 273.1 Hz), 114.6. **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) δ –62.7. **HRMS** (ESI+) calculated for $[C_{13}H_{10}BrF_3N]^+$ 315.9943 *m/z*; found $[M + H]^+$ 315.9937 *m/z*.

2'-Bromo-[1,1'-biphenyl]-3-amine

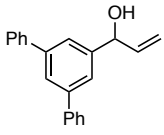


A two-necked round bottom flask equipped with condenser and stirring bar was charged with 1-iodo-3-nitrobenzene (10 g, 40.2 mmol, 1.0 equiv), 2-bromophenyl boronic acid (8.5 g, 42.2 mmol, 1.05 equiv), Na_2CO_3 (17.03 g, 161 mmol, 4.0 equiv), methyltrioctylammonium chloride (1.6 g, 4.02 mmol, 0.1 equiv), $Pd(PPh_3)_4$ (0.5 g, 0.40 mmol, 1 mol %) and toluene (50 mL) and water (25 mL) were added. The reaction mixture was stirred at 70 ºC for 60 h. The reaction was monitored by TLC (cyclohexane/Et_2O 10:1) and GC-MS analysis. After full conversion of the starting material the reaction was diluted with EtOAc. The phases were separated, the organic phase was washed with water (2x 250 mL), dried over Na_2SO_4, filtered and concentrated. The crude product was taken into the next step without further purification.

2-Bromo-3'-nitro-1,1'-biphenyl (1.0 g, 3.6 mmol, 1.0 equiv) was dissolved in acetic acid (6 mL) and water (2 mL). Iron powder (2.0 g, 36.0 mmol, 10 equiv) was added at 80 ºC (attention: foaming). The mixture was stirred for 1 h at the same temperature and the solvent was removed under reduced pressure. The residue was partially dissolved in CH_2Cl_2 (35 mL) and sat. $NaHCO_3$ (20 mL), and NaOH (200 mL, 10%) were added until basic pH was obtained. The phases were separated, the aqueous phase was extracted with CH_2Cl_2 (2x 100 mL) and the organic phase was washed with water (2x 100 mL). The organic phase was dried over Na_2SO_4 and concentrated. The crude product was purified by flash column chromatography (cyclohexane/CH_2Cl_2 1:1) to afford the title compound (0.90 g, 3.5 mmol, 95%, two steps) as a yellow solid.

M.p. = 52 – 54 °C (cyclohexane/CH_2Cl_2). **^{1}H NMR** (400 MHz $CDCl_3$) δ 7.65 (d, J = 8.0 Hz, 1H), 7.36 – 7.29 (m, 2H), 7.24 – 7.15 (m, 2H), 6.82 – 6.76 (m, 1H), 6.74 – 6.69 (m, 2H), 3.72 (br s, 2H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 146.3, 143.2, 142.6, 133.4, 131.5, 129.3, 129.0, 127.6, 122.9, 120.2, 116.5, 114.7. **HRMS** (ESI+) calculated for $[C_{12}H_{11}BrN]^+$ 248.0069, found $[M + H]^+$ 248.0070.

1-([1,1':3',1''-Terphenyl]-5'-yl)prop-2-en-1-ol



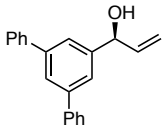
[1,1':3',1"-Terphenyl]-5'-carbaldehyde[132] (1.9 g, 7.4 mmol, 1.0 equiv) was dissolved in THF (52 mL) in a flame-dried two-necked 250 mL round bottom flask and the solution was cooled to –78 °C. Vinylmagnesium bromide (8.1 mL, 8.1 mmol, 1.1 equiv, 1M in THF) was added dropwise to the solution and the reaction mixture was stirred at the same temperature for 2 h. The reaction was monitored by TLC (cyclohexane/EtOAc 4:1) and after full conversion of the

132. Barker, C. A.; Zeng, X.; Bettington, S.; Batsanov, A. S.; Bryce, M. R.; Beeby. A. *Chem. Eur. J.* **2007**, *13*, 6710–6717.

starting material the reaction was allowed to warm up to 24 ºC, diluted with Et_2O and quenched with sat. NH_4Cl solution. The aqueous phase was extracted with Et_2O (3x) and the combined organic phases were dried over Na_2SO_4, filtered and concentrated. The crude was purified by flash column chromatography (cyclohexane/EtOAc 7:1) to yield the title compound (1.75 g, 6.1 mmol, 83%) as a white solid.

M.p. = 100 – 102 °C (cyclohexane/EtOAc). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.74 (t, *J* = 1.8 Hz, 1H), 7.68 – 7.63 (m, 4H), 7.60 (d, *J* = 1.7 Hz, 2H), 7.49 – 7.44 (m, 4H), 7.41 – 7.36 (m, 2H), 6.15 (ddd, *J* = 17.1, 10.3, 6.0 Hz, 1H), 5.45 (dt, *J* = 17.1, 1.4 Hz, 1H), 5.38 – 5.34 (m, 1H), 5.26 (dt, *J* = 10.3, 1.3 Hz, 1H), 2.06 (d, *J* = 3.4 Hz, 1H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 143.8, 142.3, 141.0, 133.5, 128.9, 127.6, 127.4, 125.7, 124.2, 74.6. **HRMS** (ESI+) calculated for $[C_{21}H_{18}NaO]^+$ 309.1250 *m/z*; found $[M + Na]^+$ 309.1245 *m/z*.

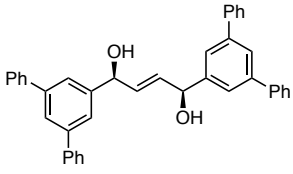
(*S*)-1-([1,1':3',1''-Terphenyl]-5'-yl)prop-2-en-1-ol



The procedure was adapted from reported procedures.[102] A 250 mL two-necked round bottom flask equipped with a stirring bar was charged with powdered 4Å molecular sieve (1.6 g) and heated to 200 ºC under high vacuum (ca 0.1 mbar) during 40 min. The flask was allowed to cool to 24 ºC under argon and novozyme 435 resin (357 mg, >5000 U/g) was added. The solids were suspended in anhydrous toluene (120 mL) and isoprenyl acetate (8.5 mL, 76 mmol, 4.55 equiv) was added followed by addition of 1-([1,1':3',1''-terphenyl]-5'-yl)prop-2-en-1-ol (4.81 g, 16.8 mmol, 1.0 equiv) in toluene (18 mL). The resulting mixture was stirred at 44 ºC for 37 h. The solvent was removed under vacuum and the crude product was purified by flash column chromatography (cyclohexane/EtOAc 20:1, then 10:1) to yield the title compound (3.33 g, 8.14 mmol, 49%) as a white solid in >99:1 *er*.

M.p. = 101 – 103 °C (cyclohexane/EtOAc). **α_D^{589}** = +6.2 deg.cm^2.g^{-1} ($CHCl_3$, c 0.98, 299 K). **HPLC** Chiralpak IA (250 × 4.6mm, 5µm) at 25 ºC, flow 1.0 mL/min, isocratic hexane/EtOH 98:2, 220 nm, t_R (major) 22.6; t_R (minor) 23.7.

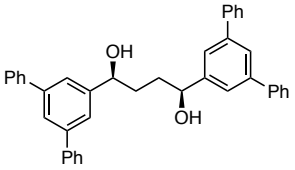
(1*S*,4*S*,*E*)-1,4-Di([1,1':3',1''-terphenyl]-5'-yl)but-2-ene-1,4-diol



(*S*)-1-([1,1':3',1''-Terphenyl]-5'-yl)prop-2-en-1-ol (2.31 g. 8.1 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (8.1 mL) and Grubbs 2nd gen. catalyst (68 mg, 81 µmol, 1 mol %) was added. The reaction mixture was stirred for 3 h at 40 ºC. The crude was purified by flash column chromatography (cyclohexane/EtOAc 2:1) and then further purified by precipitation from cold *n*hexane, filtered and dried to afford the title compound (1.31 g, 2.4 mmol, 60%) as a white solid.

M.p. = 145 – 147 °C (hexane/Et_2O). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.73 (t, *J* = 1.7 Hz, 2H), 7.62 – 7.54 (m, 12H), 7.43 – 7.37 (m, 8H), 7.37 – 7.32 (m, 4H), 6.16 (dd, *J* = 3.4, 1.6 Hz, 2H), 5.36 (s, 2H), 2.56 (s, 2H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 143.8, 142.3, 141.0, 133.5, 128.9, 127.6, 127.4, 125.8, 124.2, 74.6. **HRMS** (ESI+) calculated for $[C_{40}H_{32}NaO_2]^+$ 567.2295 *m/z*; found $[M + Na]^+$ 567.2283 *m/z*. **α_D^{589}** = +22.8 deg.cm^2.g^{-1} ($CHCl_3$, c 1.0, 298 K).

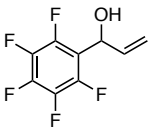
(1*S*,4*S*)-1,4-Di([1,1':3',1''-terphenyl]-5'-yl)butane-1,4-diol



A 20 mL microwave vial was charged with PtO_2 (12 mg, 0.06 mmol, 5 mol %) and evacuated and back-filled with argon (3x). A solution of (1*S*,4*S*,*E*)-1,4-di([1,1':3',1''-terphenyl]-5'-yl)but-2-ene-1,4-diol (0.59 g, 1.1 mmol, 1.0 equiv) in EtOAc (10.9 mL) was added and the reaction mixture was evacuated and back-filled with hydrogen. The reaction was stirred at 24 ºC for 1 h under hydrogen atmosphere (1 atm). The reaction was monitored by ^{1}H NMR analysis and after full conversion of the starting material, the reaction mixture was filtered over Celite® and concentrated. The crude was purified by flash column chromatography (cyclohexane/EtOAc 3:1) to yield the title compound (0.56 g, 1.0 mmol, 94%) as a white solid.

M.p. = 83 – 85 °C (cyclohexane/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71 (t, *J* = 1.7 Hz, 2H), 7.66 – 7.60 (m, 8H), 7.57 (d, *J* = 1.7 Hz, 4H), 7.48 – 7.40 (m, 8H), 7.40 – 7.33 (m, 4H), 4.92 – 4.86 (m, 2H), 2.41 (br s, 2H), 2.16 – 1.96 (m, 4H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 145.9, 142.2, 141.1, 128.9, 127.6, 127.4, 125.6, 123.7, 74.9, 36.2. **HRMS** (ESI+) calculated for $[C_{40}H_{34}NaO_2]^+$ 569.2451 *m/z*; found $[M + Na]^+$ 569.2459 *m/z*. **α_D^{589}** = –7.6 deg.cm^2.g^{-1} ($CHCl_3$, c 1.0, 297 K).

1-(Perfluorophenyl)prop-2-en-1-ol

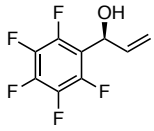


2,3,4,5,6-Pentafluorobenzaldehyde (3.2 mL, 25.5 mmol, 1.0 equiv) was dissolved in THF (128 mL) in a flame-dried 500 mL two-necked round bottom flask. The solution was cooled to –78 ºC and vinylmagnesium bromide (28.1 mL, 28.1 mmol, 1.1 equiv, 1M in THF) was added dropwise. The reaction mixture was stirred at the same temperature for 1 h. The reaction was monitored by TLC (cyclohexane/Et_2O 10:1). The reaction was allowed to warm to 24 ºC, diluted with Et_2O and quenched with sat. NH_4Cl solution. The phases were separated and the aqueous phase was extracted with Et_2O (3x). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. The crude was purified by flash column

chromatography (pentane/Et_2O 10:1) to yield the title compound (4.7 g, 20.8 mmol, 79%) as a colorless oil.

^{1}H NMR (500 MHz, CD_3OD) δ 6.27 – 6.18 (m, 1H), 5.56 (d, *J* = 6.0 Hz, 1H), 5.36 (d, *J* = 17.1, 1H), 5.25 (dt, *J* = 10.4, 1.3 Hz, 1H). **^{13}C{^{1}H} NMR** (101 MHz, CD_3OD) δ 144.8 (dm, *J* = 248.4 Hz), 140.6 (dm, *J* = 251.5 Hz), 137.5 (dm, *J* = 250.4 Hz), 137.2, 117.3 – 116.7 (m), 115.4, 65.8. **^{19}F{^{1}H} NMR** (471 MHz, CD_3OD) δ –145.0 – –145.2 (m), –158.9 (t, *J* = 20.0 Hz), –165.4 – –165.6 (m). **HRMS** (APCI+) calculated for $[C_9H_4F_5]^+$ 207.0228 *m/z*; found $[M - OH]^+$ 207.0222 *m/z*.

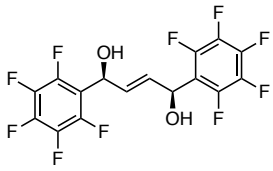
(*S*)-1-(Perfluorophenyl)prop-2-en-1-ol[102]



A 250 mL two-necked round bottom flask equipped with a stirring bar was charged with powdered 4Å molecular sieve (1.6 g) and heated to 200 ºC under high vacuum (0.1 mbar) during 40 min. The flask was allowed to cool to 24 ºC under argon and novozyme 435 resin (351 mg, >5000 U/g) was added. The solids were suspended in anhydrous toluene (137 mL) and isoprenyl acetate (8.3 mL, 74.9 mmol, 4.55 equiv) was added followed by addition of 1-(perfluorophenyl)prop-2-en-1-ol (3.7 g, 16.5 mmol, 1.0 equiv) in toluene (5 mL). The resulting mixture was stirred at 45 ºC for 48 h. The solvent was removed under vacuum and the crude product was purified by flash column chromatography (cyclohexane/EtOAc 30:1) to yield the title compound as a colorless oil (1.6 g, 7.1 mmol, 43%) in 99:1 *er*.

α_D^{589} = +17.9 deg.cm^2.g^{-1} ($CHCl_3$, c 0.9, 298 K). **HPLC** Chiralpak IA (250 × 4.6mm, 5µm) at 25 ºC, flow 1.0 mL/min, isocratic hexane/*i*PrOH 98:2, 254 nm, t_R (major) 9.9; t_R (minor) 10.9.

(1*S*,4*S*,*E*)-1,4-Bis(perfluorophenyl)but-2-ene-1,4-diol

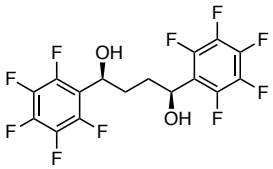


(*S*)-1-(Perfluorophenyl)prop-2-en-1-ol (3.0 g, 13.4 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (13.4 mL, 1M) and Grubbs 2nd gen. catalyst (57 mg, 0.067 mmol, 0.5 mol %) was added. The reaction mixture was stirred for 2 h at 40 ºC. The crude was directly loaded on silica and purified by flash column chromatography (cyclohexane/EtOAc 5:1). The compound was further purified by precipitation from $CHCl_3$ to afford the title compound (1.54 g, 3.7 mmol, 55%) as a white solid.

M.p. = 125 – 127 °C (cyclohexane/EtOAc). **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 6.19 – 6.10 (m, 2H), 5.68 – 5.59 (m, 2H), 2.55 (d, *J* = 6.7 Hz, 2H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 144.8 (dm, *J* = 248.9 Hz), 141.0 (dm, *J* = 253.8 Hz), 137.7 (dm, *J* = 252.7 Hz), 131.1, 115.8 – 115.2 (m), 65.4. **^{19}F{^{1}H} NMR** (471 MHz, CD_2Cl_2) δ –143.7 (dd, *J* = 21.6, 7.6 Hz), –155.3 (t, *J* = 20.7 Hz), –162.3 – –162.6 (m). **HRMS** (APCI+) calculated for $[C_{16}H_5F_{10}O]^+$

403.0175 *m/z*; found $[M - OH]^+$ 403.0168 *m/z*. $\alpha_D^{589} = -6.7$ deg.cm^2.g^{-1} (CH_2Cl_2, c 1.1, 298 K).

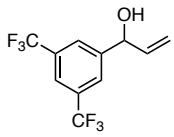
(1*S*,4*S*)-1,4-Bis(perfluorophenyl)butane-1,4-diol



A 100 mL round bottom flask equipped with a stirring bar was charged with PtO_2 (46 mg, 0.21 mmol, 5 mol %) and the flask was evacuated and back filled with argon (3x). Then, a solution of (1*S*,4*S*,*E*)-1,4-bis(perfluorophenyl)but-2-ene-1,4-diol (1.72 g, 4.1 mmol, 1.0 equiv) in EtOAc (41 mL) was added. The reaction mixture was evacuated and back filled with hydrogen (3x) and stirred at 24 ºC for 1 h under hydrogen atmosphere (1 atm). The reaction was monitored by ^{1}H NMR and after full conversion of the starting material the reaction was degassed with argon and filtered over Celite®. The solvent was removed under vacuum and the crude was purified by flash column chromatography (cyclohexane/EtOAc 3:1) to afford the title compound (1.67 g, 3.96 mmol, 97%) as a white solid.

M.p. = 104 – 106 °C (EtOAc). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.16 – 5.06 (m, 1H), 2.68 (d, *J* = 6.7 Hz, 2H), 2.35 – 2.20 (m, 2H), 1.92 – 1.80 (m, 2H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 144.7 (dm, *J* = 248.3 Hz), 140.7 (dm, *J* = 254.7 Hz), 137.7 (dm, *J* = 253.7 Hz), 116.8 – 116.3 (m), 66.0, 33.5. **^{19}F{^{1}H} NMR** (376 MHz, CD_3OD) δ –147.0 (dd, *J* = 21.5, 7.9 Hz), –160.7 (dt, *J* = 29.4, 20.0 Hz), –166.9 – –167.1 (m). **HRMS** (ESI+) calculated for $[C_{16}H_8F_{10}NaO_2]^+$ 445.0257 *m/z*; found $[M + Na]^+$ 445.0248 *m/z*. α_D^{589} = +6.5 deg.cm^2.g^{-1} ($CHCl_3$, c 1.22, 299 K).

1-(3,5-Bis(trifluoromethyl)phenyl)prop-2-en-1-ol

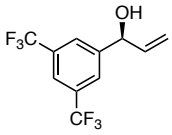


A 250 mL two-necked round bottom flask equipped with a stirring bar was flame-dried, charged with 3,5-bis(trifluoromethyl)benzaldehyde (3.4 mL, 20.7 mmol, 1.0 equiv) and THF (103 mL) was added under an argon atmosphere. Vinylmagnesium bromide (23.0 mL, 23 mmol, 1.1 equiv, 1M in THF) was added at –78 ºC dropwise and the resulting mixture was stirred for 2 h at the same temperature. The reaction was monitored by TLC (cyclohexane/Et_2O 5:1) and GC-MS analysis. The reaction was allowed to warm up to 24 ºC, diluted with Et_2O and quenched with NH_4Cl. The aqueous phase was extracted with Et_2O (3x 150 mL), dried over Na_2SO_4 and concentrated. The crude was purified by flash column chromatography (cyclohexane/EtOAc 10:1) to afford the title compound (4.5 g, 20.3 mmol, 79%) as a white solid.

M.p. 36 – 38 ºC (cyclohexane/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.85 (s, 2H), 7.80 (s, 1H), 6.05 – 5.95 (m, 1H), 5.44 (dt, *J* = 17.2, 1.1 Hz, 1H), 5.35 – 5.30 (m, 2H), 2.07 (br s, 1H).**^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 145.0, 139.1, 131.9 (q, *J* = 33.3 Hz), 126.6 (d,

J = 4.1 Hz), 123.5 (q, *J* = 272.6), 121.7 (p, *J* = 3.9 Hz), 117.6, 74.5. **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) δ –63.0. **HRMS** (EI+) calculated for $[C_{11}H_7F_6O]^+$ 269.0401 *m/z*; found $[M - H]^+$ 269.0460 *m/z*.

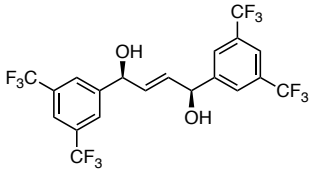
(*S*)-1-(3,5-Bis(trifluoromethyl)phenyl)prop-2-en-1-ol[102]



A 250 mL two-necked round bottom flask equipped with a stirring bar was charged with powdered 4Å molecular sieve (2.5 g) and heated to 200 ºC under high vacuum (ca 0.1 mbar) during 40 minutes. The flask was allowed to cool to 24 ºC under argon and novozyme 435 resin (548 mg, >5000 U/g) was added. The solids were suspended in anhydrous toluene (222 mL) and isoprenyl acetate (13.0 mL, 117 mmol, 4.55 equiv) was added followed by addition of 1-(3,5-bis(trifluoromethyl)phenyl)prop-2-en-1-ol (6.95 g, 25.7 mmol, 1.0 equiv) in toluene (7 mL). The resulting mixture was stirred at 45 ºC for 16 h. The solvent was removed under vacuum and the crude product was purified by flash column chromatography (cyclohexane/EtOAc 20:1) to yield the title compound (3.43 g, 12.7 mmol, 49%) as a white solid in >99:1 *er*.

M.p. = 51 – 53 ºC (cyclohexane/EtOAc). $\boldsymbol{\alpha_D^{589}}$ = +26.0 deg.cm^2.g^{-1} ($CHCl_3$, c 1.1, 298 K). **HPLC** Chiralpak OD-H (250 × 4.6mm, 5μm) at 25 ºC, flow 1.0 mL/min, isocratic hexane/*i*PrOH 99:1, 220 nm, t_R (major) 12.4; t_R (minor) 13.8.

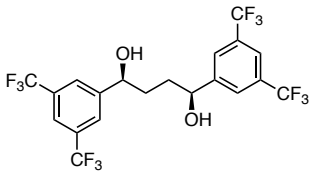
(1*S*,4*S*,*E*)-1,4-Bis(3,5-bis(trifluoromethyl)phenyl)but-2-ene-1,4-diol



(*S*)-1-(3,5-Bis(trifluoromethyl)phenyl)prop-2-en-1-ol (3.4 g, 12.4 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (12.5 mL, 1M) and Grubbs 2nd gen. catalyst (106 mg, 0.12 mmol, 1 mol %) was added. The reaction mixture was stirred for 3 h at 40 ºC. The product was precipitated from cold *n*hexane and filtered to afford the title compound (2.4 g, 4.7 mmol, 75%) as a white solid.

M.p.= 168 – 170 ºC (*n*hexane). **^{1}H NMR** (400 MHz, CD_3OD) δ 7.95 (s, 4H), 7.86 (s, 2H), 6.08 – 5.99 (m, 2H), 5.45 – 5.35 (m, 2H). **^{13}C{^{1}H} NMR** (101 MHz, CD_3OD) δ 148.5, 134.5, 132.8 (q, *J* = 33.2 Hz), 127.9 – 127.5 (m), 124.9 (q, *J* = 271.7 Hz) 122.4 – 121.6 (m), 73.5. **^{19}F{^{1}H} NMR** (376 MHz, CD_3OD) δ –64.5. **HRMS** (ESI–) calculated for $[C_{20}H_{11}F_{12}O_2]^-$ 511. 0573 *m/z*; found $[M - H]^-$ 511.0586 *m/z*. $\boldsymbol{\alpha_D^{589}}$ = +12.1 deg.cm^2.g^{-1} (MeOH, c 0.95, 298 K).

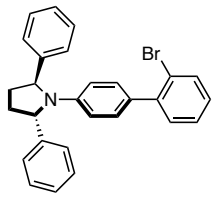
(1*S*,4*S*)-1,4-Bis(3,5-bis(trifluoromethyl)phenyl)butane-1,4-diol



A 100 mL round bottom flask equipped with a stirring bar was charged with PtO_2 (53 mg, 0.233 mmol, 5 mol %) and the flask was evacuated and back filled with argon (3x). Then, a solution of (1*S*,4*S*,*E*)-1,4-bis(3,5-bis(trifluoromethyl)phenyl)but-2-ene-1,4-diol (2.4 g, 4.67 mmol, 1.0 equiv) in EtOAc (47 mL) was added. The reaction mixture was evacuated and back filled with hydrogen (3x) and stirred at 24 ºC for 1 h under hydrogen atmosphere (1 atm). The reaction was monitored by TLC (cyclohexane/EtOAc 2:1) and ^{1}H NMR. After full conversion of the starting material the reaction was degassed with argon and filtered over Celite®. The solvent was removed under vacuum and the crude was purified by flash column chromatography (cyclohexane/EtOAc 3:1) to afford the title compound (2.3 g, 4.54 mmol, 97%) as a white solid.

M.p. = 116 – 118 °C (cyclohexane/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.82 (s, 4H), 7.80 (s, 2H), 4.98 – 4.86 (m, 2H), 3.03 (br s, 2H), 2.05 – 1.82 (m, 4H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 147.1, 132.0 (q, *J* = 33.4 Hz), 126.2 – 125.9 (m), 123.4 (q, J = 271.5 Hz) 121.8 (p, *J* = 3.8 Hz), 73.5, 36.1. **^{19}F{^{1}H} NMR** (376 MHz, CD_2Cl_2) δ –63.3. **HRMS** (ESI–) calculated for $[C_{20}H_{13}F_{12}O_2]^-$ 513. 0729 *m/z*; found $[M - H]^-$ 513.0738 *m/z*. **α_D^{589}** = –36.2 deg.cm^2.g^{-1} ($CHCl_3$, 0.64, 298 K).

(2*S*,5*S*)-1-(2'-Bromo-[1,1'-biphenyl]-4-yl)-2,5-diphenylpyrrolidine

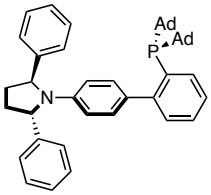


To a solution of (1*R*,4*R*)-1,4-diphenylbutane-1,4-diol[97] (0.20 g, 0.83 mmol, 1.0 equiv) in CH_2Cl_2 (8.3 mL) at –20 °C were added NEt_3 (0.35 mL, 2.48 mmol, 3.0 equiv) and methanesulfonyl chloride (0.17 mL, 2.15 mmol, 2.6 equiv) under an anhydrous argon atmosphere. The mixture was stirred for 2.5 h at –20 °C. Then, a solution of 2'-bromo-[1,1'-biphenyl]-4-amine (1.02 g, 4.1 mmol, 5.0 equiv) in CH_2Cl_2 (1.5 mL) was added and the resulting solution was stirred at 24 ºC overnight. The volatiles were removed under reduced pressure and the organic materials were dissolved in EtOAc. The organic phase was washed with brine and sat. $NaHCO_3$, dried over Na_2SO_4 and concentrated. The excess of aniline was removed by flash column chromatography (cyclohexane/CH_2Cl_2 1:1). The title compound was recrystallized from CH_2Cl_2/Et_2O to yield the title compound (94 mg, 0.21 mmol, 52%) as a white crystalline solid.

M.p. = 130 – 132 °C (CH_2Cl_2/Et_2O). **^{1}H NMR** (400 MHz, CD_2Cl_2) δ 7.58 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.38 – 7.33 (m, 4H), 7.30 – 7.20 (m, 8H), 7.11 – 7.04 (m, 3H), 6.43 – 6.37 (m, 2H), 5.27 (d, *J* = 7.3 Hz, 2H), 2.66 – 2.54 (m, 2H), 1.88 – 1.75 (m, 2H). **^{13}C{^{1}H} NMR** (101 MHz, CD_2Cl_2) δ 145.1, 144.6, 143.0, 133.6, 132.0, 130.3, 129.1, 128.7, 128.3, 127.9,

127.3, 126.7, 123.1, 113.7, 63.9, 32.8. **HRMS** (ESI+) calculated for $[C_{28}H_{25}BrN]^+$ *m/z* 454.1165; found $[M + H]^+$ *m/z* 454.1175. α_D^{589} = –93.2 deg.cm^2.g^{-1} ($CHCl_3$, c 0.9, 300 K).

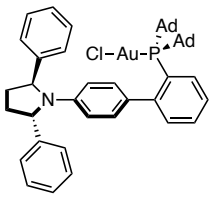
Ligand L_A

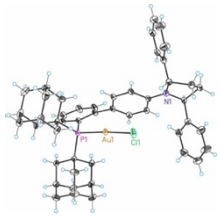


A flame-dried 20 mL Schlenk flask was charged with (2*S*,5*S*)-1-(2'-bromo-[1,1'-biphenyl]-4-yl)-2,5-diphenylpyrrolidine (0.40 g, 0.88 mmol, 1.0 equiv), $Pd(OAc)_2$ (9.9 mg, 0.04 mmol, 5 mol %), dppf (29 mg, 0.05 mmol, 6 mol %), NaO*t*Bu (102 mg, 1.06 mmol, 1.2 equiv) and toluene (4.4 mL), the resulting suspension was stirred for 15 min at 24 ºC. Di(1-adamantyl)phosphine (293 mg, 0.97 mmol, 1.1 equiv) was added and the reaction mixture was stirred at 120 ºC for 16 h. Then, the reaction was allowed to cool to 24 ºC and the crude was purified by flash column chromatography (cyclohexane/CH_2Cl_2 3:1, then cyclohexane/Et_2O 40:1) to yield ligand $\mathbf{L_A}$ (157 mg, 0.23 mmol, 72%) as a white solid.

M.p. = 173 – 175 °C (cyclohexane/Et_2O). **^{1}H NMR** (400 MHz, $CDCl_3$) 7.82 – 7.76 (m, 1H), 7.35 – 728 (m, 4H), 7.28 – 7.26 (m, 3H), 7.26 – 7.24 (m, 2H), 7.24 – 7.16 (m, 4H), 6.94 – 6.88 (m, 2H), 6.32 – 6.27 (m, 2H), 5.25 (d, *J* = 7.0 Hz, 2H), 2.65 – 2.46 (m, 2H), 2.05 – 1.91 (m, 5H), 1.91 – 1.86 (m, 3H), 1.84 – 1.79 (m, 2H), 1.76 (br s, 3H), 1.70 – 1.64 (m, 10H), 1.58 – 1.53 (m, 8H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 152.1 (d, *J* = 31.1 Hz), 144.2, 143.6, 136.8 (d, *J* = 2.9 Hz), 133.1 (d, *J* = 27.4 Hz), 131.5 (d, *J* = 4.8 Hz), 131.2 (d, *J* = 6.0 Hz), 131.1 (d, *J* = 6.9 Hz). 128.5, 128.2, 126.6, 126.5, 124.4, 112.7, 63.4, 42.5 (d, *J* = 13.5 Hz), 41.5 (d, *J* = 12.9 Hz), 37.6 (d, *J* = 26.1 Hz) 37.2 (d, *J* = 26.9 Hz), 37.0 (d, *J* = 10.0 Hz), 32.6, 29.1 (d, *J* = 8.6 Hz), 28.9 (d, *J* = 8.5 Hz). **^{31}P{^{1}H} NMR** (162 MHz, $CDCl_3$) δ 24.5. **HRMS** (ESI+) calculated for $[C_{48}H_{55}NP]^+$ 676.4067 *m/z*; found $[M + H]^+$ 676.4042 *m/z*. α_D^{589} = –47.5 deg.cm^2.g^{-1} ($CHCl_3$, c 1.0, 298 K).

Complex (*S*,*S*)-A

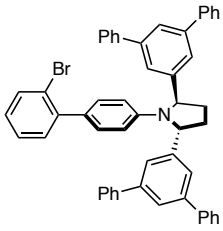




[Me_2SAuCl] (100 mg, 0.15 mmol, 1.0 equiv) and ligand $\mathbf{L_A}$ (44 mg, 0.15 mmol, 1.0 equiv) were dissolved in CH_2Cl_2 (1.5 mL) under an atmosphere of argon. The reaction mixture was stirred at 24 ºC for 30 min. The mixture was filtered through a syringe filter and concentrated. The residue was dissolved in CH_2Cl_2, filtered through a path of neutral Al_2O_3 and concentrated. The residue was dissolved in a minimal amount of CH_2Cl_2 and precipitated from Et_2O to afford complex (*S*,*S*)-**A** (121 mg, 0.13 mmol, 90%) as a white solid.

M.p. = >260 °C (decomposition; Et_2O/MeOH). **^{1}H NMR** (400 MHz, CD_2Cl_2) δ 7.81 (td, *J* = 7.2, 2.1 Hz, 1H), 7.45 – 7.38 (m, 6H), 7.37 – 7.32 (m, 4H), 7.26 – 7.21 (m, 2H), 7.19 – 7.15 (m, 1H), 6.81 – 6.74 (m, 2H), 6.35 – 6.28 (m, 2H), 5.24 (d, *J* = 6.9 Hz, 2H), 2.65 – 2.49 (m, 2H), 2.31 – 2.22 (m, 3H), 2.22 – 2.15 (m, 3H), 2.09 – 1.93 (m, 9H), 1.93 – 1.87 (m, 3H), 1.78 – 1.72 (m, 2H), 1.70 (s, 6H), 1.61 (s, 6H). **^{13}C{^{1}H} NMR** (101 MHz, CD_2Cl_2) δ 151.2 (d, *J* = 13.2 Hz), 144.5 (d, *J* = 107.6 Hz), 134.6 (d, *J* = 2.5 Hz), 134.2 (d, *J* = 7.2 Hz), 130.0 (d, *J* = 2.3 Hz), 129.9, 129.4 (d, *J* = 6.6 Hz), 129.3, 128.4, 126.6, 126.5, 125.5 (d, *J* = 6.6 Hz), 123.4 (d, *J* = 44.7 Hz), 113.7 (d, *J* = 74.3 Hz), 63.5, 42.6 – 42.3 (m), 42.5 (d, *J* = 2.6 Hz), 41.8 (d, *J* = 2.6 Hz), 36.3 (d, *J* = 9.5 Hz), 36.2 (d, *J* = 9.5 Hz), 32.4, 28.8 (d, *J* = 13.8), 28.7 (d, *J* = 13.9). **^{31}P{^{1}H} NMR** (202 MHz, $CDCl_3$) δ 65.1. **HRMS** (ESI+) calculated for $[C_{48}H_{55}AuClNP]^+$ 908.3421 *m/z*; found $[M + H]^+$ 908.3393 *m/z*. **α_D^{589}** = – 57.1 deg.cm^2.g^{-1} ($CHCl_3$, c 0.8, 299 K).

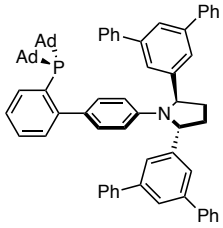
(2*R*,5*R*)-2,5-Di([1,1':3',1''-terphenyl]-5'-yl)-1-(2'-bromo-[1,1'-biphenyl]-4-yl)pyrrolidine



To a solution of (1*S*,4*S*)-1,4-di([1,1':3',1"-terphenyl]-5'-yl)butane-1,4-diol (1.21 g, 2.21 mmol, 1.0 equiv) in CH_2Cl_2 (22 mL) at –20 °C were added NEt_3 (0.93 mL, 6.64 mmol, 3.0 equiv) and methanesulfonyl chloride (0.45 mL, 5.75 mmol, 2.6 equiv) under anhydrous N_2 atmosphere. The mixture was stirred for 2.5 h at –20 °C. Then, a solution of 2'-bromo-[1,1'-biphenyl]-4-amine (2.7 g, 10.84 mmol, 4.9 equiv) in CH_2Cl_2 (4 mL) was added and the resulting solution was stirred at 24 ºC overnight. The volatile products were removed under reduced pressure and the organic materials were dissolved in EtOAc. The organic phase was washed with brine and sat. $NaHCO_3$, dried over Na_2SO_4 and concentrated. The excess aniline was removed by flash column chromatography (cyclohexane/CH_2Cl_2 3:1, then 1:1). The title compound was further purified by washing with CH_2Cl_2/Et2O mixtures to yield the title compound (973 mg, 1.3 mmol, 58%) as a white solid.

M.p. = 228 – 230 °C (CH_2Cl_2/pentane). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.72 – 7.68 (m, 2H), 7.64 – 7.59 (m, 9H), 7.50 – 7.44 (m, 12H), 7.41 – 7.35 (m, 4H), 7.29 – 7.24 (m, 2H), 7.18 – 7.14 (m, 2H), 7.11 – 7.06 (m, 1H), 6.59 – 6.54 (m, 2H), 5.44 (d, *J* = 6.8 Hz, 2H), 2.83 – 2.63 (m, 2H), 2.11 – 1.97 (m, 2H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 144.9, 144.7, 143.1, 142.2, 141.4, 133.1, 131.4, 130.1, 129.0, 127.8, 127.6, 127.5, 127.3, 124.9, 124.3, 123.3, 113.7, 63.6, 32.8. **HRMS** (ESI+) calculated for $[C_{52}H_{41}BrN]^+$ 758.2417 *m/z*; found $[M + H]^+$ 758.2431 *m/z*. **α_D^{589}** = +75.0 deg.cm^2.g^{-1} ($CHCl_3$, c 0.95, 299 K).

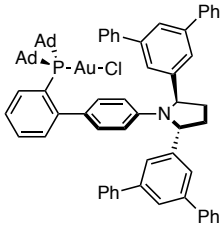
Ligand L_B



A flame-dried 10 mL Schlenk flask was charged with (2*R*,5*R*)-2,5-di([1,1':3',1"-terphenyl]-5'-yl)-1-(2'-bromo-[1,1'-biphenyl]-4-yl) pyrrolidine (170 mg, 0.22 mmol, 1.0 equiv), $Pd(OAc)_2$ (2.5 mg, 11 µmol, 5 mol %), dppf (7.5 mg, 13 µmol, 6 mol %), NaO*t*Bu (26 mg, 0.27 mmol, 1.2 equiv) and toluene (1.2 mL) and the resulting suspension was stirred for 15 min at 24 ºC. Di(1-adamantyl)phosphine (75 mg, 0.25 mmol, 1.1 equiv) was added and the reaction mixture was stirred at 120 ºC for 16 h. Then, the reaction was allowed to cool to 24 ºC and the solids were removed by filtration. The crude was dissolved in EtOAc and activated charcoal was added. The mixture was stirred for 15 min at 24 ºC, filtered over Celite® and concentrated. The residue was dissolved in Et_2O and precipitated with MeOH to yield ligand $\mathbf{L_B}$ (140 mg, 0.14 mmol, 64%) as a white solid.

M.p. = > 110 °C (decomposition; methanol). **^{1}H NMR** (400 MHz, CD_2Cl_2) δ 7.81 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.75 – 7.71 (m, 2H), 7.69 – 7.62 (m, 8H), 7.55 – 7.51 (m, 4H), 7.50 – 7.43 (m, 8H), 7.40 – 7.34 (m, 4H), 7.29 – 7.18 (m, 2H), 7.17 – 7.11 (m, 1H), 7.02 – 6.95 (m, 2H), 6.53 (dd, *J* = 8.7, 1.8 Hz, 2H), 5.49 (d, *J* = 6.6 Hz, 2H), 2.86 – 2.71 (m, 2H), 2.07 – 1.95 (m, 2H), 1.94 – 1.87 (m, 3H), 1.84 (br s, 6H), 1.78 – 1.68 (m, 8H), 1.64 (br s, 6H), 1.57 – 1.48 (m, 7H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 152.3 (d, *J* = 32.0 Hz), 145.5, 143.5, 142.1, 141.4, 136.7 (d, *J* = 2.6 Hz), 133.6, 133.4, 131.8 (d, *J* = 7.0 Hz), 131.4 (d, *J* = 4.3 Hz), 131.2 (d, *J* = 5.9 Hz), 128.9, 128.1, 127.5, 124.7, 124.5, 124.3, 113.0, 63.6, 42.4 (d, *J* = 13.5 Hz), 41.7 (d, *J* = 13.2 Hz), 37.5 (d, *J* = 29.0 Hz), 37.3 (d, J = 29.0 Hz), 37.1, 37.0, 32.9, 29.1 (d, *J* = 8.6 Hz), 28.9 (d, *J* = 8.5 Hz). **^{31}P{^{1}H} NMR** (162 MHz, $CDCl_3$) δ 24.8. **HRMS** (ESI+) calculated for $[C_{72}H_{71}NP]^+$ 980.5319 *m/z*; found $[M + H]^+$ 980.5300 *m/z*. α_D^{589} = +33.1 deg.cm^2.g^{-1} ($CHCl_3$, c 0.96, 302 K).

Complex (*R*,*R*)-B

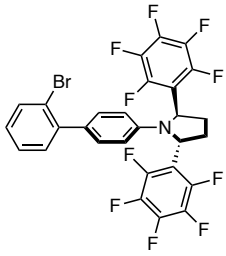


$[Me_2SAuCl]$ (14 mg, 46 µmol, 1.0 equiv) and ligand $\mathbf{L_B}$ (45 mg, 46 µmol, 1.0 equiv) were dissolved in CH_2Cl_2 (1.0 mL) under an atmosphere of argon. The reaction mixture was stirred at 24 ºC for 15 min. The mixture was filtered through a syringe filter and concentrated. The residue was dissolved in CH_2Cl_2, filtered through a path of neutral Al_2O_3 and concentrated to yield complex (*R*,*R*)-**B** (38 mg, 31 µmol, 62%) as a white solid.

M.p. = > 160 °C (decomposition; pentane/hexane). **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 7.81 (td, *J* = 7.3, 1.6 Hz, 1H), 7.76 – 7.70 (m, 10H), 7.62 (s, 4H), 7.50 – 7.44 (m, 8H), 7.44 – 7.39 (m, 2H), 7.39 – 7.35 (m, 4H), 7.22 (ddd, *J* = 7.5, 4.3, 1.7 Hz, 1H), 6.89 (dd, *J* = 8.5,

2.2 Hz, 1H), 6.82 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.57 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.53 (dd, *J* = 8.5, 2.6 Hz, 1H), 5.48 (d, *J* = 6.5 Hz, 2H), 2.84 – 2.73 (m, 2H), 2.32 – 2.24 (m, 3H), 2.24 – 2.17 (m, 3H), 2.07 – 1.94 (m, 9H), 1.94 – 1.90 (m, 2H), 1.89 – 1.83 (m, 3H), 1.74 – 1.64 (m, 6H), 1.58 – 1.50 (m, 6H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 151.8 (d, *J* = 13.0 Hz), 146.3, 145.7, 142.5, 141.7, 135.1 (d, *J* = 2.1 Hz), 134.6 (d, *J* = 7.1 Hz), 130.6 (d, *J* = 2.0 Hz), 130.3 (d, *J* = 6.6 Hz), 130.2, 130.0, 129.3, 128.0, 127.9, 126.1 (d, *J* = 6.6 Hz), 125.0, 124.7, 124.5, 124.2, 116.1, 113.9, 64.7, 43.3 (d, *J* = 23.7 Hz), 43.1 (d, *J* = 2.5 Hz), 42.7 (d, *J* = 23.4 Hz), 42.3 (d, *J* = 2.4 Hz), 36.8 (d, *J* = 21.4 Hz), 33.3, 29.4 (d, *J* = 9.8 Hz), 29.2 (d, *J* = 9.8 Hz). **^{31}P{^{1}H} NMR** (162 MHz, CD_2Cl_2) δ 65.3. **HRMS** (ESI+) calculated for $[C_{72}H_{70}AuNP]^+$ 1176.4906 *m/z*; found $[M - Cl]^+$ 1176.4909 *m/z*. **α_D^{589}** = +66.6 deg.cm^{2}g^{-1} ($CHCl_3$, c 0.87, 302 K).

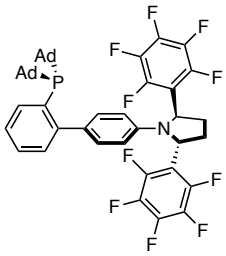
(2*R*,5*R*)-1-(2'-Bromo-[1,1'-biphenyl]-4-yl)-2,5-bis(perfluorophenyl)pyrrolidine



To a solution of (1*S*,4*S*)-1,4-bis(perfluorophenyl)butane-1,4-diol (1.5 g, 3.6 mmol, 1.0 equiv) in CH_2Cl_2 (36 mL) at –20 °C were added NEt_3 (1.5 mL, 10.8 mmol, 3.0 equiv) and methanesulfonyl chloride (0.72 mL, 9.4 mmol, 2.6 mmol) under anhydrous N_2 atmosphere. The mixture was stirred for 2.5 h at –20 °C. Then, a solution of 2'-bromo-[1,1'-biphenyl]-4-amine (4.4 g, 17.6 mmol, 4.9 equiv) in CH_2Cl_2 (3 mL) was added and the resulting solution was stirred at 24 ºC overnight. The volatiles were removed under reduced pressure and the organic materials were dissolved in EtOAc. The organic phase was washed with sat. $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated. The excess aniline was removed by flash column chromatography (cyclohexane/CH_2Cl_2 2:1, then 1:1) and the obtained compound was further purified by flash column chromatography (cyclohexane/toluene 20:1) to yield the title compound (815 mg, 1.28 mmol, 36%) as a white solid.

M.p. = 182 – 184 ºC **(**cyclohexane/toluene). **^{1}H NMR** (400 MHz, CD_2Cl_2) δ 7.63 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.33 (td, *J* = 7.5, 1.3 Hz, 1H), 7.26 (dd, *J* = 7.7, 1.9 Hz, 1H), 7.22 – 7.18 (m, 2H), 7.16 (ddd, *J* = 8.0, 7.2, 1.9 Hz, 1H), 6.52 – 6.46 (m, 2H), 5.64 – 5.54 (m, 2H), 2.94 – 2.77 (m, 2H), 2.28 – 2.12 (m, 2H). **^{13}C{^{1}H} NMR** (101 MHz, CD_2Cl_2) δ 145.3 (dm, *J* = 247.1 Hz), 143.3, 142.6, 140.9 (dm, *J* = 251.7 Hz), 138.4 (dm, *J* 250.6 Hz), 133.7, 131.9, 131.0, 128.7, 128.0, 123.0, 117.5 – 116.9 (m), 113.0, 54.8, 33.3. **^{19}F{^{1}H} NMR** (376 MHz, CD_2Cl_2) δ –145.7, –156.6 (t, *J* = 20.9 Hz), –162.5 (td, *J* = 21.4, 6.7 Hz). **HRMS** (ESI+) calculated for $[C_{28}H_{15}BrF_{10}N]^+$ 634.0223 *m/z*; found $[M + H]^+$ 634.0220 *m/z*. **α_D^{589}** = +80.9 deg.cm^2.g^{-1} ($CHCl_3$, c 1.07, 300 K).

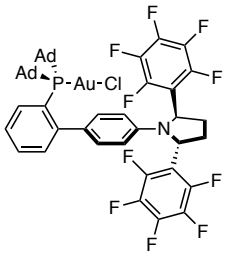
Ligand L$_C$



A flame-dried 10 mL Schlenk flask was charged with (2*R*,5*R*)-1-(2'-bromo-[1,1'-biphenyl]-4-yl)-2,5-bis(perfluorophenyl)pyrrolidin (150 mg, 0.24 mmol, 1.0 equiv), $Pd(OAc)_2$ (2.7 mg, 12 µmol, 5 mol %), dppf (7.9 mg, 14 µmol, 6 mol %), NaO*t*Bu (27 mg, 0.28 mmol, 1.2 equiv) and toluene (1.2 mL) and the resulting suspension was stirred for 15 min at 24 ºC. Di(1-adamantyl)phosphine (79 mg, 0.26 mmol, 1.1 equiv) was added and the reaction mixture was stirred at 120 ºC for 16 h. Then, the reaction was allowed to cool to 24 ºC and the crude was purified by flash column chromatography (cyclohexane/CH_2Cl_2 3:1, then cyclohexane/Et_2O 40:1) to yield ligand **L$_C$** (90 mg, 0.105 mmol, 45%) as a white solid.

M.p. = 138 – 140 °C (cyclohexane/ Et_2O). **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 7.83 (d, *J* = 7.5 Hz, 1H), 7.32 – 7.22 (m, 2H), 7.12 (ddd, *J* = 7.1, 4.0, 1.2 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 2H), 6.39 (d, *J* = 8.5 Hz, 2H), 5.58 (d, *J* = 6.5 Hz, 2H), 2.90 – 2.74 (m, 2H), 2.23 – 2.14 (m, 2H), 1.91 – 1.84 (m, 7H), 1.84 – 1.79 (m, 7H), 1.79 – 1.70 (m, 6H), 1.66 (s, 7H), 1.63 – 1.60 (m, 3H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 151.9 (d, *J* = 32.1 Hz), 145.5 (dm, *J* = 246.9 Hz), 142.4, 140.7 (dm, *J* = 252.7 Hz), 138.3 (dm, *J* = 250.8 Hz), 137.3 (d, *J* = 2.6 Hz), 134.5 (d, *J* = 7.0 Hz), 134.0, 133.8, 132.1 (d, *J* = 4.1 Hz), 131.2 (d, *J* = 6.0 Hz), 128.7, 125.5, 117.5 (t, *J* = 14.1 Hz), 112.7, 54.8, 42.5 (d, *J* = 13.1 Hz), 42.3 (d, *J* = 13.1 Hz), 37.8 (d, *J* = 9.9 Hz), 37.6 (d, *J* = 10.1 Hz), 37.5 (d, *J* = 7.4 Hz), 33.2, 29.62 (d, *J* = 8.6 Hz), 29.55 (d, *J* = 8.5 Hz). **^{31}P{^{1}H} NMR** (162 MHz, CD_2Cl_2) δ 24.7. **^{19}F{^{1}H} NMR** (376 MHz, CD_2Cl_2) δ –145.3 (dd, *J* = 22.6, 7.8 Hz), –156.7 (t, *J* = 21.0 Hz), –162.7 (t, *J* = 21.2 Hz). **HRMS** (ESI+) calculated for $[C_{48}H_{45}F_{10}NP]^+$ 856.3124 *m/z*; found $[M + H]^+$ 856.3099 *m/z*. **α_D^{589}** = +60.7 deg.cm^2.g^{-1} ($CHCl_3$, c 1.0, 299 K).

Complex (*R*,*R*)-C

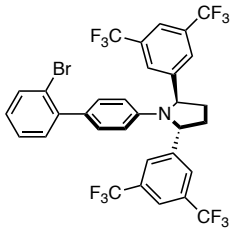


[Me_2SAuCl] (13 mg, 43 µmol, 1.0 equiv) and ligand **L$_C$** (37.2 mg, 43 µmol, 1.0 equiv) were dissolved in CH_2Cl_2 (0.44 mL) under an atmosphere of argon. The reaction mixture was stirred at 24 ºC for 15 min. The mixture was filtered through a syringe filter and concentrated. The residue was dissolved in CH_2Cl_2, filtered through a path of neutral Al_2O_3 and concentrated to yield complex (*R*,*R*)-**C** (36 mg, 33 µmol, 76%) as a white solid.

M.p. = 202 – 204 °C (CH_2Cl_2/Et_2O). **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 7.89 – 7.83 (m, 1H), 7.49 – 7.42 (m, 2H), 7.17 – 7.12 (m, 1H), 6.95 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.79 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.55 (dd, *J* = 8.4, 2.8 Hz, 1H), 6.42 (dd, *J* = 8.4, 2.8 Hz, 1H), 5.63 (d, *J* = 7.5 Hz, 2H), 2.98 – 2.85 (m, 2H), 2.21 – 2.14 (m, 8H), 2.14 – 2.06 (m, 7H), 2.00 (br s, 7H), 1.70 (br s, 10H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 151.2 (d, *J* = 13.5 Hz), 145.4 (dm, *J*

= 248.0 Hz), 143.9, 140.7 (dm, *J* = 251.2 Hz), 138.3 (dm, *J* = 250.3 Hz), 135.2 (d, *J* = 2.3 Hz), 134.8 (d, *J* = 7.3 Hz), 132.5 (d, *J* = 6.6 Hz), 130.9 (d, *J* = 6.6 Hz), 130.6 (d, *J* = 2.1 Hz), 126.4 (d, *J* = 6.6 Hz), 124.6, 124.2, 117.4 (t, *J* = 14.2 Hz), 113.3 (d, *J* = 13.5 Hz), 54.5, 43.1 (d, *J* = 23.8 Hz), 42.74 (d, *J* = 23.8 Hz), 42.74 (d, *J* = 2.5 Hz), 42.5 (d, *J* = 2.4 Hz), 36.9, 33.3, 29.4 (d, *J* = 12.3 Hz), 29.3 (d, *J* = 11.9 Hz). **^{31}P{^{1}H} NMR** (203 MHz, CD_2Cl_2) δ 64.8. **^{19}F{^{1}H} NMR** (471 MHz, CD_2Cl_2) δ –142.9 – –146.3 (m), –157.4 (t, *J* = 20.9 Hz), –160.8 – –164.5 (m). **HRMS** (ESI+) calculated for $[C_{48}H_{44}AuClF_{10}NNaP]^+$ 1110.2298 *m/z*; found $[M + H]^+$ 1110.2275 *m/z*. **Elemental analysis** calculated for $C_{48}H_{45}AuClF_{10}NP$: C 52.98; H 4.08; N 1.29; found: C 53.04; H 4.25; N 1.49. **α_D^{589}** = +49.9 deg.cm^2.g^{-1} ($CHCl_3$, c 1.1, 297 K).

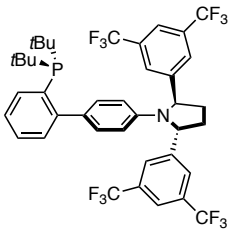
(2*R*,5*R*)-2,5-Bis(3,5-bis(trifluoromethyl)phenyl)-1-(2'-bromo-[1,1'-biphenyl]-4-yl)pyrrolidine



To a solution of (1*S*,4*S*)-1,4-bis(3,5-bis(trifluoromethyl) phenyl)butane-1,4-diol (2.4 g, 4.61 mmol, 1.0 equiv) in CH_2Cl_2 (46 mL) at –20 °C were added NEt_3 (1.93 mL, 13.8 mmol, 3.0 equiv) and methanesulfonyl chloride (0.93 mL, 12.0 mmol, 2.6 equiv) under an atmosphere of argon. The mixture was stirred for 2.5 h at –20 °C. Then, a solution of 2'-bromo-[1,1'-biphenyl]-4-amine (5.6 g, 22.6 mmol, 4.9 equiv) in CH_2Cl_2 (22.5 mL) was added and the resulting mixture was stirred at 24 ºC overnight. The volatile products were removed under reduced pressure and the organic materials were extracted with EtOAc. The combined organic phases were washed with brine and sat. $NaHCO_3$, dried over Na_2SO_4 and concentrated. The excess aniline was removed by flash column chromatography (cyclohexane/CH_2Cl_2 1:1) and the obtained compound was purified by flash column chromatography (cyclohexane/EtOAc 20:1) to afford the title compound (1.31 g, 1.80 mmol, 39%) as a white solid.

M.p. = 68 – 70 °C (cyclohexane/EtOAc). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.80 (s, 2H), 7.67 (s, 4H), 7.58 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.30 – 7.21 (m, 2H), 7.15 – 7.06 (m, 3H), 6.32 (d, *J* = 8.8 Hz, 2H), 5.45 (d, *J* = 7.1 Hz, 2H), 2.66 – 2.54 (m, 2H), 2.00 – 1.89 (m, 2H).**^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 146.2, 142.8, 142.3, 133.2, 132.3 (q, *J* = 33.3 Hz), 131.3, 130.7, 130.5, 128.2, 127.4, 126.4, 123.4 (q, J = 273.2 Hz), 123.1, 121.7 – 121.4 (m), 113.6, 62.7, 32.3. **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) δ –62.9. **HRMS** (ESI+) calculated for $[C_{32}H_{21}BrF_{12}N]^+$ 726.0660 *m/z*; found $[M + H]^+$ 726.0647 *m/z*. **α_D^{589}** = +26.0 deg.cm^2.g^{-1} ($CHCl_3$, c 0.95, 297 K).

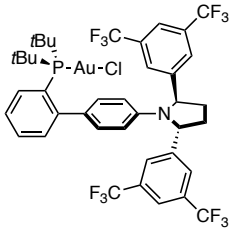
Ligand L_D

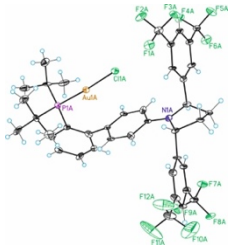


A flame-dried 10 mL Schlenk flask was charged with (2*R*,5*R*)-2,5-bis(3,5-bis(trifluoromethyl)phenyl)-1-(2'-bromo-[1,1'-biphenyl]-4-yl)pyrrolidine (150 mg, 0.21 mmol, 1.0 equiv), $Pd(OAc)_2$ (2.32 mg, 10.3 µmol, 5 mol %), dppf (6.9, 0.012 mmol, 6 mol %), NaO*t*Bu (24 mg, 0.25 mmol, 1.2 equiv) and toluene (1 mL) and the resulting suspension was stirred for 15 min at 24 ºC. Di-*tert*-butylphosphane (42 µL, 0.227 mmol, 1.1 equiv) was added and the reaction mixture was stirred at 120 ºC for 16 h. Then, the reaction was allowed to cool to 24 ºC and the crude was purified by flash column chromatography (cyclohexane/CH_2Cl_2 3:1, then cyclohexane/Et_2O 40:1) to yield ligand **L_D** (157 mg, 0.198 mmol, 96%) as a white solid.

M.p. = 172 – 174 °C (pentane). **^{1}H NMR** (400 MHz, CD_2Cl_2) δ 7.85 – 7.79 (m, 3H), 7.73 (s, 4H), 7.32 – 7.27 (m, 1H), 7.26 – 7.21 (m, 1H), 7.15 (ddd, *J* = 7.6, 4.2, 1.7 Hz, 1H), 7.02 – 6.97 (m, 2H), 6.31 – 6.25 (m, 2H), 5.47 (d, *J* = 7.2 Hz, 2H), 2.68 – 2.50 (m, 2H), 1.98 – 1.84 (m, 2H), 1.13 (d, *J* = 11.5 Hz, 9H), 0.96 (d, *J* = 11.5 Hz, 9H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 151.3 (d, *J* = 31.3 Hz), 147.2, 142.5, 136.5, 136.3, 136.1 (d, *J* = 3.0 Hz), 133.4 (d, *J* = 6.7 Hz), 132.5 (d, *J* = 4.5 Hz), 132.3 (q, *J* = 33.5 Hz), 131.2 (d, *J* = 5.8 Hz), 128.9, 127.3 – 127.0 (m), 125.8, 124.1 (q, *J* = 273.0 Hz), 122.0 – 121.5 (m), 113.3, 63.2, 33.2, 33.0, 32.9, 32.7, 31.2 (d, *J* = 15.8 Hz), 30.6 (d, *J* = 15.5 Hz).**^{31}P{^{1}H} NMR** (203 MHz, CD_2Cl_2) δ 21.2. **^{19}F{^{1}H} NMR** (376 MHz, CD_2Cl_2) δ –63.2. **HRMS** (ESI+) calculated for $[C_{40}H_{39}F_{12}NP]^+$ 792.2623 *m/z*; found $[M + H]^+$ 792.2629 *m/z*. **α_D^{589}** = +25.8 deg.cm^2.g^{-1} ($CHCl_3$, c 1.03, 298 K).

Complex (*R*,*R*)-D



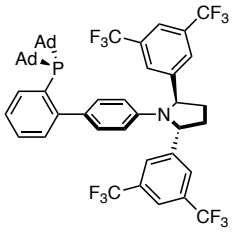


[Me_2SAuCl] (15 mg, 51 µmol, 1.0 equiv) and ligand **L_D** (40 mg, 51 µmol, 1.0 equiv) were dissolved in CH_2Cl_2 (0.51 mL) under an atmosphere of argon. The reaction mixture was stirred at 24 ºC for 15 min. The mixture was filtered through a syringe filter and concentrated. The residue was dissolved in CH_2Cl_2, filtered through a path of neutral Al_2O_3 and concentrated to yield complex (*R*,*R*)-**D** (49 mg, 48 µmol, 94%) as a white solid.

M.p. = 259 – 262 °C (CH_2Cl_2/Pentane). **^{1}H NMR** (400 MHz, CD_2Cl_2) δ 7.90 (s, 4H), 7.85 – 7.77 (m, 3H), 7.49 – 7.38 (dtt, *J* = 20.2, 7.6, 1.4 Hz, 2H), 7.27 – 7.22 (m, 1H), 6.92 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.74 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.28 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.21 (dd, *J* = 8.4, 2.7 Hz, 1H), 5.50 (d, *J* = 6.8 Hz, 2H), 2.67 – 2.53 (m, 2H), 1.91 – 1.79 (m, 2H), 1.45 (d, *J* = 15.5 Hz, 9H), 1.19 (d, *J* = 15.6 Hz, 9H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ

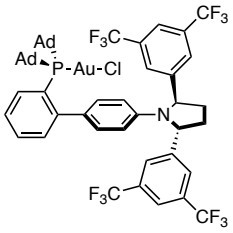
150.6 (d, *J* = 12.9 Hz), 147.2, 144.0, 134.3 (d, *J* = 2.9 Hz), 133.9 (d, *J* = 7.2 Hz), 132.2 (q, *J* = 33.2 Hz), 130.98 (d, *J* = 6.8 Hz), 130.96 (d, *J* = 2.3 Hz), 130.4, 130.2, 127.5 – 127.4 (m), 127.0 (d, *J* = 22.5 Hz), 126.8 (d, *J* = 16.5 Hz), 124.1 (q, *J* = 273.3 Hz), 121.8 – 121.4 (m), 116.3, 114.0, 63.7, 38.3 (d, *J* = 25.8 Hz), 37.8 (d, *J* = 25.4 Hz), 32.7, 31.9 (d, *J* = 6.8 Hz), 30.4 (d, *J* = 6.7 Hz).**^{31}P{^{1}H} NMR** (162 MHz, CD_2Cl_2) δ 63.3. **^{19}F{^{1}H} NMR** (376 MHz, CD_2Cl_2) δ –62.8. **HRMS** (ESI+) calculated for $[C_{40}H_{38}AuClF_{12}NNaP]^+$ 1046.1797 *m/z*; found $[M + Na]^+$ 1046.1797 *m/z*. **Elemental analysis** calculated for $C_{40}H_{38}AuClF_{12}NP$: C 46.91; H 3.74; N 1.37; found: C 46.87; H 3.81; N 1.47. **α_D^{589}** = +34.0 deg.cm^2.g^{-1} ($CHCl_3$, c 1.1, 297 K).

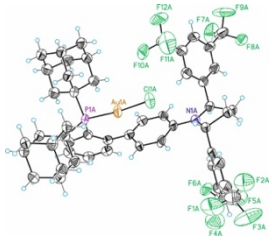
Ligand L$_E$



A flame-dried 10 mL Schlenk flask was charged with (2*R*,5*R*)-2,5-bis(3,5-bis(trifluoromethyl)phenyl)-1-(2'-bromo-[1,1'-biphenyl]-4-yl)pyrrolidine (400 mg, 0.55 mmol, 1.0 equiv), $Pd(OAc)_2$ (6.18 mg, 0.028 mmol, 5 mol %), dppf (18 mg, 0.033 mmol, 6 mol %), NaO*t*Bu (64 mg, 0,661 mmol, 1.2 equiv) and toluene (2.75 mL), the resulting suspension was stirred for 15 min at 24 ºC. Di(1-adamantyl)phosphine (183 mg, 0.606 mmol, 1.1 equiv) was added and the reaction mixture was stirred at 120 ºC for 16 h. Then, the reaction was allowed to cool to 24 ºC and the crude was purified by flash column chromatography (cyclohexane/CH_2Cl_2 3:1, then cyclohexane/Et_2O 40:1) to yield ligand **L$_E$** (493 mg, 0.520 mmol, 94%) as a white solid. **M.p. =** 174 – 176 °C (cyclohexane/Et_2O). **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 7.88 – 7.79 (m, 3H), 7.75 (s, 4H), 7.34 – 7.27 (m, 1H), 7.24 (td, *J* = 7.4, 1.6 Hz, 1H), 7.14 (ddd, *J* = 7.6, 4.1, 1.6 Hz, 1H), 7.02 – 6.94 (m, 2H), 6.33 – 6.25 (m, 2H), 5.48 (d, *J* = 7.2 Hz, 2H), 2.68 – 2.50 (m, 2H), 1.96 – 1.90 (m, 5H), 1.89 – 1.83 (m, 6H), 1.80 – 1.73 (m, 4H), 1.73 – 1.71 (m, 3H), 1.70 – 1.63 (m, 10H), 1.63 – 1.56 (m, 5H), 1.55 – 1.51 (m, 1H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 151.9 (d, *J* = 31.4 Hz), 147.2, 142.4, 137.4 (d, *J* = 2.5 Hz), 133.9, 133.64 (d, *J* = 2.1 Hz), 133.59, 132.4 (d, *J* = 4.8 Hz), 132.3 (q, *J* = 33.2 Hz), 131.4 (d, *J* = 5.9 Hz), 128.7, 127.2 – 127.0 (m), 125.4, 124.0 (q, *J* = 273.0 Hz), 121.8 (p, *J* = 3.7 Hz), 113.2, 63.2, 42.7 (d, *J* = 13.3 Hz), 42.1 (d, *J* = 13.0 Hz), 38.0, 37.8 (d, *J* = 2.7 Hz), 37.5, 37.4, 32.6, 29.6 (d, *J* = 8.6 Hz), 29.5 (d, *J* = 8.5 Hz). **^{31}P{^{1}H} NMR** (203 MHz, CD_2Cl_2) δ 24.0. **^{19}F{^{1}H} NMR** (471 MHz, CD_2Cl_2) δ –63.1. **HRMS** (ESI+) calculated for $[C_{52}H_{51}F_{12}NP]^+$ 948.3562 *m/z*; found $[M + H]^+$ 948.3562 *m/z*. **α_D^{589}** = +26.7 deg.cm^2.g^{-1} ($CHCl_3$, c 0.97, 300 K).

Complex (*R*,*R*)-E

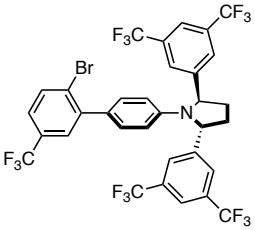




[Me2SAuCl] (31 mg, 0.11 mmol, 1.0 equiv) and ligand **L$_E$** (101 mg, 0.11 mmol, 1.0 equiv) were dissolved in CH_2Cl_2 (1.1 mL) under an atmosphere of argon. The reaction mixture was stirred at 24 ºC for 15 min. The mixture was filtered through a syringe filter and concentrated. The residue was dissolved in CH_2Cl_2, filtered through a path of neutral Al_2O_3 and concentrated to yield complex (*R*,*R*)-**E** (114 mg, 0.097 mmol, 90%) as a white solid.

M.p. = >245 °C (decomposition; CH_2Cl_2/Et_2O). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.89 (s, 4H), 7.82 – 7.75 (m, 3H), 7.48 – 7.37 (m, 2H), 7.31 – 7.26 (m, 1H), 6.91 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.70 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.28 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.17 (dd, *J* = 8.4, 2.7 Hz, 1H), 5.49 (d, *J* = 6.6 Hz, 2H), 2.67 – 2.51 (m, 2H), 2.28 – 2.17 (m, 6H), 2.00 – 1.88 (m, 12H), 1.87 – 1.83 (m, 2H), 1.73 – 1.63 (m, 6H), 1.63 – 1.55 (m, 6H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 150.8 (d, *J* = 12.5 Hz), 146.5, 143.5, 134.5 (d, *J* = 2.2 Hz), 133.8 (d, *J* = 7.0 Hz), 132.0 (q, *J* = 33.2 Hz), 130.7 (d, *J* = 6.5 Hz), 130.4 (d, *J* = 1.9 Hz), 130.0, 129.7, 126.9, 125.9 (d, *J* = 6.6 Hz), 124.3, 124.0, 123.5 (q, *J* = 272.83 Hz), 121.5 – 120.8 (m), 115.9, 113.5, 63.3, 43.0 (d, *J* = 23.5 Hz), 42.8 (d, *J* = 2.5 Hz), 42.1 (d, *J* = 23.3 Hz), 41.6 (d, *J* = 2.4 Hz), 36.5, 36.3, 32.5, 28.9 (d, *J* = 9.8 Hz), 28.6 (d, *J* = 9.9 Hz). **^{31}P{^{1}H} NMR** (162 MHz, $CDCl_3$) δ 64.9. **^{19}F{^{1}H} NMR** (471 MHz, $CDCl_3$) δ –62.3. **HRMS** (ESI+) calculated for $[C_{52}H_{50}AuClF_{12}NNaP]^+$ 1202.2736 *m/z*; found $[M + Na]^+$ 1202.2764 *m/z*. **Elemental analysis** calculated for $C_{52}H_{50}AuClF_{12}NP$: C 52.91; H 4.27; N 1.19; found: C 52.89; H 4.51; N 1.20. **α_D^{589}** = +42.4 deg.cm^2.g^{-1} ($CHCl_3$, c 1.24, 299 K).

(2*R*,5*R*)-2,5-Bis(3,5-bis(trifluoromethyl)phenyl)-1-(2'-bromo-5'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)pyrrolidine

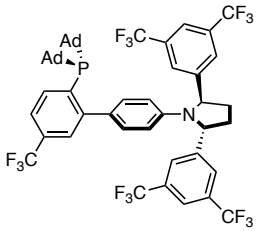


To a solution of (1*S*,4*S*)-1,4-bis(3,5-bis(trifluoromethyl)phenyl)butane-1,4-diol (200 mg, 0.389 mmol, 1.0 equiv) in CH_2Cl_2 (3.9 mL) at –20 °C were added NEt_3 (0.163 mL, 1.17 mmol, 3.0 equiv) and methanesulfonyl chloride (0.078 mL, 1.01 mmol, 2.6 equiv) under an atmosphere of argon. The mixture was stirred for 2.5 h at –20 °C. Then, a solution of 2'-Bromo-5'-(trifluoromethyl)-[1,1'-biphenyl]-4-amine (602 mg, 1.91 mmol, 4.9 equiv) in CH_2Cl_2 (2 mL) was added and the resulting mixture was stirred at 24 °C overnight. The volatile products were removed under reduced pressure and the organic materials were dissolved in EtOAc (15 mL). The organic phase was washed with sat. $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated. The excess aniline was removed by flash column

chromatography (cyclohexane/CH_2Cl_2 1:1, then 2:1) and the obtained compound was purified by flash column chromatography (cyclohexane/EtOAc 20:1) to give the title compound (114 mg, 0.136 mmol, 35%) as a white foam.

M.p. = 73 – 76 °C (CH_2Cl_2). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.82 (s, 2H), 7.71 (d, *J* = 8.3 Hz, 1H), 7.68 (s, 4H), 7.48 (d, *J* = 1.8 Hz, 1H), 7.34 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.13 (d, *J* = 8.7 Hz, 2H), 6.35 (d, *J* = 8.7 Hz, 2H), 5.46 (d, *J* = 6.9 Hz, 2H), 2.68 – 2.56 (m, 2H), 2.02 – 1.90 (m, 2H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 146.0, 143.3, 143.2, 133.8, 132.4 (q, *J* = 33.4 Hz), 130.5, 130.0 (q, *J* = 32.8 Hz), 129.3, 127.9 (q, *J* = 3.6 Hz), 127.0, 126.5 – 126.2 (m), 124.7 (q, *J* = 3.6 Hz), 124.0 (q, *J* = 272.1 Hz), 123.4 (q, *J* = 272.1 Hz), 121.8 – 121.5 (m), 113.7, 62.8, 32.3. **^{19}F{^{1}H} NMR** (471 MHz, $CDCl_3$) δ –62.7, –62.8. **HRMS** (ESI+) calculated for $[C_{33}H_{19}BrF_{15}NNa]^+$ 816.0354 *m/z*; found $[M + Na]^+$ 816.0363 *m/z*. **α_D^{589}** = +26.1 deg.cm^2.g^{-1} ($CHCl_3$, c 1.0, 300 K).

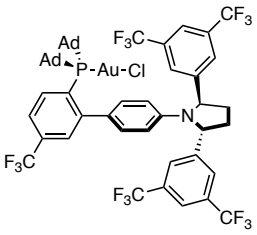
Ligand L_F

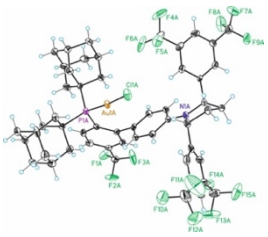


A flame-dried 10 mL Schlenk flask was charged with (2R,5R)-2,5-bis(3,5-bis(trifluoromethyl)phenyl)-1-(2'-bromo-5'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)pyrrolidine (109 mg, 0.137 mmol, 1.0 equiv), $Pd(OAc)_2$ (1.54 mg, 6.86 μmol, 5 mol %), dppf (4.56 mg, 8.23 μmol, 6 mol %), NaO*t*Bu (15.8 mg, 0.165 mmol, 1.2 equiv) and toluene (1 mL) and the resulting suspension was stirred for 15 min at 24 ºC. Di-(1-adamantyl)phosphine (45.6 mg, 0.151 mmol, 1.1 equiv) was added and the reaction mixture was stirred at 120 °C for 14 h. Then, the reaction was allowed to cool to 24 °C and the crude was purified by flash column chromatography (cyclohexane/CH_2Cl_2 4:1, then cyclohexane/Et_2O 40:1) to yield ligand **L_F** (134 mg, 0.121 mmol, 88%) as an off-white foam.

M.p. = 173 – 178 °C (cyclohexane/Et_2O). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.9 Hz, 1H), 7.80 (s, 2H), 7.70 (s, 4H), 7.49 – 7.43 (m, 2H), 6.99 (d, *J* = 8.0 Hz, 2H), 6.26 (d, *J* = 8.6 Hz, 2H), 5.47 (d, *J* = 7.0 Hz, 2H), 2.65 – 2.53 (m, 2H), 1.97 – 1.82 (m, 11H), 1.81 – 1.76 (m, 3H), 1.73 – 1.63 (s, 12H), 1.63 – 1.51 (m, 6H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 151.9 (d, *J* = 31.5 Hz), 146.3, 142.1, 138.7 (d, *J* = 33.5 Hz), 137.1 (d, *J* = 2.6 Hz), 132.2 (q, *J* = 33.3 Hz), 132.1 (d, *J* = 5.0 Hz), 131.8 (d, *J* = 3.0 Hz), 130.2 (q, *J* = 32.4 Hz), 127.4 – 127.2 (m), 126.6 – 126.4 (m), 124.4 (q, *J* = 273.0 Hz), 123.4 (q, *J* = 273.0 Hz), 121.5 – 121.3 (m), 121.3 – 121.1 (m), 113.0, 62.6, 42.2 (d, *J* = 13.4 Hz), 41.6 (d, *J* = 13.0 Hz), 37.6 (d, *J* = 27.0 Hz), 37.3 (d, *J* = 27.6 Hz), 37.0 (d, *J* = 16.9 Hz), 32.4, 29.0 (d, *J* = 8.6 Hz), 28.8 (d, *J* = 8.5 Hz). **^{31}P{^{1}H} NMR** (202 MHz, $CDCl_3$) δ 20.3. **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) δ –62.7, –62.8. **HRMS** (ESI+) calculated for $[C_{53}H_{50}F_{15}NP]^+$ 1016.3436; found $[M + H]^+$ 1016.3457. **α_D^{589}** = +23.8 deg.cm^2.g^{-1} ($CHCl_3$, c 1.0, 300 K).

Complex (*R*,*R*)-F

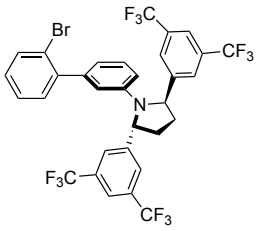




[Me_2SAuCl] (35.4 mg, 0.120 mmol, 1.0 equiv) and ligand $\mathbf{L_F}$ (122 mg, 0.120 mmol, 1.0 equiv) were dissolved in CH_2Cl_2 (1.2 mL) under an atmosphere of argon. The reaction mixture was stirred at 24 ºC for 15 min. The mixture was filtered through a syringe filter and concentrated. The residue was dissolved in CH_2Cl_2, filtered through a path of neutral Al_2O_3 and concentrated to yield complex (*R*,*R*)-**F** (146 mg, 0.115 mmol, 95%) as a white solid.

M.p. = >306 °C (decomposition; pentane/Et_2O). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.96 – 7.84 (m, 5H), 7.79 (s, 2H), 7.65 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.55 (dd, *J* = 3.7, 2.1 Hz, 1H), 6.92 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.70 (dd, *J* = 8.5, 2.2 Hz, 1H), 6.30 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.19 (dd, *J* = 8.5, 2.7 Hz, 1H), 5.49 (d, *J* = 6.9 Hz, 2H), 2.67 – 2.55 (m, 2H), 2.27 – 2.16 (m, 6H), 2.03 – 1.82 (m, 14H), 1.74 – 1.53 (m, 12H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 151.6 (d, *J* = 12.8 Hz), 146.3, 143.9, 134.9 (d, *J* = 2.4 Hz), 132.1 (qd, *J* = 33.2, 2.1 Hz), 132.0 (q, *J* = 32.5 Hz), 130.4 – 130.1 (m), 129.9, 129.6, 129.2 (d, *J* = 6.2 Hz), 128.8 (d, *J* = 40.9 Hz), 127.0 – 126.8 (m), 123.6 (q, *J* = 274.4 Hz), 123.5 (q, *J* = 272.1 Hz), 122.4 – 122.3 (m), 121.4 – 121.1 (m), 116.1, 113.7, 63.3, 43.3 (d, *J* = 22.3 Hz), 42.8 (d, *J* = 2.5 Hz), 42.4 (d, *J* = 22.2 Hz), 41.6 (d, *J* = 2.3 Hz), 36.3 (d, *J* = 19.2 Hz), 32.5, 28.8 (d, *J* = 9.8 Hz), 28.5 (d, *J* = 9.9 Hz). **^{31}P{^{1}H} NMR** (203 MHz, $CDCl_3$) δ 64.9. **^{19}F{^{1}H} NMR** (471 MHz, $CDCl_3$) δ –62.4, –63.1. **HRMS** (ESI+) calculated for $[C_{53}H_{49}AuClF_{15}NNaP]^+$ 1270.2610 *m/z*; found $[M + Na]^+$ 1270.2583 *m/z*. **Elemental analysis** calculated for $C_{53}H_{49}AuClF_{15}NP$: C 50.99; H 3.96; N 1.12; found: C 50.99; H 3.96; N 1.19. $\boldsymbol{\alpha_D^{589}}$ = +40.2 deg.cm^2.g^{-1} ($CHCl_3$, c 1.0, 301 K).

(2*R*,5*R*)-2,5-Bis(3,5-bis(trifluoromethyl)phenyl)-1-(2'-bromo-[1,1'-biphenyl]-3-yl)pyrrolidine

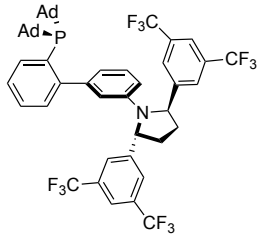


A 25 mL flame-dried two necked round bottom flask was charged with solution of 1,4-bis(3,5-bis(trifluoromethyl)phenyl)butane-1,4-diol (360 mg, 0.7 mmol, 1.0 equiv) in CH_2Cl_2 (6 mL) at –20 °C. NEt_3 (0.40 mL, 2.80 mmol, 4.0 equiv) and methanesulfonyl chloride (0.11 mL, 1.40 mmol, 2.0 equiv) were added under argon atmosphere and the mixture was stirred for 2.5 h at –20 °C. 2'-Bromo-[1,1'-biphenyl]-3-amine (870 mg, 3.50 mmol, 5.0 equiv) was then added and the solution was stirred for 20 h at 24 ºC. The reaction was quenched with sat. NH_4Cl and the aqueous phase was extracted with EtOAc. After evaporation of the solvent, the crude was purified by flash column chromatography

(cyclohexane/CH_2Cl_2 1:1) to afford the title compound (163 mg, 0.224 mmol, 32%) as a white solid.

M.p. = 55 – 57 °C (cyclohexane/CH_2Cl_2).**^{1}H NMR** (500 MHz $CDCl_3$) δ 7.78 (s, 2H), 7.66 (s, 4H), 7.51 (dd, *J* = 7.9, 1.0 1H), 7.26 – 7.23 (m, 1H), 7.15 – 7.09 (m, 3H), 6.63 (d, *J* = 8.0 Hz, 1H), 6.38 – 6.34 (m, 1H), 6.32 (dd, *J* = 8.3, 2.5 Hz, 1H), 5.43 (d, *J* = 7.2 Hz, 2H), 2.64 – 2.54 (m, 2H), 1.97 – 1.88 (m, 2H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 146.3, 142.8 (d, *J* = 2.8 Hz), 142.2, 133.2, 132.2 (q, *J* = 33.3 Hz), 131.1, 129.4, 128.7, 127.3, 126.6 – 126.4 (m), 123.4 (q, *J* = 273.2 Hz), 122.5, 121.5 (p, *J* = 3.7 Hz), 118.9, 115.8, 113.5, 62.6, 32.3. **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) δ –62.5. **HRMS** (ESI+) calculated for $[C_{32}H_{21}BrF_{12}N]^+$ 726.0660 *m/z*; found $[M + H]^+$ 726.0683 *m/z*. α_D^{589} = –54.92 deg.cm^2.g^{-1} ($CHCl_3$, c 1.00, 300 K).

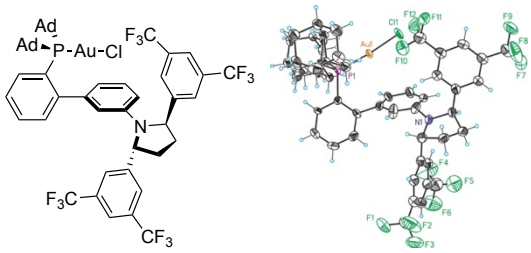
Ligand L_G



A 10 mL Schlenk flask was charged with (2*R*,5*R*)-2,5-bis(3,5-bis(trifluoromethyl)phenyl)-1-(2'-bromo-[1,1'-biphenyl]-3-yl) pyrrolidine (100 mg, 0.14 mmol), $Pd(OAc)_2$ (1.55 mg, 6.88 μmol, 5 mol %), NaO*t*Bu (15.88 mg, 0.17 mmol, 1.2 equiv), dppf (4.60 mg, 8.26 μmol, 5 mol %) and toluene (0.69 mL). The resulting suspension was stirred for 15 min at 24 ºC. Di(adamantan-1-yl)phosphane (46 mg, 0.151 mmol, 1.1 equiv) was added and the resulting mixture was stirred at 120 ºC for 24 h. Then, the reaction was allowed to cool to 24 ºC, filtered through syringe filter and washed with EtOAc. The crude product was purified by flash column chromatography (cyclohexane/CH_2Cl_2 3:1, then cyclohexane/Et_2O 40:1) to afford ligand **L_G** (78 mg, 0.14 mmol, 60%) as a white solid.

M.p. = 114 – 116 °C (cyclohexane/CH_2Cl_2/Et_2O). **^{1}H NMR** (500 MHz $CDCl_3$) δ 7.84 – 7.80 (m, 1H), 7.76 (s, 2H), 7.65 (s, 4H), 7.27 – 7.24 (m, 2H), 7.04 – 6.98 (m, 2H), 6.57 (d, *J* = 7.4Hz, 1H), 6.32 (s, 1H), 6.23 (dd, *J* = 8.2, 2.1 Hz, 1H), 5.46 (d, *J* = 7.0 Hz, 2H), 2.60 – 2.50 (m, 2H), 1.98 – 1.86 (m, 12H), 1.77 – 1.61 (m, 15H), 1.61 – 1.48 (m, 5H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 151.9 (d, *J* = 31.8 Hz), 146.5, 144.9 (d, *J* = 6.8 Hz), 142.1, 136.8 (d, *J* = 2.7 Hz), 133.2 (d, *J* = 29.5 Hz), 132.1 (q, *J* = 33.2 Hz), 130.5 (d, *J* = 6.0 Hz), 128.1 (d, *J* = 16.5 Hz), 126.6 – 126.4 (m), 125.3, 123.4 (q, *J* = 274.8 Hz), 121.5 – 121.2 (m), 121.0 (d, *J* = 3.5 Hz), 117.3 (d, *J* = 5.2 Hz), 112.6, 62.4, 42.4 (d, *J* = 13.6 Hz), 41.5 (d, *J* = 13.1 Hz), 37.4, 37.2, 36.99, 36.95 (d, *J* = 4.4 Hz), 32.3, 29.0 (d, *J* = 8.5 Hz), 28.9 (d, *J* = 8.6 Hz). **^{31}P{^{1}H} NMR** (162 MHz, $CDCl_3$) δ 24.6. **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) δ –62.8. **HRMS** (ESI+) calculated for $[C_{52}H_{51}F_{12}NP]^+$ 948.3562 *m/z*; found $[M + H]^+$ 948.3565 *m/z*. α_D^{589} = +20.7 deg.cm^2.g^{-1} ($CHCl_3$, c 0.65, 302 K).

Complex (*R*,*R*)-G

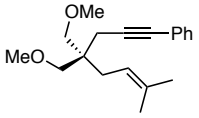


[Me_2SAuCl] (6 mg, 0.021 mmol, 1.0 equiv) and ligand $\mathbf{L_G}$ (20 mg, 0.021 mmol, 1.0 equiv) were dissolved in CH_2Cl_2 (0.4 mL) under an atmosphere of argon. The reaction mixture was stirred at 24 ºC for 15 min. The mixture was dissolved in CH_2Cl_2, filtered through a path of neutral Al_2O_3 and concentrated to yield complex (*R*,*R*)-**G** (24 mg, 0.021 mmol, 96%) as a white solid in a 5:1 mixture of rotamers. The significant ^{1}H NMR shifts of the minor rotamer were assigned by 2D NOE experiments.

M.p. = > 95 °C (decomposition; CH_2Cl_2). **Major rotamer**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 12.7 Hz, 7H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.34 – 7.29 (m, 1H), 6.98 (t, *J* = 7.9 Hz, 1H), 6.42 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.32 (d, *J* = 7.4 Hz, 1H), 6.08 (s, 1H), 5.47 (d, *J* = 5.2 Hz, 2H), 2.57 – 2.45 (m, 2H), 2.20 – 1.99 (m, 6H), 1.96 (br s, 3H), 1.79 – 1.61 (m, 14H), 1.60 – 1.50 (s, 6H), 1.46 – 1.38 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 150.9 (d, *J* = 13.6 Hz), 146.3, 143.7 – 143.6 (m), 143.5, 134.2 (d, *J* = 2.5 Hz), 133.3 (d, *J* = 7.3 Hz), 131.8 (q, *J* = 32.7 Hz), 130.1 (d, *J*= 2.5 Hz), 128.7, 126.6 – 126.3 (m), 126.1 (d, *J* = 6.4 Hz), 124.2, 123.9, 123.3 (q, *J* = 274.1 Hz), 121.4 – 121.1 (m), 119.6, 115.1, 112.8, 62.5, 42.2 – 42.0 (m), 41.5 (d, *J* = 2.7 Hz), 36.1 (d, *J* = 40.3 Hz), 32.0, 28.5 (d, *J* = 9.9 Hz), 28.3 (d, *J* = 9.7 Hz). **^{31}P{^{1}H} NMR** (162 MHz, $CDCl_3$) δ 64.4. **^{19}F{^{1}H} NMR** (471 MHz, $CDCl_3$) δ –62.4. **Minor rotamer** (only significant signals): **^{1}H NMR** (400 MHz, $CDCl_3$) 7.36 (d, *J* = 7.7 Hz, 0.2H), 7.08 (t, *J* = 7.9 Hz, 0.2H), 6.71 (dd, *J* = 8.3, 3.3 Hz, 0.2H), 6.51 (dd, *J* = 8.2, 2.2 Hz, 0.2H), 5.87 (s, 0.2H), 5.32 (d, *J* = 7.0 Hz, 0.4H), 2.65 – 2.58 (m, 0.2H), 1.85 (d, *J* = 6.4 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 150.8 (d, *J* = 13.2 Hz), 143.0 (d, *J* = 6.4 Hz), 134.2 (d, *J* = 2.1 Hz), 133.1 (d, *J* = 7.5 Hz), 132.0 (q, *J* = 33.3 Hz), 129.7, 126.0 (d, *J* = 6.7 Hz), 123.3 (q, *J* = 272.6 Hz), 119.4, 116.2, 113.7, 63.3, 42.3, 41.9, 32.4, 28.7 (d, *J* = 9.7 Hz). **^{31}P{^{1}H} NMR** (162 MHz, $CDCl_3$) δ 64.3. **^{19}F{^{1}H} NMR** (471 MHz, $CDCl_3$) δ, –62.5. **HRMS** (ESI+) calculated for $[C_{52}H_{50}AuClF_{12}NNaP]^+$ 1202.2736 *m/z*; found $[M + Na]^+$ 1202.2719 *m/z*. $\boldsymbol{\alpha_D^{589}}$ = –27.2 deg.cm^2.g^{-1} ($CHCl_3$, c 0.51, 302 K).

Enantioselective Synthesis of Cyclopenta[b]naphthalene

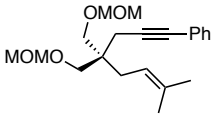
(4,4-Bis(methoxymethyl)-7-methyloct-6-en-1-yn-1-yl)benzene



A solution of 2-(3-methylbut-2-en-1-yl)-2-(3-phenylprop-2-yn-1-yl)propane-1,3-diol[133] (0.56 g, 2.18 mmol, 1.0 equiv) in THF (7 mL) was added to a suspension of NaH (0.21 g, 5.2 mmol, 2.4 equiv, 60% in mineral oil) in THF (7 mL) at 0 ºC. After stirring for 10 min MeI (0.41 mL 6.54 mmol, 3.0 equiv) was added slowly. The reaction was stirred at 24 ºC for 1 h, then diluted with Et_2O and quenched with sat. NH_4Cl solution. The aqueous phase was extracted with Et_2O (3x) and the combined organic phases were dried over Na_2SO_4, filtered and concentrated. The crude was purified by flash column chromatography (cyclohexane/EtOAc 30:1) to afford the title compound (0.56 g, 1.95 mmol, 90%) as a colorless oil.

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.42 – 7.35 (m, 2H), 7.33 – 7.25 (m, 3H), 5.22 – 5.15 (m, 1H), 3.32 (s, 6H), 3.30 – 3.23 (m, 4H), 2.37 (s, 2H), 2.13 (d, *J* = 7.9 Hz, 2H), 1.73 (s, 3H), 1.66 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, CD_2Cl_2) δ 135.0, 132.0, 128.8, 128.1, 124.7, 119.8, 88.2, 82.7, 74.9, 59.6, 43.6, 30.8, 26.4, 23.5, 18.1. **HRMS** (APCI+) calculated for $[C_{19}H_{27}O_2]^+$ 287.2006 *m/z*; found $[M + H]^+$ 287.2010 *m/z*.

6-(3-Methylbut-2-en-1-yl)-6-(3-phenylprop-2-yn-1-yl)-2,4,8,10-tetraoxaundecane

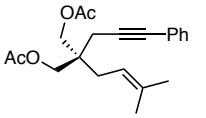


To a stirred mixture 2-(3-methylbut-2-en-1-yl)-2-(3-phenylprop-2-yn-1-yl)propane-1,3-diol[133] (60 mg, 0.23 mmol, 1.0 equiv) and DIPEA (0.16 mL, 0.92 mmol, 4.0 equiv) in CH_2Cl_2 (2.3 mL) was added MOMCl (0.053 mL, 0.69 mmol, 3.0 equiv) at 24 ºC and the reaction was stirred for 24 h. HCl (5%) was added to the mixture and the aqueous phase was extracted with CH_2Cl_2 (3x). The combined organic phases were washed with sat. $NaHCO_3$ (2x) and brine, dried over Na_2SO_4, filtered and evaporated. The crude was purified by flash column chromatography (cyclohexane/EtOAc 20:1) to yield the title compound (68 mg, 0.19 mmol, 85%) as a colorless oil.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.40 – 7.37 (m, 2H), 7.32 – 7.26 (m, 3H), 5.25 – 5.20 (m, 1H), 4.61 (s, 4H), 3.46 (q, *J* = 9.3 Hz, 4H), 3.35 (s, 6H), 2.44 (s, 2H), 2.20 (d, *J* = 7.8 Hz, 2H), 1.74 (s, 3H), 1.67 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 135.1, 132.0, 128.8, 128.1, 124.6, 119.6, 97.4, 87.9, 82.8, 69.9, 55.5, 43.0, 30.8, 26.4, 23.5, 18.2. **HRMS** (APCI+) calculated for $[C_{21}H_{31}O_4]^+$ 347.2217 *m/z*; found $[M + H]^+$ 347.2218 *m/z*.

133. Surendra, K.; Corey, E. J. *J. Am. Chem. Soc.* **2014**, *136*, 10918–10920.

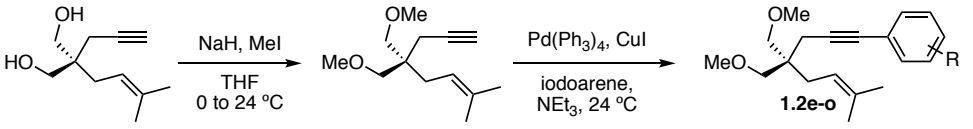
2-(3-Methylbut-2-en-1-yl)-2-(3-phenylprop-2-yn-1-yl)propane-1,3-diyl diacetate



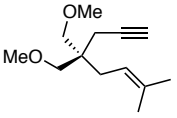
2-(3-methylbut-2-en-1-yl)-2-(3-phenylprop-2-yn-1-yl)propane-1,3-diol[133] (100 mg, 0.39 mmol, 1.0 equiv), acetyl chloride (58 μL, 0.81 mmol, 2.1 equiv) and DMAP (71 mg, 0.58 mmol, 1.5 equiv) were dissolved in CH_2Cl_2 (4 mL) and NEt_3 (0.16 mL, 1.16 mmol, 3.0 equiv) was added. The mixture was stirred at 24 ºC for 3 h. Water was added to the mixture and the aqueous phase was extracted with CH_2Cl_2 (3x). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude was purified by flash column chromatography (cyclohexane/EtOAc 20:1) to afford the title compound (102 mg, 0.3 mmol, 77%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.33 (m, 2H), 7.30 – 7.23 (m, 3H), 5.19 – 5.08 (m, 1H), 4.15 – 3.99 (m, 4H), 2.46 (s, 2H), 2.23 (d, *J* = 7.9 Hz, 2H), 2.07 (s, 6H), 1.73 (s, 3H), 1.64 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 170.9, 136.1, 131.7, 128.4, 128.0, 123.6, 117.7, 85.4, 83.4, 65.9, 41.2, 30.3, 26.2, 23.2, 21.0, 18.0. **HRMS** (ESI+) calculated for $[C_{21}H_{26}NaO_4]^+$ 365.1723 *m/z*; found $[M + Na]^+$ 365.1721 *m/z*.

Synthesis of 1,6-enynes 1.2a-o



4,4-Bis(methoxymethyl)-7-methyloct-6-en-1-yne



A solution of 2-(3-methylbut-2-en-1-yl)-2-(prop-2-yn-1-yl)propane-1,3-diol[134] (1.0 g, 5.5 mmol, 1.0 equiv) in THF (18 mL) was added to a suspension of NaH (0.53 g, 13,2 mmol, 2.4 equiv, 60% in mineral oil) in THF (18 mL) at 0 ºC. After stirring the mixture for 10 min MeI (1.0 mL, 16.5 mmol, 3.0 equiv) was added slowly. The reaction was stirred at 24 ºC for 1 h, then diluted with Et_2O and quenched with sat. NH_4Cl solution. The aqueous phase was extracted with Et_2O (3x) and the combined organic phases were dried over Na_2SO_4, filtered and concentrated. The crude was purified by flash column chromatography (cyclohexane/EtOAc 50:1) to afford the title compound (1.1 g, 5.2 mmol, 94%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.14 – 5.07 (m, 1H), 3.31 (s, 6H), 3.25 – 3.18 (m, 4H), 2.19 – 2.16 (m, 2H), 2.08 (d, *J* = 7.9 Hz, 2H), 1.94 (t, *J* = 2.7 Hz, 1H), 1.71 (s, 3H), 1.62 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 134.6, 119.2, 81.8, 74.4, 70.0, 59.3, 42.6, 30.1, 26.2,

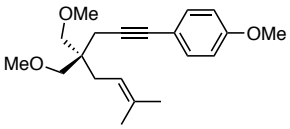
134. Benedetti, E.; Simonneau, A.; Hours, A.; Amouri, H.; Penoni, A.; Palmisano, G.; Malacria, M.; Goddard, J.; Fensterbank, L. *Adv. Synth. Catal.* **2011**, *353*, 1908–1912.

22.1, 17.8. **HRMS** (ESI+) calculated for $[C_{13}H_{22}NaO_2]^+$ 233.1512 *m/z*; found $[M + Na]^+$ 233.1503 *m/z*.

General procedure A: Sonogashira coupling

$Pd(PPh_3)_2Cl_2$ (1 mol %) and copper(I) iodide (2 mol %) were sequentially added to a stirred solution of the terminal alkyne (1.0 equiv) in NEt_3 (0.25 M) under argon at 24 ºC and the mixture was stirred for 10 min. Then, iodoarene (1.2 equiv) was added and the mixture was stirred for the corresponding time. The reaction was quenched with sat. NH_4Cl and extracted with EtOAc (3x). The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography to yield the desired Sonogashira coupling products.

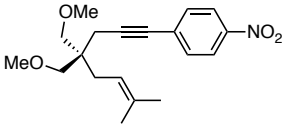
1-(4,4-Bis(methoxymethyl)-7-methyloct-6-en-1-yn-1-yl)-4-methoxybenzene



The title compound (colorless oil, 241 mg, 0.76 mmol, 80%) was synthesized following general procedure **A** using 4,4-bis(methoxymethyl)-7-methyloct-6-en-1-yne (200 mg, 1 mmol) whereby the reaction was stirred for 2 h. Purification was performed by flash column chromatography (cyclohexane/EtOAc 60:1, then toluene/CH_2Cl_2 4:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.31 (m, 2H), 6.84 – 6.79 (m, 2H), 5.21 – 5.15 (m, 1H), 3.80 (s, 3H), 3.34 (s, 6H), 3.32 – 3.26 (m, 4H), 2.37 (s, 2H), 2.15 (d, *J* = 7.9 Hz, 2H), 1.75 – 1.72 (m, 3H), 1.68 – 1.64 (m, 3H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 159.2, 134.6, 133.0, 119.5, 116.5, 114.0, 85.9, 82.1, 74.7, 59.5, 55.4, 43.2, 30.4, 26.3, 23.1, 17.9. **HRMS** (ESI+) calculated for $[C_{20}H_{28}NaO_3]^+$ 339.1931 *m/z*; found $[M + Na]^+$ 339.1926 *m/z*.

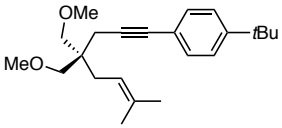
1-(4,4-Bis(methoxymethyl)-7-methyloct-6-en-1-yn-1-yl)-4-nitrobenzene



The title compound (colorless oil, 142 mg, 0.43 mmol, 91%) was synthesized following general procedure **A** using 4,4-bis(methoxymethyl)-7-methyloct-6-en-1-yne (99 mg, 0.47 mmol) whereby the reaction was stirred for 18 h. Purification was performed by flash column chromatography (cyclohexane/EtOAc 60:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 – 8.10 (m, 2H), 7.57 – 7.47 (m, 2H), 5.20 – 5.12 (m, 1H), 3.35 (s, 6H), 3.31 – 3.25 (m, 4H), 2.45 (s, 2H), 2.15 (d, *J* = 7.9 Hz, 2H), 1.74 (s, 3H), 1.65 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 146.8, 135.0, 132.4, 131.3, 123.7, 119.1, 94.3, 81.1, 74.6, 59.5, 43.2, 30.5, 26.3, 23.4, 17.9. **HRMS** (ESI+) calculated for $[C_{19}H_{25}NNaO_4]^+$ 354.1676 *m/z*; found $[M + Na]^+$ 354.1690 *m/z*.

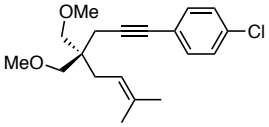
1-(4,4-Bis(methoxymethyl)-7-methyloct-6-en-1-yn-1-yl)-4-(*tert*-butyl)benzene



The title compound (colorless oil, 160 mg, 0.47 mmol, 94%) was synthesized following general procedure **A** using 4,4-bis(methoxymethyl)-7-methyloct-6-en-1-yne (105 mg, 0.5 mmol) whereby the reaction was stirred for 3 h. Purification was performed by flash column chromatography (hexane/EtOAc 70:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.28 (m, 4H), 5.22 – 5.14 (m, 1H), 3.37 – 3.33 (m, 6H), 3.32 – 3.25 (m, 4H), 2.40 – 2.37 (m, 2H), 2.15 (d, *J* = 7.8 Hz, 2H), 1.74 (s, 3H), 1.67 (s, 3H), 1.33 – 1.28 (m, 9H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 150.8, 134.6, 131.4, 125.3, 121.3, 119.5, 86.8, 82.4, 74.7, 59.5, 43.2, 34.8, 31.4, 30.4, 26.3, 23.1, 17.9. **HRMS** (ESI+) calculated for $[C_{23}H_{34}NaO_2]^+$ 365.2451 *m/z*; found $[M + Na]^+$ 365.2451 *m/z*.

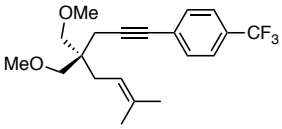
1-(4,4-Bis(methoxymethyl)-7-methyloct-6-en-1-yn-1-yl)-4-chlorobenzene



The title compound (yellowish oil, 146 mg, 0.455 mmol, 87%) was synthesized following general procedure **A** using 4,4-bis(methoxy-methyl)-7-methyloct-6-en-1-yne (110 mg, 0.523 mmol) whereby the reaction was stirred for 15 h. Purification was performed by flash column chromatography (cyclohexane/EtOAc 40:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.29 (m, 2H), 7.27 – 7.23 (m, 2H), 5.20 – 5.13 (m, 1H), 3.34 (s, 6H), 3.31 – 3.24 (m, 4H), 2.38 (s, 2H), 2.14 (d, *J* = 7.9 Hz, 1H), 1.73 (s, 3H), 1.65 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 134.7, 133.6, 132.9, 128.6, 122.8, 119.3, 88.8, 81.3, 74.6, 59.5, 43.2, 30.4, 26.3, 23.1, 17.9. **HRMS** (ESI+) calculated for $[C_{19}H_{25}ClNaO_2]^+$ 343.1435 *m/z*; found $[M + Na]^+$ 343.1445 *m/z*.

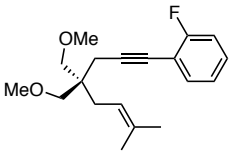
1-(4,4-Bis(methoxymethyl)-7-methyloct-6-en-1-yn-1-yl)-4-(trifluoromethyl)benzene



The title compound (colorless oil, 159 mg, 0.449 mmol, 86%) was synthesized following general procedure **A** using 4,4-bis(methoxymethyl)-7-methyloct-6-en-1-yne (110 mg, 0.523 mmol) whereby the reaction was stirred for 15 h. Purification was performed by flash column chromatography (cyclohexane/EtOAc 40:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.3 Hz, 1H), 7.49 (d, *J* = 8.2 Hz, 1H), 5.20 – 5.14 (m, 1H), 3.35 (s, 6H), 3.32 – 3.25 (m, 4H), 2.42 (s, 2H), 2.16 (d, *J* = 7.9 Hz, 1H), 1.74 (s, 3H), 1.66 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 134.8, 131.9, 129.4 (q, *J* = 32.7 Hz), 128.2 – 128.1 (m), 125.3 (q, *J* = 3.8 Hz), 124.2 (q, *J* = 272.0 Hz), 119.2, 90.7, 81.3, 74.6, 59.5, 43.2, 30.4, 26.3, 23.2, 17.9. **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) δ –62.8. **HRMS** (ESI+) calculated for $[C_{20}H_{25}F_3NaO_2]^+$ 377.1699 *m/z*; found $[M + Na]^+$ 377.1717 *m/z*.

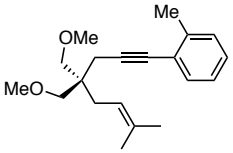
1-(4,4-Bis(methoxymethyl)-7-methyloct-6-en-1-yn-1-yl)-2-fluorobenzene



The title compound (colorless oil, 269 mg, 0.88 mmol, 93%) was synthesized following general procedure **A** using 4,4-bis(methoxymethyl)-7-methyloct-6-en-1-yne (200 mg, 1 mmol) whereby the reaction was stirred for 6 h. Purification was performed by flash column chromatography (cyclohexane/EtOAc 100:1).

^{1}H NMR (400 MHz, C_6D_6) δ 7.34 – 7.28 (m, 1H), 6.75 – 6.68 (m, 2H), 6.67 – 6.59 (m, 1H), 5.44 – 5.33 (m, 1H), 3.40 (q, *J* = 8.7 Hz, 4H), 3.16 (s, 6H), 2.65 (s, 2H), 2.48 (d, *J* = 7.9 Hz, 2H), 1.72 – 1.70 (m, 3H), 1.70 – 1.68 (m, 3H). **^{13}C{^{1}H} NMR** (101 MHz, C_6D_6) δ 163.6 (d, *J* = 250.0 Hz), 134.4, 133.7 (d, *J* = 1.5 Hz), 129.3 (d, *J* = 7.8 Hz), 124.0 (d, *J* = 3.7 Hz), 120.2, 115.6 (d, *J* = 21.1 Hz), 113.3 (d, *J* = 15.9 Hz), 94.2 (d, *J* = 3.3 Hz), 76.3, 74.6, 59.0, 43.6, 30.8, 26.3, 23.8, 17.9. **^{19}F{^{1}H} NMR** (376 MHz, C_6D_6) δ –110.6. **HRMS** (ESI+) calculated for $[C_{19}H_{25}FNaO_2]^+$ 327.1731 *m/z*; found $[M + Na]^+$ 327.1733 *m/z*.

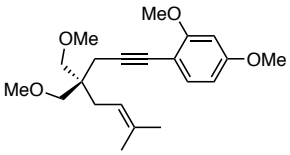
1-(4,4-Bis(methoxymethyl)-7-methyloct-6-en-1-yn-1-yl)-2-methylbenzene



The title compound (colorless oil, 242 mg, 0.81 mmol, 85%) was synthesized following general procedure **A** using 4,4-bis(methoxymethyl)-7-methyloct-6-en-1-yne (200 mg, 1 mmol) whereby the reaction was stirred for 2 h. Purification was performed by flash column chromatography (cyclohexane/EtOAc 80:1, then toluene/CH_2Cl_2 1:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.3 Hz, 1H), 7.20 – 7.14 (m, 2H), 7.14 – 7.07 (m, 1H), 5.22 – 5.15 (m, 1H), 3.35 (s, 6H), 3.33 – 3.27 (m, 4H), 2.45 (s, 2H), 2.44 (s, 3H), 2.17 (d, *J* = 7.9 Hz, 2H), 1.74 (s, 3H), 1.66 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 140.0, 134.7, 132.1, 129.4, 127.6, 125.6, 124.1, 119.4, 91.5, 81.3, 74.7, 59.4, 43.2, 30.4, 26.3, 23.3, 21.0, 17.9. **HRMS** (ESI+) calculated for $[C_{20}H_{28}NaO_2]^+$ 323.1982 *m/z*; found $[M + Na]^+$ 323.1978 *m/z*.

1-(4,4-Bis(methoxymethyl)-7-methyloct-6-en-1-yn-1-yl)-2,4-dimethoxybenzene

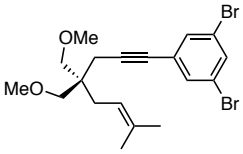


The title compound (pale yellow oil, 193 mg, 0.56 mmol, 78%) was synthesized following general procedure **A** using 4,4-bis(methoxymethyl)-7-methyloct-6-en-1-yne (150 mg, 0.7 mmol) whereby the reaction was stirred for 7 h. Purification was performed by flash column chromatography (cyclohexane/EtOAc 60:1, then 20:1).

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.28 – 7.23 (m, 1H), 6.45 – 6.40 (m, 2H), 5.22 – 5.15 (m, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.32 (s, 6H), 3.30 – 3.24 (m, 4H), 2.36 (s, 2H), 2.13 (d, *J* = 7.9 Hz, 2H), 1.73 (s, 3H), 1.65 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, CD_2Cl_2) δ 161.9, 161.2, 134.9, 134.4, 120.0, 106.3, 105.2, 98.9, 90.2, 78.8, 74.9, 59.5, 56.2, 56.0, 43.6, 30.7, 26.4,

23.7, 18.0. **HRMS** (ESI+) calculated for $[C_{21}H_{30}NaO_4]^+$ 369.2036 *m/z*; found $[M + Na]^+$ 369.2035 *m/z*.

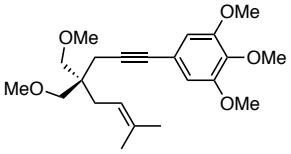
1-(4,4-Bis(methoxymethyl)-7-methyloct-6-en-1-yn-1-yl)-3,5-dibromobenzene



The title compound (brown oil, 294 mg, 0.66 mmol, 93%) was synthesized following general procedure **A** using 4,4-bis(methoxymethyl)-7-methyloct-6-en-1-yne (150 mg, 0.71 mmol) whereby the reaction was stirred for 18 h. Purification was performed by flash column chromatography (cyclohexane/EtOAc 70:1).

^{1}H NMR (500 MHz, C_6D_6) δ 7.39 (d, *J* = 1.8 Hz, 2H), 7.28 (t, *J* = 1.7 Hz, 1H), 5.35 – 5.29 (m, 1H), 3.32 – 3.27 (m, 4H), 3.12 (s, 6H), 2.55 (s, 2H), 2.37 (d, *J* = 7.9 Hz, 2H), 1.71 (s, 3H), 1.64 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, C_6D_6) δ 134.6, 133.6, 133.3, 128.4, 123.0, 119.9, 91.5, 80.2, 74.5, 59.0, 43.5, 30.9, 26.3, 23.4, 17.9. **HRMS** (ESI+) calculated for $[C_{19}H_{24}Br_2NaO_2]^+$ 465.0035 *m/z*; found $[M + Na]^+$ 465.0057 *m/z*.

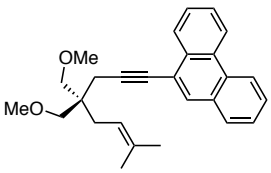
5-(4,4-Bis(methoxymethyl)-7-methyloct-6-en-1-yn-1-yl)-1,2,3-trimethoxybenzene



The title compound (pale yellow oil, 154 mg, 0.41 mmol, 83%) was synthesized following general procedure **A** using 4,4-bis(methoxymethyl)-7-methyloct-6-en-1-yne (105 mg, 0.5 mmol) whereby the reaction was stirred for 3 h. Purification was performed by flash column chromatography (cyclohexane/EtOAc 30:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.63 (s, 2H), 5.18 (tm, *J* = 6.5 Hz, 1H), 3.84 (s, 6H), 3.83 (s, 3H), 3.35 (s, 6H), 3.32 – 3.25 (m, 4H), 2.39 (s, 2H), 2.16 (d, *J* = 7.9 Hz, 2H), 1.74 (s, 3H), 1.67 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 153.2, 138.5, 134.6, 119.4, 109.0, 86.7, 82.4, 74.7, 61.1, 59.5, 56.3, 43.2, 30.4, 26.3, 23.1, 17.9. **HRMS** (ESI+) calculated for $[C_{22}H_{33}O_5]^+$ 377.2323 *m/z*; found $[M + H]^+$ 377.2331 *m/z*.

9-(4,4-Bis(methoxymethyl)-7-methyloct-6-en-1-yn-1-yl)phenanthrene

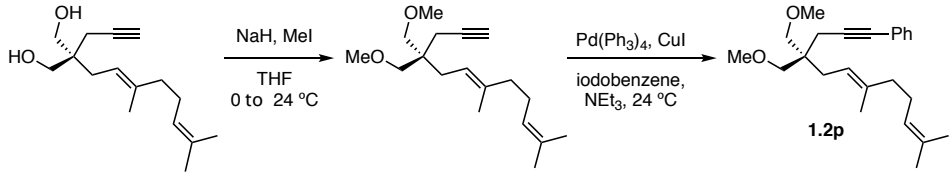


The title compound (colorless gum, 154 mg, 0.4 mmol, 80%) was synthesized following general procedure **A** using 4,4-bis(methoxymethyl)-7-methyloct-6-en-1-yne (100 mg, 0.5 mmol) whereby the reaction was stirred for 20 h. Purification was performed by flash column chromatography (pentane/EtOAc 100:1, then CH_2Cl_2/pentane 3:1).

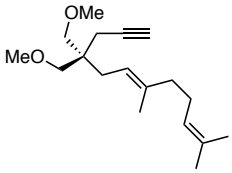
^{1}H NMR (400 MHz, C_6D_6) δ 8.84 (dd, *J* = 8.1, 1.1 Hz, 1H), 8.44 (d, *J* = 8.2 Hz, 1H), 8.37 (d, *J* = 8.2 Hz, 1H), 8.00 (s, 1H), 7.55 – 7.49 (m, 2H), 7.47 – 7.39 (m, 1H), 7.37 – 7.32 (m, 1H), 7.31 – 7.26 (m, 1H), 5.51 – 5.43 (m, 1H), 3.48 (q, *J* = 8.7 Hz, 4H), 3.20 (s, 6H), 2.82 (s, 2H), 2.57 (d, *J* = 7.9 Hz, 2H), 1.76 – 1.73 (m, 3H), 1.73 – 1.70 (m, 3H). **^{13}C{^{1}H} NMR**

(101 MHz, C_6D_6) δ 134.5, 132.4, 132.0, 131.9, 130.8, 130.5, 128.7, 127.6, 127.3, 127.23, 127.19, 127.1, 123.2, 123.0, 121.3, 120.2, 93.0, 81.3, 74.9, 59.1, 43.7, 31.1, 26.3, 24.0, 18.0. **HRMS** (ESI+) calculated for $[C_{27}H_{30}NaO_2]^+$ 409.2138 *m/z*; found $[M + Na]^+$ 409.2129 *m/z*.

Synthesis of 1,6-enyne 1.2p



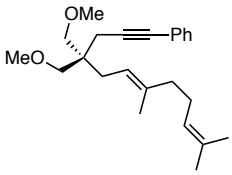
(*E*)-4,4-Bis(methoxymethyl)-7,11-dimethyldodeca-6,10-dien-1-yne



A solution of (*E*)-2-(3,7-dimethylocta-2,6-dien-1-yl)-2-(prop-2-yn-1-yl)propane-1,3-diol[135] (2.0 g, 8.0 mmol, 1.0 equiv) in THF (26 mL) was added to a suspension of NaH (0.67 g, 16.8 mmol, 2.1 equiv, 60% in mineral oil) in THF (26 mL) at 0 ºC. After stirring for 10 min MeI (1.5 mL, 23.9 mmol, 3.0 equiv) was added slowly. The reaction was stirred at 24 ºC for 1 h, then diluted with Et_2O and quenched with sat. NH_4Cl solution. The aqueous phase was extracted with Et_2O (3x) and the combined organic phases were dried over Na_2SO_4, filtered and concentrated. The crude was purified by flash column chromatography (cyclohexane/EtOAc 40:1) to afford the title compound (1.8 g, 6.5 mmol, 81%) as a colorless oil.

NMR (400 MHz, $CDCl_3$) δ 5.16 – 5.04 (m, 2H), 3.32 (s, 6H), 3.26 – 3.19 (m, 4H), 2.18 (d, *J* = 2.7 Hz, 2H), 2.14 – 2.06 (m, 4H), 2.05 – 1.99 (m, 2H), 1.95 (t, *J* = 2.7 Hz, 1H), 1.70 – 1.66 (m, 3H), 1.64 – 1.59 (m, 6H). **$^{13}C\{^1H\}$ NMR** (101 MHz, $CDCl_3$) δ 138.2, 131.4, 124.6, 119.4, 81.8, 74.4, 70.0, 59.4, 42.6, 40.2, 30.0, 26.7, 25.9, 22.1, 17.9, 16.0. **HRMS** (ESI+) calculated for $[C_{18}H_{30}NaO_2]^+$ 301.2138 *m/z*; found $[M + Na]^+$ 301.2130 *m/z*.

(*E*)-(4,4-Bis(methoxymethyl)-7,11-dimethyldodeca-6,10-dien-1-yn-1-yl)benzene

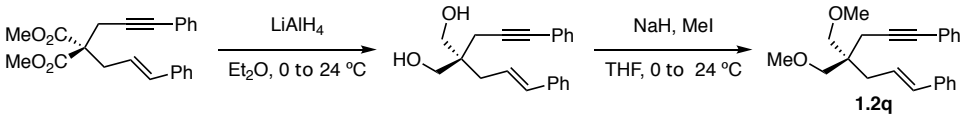


The title compound (colorless oil, 291 mg, 0.8 mmol, 89%) was synthesized following general procedure **A** using (*E*)-4,4-bis(methoxymethyl)-7,11-dimethyldodeca-6,10-dien-1-yne (258 mg, 0.9 mmol) whereby the reaction was stirred overnight. Purification was performed by flash column chromatography (cyclohexane/EtOAc 50:1).

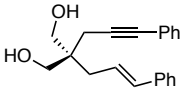
135. Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Jiménez-Núñez, E.; Buñuel, E.; Cárdenas, D. J.; Echavarren, A. M.. *Chem. Eur. J.* **2006**, *12*, 1694–1702.

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.42 – 7.36 (m, 2H), 7.33 – 7.25 (m, 3H), 5.22 – 5.14 (m, 1H), 5.14 – 5.06 (m, 1H), 3.32 (s, 6H), 3.30 – 3.23 (m, 4H), 2.37 (s, 2H), 2.17 – 2.08 (m, 4H), 2.07 – 2.02 (m, 2H), 1.68 (s, 3H), 1.65 (s, 3H), 1.61 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, CD_2Cl_2) δ 138.6, 132.0, 131.8, 128.8, 128.1, 125.0, 124.8, 120.0, 88.2, 82.7, 74.9, 59.6, 43.7, 40.7, 30.6, 27.2, 26.0, 23.4, 18.0, 16.3. **HRMS** (ESI+) calculated for $[C_{24}H_{34}NaO_2]^+$ 377.2451 *m/z*; found $[M + Na]^+$ 377. 2458 *m/z*.

Synthesis of 1,6-enyne 1.2q



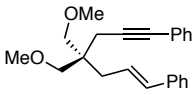
2-Cinnamyl-2-(3-phenylprop-2-yn-1-yl)propane-1,3-diol



A solution of dimethyl 2-cinnamyl-2-(3-phenylprop-2-yn-1-yl)malonate[136] (250 mg, 0.69 mmol, 1.0 equiv) in Et_2O (5 mL) was added dropwise to a suspension of $LiAlH_4$ (105 mg, 2.8 mmol, 4.0 equiv) in Et_2O (2 mL) at 0 ºC. The reaction was stirred for 1 h and after consumption of the starting material the reaction was quenched with HCl (0.5 M). After stirring for 30 min the mixture was filtered over Celite® and the organic phase was separated. The aqueous phase was extracted with Et_2O (3x) and the combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude was purified by flash column chromatography (cyclohexane/EtOAc 2:1, then 1:1) to yield the title compound (201 mg, 0.66 mmol, 95%) as a white solid.

M.p. = 75 – 77 °C (cyclohexane/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 – 7.39 (m, 2H), 7.39 – 7.34 (m, 2H), 7.33 – 7.27 (m, 5H), 7.25 – 7.19 (m, 1H), 6.52 (d, *J* = 15.7 Hz, 1H), 6.29 (dt, *J* = 15.6, 7.7 Hz, 1H), 3.84 – 3.72 (m, 4H), 2.52 (s, 2H), 2.39 (d, *J* = 7.7 Hz, 2H), 2.36 – 2.17 (br s, 2H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 137.4, 133.8, 131.8, 128.7, 128.4, 128.0, 127.4, 126.3, 125.2, 123.7, 86.5, 83.5, 68.0, 43.5, 35.7, 22.9. **HRMS** (ESI+) calculated for $[C_{21}H_{22}NaO_2]^+$ 329.1512 *m/z*; found $[M + Na]^+$ 329.1528 *m/z*.

(*E*)-(4,4-Bis(methoxymethyl)hept-1-en-6-yne-1,7-diyl)dibenzene



A solution of 2-cinnamyl-2-(3-phenylprop-2-yn-1-yl)propane-1,3-diol (100 mg, 0.33 mmol, 1.0 equiv) in THF (2 mL) was added to a suspension of NaH (31 mg, 0.78 mmol, 2.4 equiv, 60% in mineral oil) in THF (1 mL) at 0 ºC. After stirring the mixture for 10 min MeI (61 μL, 0.98 mmol, 3.0 equiv) was added slowly. The reaction was stirred at 24 ºC for 30 min and then quenched

136. Nieto-Oberhuber, C.; López, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127,* 6178–6179.

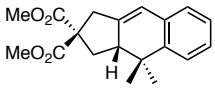
with sat. NH_4Cl. The aqueous phase was extracted with EtOAc (3x) and the combined organic phases were dried over Na_2SO_4, filtered and concentrated. The crude was purified by flash column chromatography (cyclohexane/EtOAc 60:1) to afford the title compound (105 mg, 0.31 mmol, 96%) as a pale-yellow oil.

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.45 – 7.39 (m, 2H), 7.39 – 7.35 (m, 2H), 7.34 – 7.26 (m, 5H), 7.23 – 7.17 (m, 1H), 6.48 (d, *J* = 15.8 Hz, 1H), 6.30 (dt, *J* = 15.6, 7.6 Hz, 1H), 3.37 – 3.32 (m, 10H), 2.45 (s, 2H), 2.40 – 2.35 (m, 2H). **^{13}C{^{1}H} NMR** (101 MHz, CD_2Cl_2) δ 138.4, 133.5, 132.1, 129.0, 128.8, 128.2, 127.5, 126.7, 126.6, 124.6, 87.7, 83.0, 75.1, 59.7, 43.5, 36.4, 23.7. **HRMS** (ESI+) calculated for $[C_{23}H_{26}NaO_2]^+$ 357.1825 *m/z*; found $[M + Na]^+$ 357.1833 *m/z*.

General procedure B: enantioselective formal [4+2] cycloaddition

The 1,6-enyne (1.0 equiv) and (*R*,*R*)-**E** (4 mol %) were dissolved in 1,2-dichloroethane and a solution of $AgPF_6$ (4 mol %) in 1,2-dichloroethane (total concentration 0.05M) was added dropwise. The reaction was stirred for the given time at 24 ºC in the dark, quenched by addition of 3 drops of NEt_3 and concentrated. The crude was purified by flash column chromatography or preparative TLC.

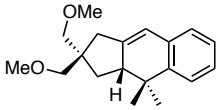
Dimethyl (*R*)-4,4-dimethyl-1,3,3a,4-tetrahydro-2*H*-cyclopenta[*b*]naphthalene-2,2-dicarboxylate



The title compound was (colorless oil, 17.6 mg, 56.0 μmol, 64%, 93:7 *er*) synthesized following general procedure **B** using dimethyl 2-(3-methylbut-2-en-1-yl)-2-(3-phenylprop-2-yn-1-yl)malonate[136] (27.0 mg, 88.0 μmol) whereby the reaction was stirred for 25 h. Purification was performed by preparative TLC (cyclohexane/CH_2Cl_2 1:1).

α_D^{589} = –14.1 deg.cm^2.g^{-1} ($CHCl_3$, c 0.79, 300 K). **UPC^2** Chiralpak IC (150 × 4.6mm, 3μm) at 35 ºC, flow 3 mL/min, isocratic CO_2/MeCN 90:10, ABRP pressure 1500 psi, 266 nm, t_R (major) 0.9; t_R (minor) 1.1. The spectral data were fully consistent with those previously reported.[136]

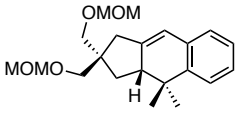
(*R*)-2,2-Bis(methoxymethyl)-4,4-dimethyl-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*b*]naphthalene



The title compound (colorless oil, 23 mg, 0.08 mmol, 92%, 94:6 *er*) was synthesized following general procedure **B** using (4,4-bis(methoxymethyl)-7-methyloct-6-en-1-yn-1-yl)benzene (25 mg, 0.087 mmol) whereby the reaction was stirred for 16 h. Purification was performed by flash column chromatography (cyclohexane/EtOAc 30:1).

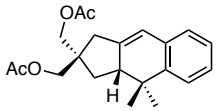
^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.31 – 7.25 (m, 1H), 7.14 – 7.07 (m, 2H), 7.00 – 6.95 (m, 1H), 6.29 – 6.25 (m, 1H), 3.36 – 3.31 (m, 5H), 3.29 (s, 3H), 3.24 – 3.19 (m, 2H), 2.74 – 2.67 (m, 1H), 2.50 – 2.42 (m, 1H), 2.33 (dt, *J* = 18.1, 2.8 Hz, 1H), 1.83 (dd, *J* = 12.6, 8.4 Hz, 1H), 1.55 (t, *J* = 12.2 Hz, 1H), 1.38 (s, 3H), 0.89 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 147.7, 145.2, 135.2, 127.0, 126.6, 126.4, 124.0, 119.2, 77.7, 75.7, 59.6, 48.9, 47.2, 38.3, 37.2, 32.1, 26.0, 22.2. **HRMS** (ESI+) calculated for $[C_{19}H_{26}NaO_2]^+$ 309.1825 *m/z*; found $[M + Na]^+$ 309.1821 *m/z*. α_D^{589} = +1.7 deg.cm^2.g^{-1} ($CHCl_3$, c 1.0, 300 K). **UPC^2** Chiralpak OJ-3 (150 × 4.6mm, 3μm) at 35 ºC, flow 2 mL/min, isocratic CO_2/*i*PrOH 98:2, ABRP pressure 2000 psi, 267 nm, t_R (major) 2.3; t_R (minor) 2.6.

(*R*)-2,2-Bis((methoxymethoxy)methyl)-4,4-dimethyl-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*b*]naphthalene



The title compound (colorless oil, 29 mg, 0.08 mmol, 91%, 93:7 *er*) was synthesized following general procedure **B** using 6-(3-methylbut-2-en-1-yl)-6-(3-phenylprop-2-yn-1-yl)-2,4,8,10-tetraoxaundecane (32 mg, 0.09 mmol) whereby the reaction was stirred for 16 h. Purification was performed by flash column chromatography (cyclohexane/EtOAc 20:1).
^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.31 – 7.26 (m, 1H), 7.15 – 7.08 (m, 2H), 7.01 – 6.96 (m, 1H), 6.31 – 6.28 (m,1H), 4.63 (s, 2H), 4.58 (s, 2H), 3.53 (q, *J* = 9.1 Hz, 2H), 3.41 (s, 2H), 3.35 (s, 3H), 3.31 (s, 3H), 2.80 – 2.70 (m, 1H), 2.55 – 2.47 (m, 1H), 2.40 (dt, *J* = 18.1, 2.9 Hz, 1H), 1.91 (dd, *J* = 12.6, 8.3 Hz, 1H), 1.59 (t, *J* = 12.2 Hz, 1H), 1.39 (s, 3H), 0.91 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 147.3, 145.1, 135.1, 127.0, 126.6, 126.4, 124.0, 119.4, 97.3, 97.2, 72.6, 70.3, 55.51, 55.47, 48.8, 46.6, 38.4, 37.2, 32.0, 26.0, 22.3. **HRMS** (ESI+) calculated for $[C_{21}H_{30}NaO_4]^+$ 369.2036 *m/z*; found $[M + Na]^+$ 369.2036 *m/z*. α_D^{589} = –3.3 deg.cm^2.g^{-1} ($CHCl_3$, c 1.0, 300 K). **UPC^2** Chiralpak IG (150 × 4.6mm, 3μm) at 35 ºC, flow 2 mL/min, isocratic CO_2/*i*PrOH 85:15, ABRP pressure 2000 psi, 267 nm, t_R (major) 2.0; t_R (minor) 2.4.

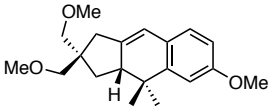
(*R*)-(4,4-Dimethyl-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*b*]naphthalene-2,2-diyl)bis(methylene) diacetate



The title compound (colorless oil, 28 mg, 0.086 mmol, 94%, 79:21 *er*) was synthesized following general procedure **B** using 2-(3-methylbut-2-en-1-yl)-2-(3-phenylprop-2-yn-1-yl)propane-1,3-diyl diacetate (32 mg, 0.87 mmol) whereby the reaction was stirred for 48 h. Purification was performed by flash column chromatography (cyclohexane/EtOAc 20:1).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.27 (m, 1H), 7.18 – 7.10 (m, 2H), 7.03 – 6.97 (m, 1H), 6.34 – 6.29 (m, 1H), 4.15 – 4.07 (m, 2H), 4.04 – 3.94 (m, 2H), 2.80 – 2.73 (m, 1H), 2.58 – 2.51 (m, 1H), 2.40 (dt, *J* = 18.2, 2.8 Hz, 1H), 2.09 (s, 3H), 2.07 (s, 3H), 1.87 (dd, *J*

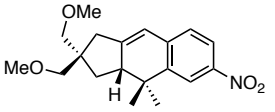
= 12.8, 8.3 Hz, 1H), 1.60 (t, *J* = 12.4 Hz, 1H), 1.39 (s, 3H), 0.91 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 171.2, 171.1, 144.4, 144.3, 134.2, 127.0, 126.4, 126.3, 123.6, 120.0, 68.1, 65.7, 48.1, 45.0, 37.7, 36.8, 31.9, 25.7, 22.0, 21.0. **HRMS** (ESI+) calculated for $[C_{21}H_{26}NaO_4]^+$ 365.1723 *m/z*; found $[M + Na]^+$ 365.1735 *m/z*. α_D^{589} = +3.1 deg.cm^2.g^{-1} ($CHCl_3$, c 1.0, 297 K). **UPC^2** Chiralpak IB (100 × 4.6mm, 3μm) at 35 ºC, flow 3 mL/min, isocratic CO_2/MeOH 90:10, ABRP pressure 1500 psi, 266 nm, t_R (minor) 0.8; t_R (major) 0.9.

(*R*)-6-Methoxy-2,2-bis(methoxymethyl)-4,4-dimethyl-2,3,3a,4-tetrahydro-1*H*-cyclopenta-[*b*]naphthalene



The title compound (colorless oil, 27.5 mg, 0.087 mmol, 97%, 96:4 *er*) was synthesized following general procedure **B** using 1-(4,4-bis(methoxymethyl)-7-methyloct-6-en-1-yn-1-yl)-4-methoxybenzene (28 mg, 0.087 mmol) whereby the reaction was stirred for 12 h. Purification was performed by flash column chromatography (cyclohexane/EtOAc 40:1).
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (d, *J* = 8.2 Hz, 1H), 6.88 (d, *J* = 2.5 Hz, 1H), 6.66 (dd, *J* = 8.2, 2.6 Hz, 1H), 6.27 – 6.20 (m, 1H), 3.80 (s, 3H), 3.38 (s, 3H), 3.37 (s, 2H), 3.32 (s, 3H), 3.27 – 3.21 (m, 2H), 2.72 – 2.63 (m, 1H), 2.47 (d, *J* = 18.0 Hz, 1H), 2.31 (dt, *J* = 17.9, 2.7 Hz, 1H), 1.83 (dd, *J* = 12.6, 8.3 Hz, 1H), 1.53 (t, *J* = 12.2 Hz, 1H), 1.36 (s, 3H), 0.89 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 158.6, 146.6, 144.1, 128.0, 126.8, 118.4, 110.9, 110.0, 75.1, 59.5, 55.4, 48.1, 46.8, 37.8, 37.1, 31.7, 25.7, 21.9. **HRMS** (ESI+) calculated for $[C_{20}H_{28}NaO_3]^+$ 339.1931 *m/z*; found $[M + Na]^+$ 339.1941 *m/z*. α_D^{589} = –21.7 deg.cm^2.g^{-1} ($CHCl_3$, c 1.0, 300 K). **UPC^2** Chiralpak OJ (150 × 4.6mm, 3μm) at 35 ºC, flow 2 mL/min, isocratic CO_2/MeOH 85:15, ABRP pressure 2000 psi, 275 nm, t_R (major) 1.4; t_R (minor) 1.5.

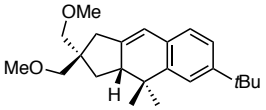
(*R*)-2,2-Bis(methoxymethyl)-4,4-dimethyl-6-nitro-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*b*]-naphthalene



The title compound (colorless oil, 29.6 mg, 0.087 mmol, 99%, 91:9 *er*) was synthesized following general procedure **B** using 1-(4,4-bis(methoxymethyl)-7-methyloct-6-en-1-yn-1-yl)-4-nitrobenzene (29.8 mg, 0.087 mmol) whereby the reaction was stirred for 12 h. Purification was performed by flash column chromatography (hexane/EtOAc 70:1).
^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.33 (d, *J* = 1.5 Hz, 1H), 7.14 (d, *J* = 7.9, 1.9 Hz, 1H), 6.91 (d, *J* = 7.9 Hz, 1H), 6.27 – 6.23 (m, 1H), 3.37 – 3.32 (m, 5H), 3.29 (s, 3H), 3.24 – 3.19 (m, 2H), 2.74 – 2.65 (m, 1H), 2.50 – 2.40 (m, 1H), 2.32 (dt, *J* = 18.0, 2.6 Hz, 1H), 1.83 (dd, *J* = 12.5, 8.4 Hz, 1H), 1.54 (t, *J* = 12.2 Hz, 1H), 1.39 (s, 3H), 1.31 (s, 9H), 0.89 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 149.9, 146.7, 144.7, 132.5, 125.9, 123.3, 121.0, 118.9,

77.8, 75.7, 59.6, 49.0, 47.2, 38.3, 37.4, 35.2, 32.1, 31.8, 26.0, 22.3. **HRMS** (ESI+) calculated for $[C_{23}H_{34}NaO_2]^+$ 365.2451 *m/z*; found $[M+Na]^+$ 365.2442 *m/z*. $\alpha_D^{589} = -17.2$ deg.cm^2.g^{-1} ($CHCl_3$, c 1.0, 300 K). **HPLC** Chiralpak OD-H (250 × 4.6mm, 5µm) at 25 ºC, flow 1.0 mL/min, isocratic hexane, 280 nm, t_R (minor) 5.6; t_R (major) 6.9.

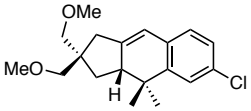
(*R*)-6-(*tert*-Butyl)-2,2-bis(methoxymethyl)-4,4-dimethyl-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*b*]naphthalene



The title compound (colorless oil, 29.6 mg, 0.087 mmol, 99%, 91:9 *er*) was synthesized following general procedure **B** using 1-(4,4-bis(methoxymethyl)-7-methyloct-6-en-1-yn-1-yl)-4-(*tert*-butyl)benzene (29.8 mg, 0.087 mmol) whereby the reaction was stirred for 12 h. Purification was performed by flash column chromatography (hexane/EtOAc 70:1).

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.33 (d, *J* = 1.5 Hz, 1H), 7.14 (d, *J* = 7.9, 1.9 Hz, 1H), 6.91 (d, *J* = 7.9 Hz, 1H), 6.27 – 6.23 (m, 1H), 3.37 – 3.32 (m, 5H), 3.29 (s, 3H), 3.24 – 3.19 (m, 2H), 2.74 – 2.65 (m, 1H), 2.50 – 2.40 (m, 1H), 2.32 (dt, *J* = 18.0, 2.6 Hz, 1H), 1.83 (dd, *J* = 12.5, 8.4 Hz, 1H), 1.54 (t, *J* = 12.2 Hz, 1H), 1.39 (s, 3H), 1.31 (s, 9H), 0.89 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 149.9, 146.7, 144.7, 132.5, 125.9, 123.3, 121.0, 118.9, 77.8, 75.7, 59.6, 49.0, 47.2, 38.3, 37.4, 35.2, 32.1, 31.8, 26.0, 22.3. **HRMS** (ESI+) calculated for $[C_{23}H_{34}NaO_2]^+$ 365.2451 *m/z*; found $[M+Na]^+$ 365.2442 *m/z*. $\alpha_D^{589} = -17.2$ deg.cm^2.g^{-1} ($CHCl_3$, c 1.0, 300 K). **HPLC** Chiralpak OD-H (250 × 4.6mm, 5µm) at 25 ºC, flow 1.0 mL/min, isocratic hexane, 280 nm, t_R (minor) 5.6; t_R (major) 6.9.

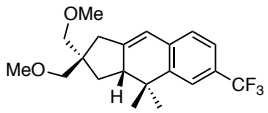
(*R*)-6-Chloro-2,2-bis(methoxymethyl)-4,4-dimethyl-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*b*]naphthalene



The title compound (colorless oil, 27 mg, 0.084 mmol, 97%, 94:6 *er*) was synthesized following general procedure **B** using 1-(4,4-bis(methoxymethyl)-7-methyloct-6-en-1-yn-1-yl)-4-chlorobenzene(27.9 mg, 0.087 mmol) whereby the reaction was stirred for 17 h. Purification was performed by preparative TLC (cyclohexane/CH_2Cl_2 1:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, *J* = 2.1 Hz, 1H), 7.08 (dd, *J* = 8.0, 2.1 Hz, 1H), 6.90 (d, *J* = 8.1 Hz, 1H), 6.24 (d, *J* = 2.4 Hz, 1H), 3.37 (s, 3H), 3.36 (s, 2H), 3.32 (s, 3H), 3.26 – 3.20 (m, 2H), 2.73 – 2.64 (m, 1H), 2.52 – 2.44 (m, 1H), 2.33 (dt, *J* = 18.2, 2.8 Hz, 1H), 1.84 (dd, *J* = 12.5, 8.4 Hz, 1H), 1.54 (t, *J* = 12.1 Hz, 1H), 1.36 (s, 3H), 0.90 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 147.5, 146.6, 133.2, 131.8, 127.1, 126.1, 124.1, 118.2, 77.3, 75.2, 59.5, 48.1, 46.8, 37.9, 37.2, 31.6, 25.6, 21.9. **HRMS** (APCI+) calculated for $[C_{19}H_{26}ClO_2]^+$ 321.1616 *m/z*; found $[M+H]^+$ 321.1615 *m/z*. $\alpha_D^{589} = -3.8$ deg.cm^2.g^{-1} ($CHCl_3$, c 1.0, 300 K). **HPLC** Chiralpak IB-N (150 × 4.6mm, 5µm) at 25 ºC, flow 0.5 mL/min, isocratic *n*heptane/M*t*BE 98:2, 280 nm, t_R (minor) 14.3; t_R (major) 16.4.

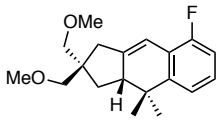
(*R*)-2,2-Bis(methoxymethyl)-4,4-dimethyl-6-(trifluoromethyl)-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*b*]naphthalene



The title compound (colorless oil, 30 mg, 0.084 mmol, 97%, 91:9 *er*) was synthesized following general procedure **B** using 1-(4,4-bis(methoxymethyl)-7-methyloct-6-en-1-yn-1-yl)-4-(trifluoromethyl)benzene (30.8 mg, 0.087 mmol) whereby the reaction was stirred for 17 h. The purification was performed by preparative TLC (cyclohexane/CH_2Cl_2 1:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.46 (m, 1H), 7.37 (ddd, *J* = 7.9, 1.9, 0.9 Hz, 1H), 7.06 (d, *J* = 7.9 Hz, 1H), 6.32 (d, *J* = 2.6 Hz, 1H), 3.38 (s, 3H), 3.37 (s, 2H), 3.33 (s, 3H), 3.28 – 3.21 (m, 2H), 2.79 – 2.71 (m, 1H), 2.52 (d, *J* = 18.4 Hz, 1H), 2.37 (dt, *J* = 18.5, 2.9 Hz, 1H), 1.87 (dd, *J* = 12.7, 8.4 Hz, 1H), 1.64 – 1.52 (m, 1H), 1.42 (s, 3H), 0.93 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 150.3, 145.2, 137.9 (d, *J* = 1.3 Hz), 128.2 (q, *J* = 31.8 Hz), 126.0, 124.7 (q, *J* = 271.7 Hz), 123.3 (q, *J* = 3.9, 3.5 Hz), 120.6 (q, *J* = 3.8 Hz), 118.3, 77.3, 75.3, 59.5, 48.3, 46.8, 38.1, 37.0, 31.5, 25.6, 21.9. **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) δ –62.2. **HRMS** (APCI+) calculated for $[C_{19}H_{22}F_3O]^+$ 323.1617 *m/z*; found $[M - CH_3O]^+$ 323.1616 *m/z*. α_D^{589} = –0.9 deg.cm^2.g^{-1} ($CHCl_3$, c 1.0, 300 K). **HPLC** Chiralpak IB-N (150 × 4.6mm, 5μm) at 25 ºC, flow 0.5 mL/min, isocratic *n*heptane/MtBE 98:2, 280 nm, t_R (minor) 12.2; t_R (major) 13.1.

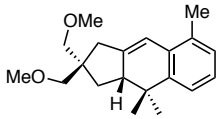
(*R*)-8-Fluoro-2,2-bis(methoxymethyl)-4,4-dimethyl-2,3,3a,4-tetrahydro-1*H*-cyclopenta-[*b*]naphthalene



The title compound (colorless oil, 23.3 mg, 0.076 mmol, 88%, 93:7 *er*) was synthesized following general procedure **B** using 1-(4,4-bis(methoxymethyl)-7-methyloct-6-en-1-yn-1-yl)-2-fluorobenzene (28 mg, 0.087 mmol) whereby the reaction was stirred for 13 h. The crude was purified by flash column chromatography (cyclohexane/EtOAc 50:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 – 7.02 (m, 2H), 6.89 – 6.80 (m, 1H), 6.56 – 6.51 (m, 1H), 3.38 (s, 3H), 3.37 (s, 2H), 3.33 (s, 3H), 3.28 – 3.21 (m, 2H), 2.77 – 2.65 (m, 1H), 2.57 – 2.48 (m, 1H), 2.36 (dt, *J* = 18.2, 2.8 Hz, 1H), 1.86 (dd, *J* = 12.6, 8.4 Hz, 1H), 1.55 (t, *J* = 12.2 Hz, 1H), 1.38 (s, 3H), 0.90 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 158.5 (d, *J* = 245.9 Hz), 147.8 (d, *J* = 1.7 Hz), 147.1 (d, *J* = 3.5 Hz), 127.0, 122.4 (d, *J* = 14.3 Hz), 119.1 (d, *J* = 2.9 Hz), 112.9 (d, *J* = 21.8 Hz), 111.0 (d, *J* = 6.3 Hz), 77.3, 75.1, 59.5 (d, *J* = 1.8 Hz), 48.1, 46.8, 38.2, 37.1, 31.6, 25.8, 21.7. **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) δ –123.2. **HRMS** (ESI+) calculated for $[C_{19}H_{25}FNaO_2]^+$ 327.1731 *m/z*; found $[M + Na]^+$ 327.1733 *m/z*. α_D^{589} = –2.0 deg.cm^2.g^{-1} ($CHCl_3$, c 1.0, 300 K). **UPC^2** Chiralpak IG (150 × 4.6mm, 3μm) at 35 ºC, flow 2 mL/min, isocratic CO_2/MeOH 95:5, ABRP pressure 2000 psi, 267 nm, t_R (minor) 2.1; t_R (major) 2.2.

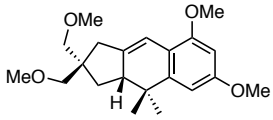
(*R*)-2,2-Bis(methoxymethyl)-4,4,8-trimethyl-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*b*]-naphthalene



The title compound (colorless oil, 22 mg, 0.073 mmol, 85%, 95:5 *er*) was synthesized following general procedure **B** using 1-(4,4-bis(methoxymethyl)-7-methyloct-6-en-1-yn-1-yl)-2-methylbenzene (26 mg, 0.087 mmol) whereby the reaction was stirred for 20 h. The crude was purified by preparative TLC (cyclohexane/CH_2Cl_2 1:1).

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.13 (d, *J* = 7.6 Hz, 1H), 7.01 (t, *J* = 7.6 Hz, 1H), 6.96 (d, *J* = 7.4 Hz, 1H), 6.51 – 6.47 (m, 1H), 3.34 (s, 5H), 3.29 (s, 3H), 3.22 (s, 2H), 2.70 – 2.62 (m, 1H), 2.55 – 2.46 (m, 1H), 2.34 (dt, *J* = 18.1, 2.8 Hz, 1H), 2.29 (s, 3H), 1.86 – 1.79 (m, 1H), 1.57 – 1.51 (m, 1H), 1.35 (s, 3H), 0.87 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 147.6, 145.3, 133.3, 133.2, 128.4, 126.5, 121.8, 116.0, 77.7, 75.6, 59.6, 48.3, 47.2, 38.7, 37.4, 32.1, 26.2, 21.9, 20.0. **HRMS** (ESI+) calculated for $[C_{20}H_{28}NaO_2]^+$ 323.1982 *m/z*; found $[M + Na]^+$ 323.1962 *m/z*. α_D^{589} = –34.7 deg.cm^2.g^{-1} ($CHCl_3$, c 1.0, 297 K). **UPC^2** Chiralpak IG (150 × 4.6mm, 3μm) at 35 ºC, flow 2 mL/min, isocratic CO_2/MeOH 90:10, ABRP pressure 2000 psi, 272 nm, t_R (minor) 1.6; t_R (major) 1.7.

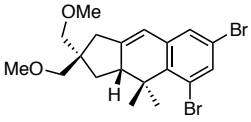
(*R*)-6,8-Dimethoxy-2,2-bis(methoxymethyl)-4,4-dimethyl-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*b*]naphthalene



The title compound (colorless oil, 27 mg, 0.078 mmol, 90%, 93:7 *er*) was synthesized following general procedure **B** using 1-(4,4-bis(methoxymethyl)-7-methyloct-6-en-1-yn-1-yl)-2,4-dimethoxybenzene (30.1 mg, 0.087 mmol) whereby the reaction was stirred for 36 h. Purification was performed by flash column chromatography (cyclohexane/EtOAc 20:1) and further purification by preparative TLC (cyclohexane/EtOAc 10:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.59 – 6.54 (m, 1H), 6.52 (d, *J* = 2.2 Hz, 1H), 6.31 (d, *J* = 2.3 Hz, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.39 – 3.35 (m, 5H), 3.31 (s, 3H), 3.26 – 3.19 (m, 2H), 2.70 – 2.60 (m, 1H), 2.54 – 2.46 (m, 1H), 2.32 (dt, *J* = 17.9, 2.9 Hz, 1H), 1.82 (dd, *J* = 12.5, 8.4 Hz, 1H), 1.50 (t, *J* = 12.1 Hz, 1H), 1.34 (s, 3H), 0.88 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 159.3, 155.6, 147.4, 143.1, 116.9, 112.4, 101.7, 95.5, 75.0, 59.5, 59.4, 55.7, 55.5, 47.8, 46.9, 38.1, 37.4, 31.7, 25.9, 21.4. **HRMS** (ESI+) calculated for $[C_{21}H_{30}NaO_4]^+$ 369.2036 *m/z*; found $[M +Na]^+$ 369.2027 *m/z*. α_D^{589} = –52.0 deg.cm^2.g^{-1} ($CHCl_3$, c 1.0, 297 K). **UPC^2** Chiralpak IG (150 × 4.6mm, 3μm) at 35 ºC, flow 2 mL/min, isocratic CO_2/MeOH 90:10, ABRP pressure 2000 psi, 272 nm, t_R (minor) 2.8; t_R (major) 3.0.

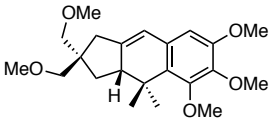
(*R*)-5,7-Dibromo-2,2-bis(methoxymethyl)-4,4-dimethyl-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*b*]naphthalene



The title compound (colorless oil, 35 mg, 0.08 mmol, 91%, 95:5 *er*) was synthesized following general procedure **B** using 1-(4,4-bis(methoxymethyl)-7-methyloct-6-en-1-yn-1-yl)-3,5-dibromobenzene (38.6 mg, 0.087 mmol) whereby the reaction was stirred for 16 h. The crude was purified by flash column chromatography (cyclohexane/EtOAc 100:1, then 50:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 2.2 Hz, 1H), 7.03 (d, *J* = 2.2 Hz, 1H), 6.14 – 6.10 (m, 1H), 3.37 (s, 3H), 3.34 (s, 2H), 3.33 (s, 3H), 3.27 – 3.21 (m, 2H), 2.85 – 2.75 (m, 1H), 2.55 – 2.46 (m, 1H), 2.35 (dt, *J* = 18.3, 2.9 Hz, 1H), 1.86 (dd, *J* = 12.6, 8.3 Hz, 1H), 1.73 (s, 3H), 1.64 – 1.55 (m, 1H), 1.03 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 148.2, 141.3, 139.6, 135.4, 128.7, 122.2, 120.0, 118.5, 75.2, 59.5, 49.8, 46.5, 40.0, 38.0, 32.4, 27.4, 18.6. **HRMS** (ESI+) calculated for $[C_{19}H_{24}Br_2NaO_2]^+$ 465.0035 *m/z*; found $[M + Na]^+$ 465.0012 *m/z*. α_D^{589} = –10.7 deg.cm^2.g^{-1} ($CHCl_3$, c 1.0, 300 K). **UPC^2** Chiralpak IG (150 × 4.6mm, 3μm) at 35 ºC, flow 2 mL/min, isocratic CO_2/MeOH 90:10, ABRP pressure 2000 psi, 278 nm, t_R (major) 4.2; t_R (minor) 4.7.

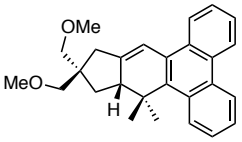
(*R*)-5,6,7-Trimethoxy-2,2-bis(methoxymethyl)-4,4-dimethyl-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*b*]naphthalene

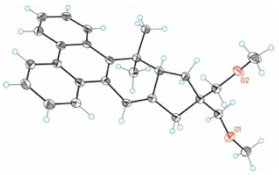


The title compound (colorless oil, 28 mg, 0.074 mmol, 85%, 96:4 *er*) was synthesized following general procedure **B** using 5-(4,4-bis(methoxymethyl)-7-methyloct-6-en-1-yn-1-yl)-1,2,3-trimethoxybenzene (32.8 mg, 0.087 mmol) whereby the reaction was stirred for 18 h. Purification was performed by flash column chromatography (cyclohexane/EtOAc 20:1) and further purification by preparative TLC (cyclohexane/EtOAc 10:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.36 (s, 1H), 6.14 (q, *J* = 2.2 Hz, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.83 (s, 3H), 3.37 (s, 3H), 3.35 (d, *J* = 1.6 Hz, 2H), 3.32 (s, 3H), 3.27 – 3.21 (m, 2H), 2.76 – 2.69 (m, 1H), 2.50 – 2.43 (m, 1H), 2.31 (dt, *J* = 18.0, 2.8 Hz, 1H), 1.86 (dd, *J* = 12.5, 8.3 Hz, 1H), 1.57 (s, 3H), 1.52 (t, *J* = 12.2 Hz, 1H), 0.95 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 153.2, 151.5, 145.7, 141.4, 131.6, 129.5, 119.1, 106.0, 75.2, 60.9, 60.7, 59.5, 56.0, 49.7, 46.5, 37.90, 37.87, 31.9, 27.4, 20.9. **HRMS** (ESI+) calculated for $[C_{22}H_{32}NaO_5]^+$ 399.2142 *m/z*; found $[M + Na]^+$ 399.2135 *m/z*. α_D^{589} = –25.6 deg.cm^2.g^{-1} ($CHCl_3$, c 1.0, 300 K). **UPC^2** Chiralpak OJ-3 (150 × 4.6mm, 3μm) at 35 ºC, flow 2 mL/min, isocratic CO_2/*i*PrOH 90:10, ABRP pressure 2000 psi, 225 nm, t_R (major) 1.7; t_R (minor) 1.9.

(*R*)-11,11-Bis(methoxymethyl)-9,9-dimethyl-9a,10,11,12-tetrahydro-9*H*-cyclopenta[*b*]triphenylene

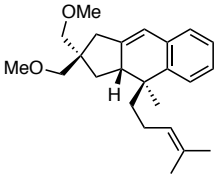




The title compound (pale yellow foam, 33 mg, 0.087 mmol, 98%, 93:7 *er*) was synthesized following general procedure **B** using 9-(4,4-bis(methoxymethyl)-7-methyloct-6-en-1-yn-1-yl)phenanthrene (33.6 mg, 0.087 mmol) whereby the reaction was stirred for 12 h. The crude was purified by flash column chromatography (pentane/EtOAc 50:1, then 10:1).

M.p. = 112 – 115 °C (benzene). **^{1}H NMR** (300 MHz, C_6D_6) δ 8.63 – 8.55 (m, 1H), 8.55 – 8.48 (m, 1H), 8.43 – 8.34 (m, 1H), 8.14 – 8.05 (m, 1H), 7.48 – 7.36 (m, 4H), 7.00 – 6.94 (m, 1H), 3.49 – 3.39 (m, 2H), 3.26 – 3.16 (m, 5H), 3.11 (s, 3H), 2.86 – 2.74 (m, 2H), 2.61 (dt, *J* = 18.0, 3.0 Hz, 1H), 1.99 (dd, *J* = 12.3, 8.7 Hz, 1H), 1.89 – 1.78 (m, 1H), 1.65 (s, 3H), 1.35 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, C_6D_6) δ 146.2, 138.5, 131.5, 131.3, 130.8, 130.5, 130.3, 126.84, 126.76, 126.2, 125.4, 125.1, 125.0, 124.1, 123.0, 115.8, 77.3, 75.2, 59.1, 59.0, 51.6, 47.2, 39.6, 38.7, 32.3, 30.1, 18.2. **HRMS** (ESI+) calculated for $[C_{27}H_{30}NaO_2]^+$ 409.2138 *m/z*; found $[M + Na]^+$ 409.2136 *m/z*. α_D^{589} = +139.6 deg.cm^2.g^{-1} ($CHCl_3$, c 1.0, 300 K). **UPC**^{2} Chiralpak IG (150 × 4.6mm, 3μm) at 35 ºC, flow 2 mL/min, isocratic CO_2/EtOH 80:20, ABRP pressure 2000 psi, 326 nm, t_R (major) 4.7; t_R (minor) 6.1.

(3a*R*,4*S*)-2,2-Bis(methoxymethyl)-4-methyl-4-(4-methylpent-3-en-1-yl)-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*b*]naphthalene

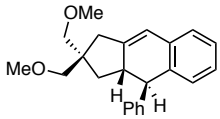


The title compound (colorless oil, 23.0 mg, 65.0 μmol, 77%, 93:7 *er*) was synthesized following general procedure **B** using (*E*)-(4,4-bis(methoxymethyl)-7,11-dimethyldodeca-6,10-dien-1-yn-1-yl) benzene (31.0 mg, 87.0 μmol) whereby the reaction was stirred for 7 d. Purification was performed by flash column chromatography (toluene/CH_2Cl_2 30:1).

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.22 – 7.19 (m, 1H), 7.15 – 7.08 (m, 2H), 6.99 (dd, *J* = 7.1, 1.7 Hz, 1H), 6.26 – 6.21 (m, 1H), 5.24 – 5.18 (m, 1H), 3.34 (s, 5H), 3.30 (s, 3H), 3.23 (s, 2H), 3.01 – 2.92 (m, 1H), 2.51 – 2.45 (m, 1H), 2.33 (dt, *J* = 18.0, 2.8 Hz, 1H), 2.05 – 1.92 (m, 3H), 1.79 (dd, *J* = 12.5, 8.3 Hz, 1H), 1.72 (s, 3H), 1.60 (s, 3H), 1.59 – 1.55 (m, 1H), 1.53 (t, *J* = 12.3 Hz, 1H), 0.87 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 147.7, 142.5, 136.1, 131.8, 126.9, 126.8, 126.5, 125.3, 124.6, 118.7, 77.8, 75.7, 59.61, 59.58, 47.2, 43.9, 40.9, 38.3, 37.2, 31.5, 26.0, 23.9, 23.3, 17.9. **HRMS** (ESI+) calculated for $[C_{24}H_{34}NaO_2]^+$ 377.2451 *m/z*; found $[M + Na]^+$ 377.2451 *m/z*. α_D^{589} = –15.5 deg.cm^2.g^{-1} ($CHCl_3$, c 1.0, 297

K). **UPC²** Chiralpak IG (150 × 4.6mm, 3µm) at 35 ºC, flow 2 mL/min, isocratic CO_2/*i*PrOH 95:5, ABRP pressure 2000 psi, 268 nm, t_R (minor) 2.3; t_R (major) 2.8.

(3a*R*,4*R*)-2,2-Bis(methoxymethyl)-4-methyl-4-phenyl-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*b*]naphthalene



The title compound (colorless oil, 17.6 mg, 0.052 mmol, 61%, 91% brsm, 81:19 *er*) was synthesized following general procedure **B** using (*E*)-(4,4-bis(methoxymethyl) hept-1-en-6-yne-1,7-diyl) dibenzene (29.1 mg, 0.087 mmol) whereby the reaction was stirred for 14 d. The crude was purified by preparative TLC (toluene/CH_2Cl_2 4:1).

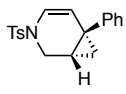
^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.42 – 7.35 (m, 2H), 7.34 – 7.25 (m, 3H), 7.13 – 7.07 (m, 1H), 7.07 – 7.01 (m, *J* = 7.4 Hz, 1H), 6.94 (t, *J* = 7.4 Hz, 1H), 6.52 (d, *J* = 7.6 Hz, 1H), 6.38 – 6.31 (m, 1H), 3.71 (d, *J* = 15.1 Hz, 1H), 3.31 (s, 3H), 3.29 (d, *J* = 2.3 Hz, 2H), 3.26 (s, 3H), 3.19 (s, 2H), 3.17 – 3.04 (m, 1H), 2.50 (s, 2H), 1.63 (dd, *J* = 13.0, 8.2 Hz, 1H), 1.34 – 1.24 (m, 1H). **^{13}C{^{1}H} NMR** (101 MHz, CD_2Cl_2) δ 149.2, 143.3, 138.9, 136.5, 130.0, 129.1, 127.4, 127.3, 127.0, 126.5, 125.7, 119.5, 77.6, 76.5, 59.6, 53.6, 47.6, 45.6, 38.4, 37.7. **HRMS** (ESI+) calculated for $[C_{23}H_{26}NaO_2]^+$ 357.1825 *m/z*; found $[M+Na]^+$ 357.1821 *m/z*. **α_D^{589}** = –15.9 deg.cm^2.g^{-1} ($CHCl_3$, c 1.0, 300 K). **UPC²** Chiralpak IG (150 × 4.6mm, 3µm) at 35 ºC, flow 2 mL/min, isocratic CO_2/*i*PrOH 76:24, ABRP pressure 2000 psi, 267 nm, t_R (major) 3.9; t_R (minor) 4.2.

Enantioselective Synthesis of azabicyclo[4.1.0]hept-4-enes

General procedure C: enantioselective synthesis of azabicyclo[4.1.0]hept-4-enes

The 1,6-Enyne (1.0 equiv) and catalyst (*R*,*R*)-**E** (4 mol %) were dissolved in toluene. A solution of $AgBF_4$ (4 mol %) in toluene (total concentration 0.05M) was added dropwise and the reaction was stirred for the given time at 40 ºC in the dark. The reaction was quenched by addition of 3 drops of NEt_3 and concentrated. The crude was purified by flash column chromatography to afford the title compounds.

(1*S*,6*S*)-6-Phenyl-3-tosyl-3-azabicyclo[4.1.0]hept-4-ene

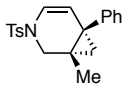


The title compound (white solid, 7 mg, 0.022 mmol, 35%, 49% brsm, 95:5 *er*) was synthesized following general procedure **C** using *N*-allyl-4-methyl-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide[137] (20 mg, 0.061 mmol) whereby the reaction was stirred for 3 d. The crude was purified by preparative TLC (toluene/CH_2Cl_2 1:1).

137. Cabrera-Lobera, N.; Rodríguez-Salamanca, P.; Nieto-Carmona, J. C.; Buñuel, E.; Cárdenas, D. J. *Chem. Eur. J.* **2018**, *24*, 784–788.

M.p. = 107 – 109 °C ($CHCl_3$). α_D^{589} = –64.3 deg.cm^2.g^{-1} ($CHCl_3$, c 0.32, 302 K). **HPLC** Chiralpak IA (250 mm × 4.6 mm, 5 μm) at 25 ºC, flow 0.9 mL/min, isocratic hexane/EtOH 90:10, 280 nm, t_R (minor) 13.3; t_R (major) 16.5. The spectral data were fully consistent with those previously reported.[138]

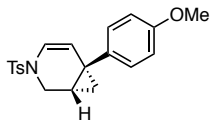
(1*S*,6*S*)-1-Methyl-6-phenyl-3-tosyl-3-azabicyclo[4.1.0]hept-4-ene



The title compound (white solid, 28.4 mg, 0.083 mmol, 89%, 90:10 *er*) was synthesized following general procedure **C** using 4-methyl-*N*-(2-methylallyl)-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide[32] (32 mg, 0.094 mmol) whereby the reaction was stirred for 24 h. The crude was purified by flash column chromatography (cyclohexene/EtOAc 30:1).

M.p. = 131 – 133 °C ($CHCl_3$). α_D^{589} = –76.7 deg.cm^2.g^{-1} ($CHCl_3$, c 1.0, 301 K). **HPLC** Chiralpak IA (250 mm × 4.6 mm, 5 μm) at 25 ºC, flow 1.0 mL/min, isocratic hexane/*i*PrOH 95:5, 254 nm, t_R (minor) 9.8; t_R (major) 10.8. The spectral data were fully consistent with those previously reported.[32]

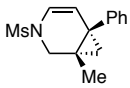
(1*S*,6*S*)-6-(4-Methoxyphenyl)-3-tosyl-3-azabicyclo[4.1.0]hept-4-ene



The title compound (white solid, 24.7 mg, 0.069 mmol, 74%, 94:6 *er*) was synthesized following general procedure **C** using *N*-allyl-*N*-(3-(4-methoxyphenyl)prop-2-yn-1-yl)-4-methylbenzenesulfonamide[137] (33.4 mg, 0.094 mmol) whereby the reaction was stirred for 16 h The crude was purified by flash column chromatography (cyclohexane/EtOAc 10:1).

M.p. = 111 – 113 °C ($CHCl_3$). α_D^{589} = –76.6 deg.cm^2.g^{-1} ($CHCl_3$, c 1.0, 302 K). **HPLC** Chiralcel OJ-H (250 mm × 4.6 mm, 5 μm) at 25 ºC, flow 1.0 mL/min, isocratic hexane/*i*PrOH 70:30, 280 nm, t_R (major) 16.9; t_R (minor) 20.8. The spectral data were fully consistent with those previously reported.[138]

(1*S*,6*S*)-1-Methyl-3-(methylsulfonyl)-6-phenyl-3-azabicyclo[4.1.0]hept-4-ene



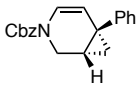
The title compound (white solid, 21.7 mg, 0.082 mmol, 88%, 74:26 *er*) was synthesized following general procedure **C** using *N*-(2-methylallyl)-*N*-(3-phenylprop-2-yn-1-yl)methanesulfonamide[32] (25 mg, 0.094 mmol) whereby the reaction was stirred for 24 h. The crude was purified by flash column chromatography (cyclohexane/EtOAc 30:1).

M.p. = 127 – 129 °C ($CHCl_3$). α_D^{589} = –52.32 deg.cm^2.g^{-1} ($CHCl_3$, c 1.0, 301 K). **HPLC** Chiralpak IC (250 mm × 4.6 mm, 5 μm) at 25 ºC, flow 1.0 mL/min, isocratic hexane/*i*PrOH

138. Brissy, D.; Skander, M.; Jullien, H.; Retailleau, P.; Marinetti, A. *Org. Lett.* **2009**, *11*, 2137–2139.

80:20, 220 nm, t_R (minor) 12.4; t_R (major) 13.2. The spectral data were fully consistent with those previously reported.[32]

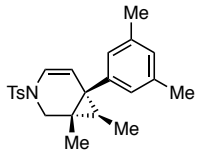
Benzyl (1*S*,6*S*)-6-phenyl-3-azabicyclo[4.1.0]hept-4-ene-3-carboxylate



The title compound (colorless gum, 16.1 mg, 0.052 mmol, 56%, 91:9 *er*) was synthesized following general procedure **C** using benzyl allyl(3-phenylprop-2-yn-1-yl)carbamate[139] (28.7 mg, 0.094 mmol) whereby the reaction was stirred for 24 h. The crude was purified by flash column chromatography (cyclohexane/EtOAc 20:1).

α_D^{589} = –84.1 deg.cm^2.g^{-1} ($CHCl_3$, c 0.7, 302 K). **HPLC** Chiralpak IA (250 mm × 4.6 mm, 5 µm) at 25 ºC, flow 1.0 mL/min, isocratic hexane/*i*PrOH 95:5, 220 nm, t_R (minor) 8.5; t_R (major) 9.5. The spectral data were fully consistent with those previously reported.[139]

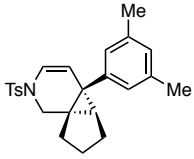
(1*S*,6*S*,7*R*)-6-(3,5-Dimethylphenyl)-1,7-dimethyl-3-tosyl-3-azabicyclo[4.1.0]hept-4-ene



The title compound (colorless gum, 31 mg, 0.081 mmol, 97%, 97:3 *er*, 10:1 dr) was synthesized following general procedure **C** using (*E*)-*N*-(3-(3,5-dimethylphenyl)prop-2-yn-1-yl)-4-methyl-*N*-(2-methylbut-2-en-1-yl)benzenesulfonamide[140] (32 mg, 0.084 mmol) whereby the reaction was stirred for 13 h. The crude was purified by preparative TLC (cyclohexane/EtOAc 10:1).

α_D^{589} = –85.8 deg.cm^2.g^{-1} ($CHCl_3$, c 1.0, 299 K). **UPC^2** Chiralpak IC (100 × 4.6mm, 3µm) at 35 ºC, flow 3 mL/min, isocratic CO_2/*i*PrOH 85:15, ABRP pressure 1500 psi, 220 nm, t_R (major) 3.9; t_R (minor) 4.5. The spectral data were fully consistent with those previously reported.[140]

(4a*S*,4b*R*,7a*S*)-4a-(3,5-Dimethylphenyl)-2-tosyl-2,4a,4b,5,6,7-hexahydro-1H-cyclopenta[1,3]cyclopropa[1,2-c]pyridine



The title compound (colorless gum, 31 mg, 0.078 mmol, 94%, 96:4 *er*) was synthesized following general procedure **C** using *N*-(cyclopent-1-en-1-ylmethyl)-*N*-(3-(3,5-dimethylphenyl)prop-2-yn-1-yl)-4-methylbenzenesulfonamide[140] (33 mg, 0.084 mmol) whereby the reaction was stirred for 16 h. The crude was purified by preparative TLC (cyclohexane/CH_2Cl_2 1:1).

139. Lin, A.; Zhang, Z.-W.; Yang, J. *Org. Lett.* **2014**, *16*, 386–389.
140. Zhang, P.-C.; Wang, Y.; Zhang, Z.-M.; Zhang, J. *Org. Lett.* **2018**, *20*, 7049–7052.

α_D^{589} = –140.3 deg.cm^2.g^{-1} ($CHCl_3$, 1.0 c, 299 K). **HPLC** Chiralpak ID (250 mm × 4.6 mm, 5 μm) at 25 ºC, flow 1.0 mL/min, isocratic hexane/*i*PrOH 95:5, 220 nm, t_R (major) 11.5; t_R (minor) 12.4. The spectral data were fully consistent with those previously reported.[140]

Enantioselective Synthesis of 1,2-Dihydronaphthalenes

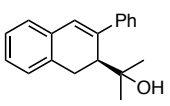
General procedure D: Protocol A for enantioselective synthesis of 1,2-dihydronaphthalenes

1,6-Enyne (1.0 equiv) and the corresponding nucleophile (2.5 equiv) were dissolved in α,α,α-trifluorotoluene (0.05M). This solution was added to a vial containing gold catalyst (*R*,*R*)-**E** (2 mol %) and $AgSbF_6$ (2 mol %) and the reaction was stirred for 24 h at 25 ºC. The reaction was quenched by addition of 1 drop of NEt_3 and concentrated. The crude was purified by flash column chromatography.

General procedure E: Protocol B for enantioselective synthesis of 1,2-dihydronaphthalenes

1,6-Enyne (1.0 equiv) and H_2O (5.0 equiv) were dissolved in α,α,α-trifluorotoluene (0.2M). This solution was added to a vial containing gold catalyst (*R*,*R*)-**E** (1 mol %) and $AgSbF_6$ (1 mol %) and the reaction was stirred for 24 h at 25 ºC. The reaction was quenched by addition of 1 drop of NEt_3 and concentrated. The crude was purified by flash column chromatography.

(*S*)-2-(3-Phenyl-1,2-dihydronaphthalen-2-yl)propan-2-ol

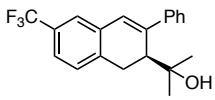


The title compound (white solid, 21.9 mg, 0.083 mmol, 68%, 97:3 *er*) was synthesized following general procedure **D** using 1-(3-methylbut-2-en-1-yl)-2-(phenylethynyl)benzene[141] (30.0 mg, 0.12 mmol). The crude was purified by flash column chromatography (pentane/CH_2Cl_2 4:1, then pentane/Et_2O 1:1).

M.p. = 138 – 140 ºC (pentane). **^{1}H NMR** (400 MHz, CD_2Cl_2) δ 7.58 – 7.50 (m, 2H), 7.43 – 7.34 (m, 2H), 7.33 – 7.25 (m, 1H), 7.21 – 7.09 (m, 4H), 6.86 (s, 1H), 3.32 – 3.19 (m, 2H), 3.11 (dd, *J* = 7.1, 2.3 Hz, 1H), 1.18 – 1.12 (m, 1H), 0.96 (s, 3H), 0.88 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 143.9, 140.9, 136.0, 135.2, 129.1, 128.4, 128.1, 127.8, 127.6, 127.2, 126.9, 126.8, 75.3, 46.0, 31.3, 29.2, 28.1. **HRMS** (ESI+) calculated for $[C_{19}H_{20}NaO]^+$ 287.1406 *m/z*; found $[M + Na]^+$ 287.1394 *m/z*. α_D^{589}= –263.5 deg.cm^2.g^{-1} ($CHCl_3$, c 0.83, 299 K). **UPC^2** Chiralpak IC (150 × 4.6mm, 3μm) at 35 ºC, flow 3 mL/min, isocratic CO_2/MeOH 95:5, ABRP pressure 1500 psi, 294 nm, t_R (major) 2.8; t_R (minor) 3.1.

141. Sanjuán, A. M.; Martínez, A.; García-García, P.; Fernández-Rodríguez, M. A.; Sanz, R. *Beilstein J. Org. Chem.* **2013**, *9,* 2242–2249.

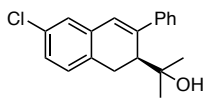
(*S*)-2-(3-Phenyl-6-(trifluoromethyl)-1,2-dihydronaphthalen-2-yl)propan-2-ol



The title compound (colorless oil, 21.9 mg, 0.066 mmol, 69%, 94:6 *er*) was synthesized following general procedure **D** using 1-(3-methylbut-2-en-1-yl)-2-(phenylethynyl)-4-(trifluoromethyl) benzene[142] (30.0 mg, 0.095 mmol). The crude was purified by flash column chromatography (pentane/CH_2Cl_2 4:1, then pentane/Et_2O 1:1).

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.56 – 7.52 (m, 2H), 7.44 – 7.41 (m, 4H), 7.34 – 7.27 (m, 2H), 6.87 (s, 1H), 3.40 (d, *J* = 16.7 Hz, 1H), 3.26 (ddt, *J* = 16.7, 8.2, 1.7 Hz, 1H), 3.16 (dd, *J* = 8.2, 1.2 Hz, 1H), 1.16 (br s, 1H), 0.95 (s, 3H), 0.88 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, CD_2Cl_2) δ 143.3, 142.8, 140.4 – 140.3 (m), 135.8, 129.2, 129.1 (q, *J* = 32.1 Hz), 128.2, 127.9, 127.22, 127.17, 125.1 (q, *J* = 272.0 Hz), 124.5 (q, *J* = 4.0 Hz), 123.1 (q, *J* = 3.8 Hz), 75.2, 45.9, 31.2, 29.4, 27.9. **^{19}F{^{1}H} NMR** (376 MHz, CD_2Cl_2) δ –62.8. **HRMS** (APCI+) calculated for $[C_{20}H_{18}F_3]^+$ 315.1355 *m/z*; found $[M - OH]^+$ 315.1355 *m/z*. α_D^{589} = –182.7 deg.cm^2.g^{-1} ($CHCl_3$, c 0.98, 299 K). **HPLC** Chiralpak OJ-H (250 mm × 4.6 mm, 5 μm) at 25 ºC, flow 1.0 mL/min, isocratic hexane/*i*PrOH 90:10, 280 nm, t_R (major) 4.3; t_R (minor) 6.5.

(*S*)-2-(6-Chloro-3-phenyl-1,2-dihydronaphthalen-2-yl)propan-2-ol

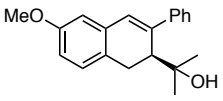


The title compound (white solid, 23.0 mg, 0.077 mmol, 43%, 95:5 *er*) was synthesized following general procedure **D** using 4-chloro-1-(3-methylbut-2-en-1-yl)-2-(phenylethynyl)benzene[142] (50.0 mg, 0.178 mmol). The crude was purified by flash column chromatography (pentane/CH_2Cl_2 2:1, then pentane/Et_2O 1:1).

M.p. = 105 – 108 ºC (pentane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55 – 7.47 (m, 2H), 7.43 – 7.35 (m, 2H), 7.33 – 7.27 (m, 1H), 7.14 – 7.05 (m, 3H), 6.77 (s, 1H), 3.28 (d, *J* = 15.9 Hz, 1H), 3.25 – 3.09 (m, 2H), 1.00 (s, 3H), 0.90 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 142.8, 141.9, 136.2, 133.7, 132.0, 128.9, 128.3, 127.8, 127.4, 126.9, 126.8, 126.1, 75.1, 45.7, 30.3, 29.2, 27.7. **HRMS** (ESI+) calculated for $[C_{19}H_{19}ClNaO]^+$ 321.1017 *m/z*; found $[M + Na]^+$ found 321.1011 *m/z*. α_D^{589} = –170.4 deg.cm^2.g^{-1} ($CHCl_3$, c 0.61, 299 K). **HPLC** Chiralpak IA (250 mm × 4.6 mm, 5 μm) at 25 ºC, flow 1.0 mL/min, isocratic hexane/*i*PrOH 90:10, 280 nm, t_R (major) 6.3; t_R (minor) 21.1.

142. The synthesis of starting materials has been performed by Joan G. Mayans.

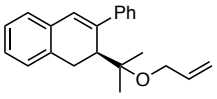
(*S*)-2-(6-Methoxy-3-phenyl-1,2-dihydronaphthalen-2-yl)propan-2-o



The title compound (white solid, 32.1 mg, 0.109 mmol, 60%, 97:3 *er*) was synthesized following general procedure **D** using 4-methoxy-1-(3-methylbut-2-en-1-yl)-2-(phenylethynyl)benzene[142] (50.0 mg, 0.181 mmol). The crude was purified by flash column chromatography (pentane/CH_2Cl_2 2:1, then pentane/Et_2O 1:1).

M.p. = 103 – 106 ºC (pentane). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.56 – 7.52 (m, 2H), 7.41 – 7.36 (m, 2H), 7.31 – 7.27 (m, 1H), 7.07 (ddd, *J* = 8.0, 1.3, 0.7 Hz, 1H), 6.82 (s, 1H), 6.73 – 6.69 (m, 2H), 3.81 (s, 3H), 3.26 – 3.15 (m, 2H), 3.11 (dd, *J* = 7.3, 1.8 Hz, 1H), 1.01 (s, 3H), 0.92 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 158.5, 143.2, 140.9, 135.6, 128.8, 128.1, 127.8, 127.5, 127.3, 126.8, 112.7, 112.2, 75.2, 55.4, 45.9, 30.1, 29.1, 27.8. **HRMS** (ESI+) calculated for $[C_{20}H_{22}NaO_2]^+$ 317.1512 *m/z*; found $[M + Na]^+$ found 317.1500 *m/z*. **α_D^{589}** = –173.0 deg.cm^2.g^{-1} ($CHCl_3$, c 1.03, 299 K). **UPC^2** Chiralpak IA (150 × 4.6mm, 3µm) at 35 ºC, flow 3 mL/min, isocratic CO_2/*i*PrOH 75:25, ABRP pressure 1500 psi, 242 nm, t_R (major) 1.3; t_R (minor) 2.8.

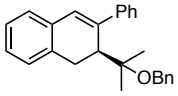
(*S*)-2-(2-(Allyloxy)propan-2-yl)-3-phenyl-1,2-dihydronaphthalene



The title compound (light-yellow solid, 23.4 mg, 0.077 mmol, 63%, 95:5 *er*) was synthesized following general procedure **D** using 1-(3-methylbut-2-en-1-yl)-2-(phenylethynyl)benzene[141] (30.0 mg, 0.12 mmol). The crude was purified by flash column chromatography (pentane/CH_2Cl_2 4:1, then pentane/Et_2O 9:1).

M.p. = 78 – 80 ºC (pentane). **^{1}H NMR** (400 MHz, CD_2Cl_2) δ 7.56 – 7.50 (m, 2H), 7.42 – 7.35 (m, 2H), 7.32 – 7.26 (m, 1H), 7.19 – 7.10 (m, 4H), 6.80 (s, 1H), 5.77 (ddt, *J* = 17.2, 10.4, 5.2 Hz, 1H), 5.16 (dq, *J* = 17.2, 1.8 Hz, 1H), 5.04 (dq, *J* = 10.4, 1.6 Hz, 1H), 3.87 (ddt, *J* = 12.5, 5.3, 1.6 Hz, 1H), 3.80 (ddt, *J* = 12.4, 5.1, 1.6 Hz, 1H), 3.40 (d, *J* = 16.4 Hz, 1H), 3.30 (d, *J* = 8.4 Hz, 1H), 3.17 (dd, *J* = 16.3, 8.4 Hz, 1H), 0.89 (s, 3H), 0.75 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 144.4, 141.2, 136.8, 136.4, 135.3, 129.0, 128.91, 128.87, 128.0, 127.6, 127.5, 127.2, 126.7, 115.3, 79.6, 62.8, 42.9, 30.4, 25.7, 23.2. **HRMS** (ESI+) calculated for $[C_{22}H_{24}NaO]^+$ 327.1719 *m/z*; found $[M + Na]^+$ 327.1712 *m/z*. **α_D^{589}** = –181.4 deg.cm^2.g^{-1} ($CHCl_3$, c 0.66, 299 K). **UPC^2** Chiralpak IC (150 × 4.6mm, 3µm) at 35 ºC, flow 3 mL/min, isocratic CO_2/MeOH 95:5, ABRP pressure 1500 psi, 293 nm, t_R (major) 1.1; t_R (minor) 1.3.

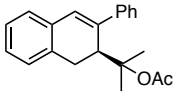
(*S*)-2-(2-(Benzyloxy)propan-2-yl)-3-phenyl-1,2-dihydronaphthalene



The title compound (white solid, 32.4 mg, 0.091 mmol, 75%, 95:5 *er*) was synthesized following general procedure **D** using 1-(3-methylbut-2-en-1-yl)-2-(phenylethynyl)benzene[141] (30.0 mg, 0.12 mmol). The crude was purified by flash column chromatography (pentane/CH_2Cl_2 4:1, then pentane/Et_2O 9:1).

M.p. = 79 – 81 ºC (pentane). **^{1}H NMR** (400 MHz, CD_2Cl_2) δ 7.57 – 7.52 (m, 2H), 7.41 – 7.34 (m, 2H), 7.31 – 7.20 (m, 4H), 7.19 – 7.11 (m, 6H), 6.82 (s, 1H), 4.39 (d, *J* = 11.2 Hz, 1H), 4.31 (d, *J* = 11.2 Hz, 1H), 3.45 (d, *J* = 16.5 Hz, 1H), 3.36 (d, *J* = 8.4 Hz, 1H), 3.19 (dd, *J* = 16.3, 8.2 Hz, 1H), 0.95 (s, 3H), 0.84 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 144.4, 141.1, 140.4, 136.5, 135.3, 129.0, 128.9, 128.6, 128.0, 127.8, 127.6, 127.50, 127.47, 127.3, 126.7, 79.9, 63.8, 43.3, 30.5, 25.6, 23.2. **HRMS** (ESI+) calculated for $[C_{26}H_{26}NaO]^+$ 377.1876 *m/z*; found $[M + Na]^+$ 377.1869 *m/z*. α_D^{589}= –137.1 deg.cm^2.g^{-1} ($CHCl_3$, c 1.19, 299 K). **UPC^2** Chiralpak IC (150 × 4.6mm, 3μm) at 35 ºC, flow 3 mL/min, isocratic CO_2/MeOH 90:10, ABRP pressure 1500 psi, 293 nm, t_R (major) 1.4; t_R (minor) 1.7.

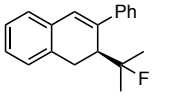
(*S*)-2-(3-Phenyl-1,2-dihydronaphthalen-2-yl)propan-2-yl acetate



The title compound (white solid, 15.3 mg, 0.050 mmol, 41%, 90:10 *er*) was synthesized following general procedure **D** using 1-(3-methylbut-2-en-1-yl)-2-(phenylethynyl)benzene[141] (30.0 mg, 0.12 mmol). The crude was purified by flash column chromatography (pentane/CH_2Cl_2 4:1, then pentane/Et_2O 2:1).

M.p. = 93 – 96 ºC (pentane). **^{1}H NMR** (400 MHz, CD_2Cl_2) δ 7.51 – 7.46 (m, 2H), 7.41 – 7.35 (m, 2H), 7.30 – 7.24 (m, 1H), 7.18 – 7.11 (m, 4H), 6.82 (s, 1H), 3.88 (dd, *J* = 8.4, 1.3 Hz, 1H), 3.27 (dd, *J* = 16.7, 8.4 Hz, 1H), 3.11 (dd, *J* = 16.7, 1.2 Hz, 1H), 1.39 (s, 3H), 1.34 (s, 3H), 1.00 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 170.8, 143.9, 140.8, 135.5, 135.2, 129.1, 128.9, 128.1, 127.5, 127.4, 127.0, 126.7, 86.0, 41.8, 31.1, 25.2, 25.0, 22.2. **HRMS** (ESI+) calculated for $[C_{21}H_{22}NaO_2]^+$ 329.1512 *m/z*; found $[M + Na]^+$ 329.1514 *m/z*. α_D^{589} = –196.4 deg.cm^2.g^{-1} ($CHCl_3$, c 0.46, 299 K). **UPC^2** Chiralpak IC (150 × 4.6mm, 3μm) at 35 ºC, flow 3 mL/min, isocratic CO_2/MeOH 95:5, ABRP pressure 1500 psi, 290 nm, t_R (major) 1.7; t_R (minor) 1.8.

(*S*)-2-(2-Fluoropropan-2-yl)-3-phenyl-1,2-dihydronaphthalene

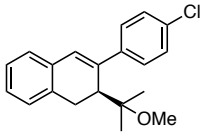


The title compound (white solid, 8.44 mg, 0.032 mmol, 40%, 96:4 *er*) was synthesized following general procedure **D** using 1-(3-methylbut-2-en-1-yl)-2-(phenylethynyl)benzene[141] (20.0 mg, 0.08 mmol) and HF·pyridine complex (5.0 equiv). The reaction was carried out in an Eppendorf vial using (*R*,*R*)-**E** (3

mol %) and $AgSbF_6$ (3 mol %). The crude was purified by flash column chromatography (pentane).

M.p. = 72 – 75 ºC (pentane). **^{1}H NMR** (400 MHz, CD_2Cl_2) δ 7.56 – 7.51 (m, 2H), 7.42 – 7.35 (m, 2H), 7.32 – 7.26 (m, 1H), 7.21 – 7.11 (m, 4H), 6.87 (s, 1H), 3.38 – 3.29 (m, 1H), 3.28 – 3.23 (m, 2H), 1.13 (d, J = 21.9 Hz, 3H), 0.94 (d, J = 22.9 Hz, 3H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 143.3, 139.6 (d, J = 6.2 Hz), 135.4, 135.0, 129.0, 128.6, 128.2, 127.8, 127.6, 127.2, 127.0, 126.9, 99.0 (d, J = 170.8 Hz), 44.4 (d, J = 22.7 Hz), 30.7 (d, J = 6.6 Hz), 27.0 (d, J = 24.0 Hz), 24.9 (d, J = 24.6 Hz). **^{19}F{^{1}H} NMR** (376 MHz, CD_2Cl_2) δ –132.9. **HRMS** (ESI+) calculated for $[C_{19}H_{19}FNa]^+$ 289.1363 *m/z*; found $[M + Na]^+$ 289.1360 *m/z*. **α_D^{589}** = –164.5 deg.cm^2.g^{-1} ($CHCl_3$, c 0.165, 299 K). **UPC^2** Chiralpak IG (150 × 4.6mm, 3μm) at 35 ºC, flow 2 mL/min, isocratic CO_2/MeOH 85:15, ABRP pressure 2000 psi, 292 nm, t_R (major) 1.9; t_R (minor) 4.6.

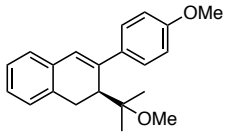
(*S*)-3-(4-Chlorophenyl)-2-(2-methoxypropan-2-yl)-1,2-dihydronaphthalene



The title compound (white solid, 67.0 mg, 0.214 mmol, 50%, 96:4 *er*) was synthesized following general procedure **D** using 1-((4-chlorophenyl)ethynyl)-2-(3-methylbut-2-en-1-yl)benzene[142] (120.0 mg, 0.427 mmol). The crude was purified by preparative TLC (pentane/Et_2O 20:1).

M.p. = 116 – 118 ºC (pentane). **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 7.48 – 7.43 (m, 2H), 7.37 – 7.33 (m, 2H), 7.16 – 7.09 (m, 4H), 6.77 (s, 1H), 3.32 (d, J = 16.1 Hz, 1H), 3.19 (d, J = 8.6 Hz, 1H), 3.12 (dd, J = 16.1, 8.4 Hz, 1H), 3.07 (s, 3H), 0.82 (s, 3H), 0.68 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 143.0, 139.9, 136.4, 134.9, 133.0, 129.2, 129.0, 128.6, 128.2, 127.6, 126.8, 126.7, 79.2, 49.1, 42.4, 30.1, 25.02, 22.7. **HRMS** (APCI+) calculated for $[C_{19}H_{18}Cl]^+$ 281.1092 *m/z*; found $[M – CH_3O]^+$ 281.1095 *m/z*. **α_D^{589}** = –205.0 deg.cm^2.g^{-1} ($CHCl_3$, c 0.50, 299 K). **HPLC** Chiralpak OJ-H (250 mm × 4.6 mm, 5 μm) at 25 ºC, flow 1.0 mL/min, isocratic hexane/*i*PrOH 90:10, 280 nm, t_R (major) 5.5; t_R (minor) 16.6.

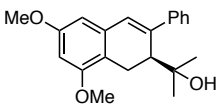
(*S*)-3-(4-Methoxyphenyl)-2-(2-methoxypropan-2-yl)-1,2-dihydronaphthalene



The title compound (white solid, 29.5 mg, 0.096 mmol, 52%, 96:4 *er*) was synthesized following general procedure **D** using 1-((4-methoxyphenyl)ethynyl)-2-(3-methylbut-2-en-1-yl)benzene[141] (51.0 mg, 0.165 mmol). The crude was purified by preparative TLC (pentane/Et_2O 20:1).

M.p. = 104 – 106 ºC (pentane). **α_D^{589}** = –221.7 deg.cm^2.g^{-1} ($CHCl_3$, c 1.19, 299 K). **HPLC** Chiralpak IA (250 × 4.6mm, 5μm), flow 1.0 mL/min, isocratic hexane/*i*PrOH 98:2, 280 nm, t_R (major) 5.9; t_R (minor) 7.3. The spectral data were fully consistent with those previously reported.[141]

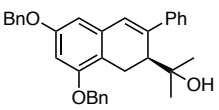
(*S*)-2-(6,8-Dimethoxy-3-phenyl-1,2-dihydronaphthalen-2-yl)propan-2-ol



The title compound (white solid, 130 mg, 0.40 mmol, 60%, 99:1 *er*) was synthesized following general procedure **E** using 1,5-dimethoxy-2-(3-methylbut-2-en-1-yl)-3-(phenylethynyl)benzene[142] (205 mg, 0.67 mmol). The crude was purified by flash column chromatography (pentane/CH_2Cl_2 2:1, pentane/Et_2O 1:1).

M.p. = 102 – 104 ºC (pentane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 – 7.52 (m, 2H), 7.41 – 7.35 (m, 2H), 7.31 – 7.25 (m, 1H), 6.79 (s, 1H), 6.37 (q, *J* = 2.4 Hz, 2H), 3.84 (s, 3H), 3.82 (s, 3H), 3.57 (d, *J* = 16.9 Hz, 1H), 3.13 (dd, *J* = 8.3, 1.2 Hz, 1H), 2.77 (dd, *J* = 17.0, 8.2 Hz, 1H), 1.02 (s, 3H), 0.92 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 159.1, 156.9, 143.3, 141.0, 136.0, 128.8, 128.0, 127.4, 126.7, 115.1, 103.4, 98.1, 75.3, 55.7, 55.5, 45.3, 28.8, 27.9, 22.8. **HRMS** (ESI+) calculated for $[C_{21}H_{24}NaO_3]^+$ 347.1618 *m/z*; found $[M + Na]^+$ 347.1626 *m/z*. $[\alpha]_D^{589}$ = –253.8 deg.cm^2.g^{-1} ($CHCl_3$, c 1.00, 299 K). **HPLC** Chiralpak IA (250 mm × 4.6 mm, 5 μm) at 25 ºC, flow 1.0 mL/min, isocratic hexane/*i*PrOH 90:10, 280 nm, t_R (major) 8.5; t_R (minor) 15.3.

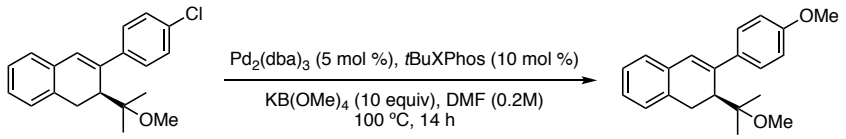
(*S*)-2-(6,8-Bis(benzyloxy)-3-phenyl-1,2-dihydronaphthalen-2-yl)propan-2-ol



The title compound (white solid, 484 mg, 1.78 mmol, 68%, 98:2 *er*) was synthesized following general procedure **E** using 1 (((4-(3-methylbut-2-en-1-yl)-5-(phenylethynyl)-1,3-phenylene)bis(oxy))bis(methylene))dibenzene[142] (1.2 g, 2.62 mmol). The crude was purified by flash column chromatography (pentane/CH_2Cl_2 2:1, pentane/Et_2O 1:1).

M.p. = 112 – 113 ºC (pentane). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.6 Hz, 2H), 7.48 – 7.27 (m, 13H), 6.80 (s, 1H), 6.53 (d, *J* = 2.3 Hz, 1H), 6.48 (d, *J* = 2.3 Hz, 1H), 5.09 (s, 2H), 5.05 (s, 2H), 3.67 (d, *J* = 17.0 Hz, 1H), 3.15 (d, *J* = 8.1 Hz, 1H), 2.83 (dd, *J* = 17.0, 8.2 Hz, 1H), 1.21 (s, 1H), 1.03 (s, 3H), 0.93 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 158.3, 156.0, 143.2, 141.2, 137.5, 137.2, 136.3, 128.8, 128.73, 128.71, 128.1, 128.0, 127.7, 127.5, 127.4, 126.7, 116.0, 105.1, 100.5, 100.1, 75.3, 70.40, 70.38, 45.3, 28.7, 28.0, 23.1. **HRMS** (ESI+) calculated for $[C_{33}H_{32}NaO_3]^+$ 499.2244 *m/z*; found $[M + Na]^+$ found 499.2265 *m/z*. $[\alpha]_D^{589}$ = –174.5 deg.cm^2.g^{-1} ($CHCl_3$, c 1.00, 299 K). **HPLC** Chiralpak IA (250 mm × 4.6 mm, 5 μm) at 25 ºC, flow 1.0 mL/min, isocratic hexane/*i*PrOH 90:10, 280 nm, t_R (major) 12.3; t_R (minor) 33.0.

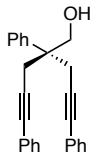
Interconversion of 1.94i into 1.94j



1.94i: 96:4 *er* — **1.94j**: 75%, 96:4 *er*

A microwave vial was charged with $Pd_2(dba)_3$ (1.46 mg, 1.59 μmol, 5 mol %), *t*BuXPhos (1.36 mg, 3.20 μmol, 10 mol %), compound **1.94i** (10 mg, 32 μmol, 1.0 equiv) $KB(OMe)_4$ (55.6 mg, 0.32 mmol, 10.0 equiv) and DMF (0.2 mL). The reaction mixture was heated to 100 ºC for 14 h. The reaction was quenched by addition of water and extracted from EtOAc (3x). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude was purified by preparative TLC (cyclohexane/Et_2O 10:1) to afford compound **1.94j** (7.4 mg, 24 μmol, 75%) as a white solid in 96:4 *er*.

2,5-Diphenyl-2-(3-phenylprop-2-yn-1-yl)pent-4-yn-1-ol



A solution of methyl 2,5-diphenyl-2-(3-phenylprop-2-yn-1-yl)pent-4-ynoate[131] (265 mg, 0.700 mmol, 1.0 equiv) in Et_2O (5 mL) was added dropwise to a suspension of $LiAlH_4$ (45 mg, 1.2 mmol, 1.7 equiv) in Et_2O (2 mL) at 0 ºC. The reaction was stirred for 1 h and after consumption of the starting material the reaction was quenched with HCl (0.5 M). After stirring for 30 min the mixture was filtered over Celite® and the organic phase was separated. The aqueous phase was extracted with Et_2O (3x) and the combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude was purified by flash column chromatography (cyclohexane/EtOAc 2:1, then 1:1) to yield the title compound (233 mg, 0.66 mmol, 95% yield) as a colorless gum.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.54 (d, *J* = 8.5 Hz, 2H), 7.42 (t, *J* = 7.7 Hz, 2H), 7.36 – 7.29 (m, 5H), 7.29 – 7.23 (m, 6H), 4.08 (d, *J* = 5.6 Hz, 2H), 3.13 – 2.98 (m, 4H), 1.72 – 1.64 (m, 1H). **^{13}C{^{1}H} NMR** (101 MHz, CD_2Cl_2) δ 142.5, 131.9, 128.8, 128.6, 128.2, 127.3, 123.9, 87.1, 83.6, 68.3, 47.2, 27.0. **HRMS** (APCI+) calculated for $[C_{26}H_{23}O]^+$ 351.1743 *m/z*; found $[M + H]^+$ 351.1743 *m/z*.

Chapter 2.

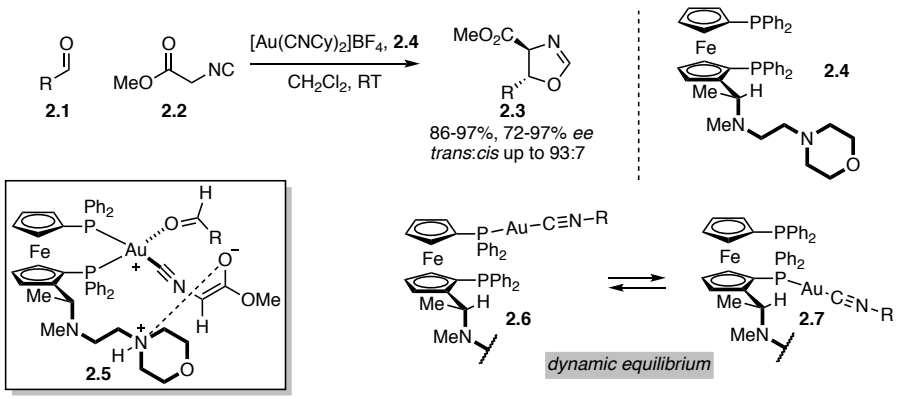
Catalyst Mode of Action and Mechanistic Considerations

Introduction

Origin of Enantioselectivity in Gold(I)-Catalyzed Transformations

Because the working mode of chiral gold(I) catalysts is not always entirely understood, the development of asymmetric methods remains a challenge. Thus, a successful enantioselective gold(I)-catalyzed transformation often implies the time-consuming screening of several ligand families and additives. Alternatively, the complete study on the working mode of a particular catalytic system would provide the required knowledge to implement new asymmetric transformations.

The first enantioselective gold(I)-catalyzed transformation was reported by Ito and Hayashi[1] describing the synthesis of chiral oxazolines **2.3** via aldol reaction of isocyanoacetates **2.2** and aldehydes **2.1** (Scheme 2.1).[1] The use of ferrocenylamine ligand **2.4** that contains both, planar and central chirality was crucial for achieving high enantioselectivities. Transition state **2.5** in which gold(I) is tetracoordinated and acts as a traditional Lewis acid activating both reaction partners **2.1** and **2.2** was proposed to explain the observed absolute and relative configurations in products **2.3**.



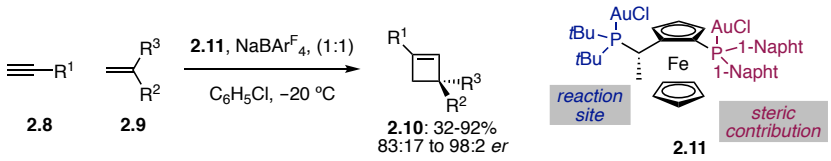
Scheme 2.1. Enantioselective gold(I)-catalyzed synthesis of oxazolines.

Additionally, the dialkylamino side chain in ligand **2.4** was suggested to assist the enolization process and stabilize the transition state through ion pair interactions. Finally, the planar rather than the central chirality in ligand **2.4** was identified to be stereodetermining, predominantly based on prior reports.[143]

143. (a) Hayashi, T.; Konishi, M.; Fukushima, M.; Mise, T.; Kagotani, M.; Tajika, M.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 180–186. (b) Hayashi, T.; Kumada, M. *Acc. Chem. Res.* **1982**, *15*, 395–401.

In a detailed mechanistic investigation, Togni[144] studied several aspects of the working model proposed by Ito and Hayashi. Indeed, control experiments excluded the presence of a tetracoordinated gold(I) species. The metal was rather suggested to be in a dynamic equilibrium between **2.6** and **2.7** in which gold(I) migrates from one coordinating phosphorous atom to the other, which is consistent with the preferred linear dicoordiantion adopted by gold(I). Finally, the high enantio- and diastereoselectivities were found to arise from an internal cooperation of both, planar and central chirality[145] and are not only steric in origin but also correlate with the electronic properties of the reacting aldehydes **2.1**.

The synthesis of chiral cyclobutenes **2.10** through [2+2] cycloaddition of alkynes **2.8** with alkenes **2.9** reported by our group involves the use of digold complexes **2.11** supported by JosiPhos-type ligands (Scheme 2.2).[112] Interestingly, the rate-determining step in this transformation depends on the substitution pattern at the alkene. More electron-rich alkenes favor the formation of (η^2-alkene)gold(I) complexes and therefore slow down the ligand exchange process with alkynes to form (η^2-alkyne)gold(I) intermediates. On the other hand, the Markovnikov-type addition to electrophilic (η^2-alkyne)gold(I) becomes rate-determining in the case of less electron-rich alkenes.

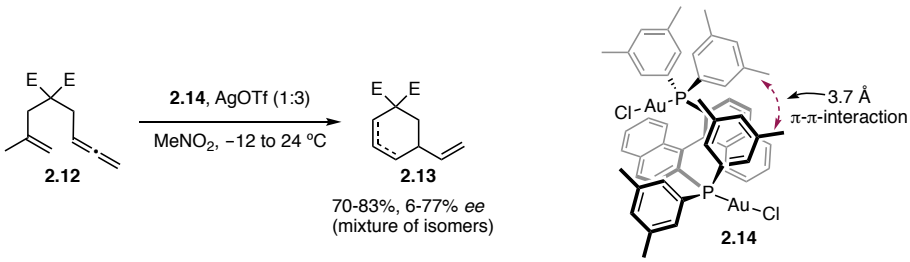


Scheme 2.2. Gold(I)-catalyzed enantioselective [2+2] cycloaddition of alkenes with alkynes.

Mechanistic investigations, including DFT calculations, have shown that the observed enantioselectivities are attributed mainly to steric effects. Additionally, the reaction takes place predominantly at the *t*Bu$_2$P-Au(I) site whereas the (naphthyl)$_2$P-AuCl moiety is essential for high stereoinduction.

In several reports, secondary non-covalent interactions have been identified to account for high enantioselectivities. An example is presented by Gagné[13] in which axially-chiral digold(I) complex **2.14** catalyzes the cycloisomerization of eneallenes **2.12** into vinylcyclohexenes **2.13** in good yields but modest enantiomeric excesses (Scheme 2.3). In this work, it was suggested that the π-π stacking between the P-bound 3,5-xylyl groups shown in the the X-ray structure of **2.14**, which presumably define the specific chiral environment, are also relevant in solution.

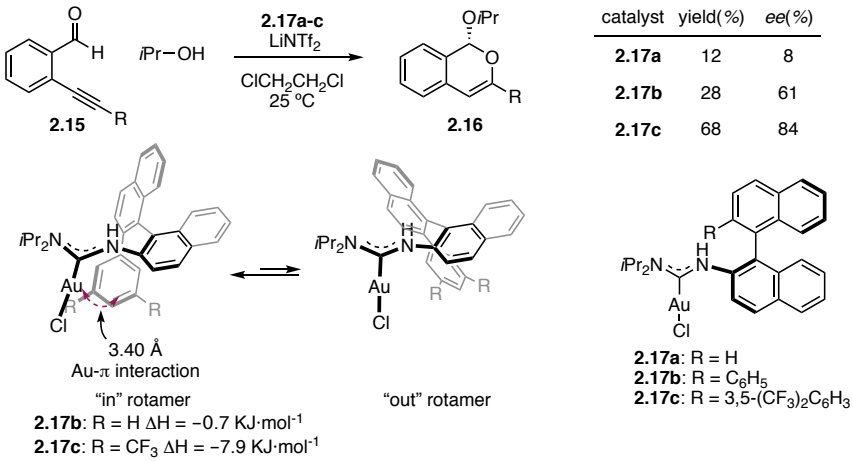
144. Togni, A.; Pastor, S. D. *J. Org. Chem.* **1990**, *55*, 1649–1664.
145. Pastor, S. D.; Togni, A. *J. Am. Chem. Soc.* **1989**, *111*, 2333–2334.



Scheme 2.3. Enantioselective eneallene cyclization.

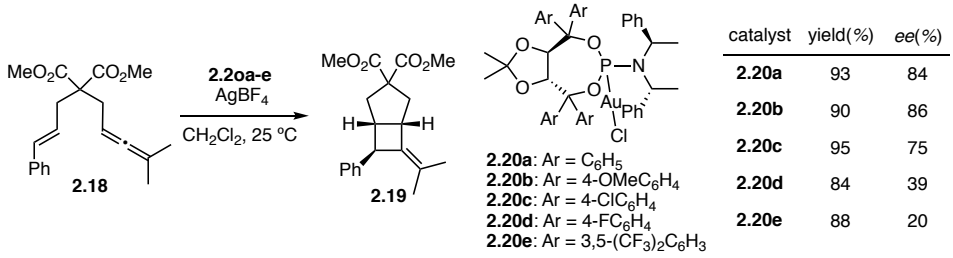
In 2012, Slaughter reported a series of chiral gold(I) complexes **2.17a-c** supported by acyclic diaminocarbene ligands[146] and their application in the enantioselective cyclization of alkynylbenzaldehydes **2.15** (Scheme 2.4).[147] In the presence of catalyst **2.17a,b,** 1*H*-isochromene **2.16** is obtained in poor to modest yields and enantiomeric excesses, whereas catalyst **2.17c** gave the expected cyclization product **2.16** in significantly improved results. A comparison of the X-ray structures of **2.17b** and **2.17c** showed that two rotameric forms of the diaminocarbene ligands can be present when coordinated to gold(I) referred respectively as the "in" and the "out" rotamer. Short distances between gold and the 3,5-$(CF_3)_2C_6H_3$ group in complex **2.17c** suggest weak electrostatic Au-π interactions (>3 Å) which favor the "in" rotamer. As a consequence of this particular conformation, the chiral environment is held close to the reactive center and thus, results beneficial in catalysis enhancing enantioselectivity and stability of the complex. DFT calculations provided further evidence for the observed preferred conformation. The "in" rotamer of **2.17c** was calculated to be 7.9 $KJ \cdot mol^{-1}$ more stable than its "out" conformer, whereas in the case of complex **2.17b** no significant difference was observed. Importantly, the "out" rotamer does not show any disfavored steric interactions which, reinforces the hypothesis that the preference for the "in" rotamer originates from electrostatic Au-π interactions, typically observed for cation-π interactions.[148]

146. Handa, S.; Slaughter, L. M. *Angew. Chem. Int. Ed.* **2012**, *51*, 2912–2915.
147. Asao, N.; Nogami, T.; Takahashi, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 764–765.
148. (a) Mecozzi, S.; West, A. P.; Dougherty, D. A. *J. Am. Chem. Soc.* **1996**, *118*, 2307–2308. (b) Mascal, M.; Kerdelhué, J.-L.; Blake, A. J.; Cooke, P. A.; Mortimer, R. J.; Teat, S. J. *Eur. J. Inorg. Chem.* **2000**, *2000*, 485–490.



Scheme 2.4. Enantioselective alkynylbenzaldehyde cyclization.

A similar electrostatic effect was noted by the group of Fürstner in the enantioselective [2+2] cycloaddition of eneallene **2.18** using chiral gold(I) complexes **2.20a-e** with TADDOL-derived monodentate phosphoramidite ligands (Scheme 2.5).[149] In general, electron-donating aryl substituents at the TADDOL backbone gave bicyclo[3.2.0]heptane **2.19** with higher enantioselectivities whereas unsatisfactory results were obtained with electron-poor aryl groups.



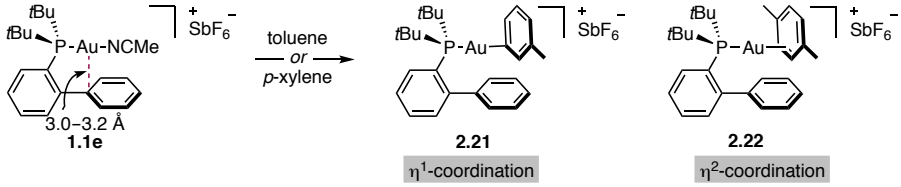
Scheme 2.5. Performance of phosphoramidite-supported gold(I) complexes **2.20a-e** in the [2+2] cycloaddition of **2.18**.

Based on crystallographic evidence, the electron rich aromatic substituents remain closer (3.2–3.8 Å) to the electron deficient gold center, probably exerting a stabilizing through-space Au-arene interaction. Thus, higher enantioselectivities are achieved.

149. Teller, H.; Flügge, S.; Goddard, R.; Fürstner, A. *Angew. Chem. Int. Ed.* **2010**, *49*, 1949–1953.

Cationic π-Gold(I) Complexes and Ligand Exchange

Gold(I) forms stable π-complexes with alkynes, alkenes, allenes, dienes and arenes.[10b,150] The first characterization of (π-arene)gold(I) complexes has been reported by our group,[151] which was followed by another contribution by the group of Bertrand.[152] η^1/η^2-Arene-gold(I) complexes **2.21** and **2.22** were synthesized by recrystallization of cationic complex **1.1e** from the appropriate aromatic solvents (Scheme 2.6). Short Au-Ar_{plane} distances (2.20–2.24 Å) were found and, interestingly, the bonding of the arene varies from η^1-coordination in toluene complex **2.21** to η^2-coordination in the case of **2.22**, with *p*-xylene complexed to gold(I) perpendicular to the Au-P bond.



Scheme 2.6. Synthesis of η^1/η^2-arene-gold(I) complexes **2.21** and **2.22**.

It is important to underline that in cationic complexes such as **1.1e** distances between gold(I) and the bottom aryl ring of the biphenyl scaffold are in the range of 3.0–3.2 Å. These values, as well as bond distances found in other gold(I) complexes,[153] are above the limit of significant gold(I)-arene interactions calculated to be 2.95 Å.[154] A covalent character for this interaction was excluded computationally as electron transfer from the arene to the metal does not occur.

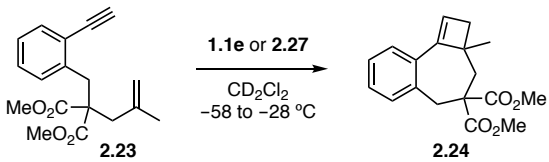
If both present, alkenes and alkynes compete for the coordination to gold whereby alkynes are selectively activated. It is noteworthy that the alkynophilicity of gold(I) complexes under homogeneous conditions is attributed to kinetic rather than thermodynamic factors as the coordinated alkynes display a significantly low LUMO.[155]

150. (a) Brooner, R. E. M.; Widenhoefer, R. A. *Angew. Chem. Int. Ed.* **2013**, *52*, 11714–11724 and references therein.
151. Herrero-Gómez, E.; Nieto-Oberhuber, C.; López, S.; Benet-Buchholz, J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 5455–5459.
152. Lavallo, V.; Frey, G. D.; Kousar, S.; Donnadieu, B.; Bertrand, G. *Proc. Natl. Acad. Sci. U. S. A.* **2007**, *104*, 13569–13573.
153. Li, Q. S.; Wan, C. Q.; Zou, R. Y.; Xu, F. B.; Song, H. Bin; Wan, X. J.; Zhang, Z. Z. *Inorg. Chem.* **2006**, *45*, 1888–1890.
154. Pérez-Galán, P.; Delpont, N.; Herrero-Gómez, E.; Maseras, F.; Echavarren, A. M. *Chem. Eur. J.* **2010**, *16*, 5324–5332.
155. García-Mota, M.; Cabello, N.; Maseras, F.; Echavarren, A. M.; Pérez-Ramírez, J.; Lopez, N. *ChemPhysChem* **2008**, *9*, 1624–1629.

However, depending on the substitution pattern the formation of (π-alkene)gold(I) complexes can be thermodynamically favored.[156,157] Indeed, Widenhofer has studied the relative binding affinities of alkynes[158] and alkenes[159] to gold(I) concluding that they strongly depend on the ancillary ligand and are predominantly affected by electronic and less by steric factors.

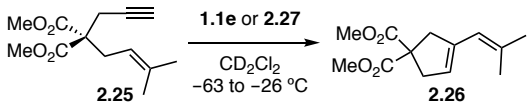
η^2-Alkyne-,[158a] η^2-alkene-,[159] η^2-allene-,[160] and η^2-(1,3-diene)-gold(I) complexes[158b] undergo ligand exchange following an associative mechanism. In cyclizations of 1,*n*-enynes ligand exchange also occurs through an associative pathway.[61,161] Our group determined the thermodynamic parameters of activation for the intramolecular [2+2] cycloaddition of 1,8-enyne **2.23** and the skeletal rearrangement of 1,6-enyne **2.25** (Scheme 2.7). [161a] The largely negative entropies of activation suggest that in both transformations an associative ligand exchange between (π-product)gold(I) complex and a molecule of incoming enyne is rate determining.

156. Nechaev, M. S.; Rayon, V. M.; Frenking, G. *J. Phys. Chem. A* **2004**, *108*, 3134–3142.
157. Jašíková, L.; Roithová, J. *Organometallics* **2012**, *31*, 1935–1942.
158. (a) Brown, T. J.; Widenhoefer, R. A. *J. Organomet. Chem.* **2011**, *696*, 1216–1220. (b) Brown, T. J.; Widenhoefer, R. A. *Organometallics* **2011**, *30*, 6003–6009.
159. (a) Brooner, R. E. M.; Widenhoefer, R. A *J. Am. Chem. Soc.* **2009**, 1*31*, 6350–6351. (b) Brooner, R. E. M.; Brown, T. J.; Widenhoefer, R. A. *Chem. Eur. J.* **2013**, *19*, 8276–8284. (c) Brown, T. J.; Dickens, M. G.; Widenhoefer, R. A. *Chem. Commun.* **2009**, *42*, 6451–6453.
160. (a) Brown, T. J.; Sugie, A.; Dickens, M. G.; Widenhoefer, R. A. *Organometallics* **2010**, *29*, 4207–4209. (b) Brown, T. J.; Sugie, A.; Leed, M. G. D.; Widenhoefer, R. A.. *Chem. Eur. J.* **2012**, *18*, 6959–6971.
161. (a) Escribano-Cuesta, A.; Pérez-Galán, P.; Herrero-Gómez, E.; Sekine, M.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *Org. Biomol. Chem.* **2012**, *10*, 6105–6111. (b) Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Cárdenas, D. J.; Buñuel, E.; Nevado, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6146–6148.



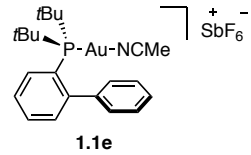
2.23 **2.24**

catalyst	$\Delta G^{\ddagger}_{298}$	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
1.1e	21.2 ± 4.4	6.3 ± 0.4	−46.4 ± 4.0
2.27	19.2 ± 4.8	11.3 ± 0.3	−26.5 ± 4.5

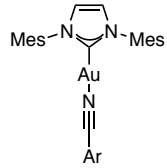


2.25 **2.26**

catalyst	$\Delta G^{\ddagger}_{298}$	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
1.1e	21.7 ± 1.1	3.7 ± 0.3	−60.6 ± 4.0
2.27	19.9 ± 2.1	13.1 ± 0.5	−22.8 ± 2.1



1.1e



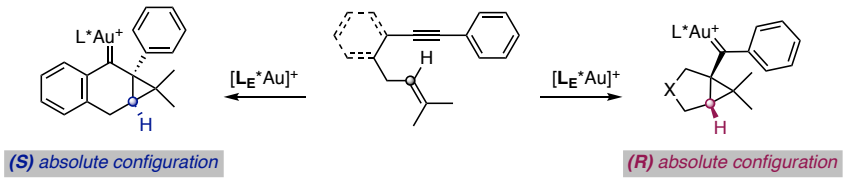
2.27: Ar = 2,4,6-$(OMe)_3C_6H_2$

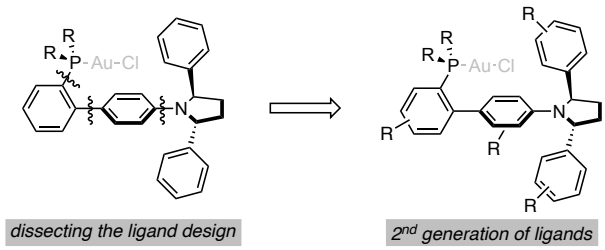
($\Delta G^{\ddagger}_{298}$ and $\Delta H^{\ddagger}$ in Kcal·mol^{-1} and $\Delta S^{\ddagger}$ in cal·mol^{-1}·K^{-1})

Scheme 2.7. Eyring analyses of intramolecular [2+2] cycloaddition and skeletal rearrangement.

Objectives

We aimed to investigate in detail the working mode of our pyrrolidinyl-biphenyl phosphine complexes, which gave products of formal [4+2] cycloaddition and 1,2-dihydronaphthalenes with opposite absolute configurations from starting 1,6-arylenynes (see **Chapter 1**).





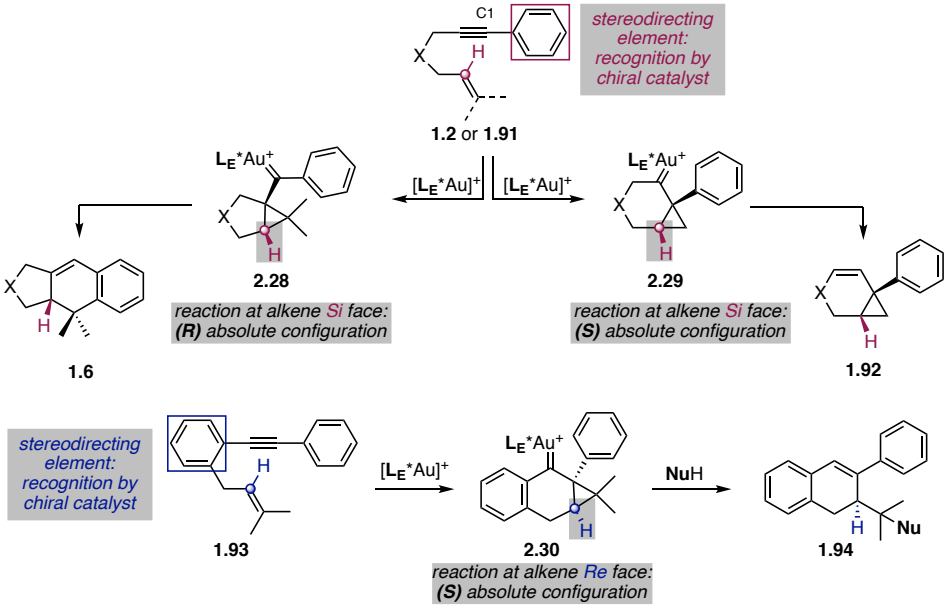
Scheme 2.8. Contradictory enantioselectivities and analysis of ligand design.

We also observed that the reactivity of our pyrrolidine-containing biphenyl phosphine gold(I) catalysts was lower than those with JohnPhos ligand in the formal [4+2] cycloaddition of 1,6-arylenynes. In order to rationalize this difference in reaction rates, we decided to perform additional mechanistic investigations.

Results and Discussion

Elucidation of the Mode of Stereoinduction

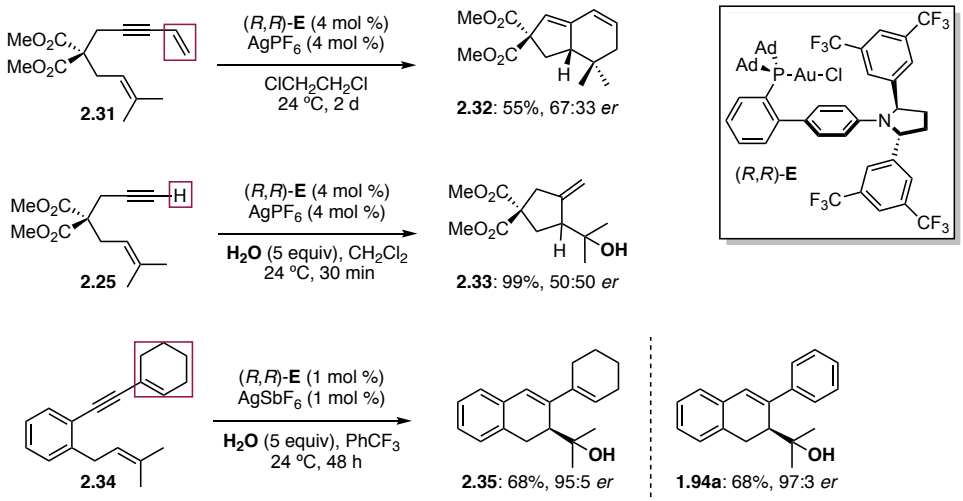
The simple catalyst design containing only one gold center and one single source of chirality allowed for the systematic investigation of the mode of stereoinduction. The geometrical arrangement of enynes **1.2**, **1.91**, and **1.93** together with their specific chiral folding inside the active catalyst define the outcoming absolute configuration in **1.6**, **1.92**, and **1.94** (Scheme 2.9). The stereodetermining step in the cyclizations of 1,6-enynes **1.2**, **1.91** and **1.93** is the formation of the corresponding cyclopropyl gold(I) carbenes **2.28**, **2.29** and **2.30**. As a logic consequence of the observed absolute stereoselectivities, the formation of **1.6** and **1.92** occurs through the preferential reaction of the (η^2-alkyne)gold(I) complex with the *Si* prochiral face of the alkene. Conversely, 1,6-enyne **1.93** is accommodated inside the chiral pocket of the catalyst in such a way that reaction at the alkene *Re* face is favored. This indicates that, despite their structural analogy, **1.2** and **1.93** must adopt distinct geometrical arrangements when coordinated to gold(I).



Scheme 2.9. Stereodirecting elements in 1,6-enynes **1.2**, **1.91**, and **1.93**.

Our working hypothesis is that, in the case of 1,6-enynes **1.2** and **1.91** the aryl group at carbon C1 is the stereocontrolling element. In contrast, the aryl group at the tether in enyne **1.93** would be the element of stereocontrol in the formation of products **1.94**.

To verify our hypothesis, we performed control experiments with dienyne **2.31** in which the aromatic substituent at the alkyne is replaced by an alkene (Scheme 2.10). In agreement with our expectations, cycloadduct **2.32** was obtained with modest 67:33 *er*, presumably due to weaker interactions between the substrate and the catalyst. Furthermore, hydroxycyclization of 1,6-enyne **2.25** bearing a terminal alkyne afforded **2.33** as a racemic mixture. On the other hand, 1,6-enyne **2.34** bearing a cyclohexenyl instead of an aryl group at the alkyne gave dihydronapthalene **2.35** in essentially the same yield and enantioselectivity obtained for **1.94a**.



Scheme 2.10. Control experiments.

The absolute configuration in **2.35** was assigned by correlation with those of **1.94a** by circular dichroism (Figure 2.1). The CD-spectra of chiral dihydronaphthalenes **1.94a** and **2.35** were measured in MeCN and show a negative Cotton effect around 240 nm.

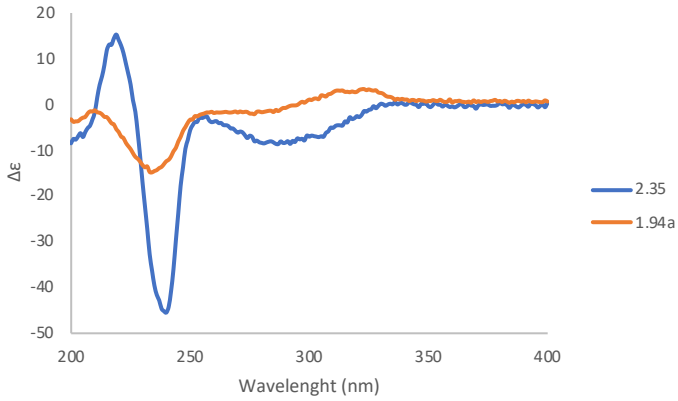
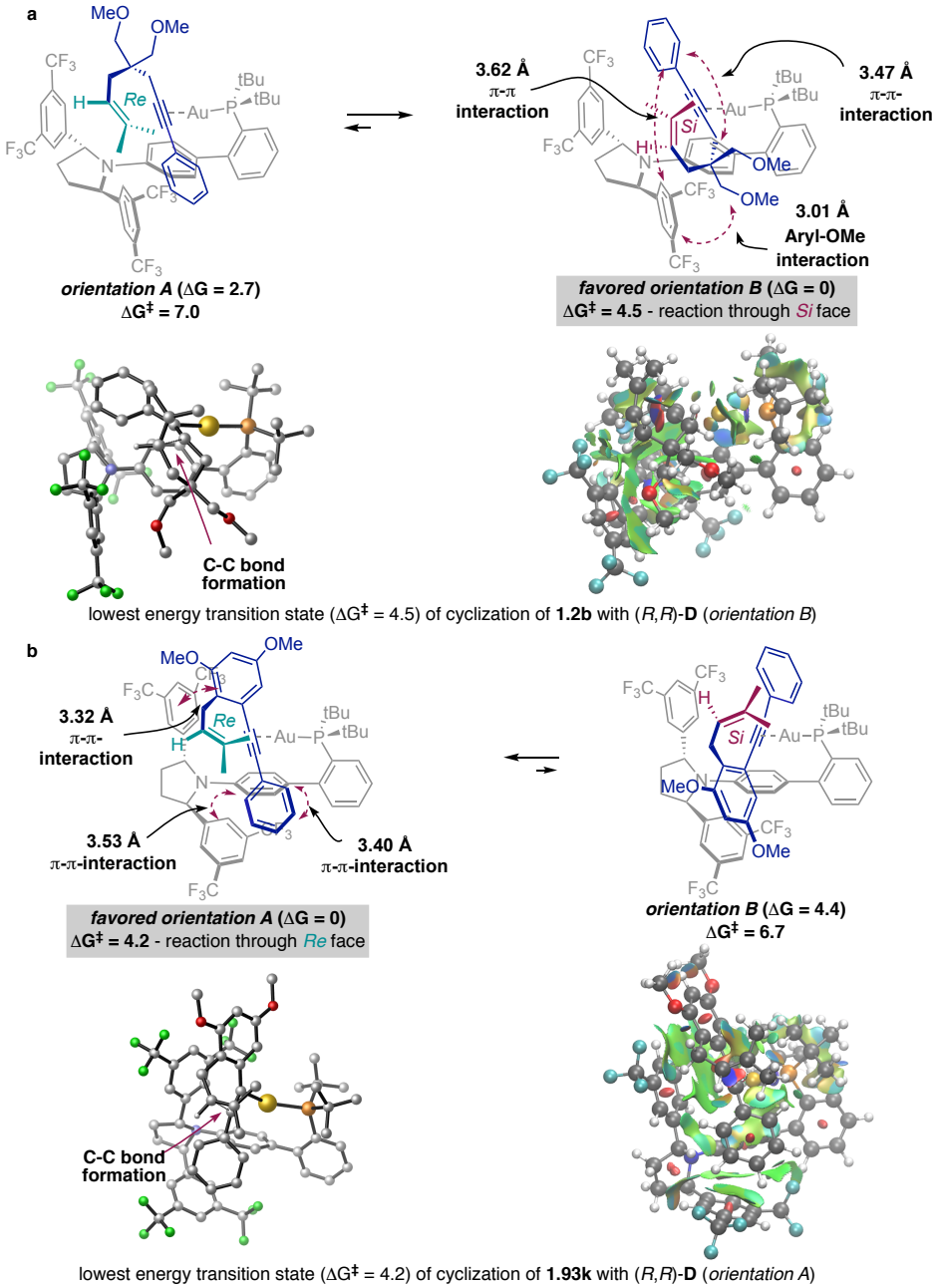


Figure 2.1. Superimposed CD-spectra of compounds **1.94a** and **2.35**.

We studied the cyclizations of **1.2b** and **1.93k** theoretically performing DFT calculations (BP86-D3/6-31G(d) (C, H, P, O, F, N) and SDD (Au), PCM = CH_2Cl_2) using catalyst (*R*,*R*)-**D** which gave similar results compared to the best catalyst (*R*,*R*)-**E**.[162] The observed enantioselectivities can originate from the combination of two different binding orientations (*A* and *B*) of the substrate bound to the gold through the alkyne and the two enantiotopic faces (*Re* and *Si*) of the olefin (Scheme 2.11). Hence, for both cyclizations four minima were calculated. In agreement with our experimental results, enyne **1.2b** reacts preferentially through the *Si* prochiral face of the alkene resulting in the formation of the *R* enantiomer whereas the absolute configuration *S* in dihydronaphthalene **1.94k** arises from the reaction of the *Re* face of the alkene. In both cases, the lowest energy transitions states were achieved from the corresponding most stable binding orientations (*B* for **1.2b** and *A* for **1.93k**). As visualized by NCI plots, attractive non-covalent interactions between stereodirecting aromatic components of the substrates and the aromatic substituents of the distal chiral pyrrolidine in complex (*R*,*R*)-**D** are the key players for the stabilization of the favored binding orientations and the corresponding transition states. Additional stabilization is provided by π-π-interactions between the substrates and the bottom ring of the biphenyl scaffold of the ligand. Thus, substrate recognition by the chiral catalyst induces one specific binding orientation stabilized by non-covalent interactions that leads to a particular enantioselective folding and consequentially, to the observed absolute configuration.[163] The complete energy diagrams including all the calculated transition states can be found in the experimental section of this chapter.

162. The DFT calculations have been performed by Imma Escofet.
163. (a) Neel, A. J.; Hilton, M. J.; Sigman, M. S.; Toste, F. D. *Nature* **2017**, *543*, 637−646. (b) Toste, F. D.; Sigman, M. S.; Miller, S. J. *Acc. Chem. Res.* **2017**, *50*, 609−615.

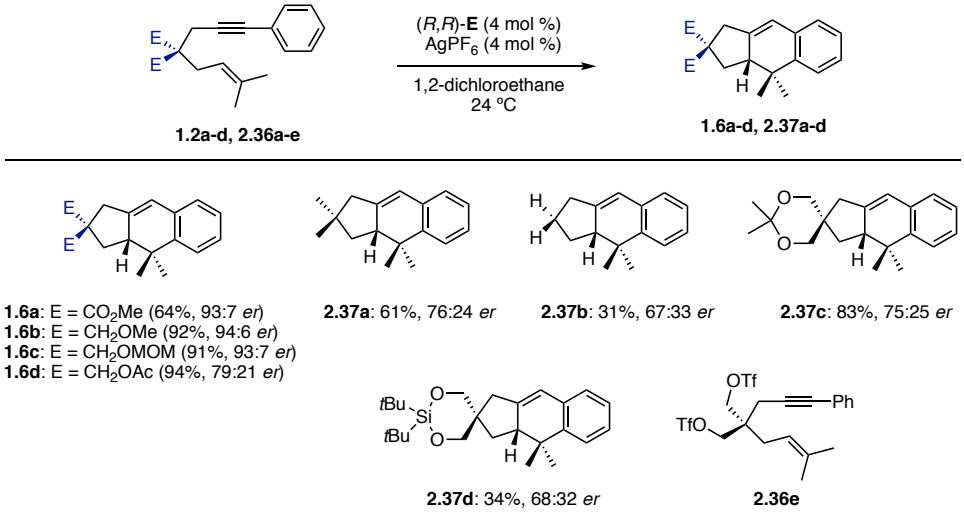


Scheme 2.11. Two most relevant binding orientations (*A* and *B*) of enynes a) **1.2b** and b) **1.93k** coordinated to (*R*,*R*)-**D** and lowest energy transitions states (CYLview representations and NCI plots). Energy values are given in kcal·mol^{-1} relative to the most stable orientation. Hydrogen atoms are omitted for clarity, with the exception of the stereocenters. Strong attractive interactions are blue (C−C bond formation), weak attractive interactions are green (non-covalent interactions), and strong repulsive interactions are red. Color code: P, orange; Au, yellow; F, cyan; O, red; C, gray; and H, white.

In the cyclization of substrate **1.2b** we found that MeO-aryl interactions further contribute to the stabilization of the transition state (Scheme 2.11a). This observation is consistent with the lower enantioselectivities obtained for diacetate **1.6d** (Table 2.1). Presumably, the more electron withdrawing OAc groups interact weakly with the aromatic substituents of the chiral pyrrolidine resulting in a drop in enantioselectivity.

Guided by this finding, we performed a structure-reactivity study modulating the tethering moiety in enynes **2.36a-e** undergoing formal [4+2] cycloaddition. Indeed, we confirmed that both the electronic and steric properties of the tether are crucial for an optimal reaction outcome. Replacing the Me-protected diols in **1.2b** with gem-dimethyl substituents induced a drop in enantiomeric ratio affording compound **2.37a** with 76:24 *er*. This result reinforces that stabilizing attractive MeO-aryl interactions play an important role in the stereoselective folding of enyne **1.2b**. In line with this trend, compound **2.37b** synthesized from the corresponding linear enyne **2.36b** was isolated in 31% yield and 67:33 *er*.

Table 2.1. Structure reactivity study and unreactive enynes.



Compounds **2.37c** and **2.37d**[133] with cyclic dimethyl acetal and cyclic bis-*tert*butylsilyl ether, respectively, were obtained with moderate enantioselectivities (68:32 and 75:25 *er*). We assume that the particular shape and bulkiness of the tethers prevents enynes **2.36c** and **2.36d** to adopt the desired binding orientation in the chiral pocket and consequentially, a less efficient enantiodiscrimination occurs. Finally, enyne **2.36e** was unreactive in presence of (*R*,*R*)-**E**, presumably as a result of the deactivation of the alkyne by the strongly electron withdrawing triflates.

We also investigated the proposed non-covalent interactions between stereodirecting moieties in enynes **1.2** and **1.93** and the ligand performing a Hammett study.[164] In the case of enynes **1.2** we plotted log(*er*) versus σ^{+}_{p} resulting in a negative slope $\rho = -0.26$, which confirms the preferential binding of the most electron rich substrates to the catalyst that bears electron deficient bis(trifluoromethyl)phenyl substituents at the chiral pyrrolidine (Figure 2.2). It is important to note the data point corresponding to **1.2g** (R = *t*Bu) was not considered for the linear regression, since Hammett parameters do not account for steric factors.[165] In this case, the key attractive interactions between substrate and ligand are disfavored because of the bulkiness of the *t*Bu substituent, thus giving **1.6g** in lower *er*.

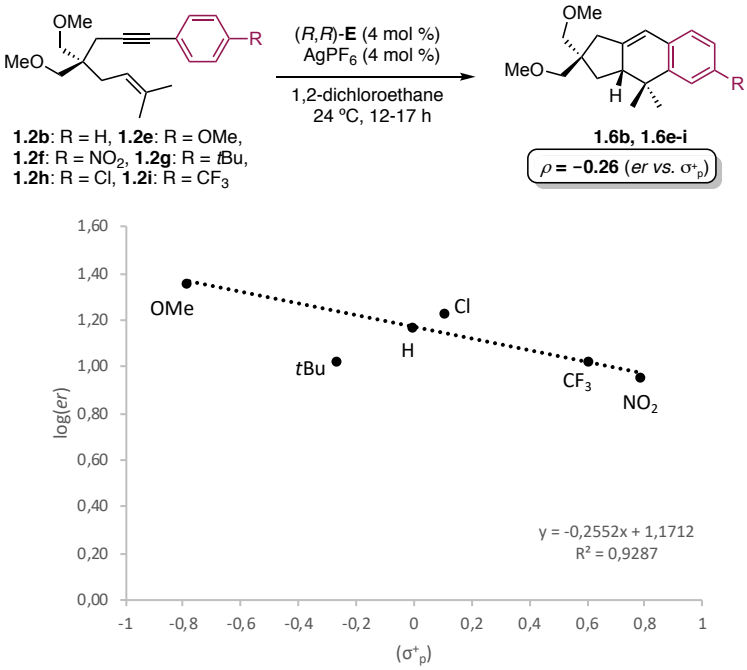


Figure 2.2. Hammett study of the formal [4+2] cycloaddition catalyzed by (*R*,*R*)-**E**.

Similarly, a Hammett correlation of log(*er*) with σ^{+}_{m} for the formation of 1,2-dihydronaphthalenes **1.94** also confirmed the dependence of the *er* on the electronic properties of the aromatic tether giving a negative slope $\rho = -0.62$ (Figure 2.3).

164. Hammett, L. P. *J. Am. Chem. Soc.* **1937**, *59*, 96–103.
165. (a) Milo, A.; Elizabeth, N. B.; Sigman, M. S. *Nature* **2014**, *507*, 210–215. (b) Santiago, C. B.; Milo, A.; Sigman, M. S. *J. Am. Chem. Soc.* **2016**, *138*, 13424-13430.

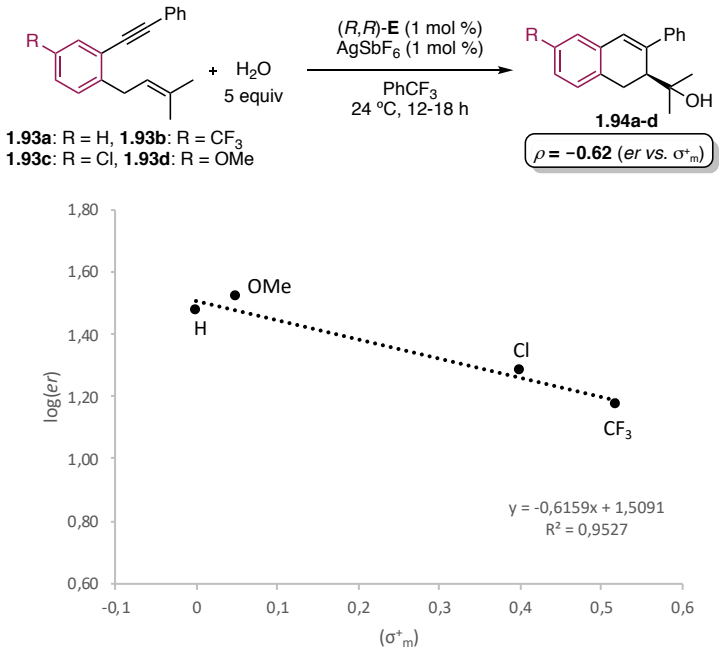
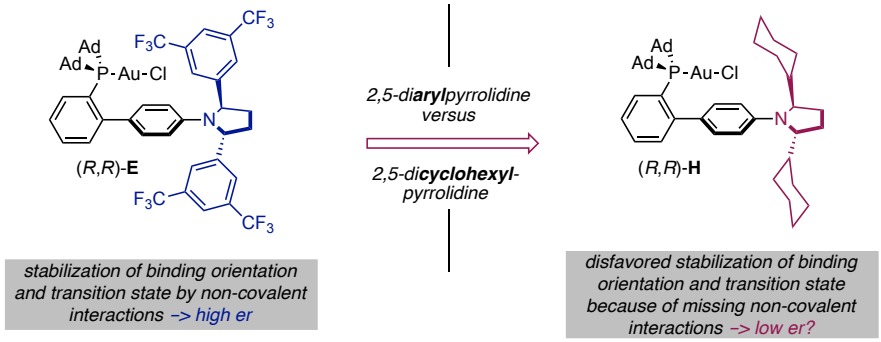


Figure 2.3. Hammett study for formation of 1,2-dihydronaphthalenes **1.94**.

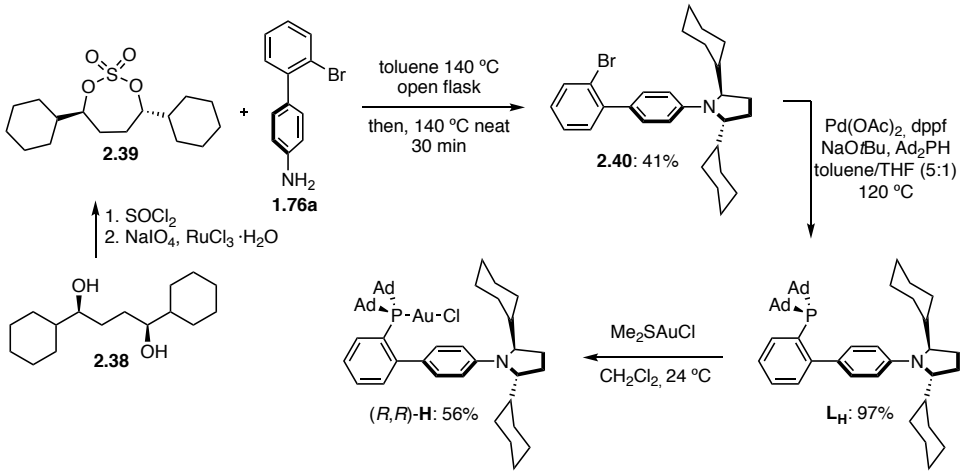
To provide further evidence for the proposed π-π-interactions we envisioned to replace the remote *trans*-2,5-diarylpyrrolidine by a *trans*-2,5-dicyclohexylpyrrolidine in complex (*R*,*R*)-**H** (Scheme 2.12). Hence, we expected that the stabilizing interactions and consequentially the optimal substrate orientation observed with (*R*,*R*)-**D**/**E** would be disfavored and products **1.6** and **1.94** would form in lower enantiomeric ratios.



Scheme 2.12. Modification of chiral C_2-symmetric pyrrolidine.

The synthesis of complex (*R*,*R*)-**H** was accomplished following a slightly modified route as described in **Chapter 1**. 1,4-Dicyclohexyl diol **2.38**, synthesized according to the

same protocol used for the preparation of 1,4-diols **1.86a-c** (see **Chapter 1**), was converted to cyclic sulfate **2.39**[166] (Scheme 2.13). Reaction of cyclic sulfate **2.39** with aniline **1.76a** led to Pyrrolidinyl-biphenyl bromide **2.40** in 41% yield adapting a reported procedure[167]. Finally, (*R*,*R*)-**H** was obtained via Pd-catalyzed coupling giving $\mathbf{L_H}$, followed by complexation with [Me_2SAuCl].

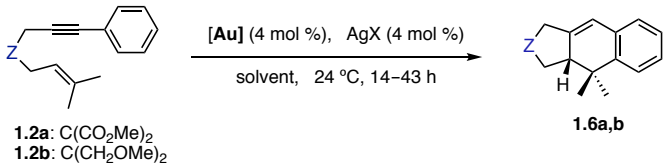


Scheme 2.13. Synthesis of (*R*,*R*)-**H**.

We studied the performance of (*R*,*R*)-**H** in the cyclization of enynes **1.2a,b**. In contrast to our predictions, (*R*,*R*)-**H** gave fused tricyclic compound **1.6a** with good 87:13 *er* and *R* absolute configuration (Table 2.2, entry 1). In comparison, employing (*S*,*S*)-**A** as the catalyst, which corresponds to the unsaturated analogue of (*R*,*R*)-**H** with opposite absolute configuration, gave *ent*-**1.2a** with lower 20:80 *er* (Table 2.2, entry 2). Complex (*R*,*R*)-**C** with *trans*-2,5-perfluorophenyl substituents at the pyrrolidine performed similarly to (*R*,*R*)-**H** giving **1.2a** with comparable 85:15 *er* (Table 2.2, entry 3). As shown before, the best results were obtained with (*R*,*R*)-**E**, affording **1.6a** with 90:10 *er* (Table 2.2, entry 4).

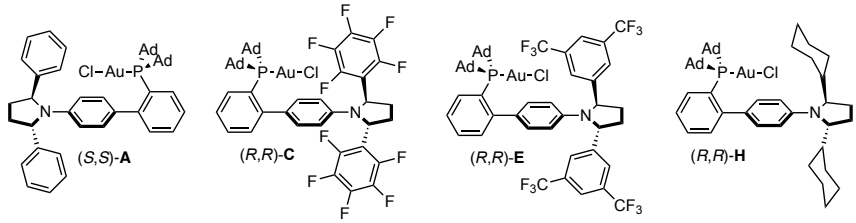
166. **2.39** was synthesized adapting a procedure from the literature: Burk, M. J.; Harper, T. G. P.; Kalberg, C. S. *J. Am. Chem. Soc.* **1995**, *117*, 4423−4424.
167. Sprott, K. T.; Corey, E. J. A. *Org. Lett.* **2003**, *5*, 2465–2467.

Table 2.2. Performance of (*R*,*R*)-**H** in the [4+2] cycloaddition of enynes **1.2**.



entry	enyne	[Au]	X	solvent	yield (%)[a]	*er*
1	**1.2a**	(*R*,*R*)-**H**	NTf_2	CH_2Cl_2	21[b]	87:13
2	**1.2a**	(*S*,*S*)-**A**	NTf_2	CH_2Cl_2	75	20:80
3	**1.2a**	(*R*,*R*)-**C**	NTf_2	CH_2Cl_2	93	85:15
4	**1.2a**	(*R*,*R*)-**E**	NTf_2	CH_2Cl_2	56	90:10
5	**1.2b**	(*R*,*R*)-**H**	PF_6	1,2-dichloroethane	90	70:30
6	**1.2b**	(*R*,*R*)-**E**	PF_6	1,2-dichloroethane	92	94:6

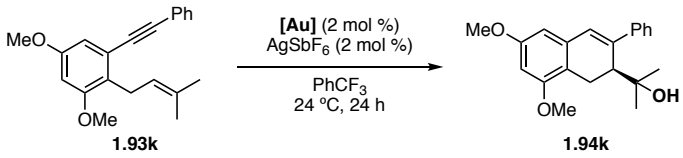
[a]Isolated yields. [b]41% brsm.



Complex (*R*,*R*)-**H** was less efficient in the cyclization of enyne **1.2b** giving **1.6b** with modest 70:30 *er*, whereas under comparable reaction conditions (*R*,*R*)-**E** gave **1.6b** with 94:6 *er* (Table 2.2, entries 5 and 6).

We also tested the performance of (*R*,*R*)-**H** in the 6-*endo*-dig hydroxycyclization of enyne **1.93k**. 1,2-Dihydronaphthalene **1.94k** was obtained with the same absolute *S* configuration as with our best catalyst (*R*,*R*)-**E** with good enantiomeric ratio and yield (89:11 *er*, 53%) (Table 2.3, entries 1 and 2). Comparing the performance of (*R*,*R*)-**H** with other catalysts showed the same trend observed in the [4+2] cycloaddition of enynes **1.2a,b** proceeding by an initial 5-*exo*-dig cyclization. Catalyst (*S*,*S*)-**A** with diphenyl substituents at the chiral pyrrolidine was less efficient (23:77 *er*) (Table 2.3, entry 3). On the other hand, (*R*,*R*)-**C** leads to **1.94k** with comparable 88:12 *er* (Table 2.3, entries 1 and 4).

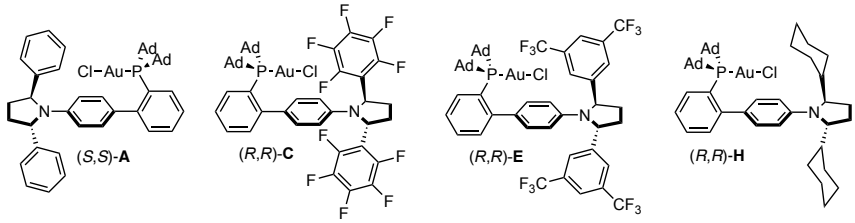
Table 2.3. Performance of (*R*,*R*)-**H** in cyclization of enyne **1.93k**.



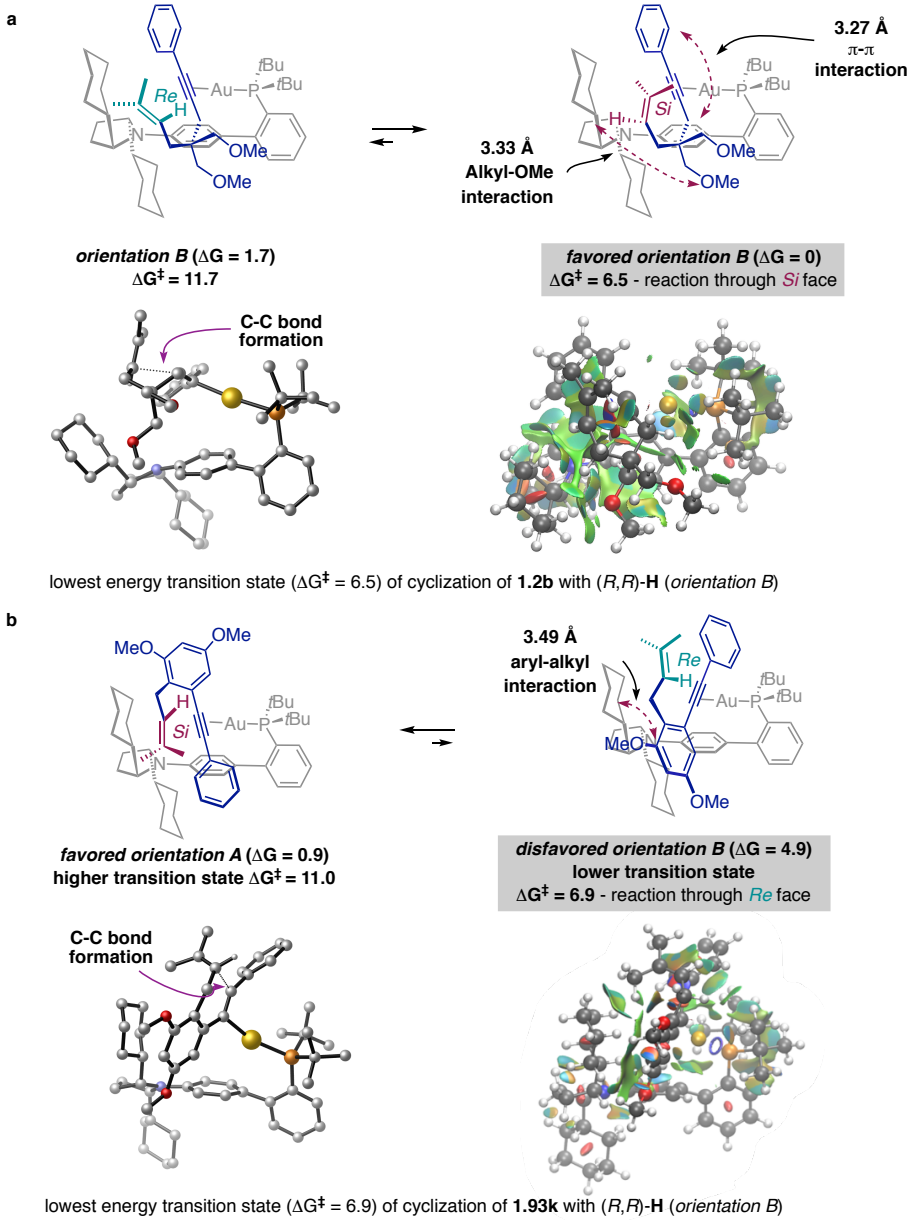
1.93k **1.94k**

entry	[Au]	yield (%)[a]	*er*
1	(*R*,*R*)-**H**	53	89:11
2	(*R*,*R*)-**E**	60	98:2
3	(*S*,*S*)-**A**	52	23:77
4	(*R*,*R*)-**C**	48	88:12

[a]Isolated yields.



To provide further understanding of the mode of action of (*R*,*R*)-**H**, we performed DFT calculations (BP86-D3/6-31G(d) (C, H, P, O, F, N) and SDD (Au), PCM = CH_2Cl_2) of both cyclizations using modified (*R*,*R*)-**H**' with di-*tert*-butylphosphine (Scheme 2.14).[162] Similarly, four minima were calculated considering two possible binding orientations of the substrate bound to gold through the alkyne (*A* and *B*) and the two prochiral faces (*Re* and *Si*) of the olefin. As found for the reaction with (*R*,*R*)-**D**, the cyclization of **1.2b** evolves via the most stable binding orientation *B* and the corresponding lowest energy transition state favoring reaction through the *Si* prochiral face of the alkene which results in the observed *R* absolute configuration in **1.6b** (Scheme 2.14a). Interestingly, the calculations with (*R*,*R*)-**H**' predict that the competing pathway (formation of *S* enantiomer) also evolves through binding orientation *B*. In addition to the previously discussed stabilizing attractive π-π-interactions between the arylalkyne moiety in **1.2b** and the bottom ring of the biphenyl scaffold, NCI plots provided evidence for stabilizing alkyl-MeO interactions (3.33 Å) between the cyclohexyl substituents of the chiral pyrrolidine and the substrate (Scheme 2.14a).

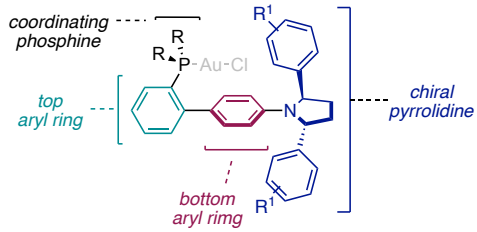


Scheme 2.14. Most relevant binding orientations (*A* and *B*) of a.) enynes **1.2b** and b.) **1.93k** coordinated to catalyst (*R*,*R*)-**H'** and lowest energy transitions states (NCI plots). Energy values are given in kcal·mol^{-1} relative to the most stable orientation. Hydrogen atoms are omitted for clarity, with the exception of the stereocenters. Strong attractive interactions are blue (C−C bond formation), weak attractive interactions are green (non-covalent interactions), and strong repulsive interactions are red. Color code: P, orange; Au, yellow; F, cyan; O, red; C, gray; and H, white.

For the cyclization of enyne **1.93k** our computational work predicts the reaction to proceed via binding orientation *B* despite being 4.9 kcal·mol^{-1} less stable than orientation *A* (Scheme 2.14b). The lowest transition state ($\Delta G^{\ddagger}$ = 6.9 kcal·mol^{-1}) is achieved via orientation *B* favoring reaction through the *Re* prochiral face of the alkene, thus leading to the formation of the observed *S* enantiomer of **1.94k** following a Curtin-Hammett scenario. Short distances between the cyclohexyl substituents of the ligand and the electron rich aryl tether in **1.93k** suggest that attractive aryl-alkyl interactions[168] to play an important role in the stabilization of the transition state. These interactions were also visualized with NCI plots. The complete energy diagrams including all the calculated transition states can be found in the experimental section of this chapter.

Analysis of the Ligand Design

To understand the working mode of our complexes, we dissected the ligand design in four parts and examined. These parts were identified as the chiral pyrrolidine, the bottom and the top aryl rings of the biaryl scaffold, and the coordinating phosphine (Scheme 2.15).



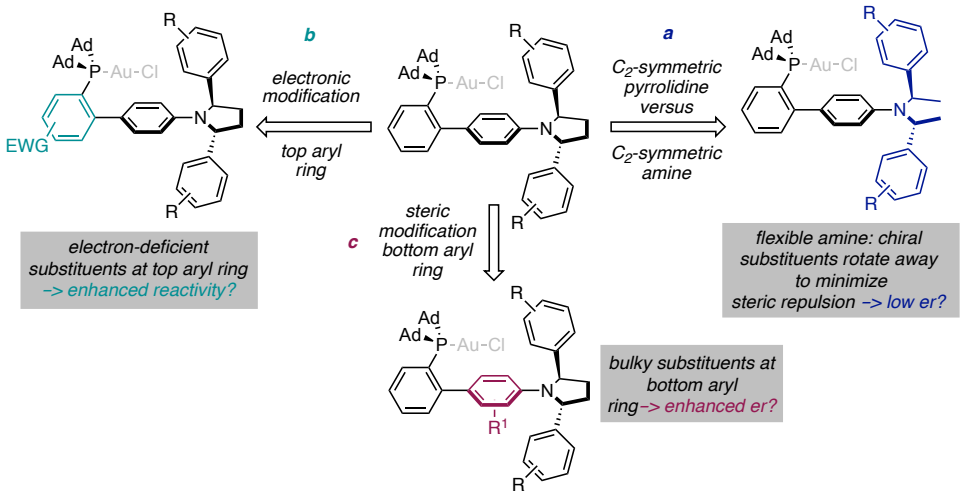
Scheme 2.15. Dissecting the ligand design.

We analyzed the single components of our ligand design synthesizing a 2nd generation of chiral biphenyl phosphine-supported complexes. Then, we examined the performance of each of the new catalysts in the formal [4+2] cycloaddition of enyne **1.2b**. The effect of different bulky groups on the coordinating phosphine was already examined ((*R*,*R*)-**E** versus (*R*,*R*)-**D**) in **Chapter 1**. Additionally, Liming Zhang[169] showed on a comparable system that replacing the bulky diadamantyl phosphines by diphenyl phosphines facilitates the rotation around the C_{aryl}–P bond leading to a drop in enantioselectivity.

We reasoned that replacing the rigid pyrrolidine ring by acyclic C_2-symmetric amines would lead to a decrease in enantioselectivity as the chiral substituents experience a higher

168. Ribas, J.; Cubero, E.; Luque, F. J.; Orozco, M. *J. Org. Chem.* **2002**, *67*, 7057–7065.
169. Ji, K.; Zheng, Z.; Wang, Z.; Zhang, L. *Angew. Chem. Int. Ed.* **2015**, *54*, 1245–1249.

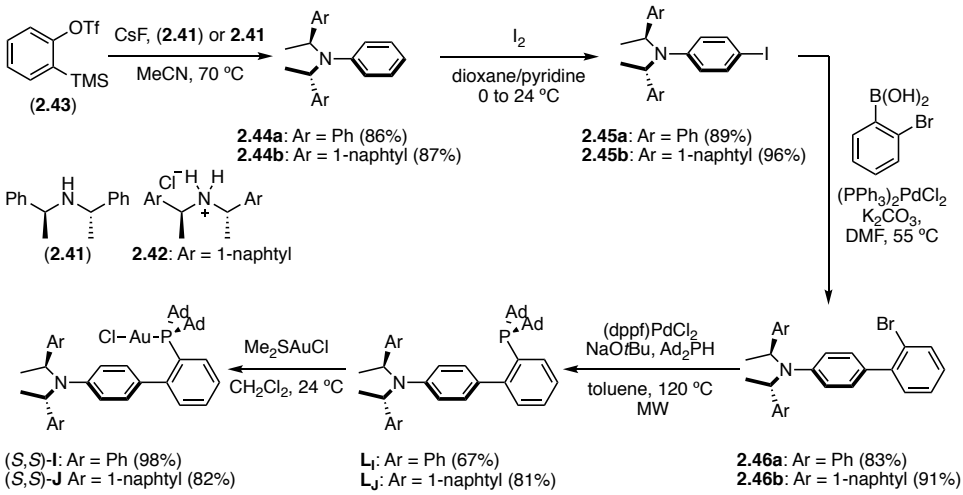
degree of flexibility (Scheme 2.16, path a). On the other hand, functionalization of the top aryl ring of the biphenyl scaffold with electron withdrawing substituents would change the electronic properties of the coordinating phosphine leading to enhanced electrophilicities of the corresponding gold(I) complexes (Scheme 2.16, path b). Finally, the introduction of substituents at the bottom aryl ring would provide additional steric bulk around the reactive center leading to higher enantioselectivities (Scheme 2.16, path c).



Scheme 2.16. Structural modifications of original ligand design.

We commenced our analysis replacing the C_2-symmetric pyrrolidine by chiral C_2-symmetric amines. The synthesis of these modified complexes (*S*,*S*)-**I** and (*S*,*S*)-**J** was carried out in 5 steps and is illustrated in scheme 2.17.[170] Phenylamines **2.44a**,**b** were synthesized in good yields (86-87%) from 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**2.43**) through *in situ* formation of benzyne[171] and nucleophilic addition of commercially available (*S*)-bis((*S*)-1-phenylethyl)amine (**2.41**) and hydrochloride **2.42**, respectively. Electrophilic iodination of **2.44a,b** gave **2.45a**,**b** (89-96%) which was followed by Pd-catalyzed Suzuki-Miyaura coupling afforded biphenylbromide precursors **2.46a,b** in good yields (83-91%). Complexes (*S*,*S*)-**I** and (*S*,*S*)-**J** were finally obtained by Pd-mediated formation of phosphine ligands $\mathbf{L_I}$ and $\mathbf{L_J}$ in 67-87% yield and subsequent complexation with [Me_2SAuCl].

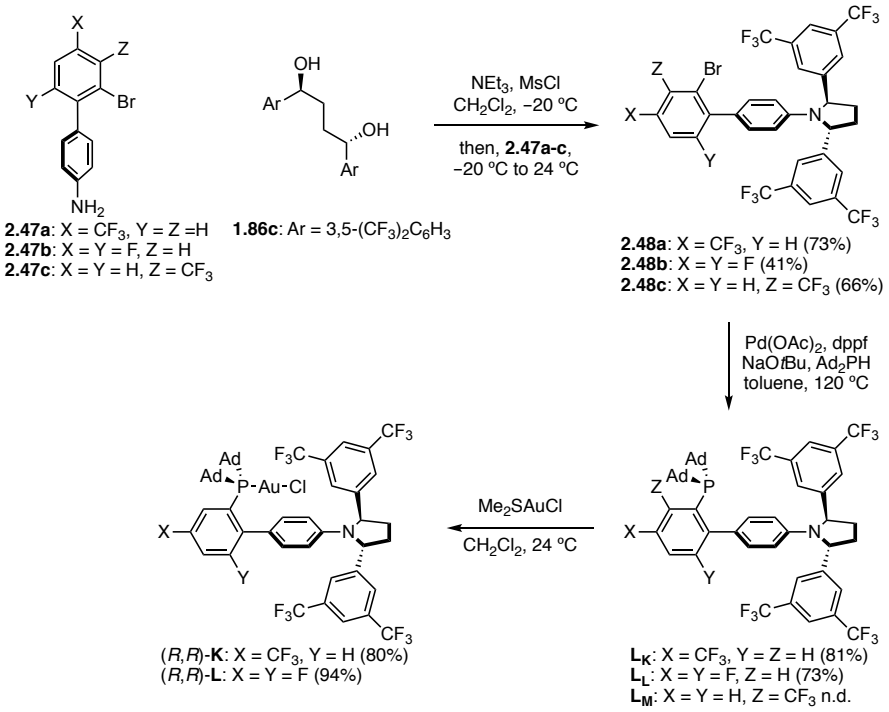
170. The synthesis of complexes (*S*,*S*)-**I** and (*S*,*S*)-**J** has been carried out by Dr. Leonardo J. Nannini.
171. (a) Takikawa, H.; Nishii, A.; Sakai, T.; Suzuki, K. *Chem. Soc. Rev.* **2018**, *47*, 8030–8056. (b) Tadross, P. M.; Stoltz, B. M. *Chem. Rev.* **2012**, *112*, 3550–3577. (c) Gampe, C. M.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2012**, *51*, 3766–3778.



Scheme 2.17. Synthesis of (*S*,*S*)-**I** and (*S*,*S*)-**J**.

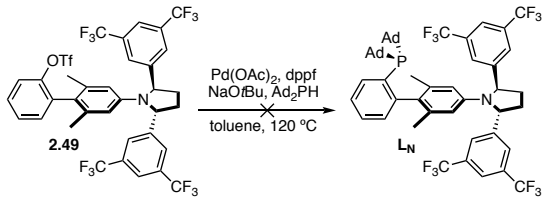
The modifications on the top aryl ring were performed following the same synthetic route discussed in **Chapter 1** starting from biphenyl anilines **2.47a-c**[172] (Scheme 2.18). However, the synthesis of ligand $\mathbf{L_M}$ could not be achieved as no conversion of precursor **2.48c** in the Pd-catalyzed introduction of the diadamantyl phosphine moiety was observed. Presumably, steric hindrance arising from the *o*-trifluoromethyl substituent prevents oxidative addition to take place.

172. See Experimental section.



Scheme 2.18. Synthesis of (*R*,*R*)-**K** and (*R*,*R*)-**L**.

Similarly, the synthesis of ligand $\mathbf{L_N}$ with a modified bottom aryl ring was unsuccessful (Scheme 2.19). Although we prepared 2',6'-dimethyl-biphenyl precursor **2.49** following a similar synthetic route the introduction of the bulky phosphine was unsuccessful presumably due to the steric hindrance provided by the methyl substituents.

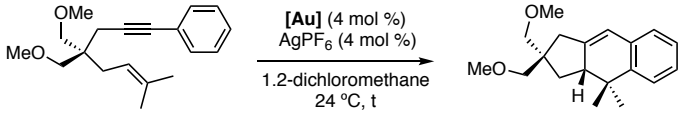


Scheme 2.19. Unsuccessful Pd-catalyzed phosphine coupling.

Next, we tested the performance of the obtained complexes in the cyclization of enyne **1.2b** (Table 2.4). In general, the entire series of 2nd generation complexes gave expected product **1.6b** in good to excellent yields (83-97%). However, complexes (*S*,*S*)-**I** and (*S*,*S*)-**J** gave **1.6b** essentially as a racemic mixture (Table 2.4, entries 2 and 3). As anticipated, the acyclic C_2-symmetric amines in (*S*,*S*)-**I** and (*S*,*S*)-**J** lack in rigidity and the chiral substituents rotate away from the reaction center to minimize steric repulsion

resulting in poor enantioinduction. In agreement with our predictions, complexes (*R*,*R*)-**K** and (*R*,*R*)-**L** containing electron-deficient substituents at the top aryl ring of the corresponding ligands gave **1.6b** with comparable 93:7 *er* although in much shorter reaction timea (Table 2.4, entry 1 versus 4 and 5).

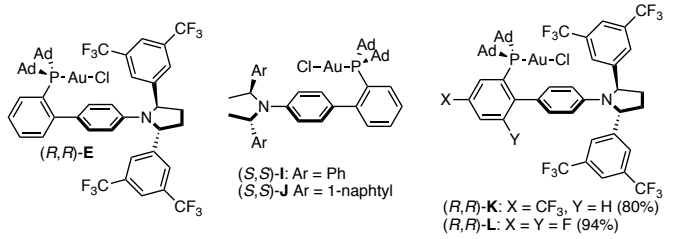
Table 2.4. Comparison of 2nd generation complexes.



1.2b 1.6b

entry	[Au]	t (*h*)	yield (*%*)[a]	*er*
1	(*R*,*R*)-**E**	16	92	94:6
2	(*S*,*S*)-**I**	6	84	51:49
3	(*S*,*S*)-**J**	6	83	48:52
4	(*R*,*R*)-**K**	35 min	97	93:7
5	(*R*,*R*)-**L**	2	95	93:7

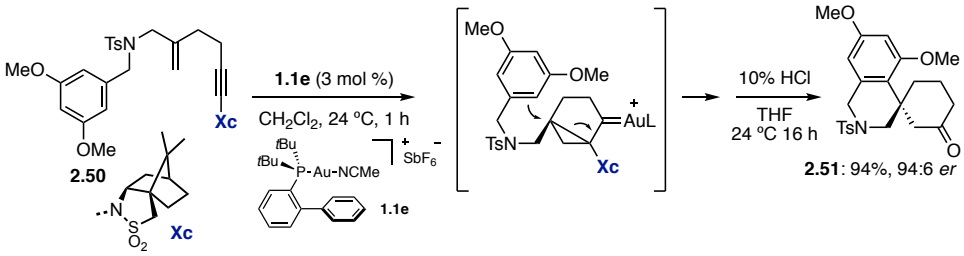
[a]Isolated yields.



Enantioselective Synthesis of Spirofused Vinyl Bromides

Recently, our group has reported gold(I)-catalyzed cyclizations of polyenynes in which the activation of terminal alkynes or bromoalkynes triggers the cascade process leading to the synthesis of steroid-like molecules. In these transformations up to four carbon–carbon bonds were built in a highly stereoselective manner in one single step.[121] However, only poor enantioselectivities were achieved using chiral catalysts. To circumvent this limitation, our group developed a diastereoselective process based on a 5-*endo*-dig cyclization of 1,5-enynes **2.50** containing chiral auxiliaries such as the Oppolzer's sultam.[173] Upon hydrolysis, chiral spirofused ketones **2.51** are obtained (Scheme 2.20).

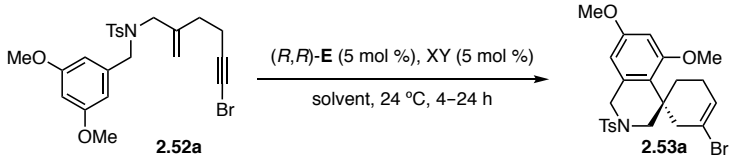
173. (a) Oppolzer, W.; Chapuis, C.; Bernardinelli, G. *Helv. Chim. Acta* **1984**, *67*, 1397. (b) Heravi, M. M.; Zadsirjan, V. *Tetrahedron: Asymmetry* **2014**, *25*, 1061.



Scheme 2.20. Diastereoselective synthesis of spirofused ketones.

Owing to the success obtained with our family of pyrrolidinyl-biphenyl phosphine-supported complexes, we envisioned to study their performance in the preparation of similar spirofused compounds. Because our catalysts perform better with disubstituted alkynes, we chose the cyclization of 1-bromo-1,5-enyne **2.52a** giving vinylbromide **2.53a** (Table 2.5).[174] Preliminary reaction optimization with (*R*,*R*)-**E** established $AgSbF_6$ and chlorobenzene as the combination of choice affording **2.53a** with good 82:18 *er* (Table 2.5, entry 7). Despite the promising results, extensive solvent screening did not improve the enantioselectivity of the reaction (Table 2.5, entries 9-18).

Table 2.5. Preliminary reaction optimization.



entry	XY	solvent	conversion (%)	*er*
1	$AgSbF_6$	CH_2Cl_2	100	70:30
2	$AgBF_4$	PhMe	100	65:35
3	$AgSbF_6$	$PhCF_3$	100	76:24
4	$NaBAr^F{}_4$	$PhCF_3$	-[a]	70:30
5	$AgNTf_2$	$PhCF_3$	100	72:28
6	AgOTf	$PhCF_3$	100	63:37
7	$AgSbF_6$	C_6H_5Cl	100	82:18
8	$AgSbF_6$	xylenes	-	80:20
9	$AgSbF_6$	C_6H_6	100	81:19
10	$AgSbF_6$	*o*-xylene	-	80:20
11	$AgSbF_6$	*p*-xylene	100	78:22
12	$AgSbF_6$	1,2-dichlorobenzene	100	76:24

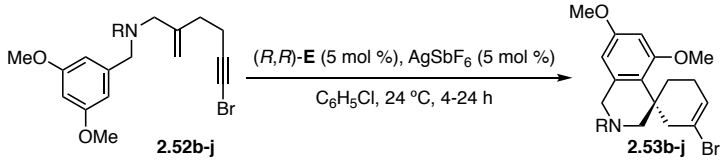
174. The optimization of reaction conditions was carried out in collaboration with Dr. Guilong Tian.

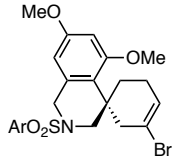
13	$AgSbF_6$	1,3-dichlorobenzene	100	78:22
14	$AgSbF_6$	C_6H_5Br	100	81:19
15	$AgSbF_6$	$Cl(CH_2)_2Cl$	100	64:36
16	$AgSbF_6$	$Cl_2(CH)_2Cl_2$	100	68:32
17	$AgSbF_6$	C_6H_5Cl:HFIP (10:1)	100	67:33
18	$AgSbF_6$	heptane	100	69:31

[a]Traces of product.

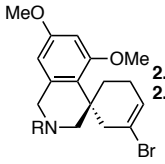
We reasoned that modifying the sulfonyl amide in **2.52a** could have a beneficial effect on the enantioselectivity, as found for the synthesis of azabicyclo[4.1.0]hept-4-enes **1.92** discussed in **Chapter 1**. Indeed, an important impact on yield was observed upon modifying the electronic and steric properties of the corresponding sulfonyl amides in **2.52b-j** (Table 2.6). Nonetheless, the enantioselectivities remained unsatisfactory.

Table 2.6. Reaction scope.





2.53b: Ar = 2-$NO_2C_6H_4$, 88%, 83:17 *er*
2.53c: Ar = 4-$CF_3C_6H_4$, 74%, 80:20 *er*
2.53d: Ar = 4-FC_6H_4, 90%, 81:19 *er*
2.53e: Ar = C_6H_5, 90%, 77:23 *er*
2.53f: Ar = 4-$OMeC_6H_4$, 85%, 79:21 *er*
2.53g: Ar = 2,4,6-(iPr)$_3C_6H_2$, 66%, 63:37 *er*
2.53h: Ar = 2,4,6-(Me)$_3C_6H_2$, 85%, 68:32 *er*



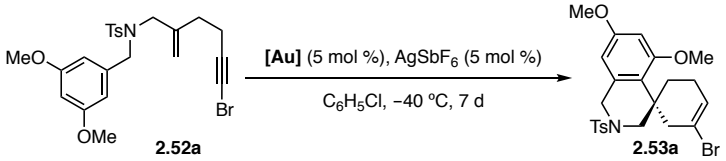
2.53i: R = Tf, 49%, 68:32 *er*
2.53j: R = Ms, 92%, 82:18 *er*

The best results were obtained with 1-bromo-1,5-enynes **2.52b-f** containing electronically-modified benzenesulfonyl amides and **2.52j** giving spirocyclic compounds **2.53b-f** and **2.53j** in 74-92% yield and 77:23-83:17 *er*. Products **2.53g,h** with sterically demanding sulfonyl amides as well as **2.53i** with strong electron-withdrawing triflimide were obtained in good 49-85% yield albeit with lower 63:37-68:32 *er*.

Thus, we continued the optimization studies with bromoenyne **2.52a** by lowering the temperature. At –40 ºC, **2.53a** was obtained with improved 91:9 *er* (Table 2.7, entry 1). However, only 20% of starting material was converted during 7 days reaction time and the remaining 1st generation catalysts gave the target product in lower enantioselectivities (Table 7, entries 2-6). The more active 2nd generation complex (*R*,*R*)-**K** was more effective

and gave **2.53a** in 61% (71% brsm) yield and with slightly improved enantiomeric ratio (92:8 *er*) (Table 2.7, entry 7).

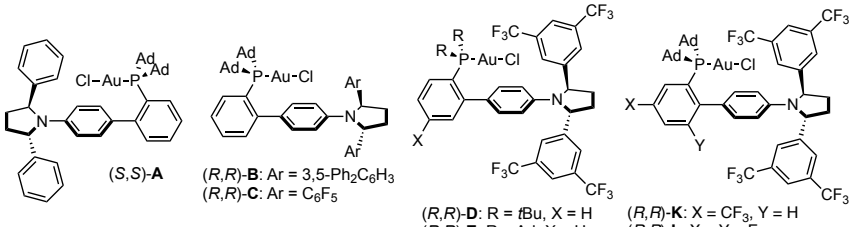
Table 2.7. Catalyst screening at –40 ºC.



2.52a **2.53a**

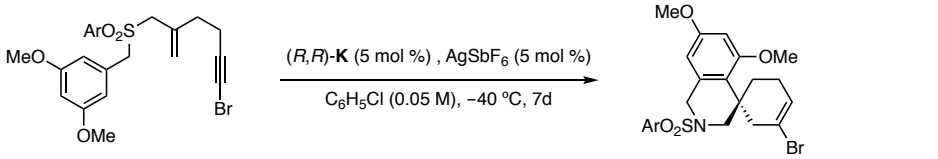
entry	[Au]	yield (%)	*er*
1	(*R*,*R*)-**E**	-[a]	91:9
2	(*S*,*S*)-**A**	n.d.[b]	39:61
3	(*R*,*R*)-**B**	n.d.	85:15
4	(*R*,*R*)-**C**	n.d.	74:26
5	(*R*,*R*)-**D**	n.d.	85:15
6	(*R*,*R*)-**F**	n.d.	90:10
7	(*R*,*R*)-**K**	61[c]	92:8
8	(*R*,*R*)-**L**	98[d]	82:18

[a]20% conversion. [b]n.d. = not determined, only traces. [c]71% brsm. [d]reaction run at 24 ºC.



We performed preliminary studies on the scope of this transformation using our optimized conditions modulating the sulfonyl amide component (Table 2.8). Spirofused vinylbromides **2.53a-d** were isolated in 18-61% yield and 90:10-92:8 *er*.

Table 2.8. Synthesis of spirofused vinyl bromides.

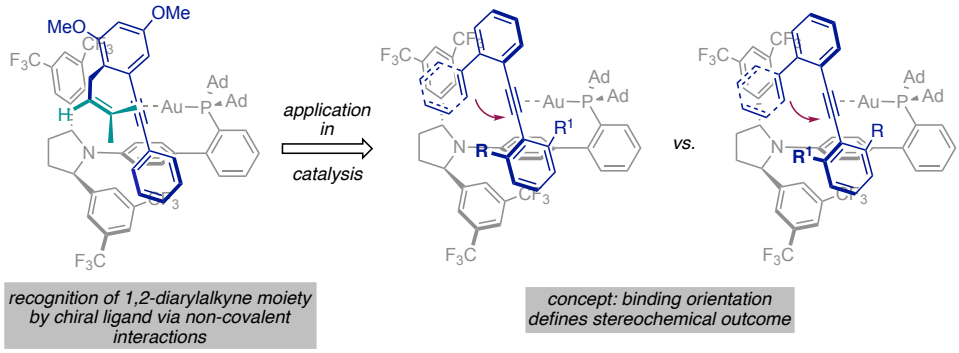


2.52a-d

2.53a: Ar = 4-MeC_6H_4, 61% (71% brsm), 92:8 *er*
2.53b: Ar = 2-$NO_2C_6H_4$, 18% (69% brsm), 90:10 *er*
2.53c: Ar = 4-$CF_3C_6H_4$, 47% (68% brsm), 92:8 *er*
2.53d: Ar = 4-FC_6H_4, 51% (80% brsm), 92:8 *er*

Synthesis of Axially-Chiral Biaryls

We also envisioned to approach the development of new asymmetric gold(I)-catalyzed transformations taking advantage of the specific mode of action and enantioinduction of our complexes. Their ability to recognize the 1,2-diarylalkyne moiety via stabilizing non-covalent interactions inducing a preferred binding orientation, represented an opportunity to develop the synthesis of axially-chiral biaryls via hydrofunctionalization of 1,2-disubstituted arylalkynes (Scheme 2.21). Conceptually, the stereochemical outcome would be defined prior to the hydrofunctionalization event by the preferred binding orientation, in which the catalyst discriminates between two conformers of the substrate.

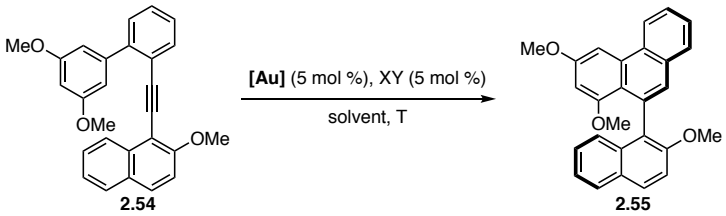


Scheme 2.21. Specific mode of enantioinduction applied in the development of new asymmetric transformations: synthesis of axially-chiral biaryls.

For preliminary studies we chose disubstituted 1-naphthyl-2-arylalkyne **2.54** as the model substrate.[175] Among the screened complexes, (*R*,*R*)-**K** performed best giving **2.55** with 70:30 *er* (Table 2.9, entry 4).

175. Kadoya, N.; Murai, M.; Ishiguro, M.; Uenishi, J.; Uemura, M. *Tetrahedron Lett.* **2013**, *54*, 512–514.

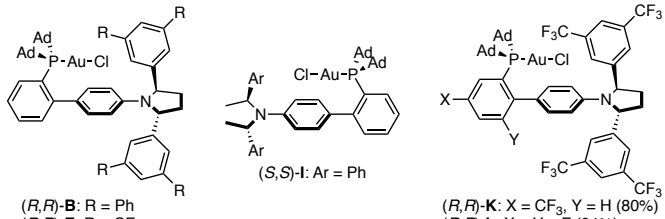
Table 2.9. Atroposelective hydroarylation of **2.54**.



2.54 **2.55**

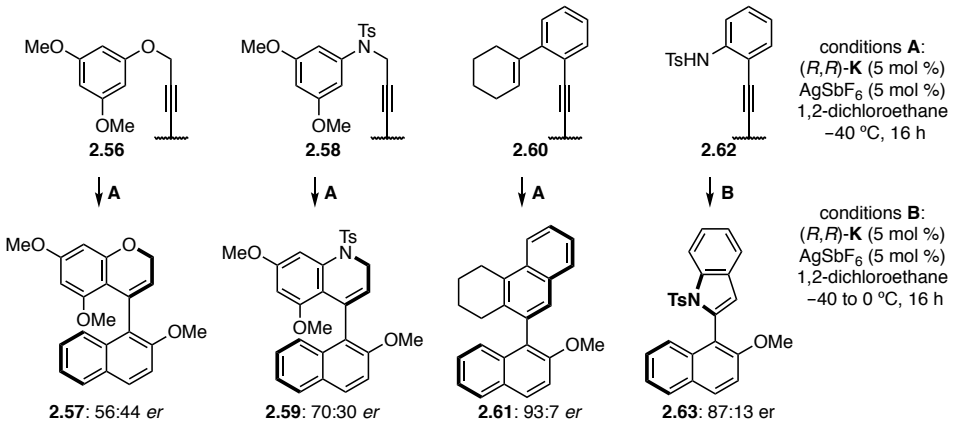
entry	[Au]	XY	solvent	T (ºC)	yield (%)[a]	*er*
1	(*R*,*R*)-**B**	$AgPF_6$	1,2-dichloroethane	24	n.d.[b]	50:50
2	(*R*,*R*)-**E**	$AgPF_6$	1,2-dichloroethane	24	n.d.	65:35
3	(*S*,*S*)-**I**	$AgNTf_2$	1,2-dichloroethane	24	n.d.	44:56
4	(*R*,*R*)-**K**	$AgPF_6$	1,2-dichloroethane	24	n.d.	70:30
5	(*R*,*R*)-**L**	$AgPF_6$	1,2-dichloroethane	24	n.d.	62:38
6	(*R*,*R*)-**K**	$AgPF_6$	1,2-dichloroethane	–40	n.d.	93:7
7	(*R*,*R*)-**K**	$NaBAr^F{}_4$	1,2-dichloroethane	–40	-[c]	-
8	(*R*,*R*)-**K**	$AgSbF_6$	1,2-dichloroethane	–40	88	94:6
9	(*R*,*R*)-**K**	$AgBF_4$	1,2-dichloroethane	–40	80	94:6
10	(*R*,*R*)-**K**	AgOTf	1,2-dichloroethane	–40	58	96:4
11	(*R*,*R*)-**K**	$AgNTf_2$	1,2-dichloroethane	–40	98	93:7
12	(*R*,*R*)-**K**	$AgSbF_6$	Toluene	–20	n.d.	74:26
13	(*R*,*R*)-**K**	$AgSbF_6$	EtOAc	–20	n.d.	83:17
14	(*R*,*R*)-**K**	$AgSbF_6$	2-chloropropane	–50	-[d]	95:5
15	(*R*,*R*)-**K**	$AgSbF_6$	CH_2Cl_2	–50	88[e]	96:4

[a]Yields determined by ^1H NMR using 1,3-benzodioxole as internal standard. [b]n.d. = not determined. Full conversion after 16 h. [c]Unreacted starting material. [d]20% conversion after 7 days reaction time. [e]Full conversion after 3 d reaction time.



Lowering the reaction temperature to –40 ºC resulted in a significantly improved 93:7 *er* (Table 2.9, entry 6). Using $AgSbF_6$ as the chloride scavenger gave the best compromise between chemical yield and enantiomeric ratio (88%, 94:6 *er*) (Table 2.9, entry 8), whereas no beneficial solvent effects were found (Table 2.9, entries 12-14). Finally, axially-chiral biaryl **2.55** was obtained in 88% yield and 96:4 *er* using (*R*,*R*)-**K** and $AgSbF_6$ in CH_2Cl_2 at –50 ºC (Table 2.9, entry 15).

To explore the limits of the atroposelective transformation we performed a structure-enantioselectivity relationship analysis maintaining the 1-ethynyl-2-methoxynaphthalene motif constant and changing the nucleophilic component (Scheme 2.22). The hydroarylation of propargyl ether **2.56** and tosyl amine **2.58** gave the corresponding products **2.57** and **2.59** with low enantiomeric ratios (56:44 and 70:30 *er*). However, 1,5-enyne **2.60** and tosyl aniline **2.62**, both containing the same 1,2-diarylalkyne motif, gave product of Friedel-Crafts-type reaction **2.61** and indole **2.63** in good 93:7 and 87:13 *er*, respectively. This study confirms that the 1,2-diarylalkyne moiety is recognized by the chiral catalyst and is essential to achieve high enantiomeric ratios.



Scheme 2.22. Structure-enantioselectivity relationship study. Yields not determined. Full conversion after 16 h.

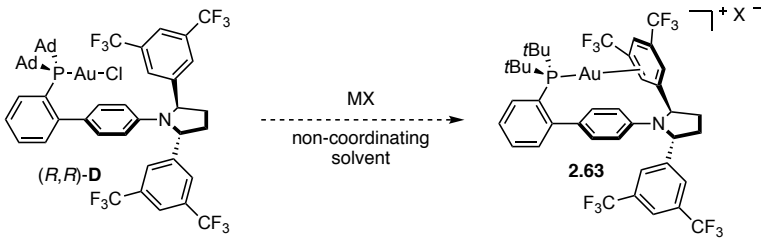
Future efforts will focus on expanding the scope of this transformations and on post functionalizations of the obtained axially-chiaral biaryls.

Mechanistic Insights on the Formal [4+2] Cycloaddition with (*R*,*R*)-D

Determination of the Catalytically Active Species

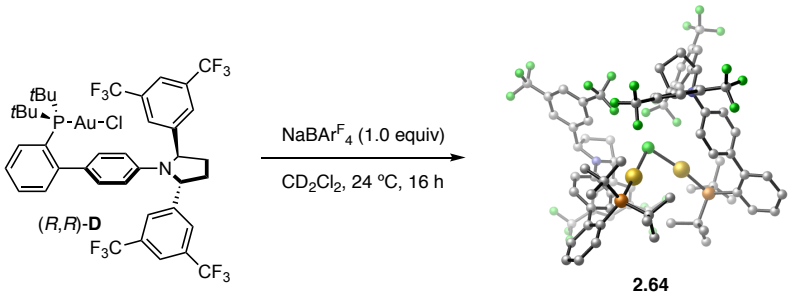
To gain further understanding on the working mode of our chiral complexes we studied the formal [4+2] cycloaddition reaction in more detail.

In view of the close proximity of the 3,5-bis(trifluoromethyl)aryl substituent at the chiral pyrrolidine in (*R*,*R*)-**D** to the gold(I) nucleus we considered the possibility that arene-gold(I) complex **2.63**, formed upon chloride abstraction, could be involved in the catalytic cycle (Scheme 2.23).



Scheme 2.23. Proposed synthesis of arene-gold(I) complex **263**.

Encouraged by previous reports on the isolation of arene-gold(I) complexes,[152,151] we treated (*R*,*R*)-**D** with one equivalent of $NaBAr^{F}{}_{4}$ in dichloromethane-d_2. However, we observed the formation of chloride-bridged digold complex **2.64** as confirmed by single-crystal X-ray diffraction (Scheme 2.24). Although chloride-bridged digold complexes have been reported,[11] the formation of **2.64** was rather unexpected considered the bulkiness of the complex bearing the C_2-symmetric diarylpyrrolidine moiety.



Scheme 2.24. Formation of chloride-bridged digold complex **2.64**. Hydrogen atoms, solvents and $BAr^{F}{}_{4}$ counteranion have been omitted for clarity.

The reaction progress was monitored by $^{31}P\{^{1}H\}$ NMR (Figure 2.4). After 4 h, (*R*,*R*)-**D** was completely converted into digold(I) complex **2.64**. To force the Au-Cl bond-breaking, a second portion of $NaBAr^{F}{}_{4}$ (0.5 equiv) was added, although no changes were observed after 16 h. Upon heating of the reaction mixture to 50 ºC for 3-6 h, the formation of a species at 67.5 ppm was observed, which was attributed to arene-gold(I) complex **2.63** based on reported chemical shifts of analogue structures.[176] Prolonged heating (22-30 h) led also to the formation of small amounts of (*R*,*R*)-**D**, indicating that (*R*,*R*)-**D**, arene-gold(I) complex **2.63** and chloride-bridged digold complex **2.64** are in equilibrium under these reaction conditions (Scheme 2.25a). Similarly, arene complexes of type **2.63** also formed with $AgSbF_6$ in the absence of coordinating reagents.

176. JohnPhosgold-arene complexes display a chemical shift at 68 ppm: Herrero-Gómez, E.; Nieto-Oberhuber, C.; López, S.; Benet-Buchholz, J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 5455–5459.

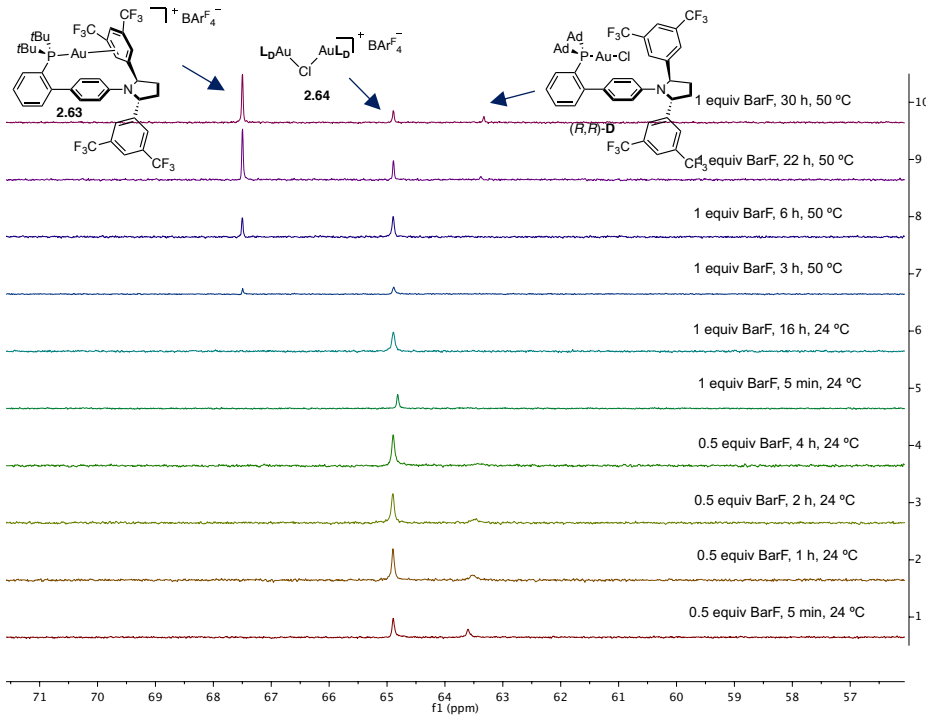
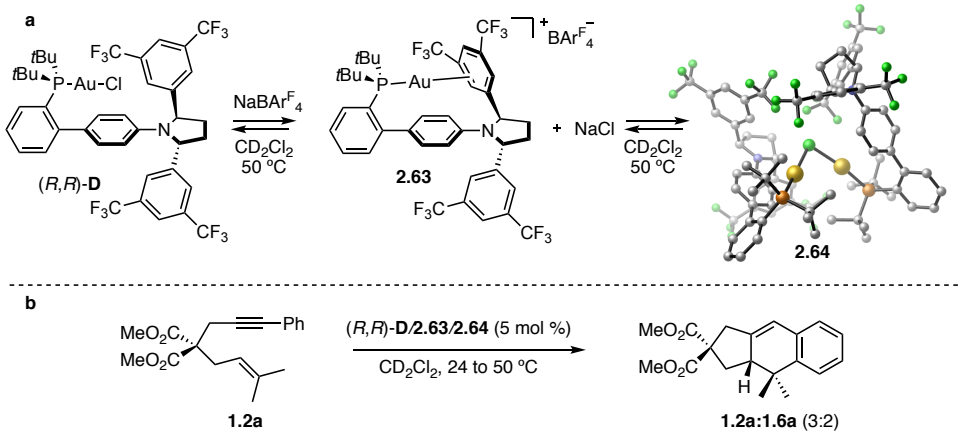


Figure 2.4. $^{31}P\{^{1}H\}$ reaction progress monitoring of the formation of **2.63** and **2.64**.

We tested the catalytic activity of the obtained mixture in the formal [4+2] cycloaddition of 1,6-enyne **1.2a** (Scheme 2.25b). At ambient temperature only unreacted starting material was recovered. Upon heating to 50 ºC for a period of 16 h, the formation of **1.6a** was observed together with a significant amount of unreacted starting enyne **1.2a**.



Scheme 2.25. a) Equilibrium between complexes (*R*,*R*)-**D**, **2.63** and **2.64** and b) performance in catalysis.

Monitoring the reaction progress by $^{31}P\{^1H\}$ NMR showed that the amount of chloride-bridged digold complex **2.64** decreases over time with the concomitant formation of arene-gold(I) complex **2.63** and (*R*,*R*)-**D** (Figure 2.5).

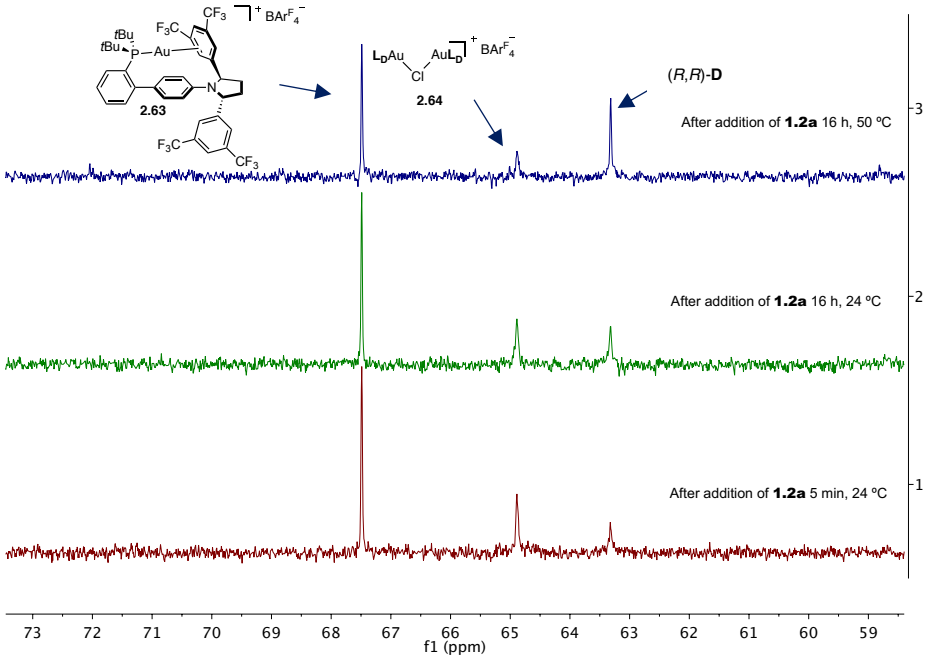
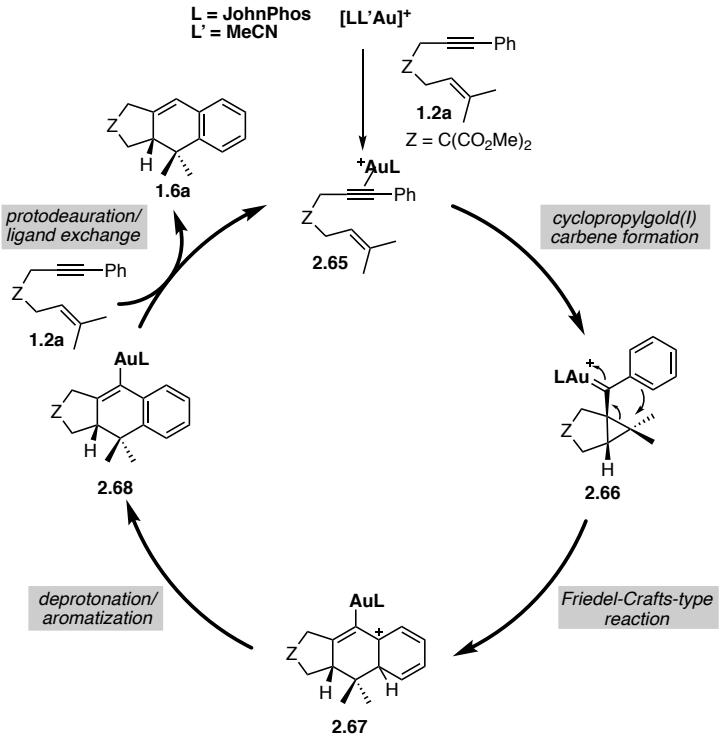


Figure 2.5. Monitoring of the progress of reaction of **1.2a** into **1.6a** by $^{31}P\{^1H\}$ NMR.

Kinetic Studies

Our group reported in 2008 a mechanistic study on the gold(I)-catalyzed formal [4+2] cycloaddition of enyne **1.2a** including experimental and computational work (Scheme 2.26).[61] The highest computed energy barrier was found for the formation of cyclopropyl gold(I) carbene **2.66**, the Friedel-Crafts-type reaction to form Wheland intermediate **2.67** is an exothermic process. The deprotonation/aromatization to give σ-gold(I) intermediate **2.68** as well as final protodeauration are energetically favored with respect to the formation of carbene **2.66**. The thermodynamic parameters of activation were determined ($\Delta G^{\ddagger}_{298}$ = 22.4 ± 0.5 kcal·mol^{-1}, $\Delta H^{\ddagger}$ = 12.6 ± 0.1 kcal·mol^{-1}, $\Delta S^{\ddagger}$ = –33.1 ± 0.5 cal·mol^{-1}·K^{-1}) and a negative entropy of activation $\Delta S^{\ddagger}$ was found, which is consistent with similar negative values observed for intramoleculat cycloaddition reactions.[177]



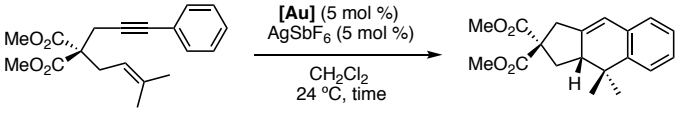
Scheme 2.26. Catalytic cycle for the formation of **1.6a**.

As presented in **Chapter 1**, the formal [4+2] cycloaddition of enyne **1.2a** with catalyst (*R*,*R*)-**E** required 24 h reaction time (**Chapter 1**, Table 2.10, entry 4). We hypothesized that

177. Diedrich, M. K.; Klärner, F.-G.; Beno, B. R.; Houk, K. N.; Senderowitz, H.; Still, W. C. *J. Am. Chem. Soc.* **1997**, *119*, 10255–10259.

the relatively low reactivity of (*R*,*R*)-**E** could be attributed to the bulkier and more electron-donating adamantyl phosphine in ligand $\mathbf{L_E}$, which reduces the electrophilicity of the catalyst. In comparison, using cationic JohnPhos gold(I) complex **1.1e** led to the formation of **1.6a** in only 1 h (Table 2.10, entry 2).[60]

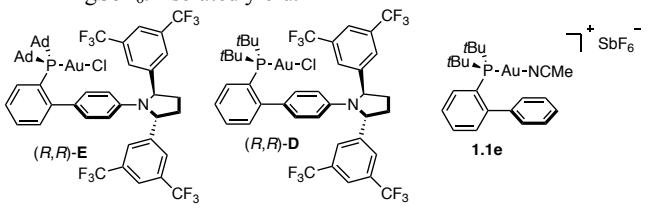
Table 2.10. Comparison of reaction times.



1.2a **1.6a**

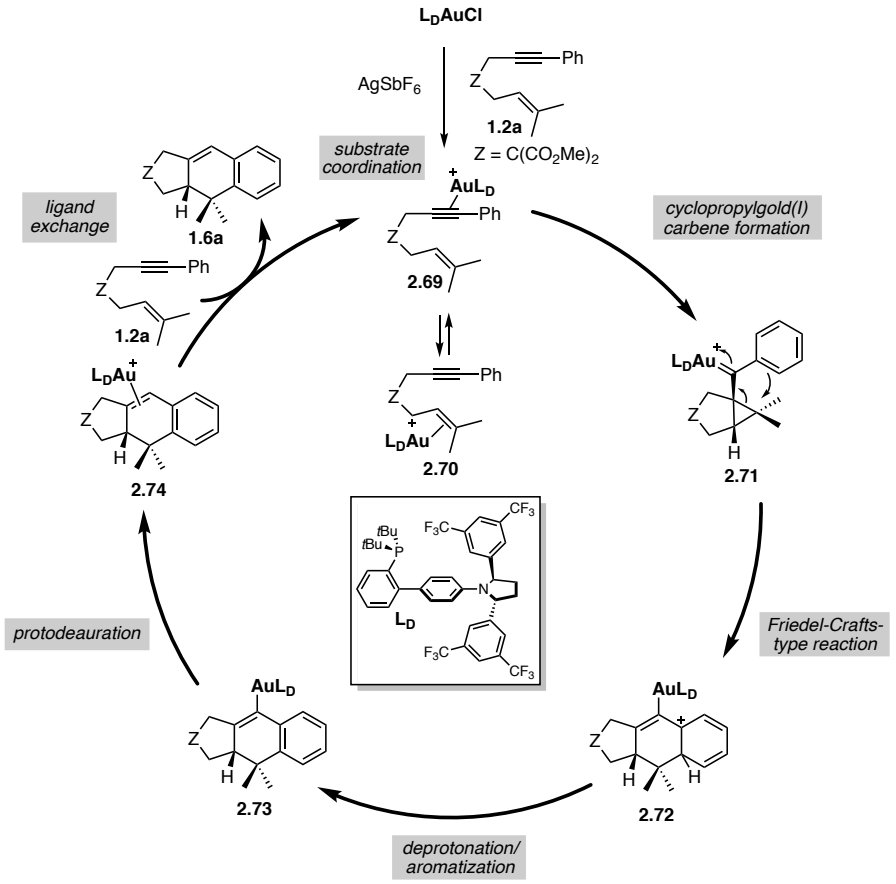
entry	[Au]	Time (*h*)	yield (*%*)[a]
1	(*R*,*R*)-**E**	24	88
2	**1.1e**[b]	1	86
3	(*R*,*R*)-**D**	6	70[c]

[a]Yields determined by ^{1}H NMR using 1,3,5-tribromobenzene as internal standard. [b]No addition of $AgSbF_6$. [c]Isolated yield.



We performed the cyclization of enyne **1.2a** with complex (*R*,*R*)-**D** with di-*tert*-butylphosphine $\mathbf{L_D}$, which corresponds to the JohnPhos equivalent among our pyrrolidinyl-biphenyl phosphine ligands. Monitoring the reaction progress by ^{1}H NMR, using 1,3,5-tribromobenzene as internal standard, showed that full conversion was only obtained after nearly 6 h reaction time. This suggests that the remote chiral pyrrolidine in (*R*,*R*)-**D** slows down the catalytic process with respect to **1.1e** (Table 2.10, entry 3). To understand the difference in reaction rates between the two catalytic systems and to determine whether the pyrrolidinyl phosphine ligands affect the reaction mechanism, we designed a series of experiments to study the single steps involved in the catalytic cycle. In addition to the elemental steps in the catalytic cycle depicted in scheme 2.26, we included the equilibrium between (π-alkyne)gold(I) complex **2.69** and (π-alkene)gold(I) complex **2.70** in our investigations (Scheme 2.27). Furthermore, protodeauration from σ-gold(I) intermediate **2.73** forming (π-alkene)gold(I) complex **2.74** and the following ligand exchange event with a molecule of starting **1.2a** were considered separately. Based on the preceding mechanistic investigations performed by our group,[61] we anticipated that under the action of (*R*,*R*)-**D**/**E**

the exothermic Friedel-Crafts-type step proceeding through a low transition state could be excluded as the rate-determining step.



Scheme 2.27. Catalytic cycle as basis for mechanistic investigation.

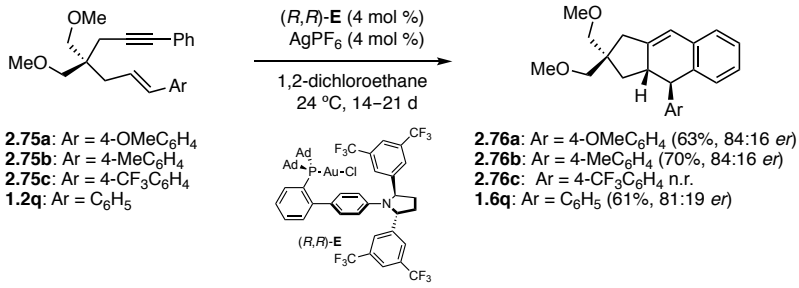
We started our mechanistic studies determining the rate constant and the overall reaction order. The formation of **1.6a** was monitored by ^{1}H NMR using enyne **1.2a**, 4 mol % of (*R*,*R*)-**D**/$AgSbF_6$ (1:1) and 1,3,5-tribromobenzene as internal standard at 25 ºC. The reaction was determined to be pseudo-first order with rate constant $k = 4.03 \cdot 10^{-4}$ s^{-1}.

We also determined the reaction order of both (*R*,*R*)-**D** and starting enyne **1.2a** using the method of initial rates. Thereby, we assumed that chloride abstraction with one equivalent of $AgSbF_6$ occurs instantaneously[10a] and the starting concentration of gold(I) chloride (*R*,*R*)-**D** corresponds to the starting concentration of active catalyst in the reaction medium.

We performed the formal [4+2] cycloaddition using a 1:1 mixture of (*R*,*R*)-**D** and $AgSbF_6$ in CD_2Cl_2 and increasing the amounts of starting enyne **1.2a**. Furthermore, we maintained the concentration of **1.2a** constant and changed the concentration of active catalyst (*R*,*R*)-**D**/$AgSbF_6$ (see experimental section). Hence, the gold(I)-catalyzed formal [4+2] cycloaddition of **1.2a** is first order in catalyst (*R*,*R*)-**D**/$AgSbF_6$ and zeroth order in **1.2a**.

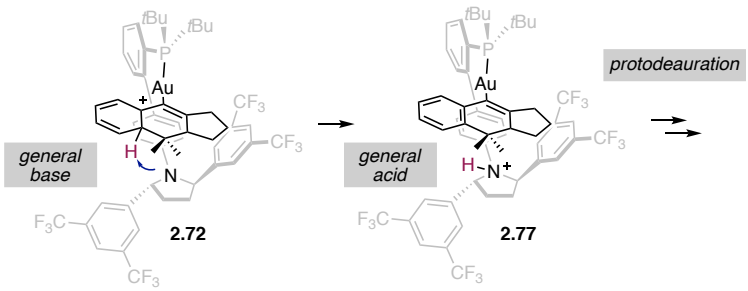
Because the binding of alkenes to gold(I) complexes in presence of alkynes can be thermodynamically favored depending on the substitution of both alkenes and alkynes,[156,159] we considered if the formation of unproductive (π-alkene)gold(I) complex **2.70** decelerates the reaction progress.

We prepared enynes **2.75a-c** with 4-substituted styrenes as the alkene, displaying different electronic properties. In the presence of (*R*,*R*)-**E**, enynes **2.75a,b** and **1.2q** were converted to the desired products **2.76a,b** and **1.6q** in comparable good yields (61-70%) and enantiomeric ratios (81:19 to 84:16 *er*) (Scheme 2.28). However, no conversion of enyne **2.75c** containing strong electron withdrawing 4-trifluoromethyl-substituted styrene was observed under these reaction conditions. Therefore, the reactivity of the enynes correlates with the nucleophilicity of the alkene. This indicates that the formation of unproductive (π-alkene)gold(I) complex **2.70**, which would be favored for the more electron-rich alkenes, does not have a significant effect on the reaction rate.



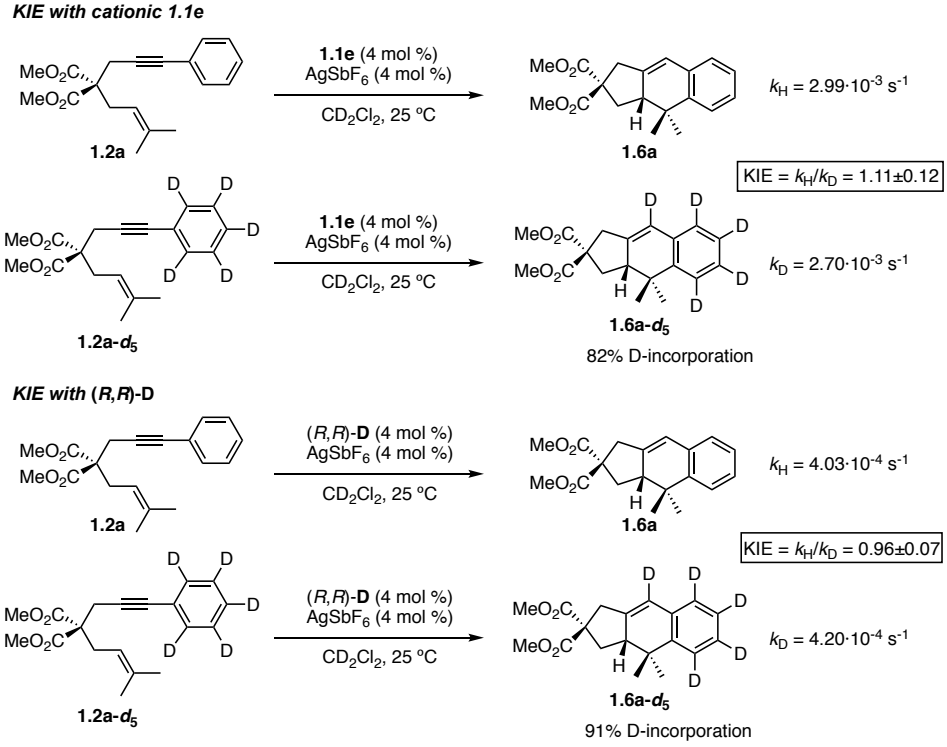
Scheme 2.28. Variation of the electronic properties in enynes **2.75a-c** and **1.2q**.

Next, we investigated the deprotonation/aromatization step from Wheland intermediate **2.72**. We hypothesized that the slightly basic pyrrolidine-nitrogen, situated directly underneath the reaction center, could be involved in this step acting firstly as a general base leading to σ-gold(I) intermediate **2.77** in which the nitrogen atom in the ligand is protonated, and in a second step as a general acid in the protodeauration step (Scheme 2.29).



Scheme 2.29. Hypothetical dual role of the pyrrolidine-nitrogen.

Thus, we performed kinetic isotope effect (KIE) studies with enyne **1.2a** and perdeuterated enyne **1.2a-*d*$_5$**. We carried out the experiments with cationic complex **1.1e** and (*R*,*R*)-**D**. A KIE = 1.1 was found when complex **1.1e** was employed as the catalyst (Scheme 2.30). This value is in agreement with reported values for transition metal-catalyzed hydroarylation reactions[178].

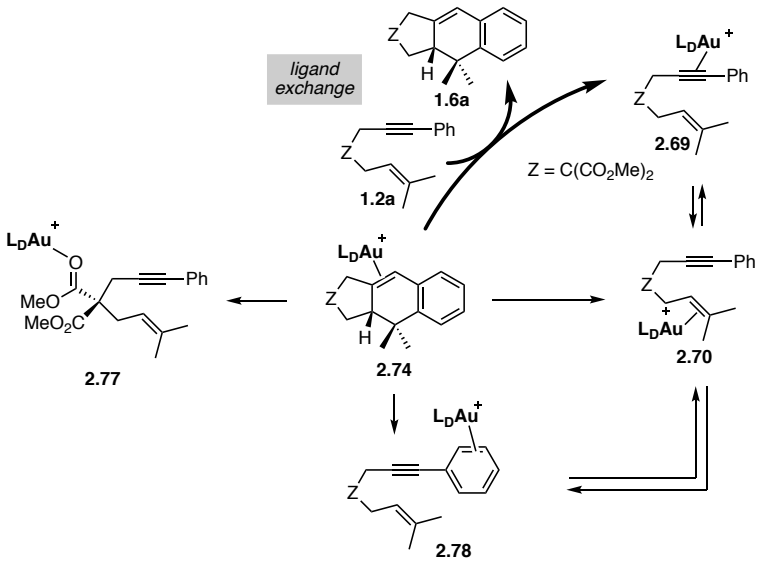


Scheme 2.30. Kinetic isotope effects (KIE) with complex **1.1e** and (*R*,*R*)-**D**.

178. (a) Tunge, J. A.; Foresee, L. N. *Organometallics* **2005**, *24*, 6440–6444. (b) Chernyak, N.; Gevorgyan, V. *J. Am. Chem. Soc.* **2008**, *130*, 5636–5637.

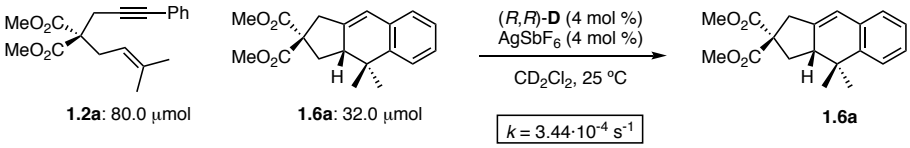
Using (*R*,*R*)-**D** as the catalyst gave a KIE = 0.96 indicating that the deprotonation/aromatization process of Wheland intermediate **2.72** is not rate-determining.

Finally, we considered that the decrease in rate observed with pyrrolidine-containing complexes (*R*,*R*)-**D**/**E** could be attributed to the ligand exchange process. The associative ligand substitution of one molecule of product **1.6a** with the concomitant coordination of a molecule of starting enyne **1.2a** can be affected by the sterically encumbered substituents of the chiral pyrrolidine. In addition to the ligand exchange event of (π-alkene)gold(I) complex **2.74** with substrate **1.2a** to form (π-alkyne)gold(I) complex **2.69** the formation of other intermediates such as **2.70**, **2.77** or **2.78** in which the substrate is coordinated to gold(I) through the alkene, the oxygen atoms of the malonate or the phenyl ring can also be involved (Scheme 2.31).



Scheme 2.31. Productive versus unproductive ligand exchange.

We found that performing the cycloaddition of enyne **1.2a** in presence of product **1.6a** (2.5:1 ratio) at the beginning of the reaction results in a drop in rate ($k = 3.44 \cdot 10^{-4}$ s^{-1} vs. $k = 4.03 \cdot 10^{-4}$ s^{-1}) (Scheme 2.32). Thus, the ligand exchange of intermediate **2.74** with a second molecule of product **1.6a** is not negligible and should become more important as the reaction preceeds.



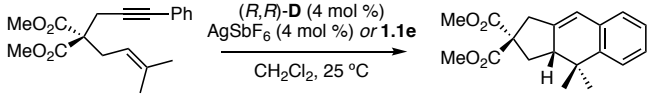
Scheme 2.32. Control experiment with product at the beginning of the reaction.

We performed an Eyring analysis considering a simplified pseudo-first order behavior to determine the thermodynamic parameters of activation (Table 2.11 and 2.12). A positive entropy of activation ($\Delta S^{\ddagger}$ = +24.5 ± 6.0 cal·mol·K^{-1}) was found, which is in contrast to that observed with JohnPhos gold(I) complex **1.1e**. This might suggest that the final ligand exchange process becomes rate-determining with (*R*,*R*)-**D**. It is important to remark that, among the several systems that we have examined in our group,[61,161] this is the first example of a gold(I)-catalyzed transformation displaying a positive entropy of activation.

Table 2.11 Pseudo-first order rate constants at different temperatures.

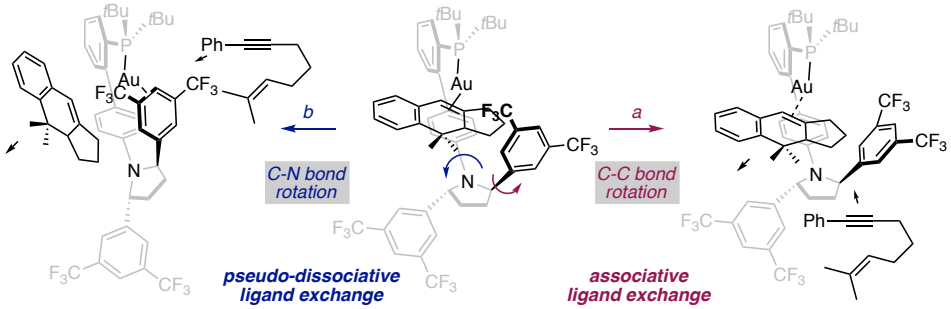
T (*ºC*)	*k* (s^{-1})
10	$5.82 \cdot 10^{-5}$
15	$9.89 \cdot 10^{-5}$
20	$3.04 \cdot 10^{-4}$
25	$4.03 \cdot 10^{-4}$
30	$7.76 \cdot 10^{-4}$
35	$8.89 \cdot 10^{-4}$
40	$9.89 \cdot 10^{-4}$
45	$1.34 \cdot 10^{-3}$

Table 2.12. Thermodynamic parameters of activation.



complex	$\Delta G^{\ddagger}_{298}$ (*kcal·mol^{-1}*)	$\Delta H^{\ddagger}$ (*kcal·mol^{-1}*)	$\Delta S^{\ddagger}$ (*cal·mol^{-1}·K^{-1}*)
(*R*,*R*)-**D**	8.1 ± 2.5	15.4 ± 1.8	+24.5 ± 6.0

We considered two plausible mechanisms for the ligand exchange. An associative ligand exchange can occur upon rotation of the aryl substituent of the chiral pyrrolidine widening the binding pocket (Scheme 2.33, path a).



Scheme 2.33. Proposed mechanisms for ligand exchange.

Alternatively, the ligand exchange could take place following a pseudo-dissociative mechanism (associative with respect to gold(I) and dissociative with respect to the substrate) (Scheme 2.33, path *b*). In this process, rotation around the C–N bond would lead to the formation of a species in which the gold(I) nucleus is stabilized by Au-π (cation-π) interactions.[148,179]

The Eyring plot in Figure 2.6 shows a break around 21 ºC. The presence of two independent straight lines establishes that there are two competing rate-determining steps.

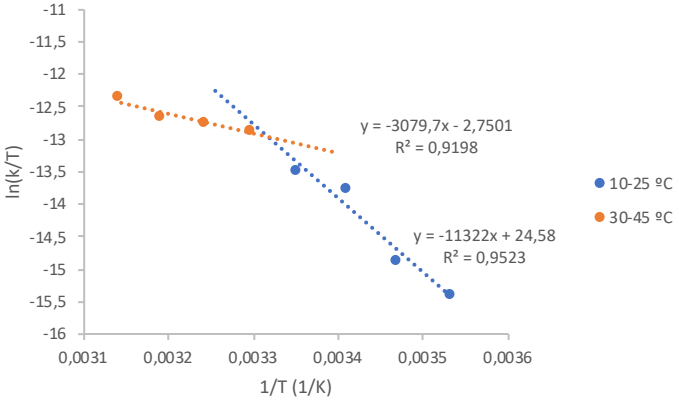


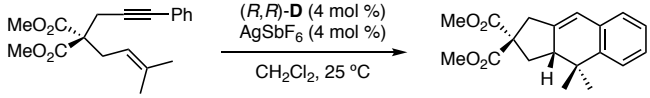
Figure 2.6. Eyring analysis at high and low temperatures.

The Gibbs free energies of activation remained similar when the temperature ranges were examined separately (Table 2.13). However, at higher temperatures ($\Delta H^{\ddagger}$ = 6.1 ± 1.3 kcal·mol^{-1}, $\Delta S^{\ddagger}$ = –5.5 ± 4.1 cal·mol^{-1}·K^{-1}) (Table 2.13, entry 2) the formation of cyclopropyl gold(I) carbene **2.71** in which two C–C bonds are formed predominates as the

179. (a) Jian Tan, X.; Liang Zhu, W.; Cui, M.; Min Luo, X.; De Gu, J.; Silman, I.; Sussman, J. L.; Liang Jiang, H.; Yun Ji, R.; Xian Chen, K. *Chem. Phys. Lett.* **2001**, *349*, 113–122. (b) Ma, J. C.; Dougherty, D. A. *Chem. Rev.* **1997**, *97*, 1303–1324.

rate-determining step. At lower temperatures, the entropy of activation is nearly double ($\Delta S^{\ddagger}$ = +48.8 ± 12.2 cal·mol^{-1}·K^{-1}) compared to the entropy of activation determined for the entire temperature range ($\Delta S^{\ddagger}$ = +24.5 ± 6.0 cal·mol^{-1}·K^{-1}) (Table 2.13 entries 2 and 3), which could suggest that the ligand exchange process prevails as the rate-determining step under these conditions.

Table 2.13. Thermodynamic parameters of activation at low and high T.



1.2a **1.6a**

entry	T(°C)	$\Delta G^{\ddagger}_{298}$ (kcal·mol^{-1})	$\Delta H^{\ddagger}$ (kcal·mol^{-1})	$\Delta S^{\ddagger}$ (cal·mol^{-1}·K^{-1})
1	**30-45**	7.7 ± 1.7	6.1 ± 1.3	–5.5 ± 4.1
2	**10-25**	7.9 ± 5.1	22.5 ± 3.6	+48.8 ± 12.2
3	**10-45**	8.1 ± 2.5	15.4 ± 1.8	+24.5 ± 6.0

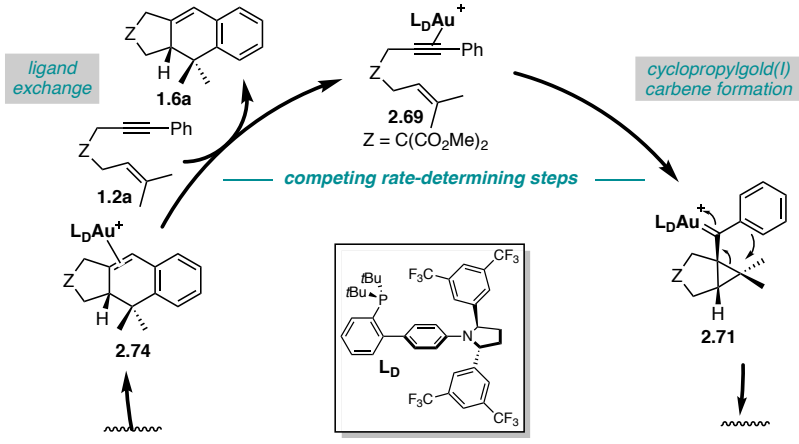
Conclusions

We have analyzed the mode of action and enantioinduction of our chiral pyrrolidinyl-biphenyl phosphine gold(I) complexes computationally and experimentally. In the cyclizations of 1,6-arylenynes, non-covalent attractive π-π interactions between stereodirecting components of the substrates and aromatic moieties of the chiral catalysts (*R*,*R*)-**D**/**E** induce a specific binding orientation inside the chiral pocket accounting for the enantioselective foldings and the observed absolute configurations.

In the case of catalyst (*R*,*R*)-**H** with C_2-symmetric 2,5-dicyclohexylpyrrolidine, high enantiomeric ratios are attributed to both, steric and electronic factors depending on the reacting 1,6-enyne. Non-covalent attractive alkyl-OMe and aryl-alkyl interactions between substrates and ligand have been found to be stabilizing in the studied cyclizations.

We synthesized a 2nd generation of chiral catalysts which allowed us to analyze the role of the single components in the original ligand design. From this study, more electrophilic complexes emerged which were applied in the spiro cyclization of 1-bromo-1,5-enynes. We have also applied the 2nd generation of chiral catalysts in the atroposelective synthesis of biaryl systems by intramolecular hydrofunctionalization.

An Eyring analysis at different temperature ranges suggests that there are two competing rate-determining steps in the formal [4+2] cycloaddition catalyzed by (*R*,*R*)-**D**: the formation of the cyclopropyl gold(I) carbene and the final ligand exchange (Scheme 2.34). Nevertheless, further experimental and computational mechanistic work would be necessary to fully confirm these preliminary conclusions.



Scheme 2.34. Competing rate-determining steps in the cyclization of **1.2a** with (*R*,*R*)-**D**.

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Experimental Section

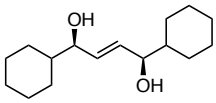
General Information

The general information is provided in the Experimental Section of **Chapter 1**. 1,2-diarylalkynes **2.54**, **2.60** and **2.62**[180] were synthesized following a reported procedure.[175]

Synthetic Procedures and Characterization of Compounds

Synthesis of Complexes

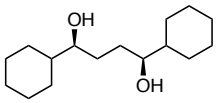
(1*R*,4*R*,E)-1,4-Dicyclohexylbut-2-ene-1,4-diol



(*S*)-1-Cyclohexylprop-2-en-1-ol[102b] (1.55 g, 11.1 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (11.0 mL, 1 M) and Grubbs 2nd gen. catalyst (47.0 mg, 55.0 μmol, 0.5 mol %) was added. The reaction mixture was stirred for 2 h at 40 ºC. The compound was purified by precipitation from cold *n*hexane to afford the title compound (882 mg, 3.49 mmol, 63%) as a white solid.

M.p. = 118 – 120 °C (*n*hexane). α_D^{589} ($CHCl_3$, c 1.0, 300 K) = –20.2 deg.cm^2.g^{-1}. The spectral data were fully consistent with those previously reported.[181]

(1*S*,4*S*)-1,4-Dicyclohexylbutane-1,4-diol

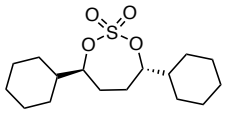


A 50 mL round bottom flask equipped with a stirring bar was charged with PtO_2 (37.0 mg, 0.160 mmol, 5 mol %) and the flask was evacuated and back filled with argon (3x). Then, a solution of (1*R*,4*R*,*E*)-1,4-dicyclohexylbut-2-ene-1,4-diol (830 mg, 3.29 mmol, 1.0 equiv) in EtOAc/MeOH (9:1, 0.08M) was added. The reaction mixture was evacuated and back filled with hydrogen (3x) and stirred at 24 ºC for 1 h under hydrogen atmosphere (1 atm). The reaction was monitored by ^{1}H NMR. After full conversion of the starting material the reaction was degassed with argon and filtered over Celite®. The solvent was removed under vacuum and the crude was purified by flash column chromatography (cyclohexane/EtOAc 3:1) to afford the title compound (755 mg, 2.96 mmol, 90%) as a white solid.

M.p. = 157 – 159 °C (cyclohexane/EtOAc). α_D^{589} ($CHCl_3$, c 1.1, 300 K) = –21.5 deg.cm^2.g^{-1}. The spectral data were fully consistent with those previously reported.[166]

180. He, Y.-P.; Wu, H.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2020**, *59*, 2105–2109.
181. Bach, J.; Berenguer, R.; Garcia, J.; López, M.; Manzanal, J.; Vilarrasa, J. *Tetrahedron* **1998**, *54*, 14947–14962.

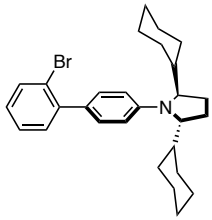
(4*S*,7*S*)-4,7-Dicyclohexyl-1,3,2-dioxathiepane 2,2-dioxide



The sulfate was synthesized according to the reported procedure starting from (1*S*,4*S*)-1,4-dicyclohexylbutane-1,4-diol (340 mg, 1.34 mmol, 1.0 equiv), $RuCl_3 \cdot H_2O$ (3.92 mg, 17 μmol, 1 mol %) and $NaIO_4$ (600 mg, 2.81 mmol, 2.1 equiv). The title compound (393 mg, 1.24 mmol, 93%) was isolated as a white powder.

M.p. = > 156 °C (decomposition; hexane/Et_2O). α_D^{589} ($CHCl_3$, c 0.9, 298 K) = –54.1 deg.cm^2.g^{-1}. The spectral data were fully consistent with those previously reported.[166]

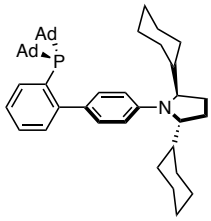
(2*R*,5*R*)-1-(2'-Bromo-[1,1'-biphenyl]-4-yl)-2,5-dicyclohexylpyrrolidine



2'-bromo-[1,1'-biphenyl]-4-amine (see **Chapter 1**) (812 mg, 3.27 mmol, 5.0 equiv) and (4*S*,7*S*)-4,7-dicyclohexyl-1,3,2-dioxathiepane 2,2-dioxide (207 mg, 0.654 mmol, 1.0 equiv) were dissolved in toluene (1.3 mL) in a 20 mL microwave vial and heated to 140 ºC until the solvent evaporated completely. The neat mixture was further heated for additional 30 min. The reaction mixture was allowed to cool to 24 ºC and dissolved in EtOAc and sat. $NaHCO_3$. The phases were separated and the aqueous phase was extracted with EtOAc (2x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude was purified by flash column chromatography (cyclohexane, then cyclohexane/CH_2Cl_2, 20:1) to yield the title compound (124 mg, 0.270 mmol, 41%) as a white solid.

M.p. = 202 – 206 °C ($CHCl_3$). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.63 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.36 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.33 – 7.26 (m, 3H), 7.13 – 7.07 (m, 1H), 6.63 – 6.55 (m, 2H), 3.86 (d, *J* = 4.8 Hz, 2H), 2.04 (td, *J* = 12.0, 2.9 Hz, 2H), 1.97 – 1.79 (m, 4H), 1.73 (d, *J* = 12.8 Hz, 2H), 1.62 (d, *J* = 11.9 Hz, 4H), 1.55 (d, *J* = 13.8 Hz 2H), 1.40 (d, *J* = 12.8 Hz, 2H), 1.31 – 1.18 (m, 2H), 1.12 – 0.96 (m, 6H), 0.95 – 0.81 (m, 2H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 144.8, 143.0, 133.4, 131.6, 130.1, 127.6, 127.4, 127.1, 122.9, 114.7, 63.1, 37.5, 30.6, 26.9, 26.8, 26.7, 26.4, 26.0. **HRMS** (ESI+) calculated for $[C_{28}H_{37}BrN]^+$ 466.2104 *m/z*; found $[M + H]^+$ 466.2108 *m/z*. α_D^{589} ($CHCl_3$, c 1.0, 298 K) = –18.7 deg.cm^2.g^{-1}.

Ligand L_H

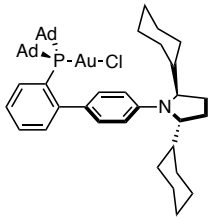


A flame-dried 10 mL Schlenk flask was charged with (2*R*,5*R*)-1-(2'-bromo-[1,1'-biphenyl]-4-yl)-2,5-dicyclohexylpyrrolidine (130 mg, 279 μmol, 1.0 equiv), $Pd(OAc)_2$ (3.13 mg, 14.0 μmol, 5 mol %), dppf (9.27 mg, 17.0 μmol, 6 mol %), NaO*t*Bu (32.0 mg, 334 μmol, 1.2 equiv), toluene (1.4 mL) and THF (0.30 mL) and the resulting

suspension was stirred for 15 min at 24 ºC. Di-(1-adamantyl)phosphine (93.0 mg, 307 μmol, 1.1 equiv) was added and the reaction mixture was stirred at 120 °C for 12 h. Then, the reaction was allowed to cool to 24 °C and the crude was purified by flash column chromatography (cyclohexane/CH_2Cl_2 3:1, then cyclohexane/EtOAc 30:1) to yield ligand $\mathbf{L_H}$ (186 mg, 0.270 mmol, 97%) as an off-white foam.

M.p. = 115 – 118 °C (cyclohexane/EtOAc). **^{1}H NMR** (400 MHz, CD_2Cl_2) δ 7.88 (d, *J* = 7.5 Hz, 1H), 7.38 – 7.31 (m, 1H), 7.30 – 7.22 (m, 2H), 7.07 (d, *J* = 8.6 Hz, 2H), 6.56 (d, *J* = 8.6 Hz, 2H), 3.89 (d, *J* = 4.4 Hz, 2H), 2.11 – 1.99 (m, 5H), 1.99 – 1.80 (m, 19H), 1.78 (d, *J* = 12.4 Hz, 2H), 1.69 (dd, *J* = 25.0, 11.1 Hz, 17H), 1.56 (d, *J* = 12.9 Hz, 2H), 1.44 (d, *J* = 11.5 Hz, 2H), 1.33 – 1.20 (m, 2H), 1.14 – 1.04 (m, 5H), 1.03 – 0.89 (m, 2H). **^{13}C{^{1}H} NMR** (101 MHz, CD_2Cl_2) δ 152.2 (d, *J* = 31.9 Hz), 143.6, 136.8 (d, *J* = 2.6 Hz), 133.2, 133.0, 131.3 (d, *J* = 4.2 Hz), 131.1 (d, *J* = 6.1 Hz), 130.5 (d, *J* = 6.8 Hz), 128.1, 124.5, 113.9, 62.9, 42.2 (d, *J* = 13.2 Hz), 41.6 (d, *J* = 12.9 Hz), 37.58 (d, *J* = 5.13 Hz), 37.54, 37.3 (d, *J* = 9.8 Hz), 37.0 (d, *J* = 6.3 Hz), 30.4, 29.1 (d, *J* = 8.6 Hz), 29.0 (d, *J* = 8.7 Hz), 26.8 (d, *J* = 12.9 Hz), 26.5 (d, *J* = 20.1 Hz), 25.8. **^{31}P{^{1}H} NMR** (162 MHz, CD_2Cl_2) δ 24.8. **HRMS** (ESI+) calculated for $[C_{48}H_{67}NP]^+$ 688.5006 *m/z*; found $[M + H]^+$ 688.5012 *m/z*. $\boldsymbol{\alpha_D^{589}}$ ($CHCl_3$, c 1.0, 297 K) = –19.5 deg.cm^2.g^{-1}.

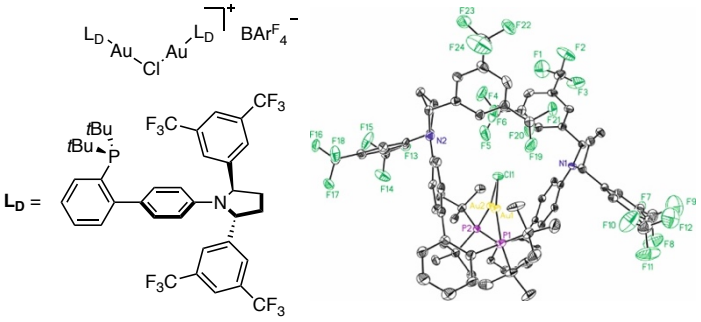
Complex (*R*,*R*)-H



[Me_2SAuCl] (17.1 mg, 58.0 μmol, 1.0 equiv) and ligand $\mathbf{L_H}$ (40 mg, 58.0 μmol, 1.0 equiv) were dissolved in CH_2Cl_2 (0.60 mL) under an atmosphere of argon. The reaction mixture was stirred at 24 ºC for 30 min. The mixture was dissolved in CH_2Cl_2, filtered through a path of neutral Al_2O_3 and concentrated to yield complex (*R*,*R*)-**C** (29.9 mg, 0.033 mmol, 56%) as a white solid.

M.p. = >225 °C brown (decomposition; MeOH/Et_2O). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.83 (t, *J* = 7.0 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.35 – 7.30 (m, 1H), 6.92 (ddd, *J* = 15.5, 8.3, 1.7 Hz, 2H), 6.63 – 6.55 (m, 2H), 3.87 (d, *J* = 5.5 Hz, 2H), 2.31 – 2.21 (m, 5H), 2.21 – 2.14 (m, 7H), 2.14 – 2.08 (m, 3H), 1.99 (d, *J* = 9.6 Hz, 7H), 1.87 – 1.78 (m, 2H), 1.74 – 1.59 (m, 18H), 1.52 (s, 2H), 1.33 – 1.22 (m, 5H), 1.11 – 0.97 (m, 4H), 0.95 – 0.79 (m, 3H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 152.2 (d, *J* = 13.9 Hz), 145.3, 135.0 (d, *J* = 7.3 Hz), 134.5, 130.2, 130.1 (d, *J* = 1.9 Hz), 129.9, 128.2 (d, *J* = 6.9 Hz), 125.4 (d, *J* = 6.7 Hz), 124.2, 123.9, 115.3, 114.4, 63.1, 42.6, 42.5 (d, *J* = 7.2 Hz), 42.3 (d, *J* = 2.6 Hz), 42.1 (d, *J* = 2.6 Hz), 36.51, 36.47, 30.7, 28.83 (d, *J* = 2.6 Hz), 28.75 (d, *J* = 2.6 Hz), 27.1 (d, *J* = 2.7 Hz), 26.8 (d, *J* = 3.9 Hz), 26.3, 26.1. **^{31}P{^{1}H} NMR** (203 MHz, $CDCl_3$) δ 65.0. **HRMS** (ESI+) calculated for $[C_{48}H_{67}AuClNP]^+$ 920.4360 *m/z*; found $[M + H]^+$ 920.4328 *m/z*. $\boldsymbol{\alpha_D^{589}}$ ($CHCl_3$, c 0.7, 299 K) = –16.0 deg.cm^2.g^{-1}.

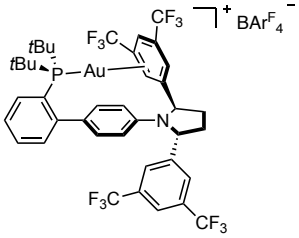
Synthesis of chloride-bridged digold complex (*R*,*R*)-D$_2$-Cl



Complex (*R*,*R*)-**D** (15.0 mg, 15.0 μmmol, 1.0 equiv) was dissolved in CD_2Cl_2 (0.6 mL) and $NaBAr^F_4$ (6.49 mg, 7.32 μmol, 0.5 equiv) was added. The reaction mixture was stirred at 24 ºC for 16 h. The yield of the title compound was calculated by ^{1}H NMR with 1,2-dibromoethane as internal standard (65%).

Characteristic signals for chloride-bridged digold(I) complex (*R*,*R*)-C$_2$-Cl: **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 7.84 – 7.76 (m, 6H), 7.75 – 7.69 (m, 8H), 7.67 (s, 6H), 7.55 (s, 4H), 7.53 – 7.41 (m, 4H), 7.26 – 7.12 (m, 2H), 6.86 (t, *J* = 6.3 Hz, 4H), 6.33 (d, *J* = 8.8 Hz, 2H), 6.13 (d, *J* = 8.2 Hz, 2H), 5.40 – 5.32 (m, 4H), 2.74 – 2.48 (t, *J* = 7.5 Hz, 4H), 2.07 – 1.85 (m, 4H), 1.42 (s, 9H), 1.38 (s, 9H), 1.34 (s, 9H), 1.30 (s, 9H). **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 162.5 (d, *J* = 50.0 Hz), 161.7 (d, *J* = 49.9 Hz), 145.8, 143.8, 135.1, 134.4, 133.4, 132.2, 132.0, 131.7 (d, *J* = 3.8 Hz), 131.0 (d, *J* = 6.7 Hz), 129.5 (d, *J* = 5.3 Hz), 129.3 (dd, *J* = 5.7, 2.8 Hz), 129.1 (dd, *J* = 5.7, 2.9 Hz), 128.2, 127.7 – 127.5 (m), 126.8, 126.0, 123.8, 123.7 (q, *J* = 273.0 Hz), 121.9 – 121.6 (m), 117.8 (dt, *J* = 7.9, 3.5 Hz), 114.9, 114.6, 63.4, 38.3 (d, *J* = 25.9 Hz), 32.2, 31.9 (d, *J* = 6.0 Hz), 30.2 (d, *J* = 6.1 Hz). **^{31}P{^{1}H} NMR** (162 MHz, CD_2Cl_2) δ 64.9. **^{19}F{^{1}H} NMR** (376 MHz, CD_2Cl_2) δ –62.8, –63.0. **HRMS** (ESI+) calculated for $[C_{80}H_{76}Au_2ClF_{24}NP]^+$ 2011.4120 *m/z*; found $[M]^+$ 2011.4094 *m/z*.

Evidence for Arene-gold(I) complex

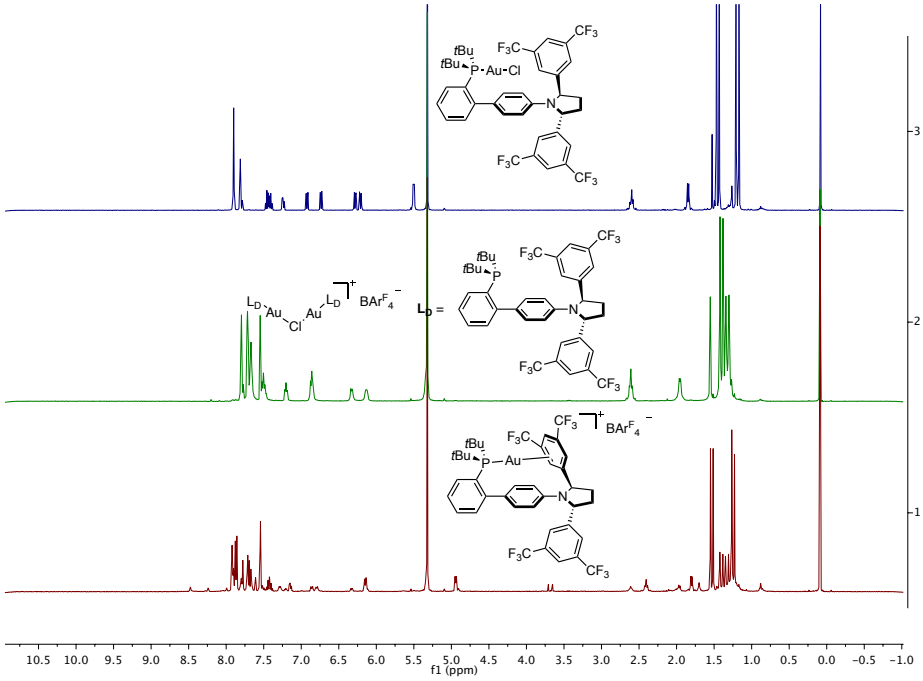


In a capped NMR tube, complex (*R*,*R*)-**D** (5.00 mg, 4.88 μmmol, 1.0 equiv) was dissolved in dry CD_2Cl_2 (0.5 mL) and $NaBAr^F_4$ (2.20 mg, 2.44 μmol, 0.5 equiv) was added. The reaction mixture was stirred at 24 ºC for 16 h until full conversion to the chloride-bridged digold complex (*R*,*R*)-**D$_2$**-Cl. The reaction was monitored by ^{31}P{^{1}H} NMR. Then, a second portion of $NaBAr^F_4$ (2.2 mg, 2.44 μmol, 0.5 equiv) was added and the reaction mixture was stirred at 50 ºC for 6 h. The obtained mixture was characterized by NMR spectroscopy and high-resolution mass analysis.

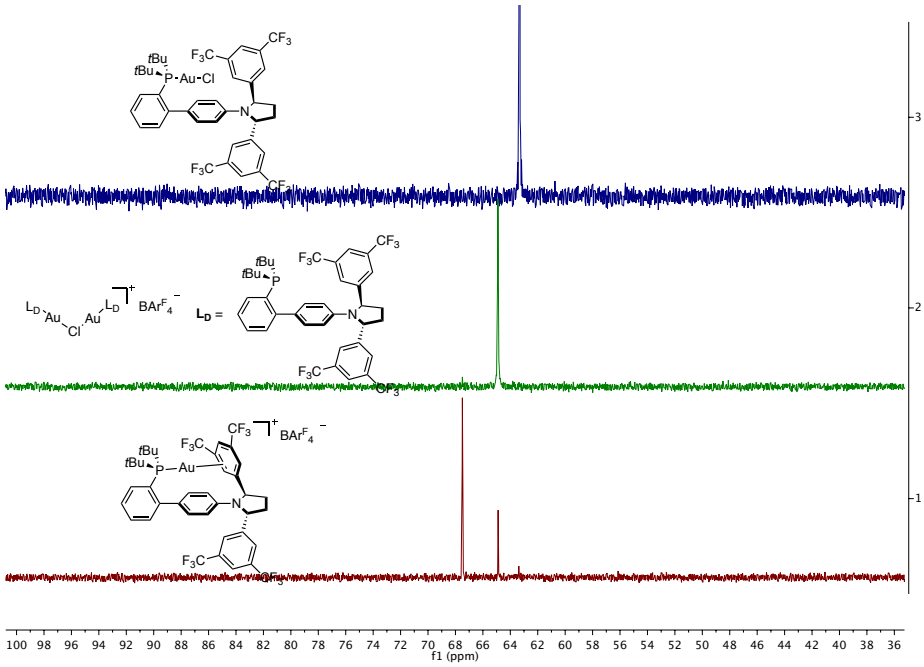
Characteristic signals for arene-gold(I) complex: **^{1}H NMR** (400 MHz, CD_2Cl_2) δ 7.94 – 7.89 (m, 5H), 7.89 – 7.85 (m, 6H), 7.61 (s, 1H), 7.47 – 7.37 (m, 2H), 7.32 – 7.24 (m, 1H), 7.18 – 7.11 (m, 1H), 6.82 – 6.77 (m, 1H), 6.15 (d, *J* = 7.6 Hz, 2H), 4.94 (d, *J* = 7.0 Hz, 2H),

2.47 – 2.33 (m, 2H), 1.86 – 1.74 (m, 2H), 1.53 (d, J = 14.4 Hz, 9H), 1.25 (d, J = 14.7 Hz, 9H). **^{31}P{^{1}H} NMR** (162 MHz, CD_2Cl_2) δ 67.5. **^{19}F{^{1}H} NMR** (376 MHz, CD_2Cl_2) δ –62.4, –63.3, –63.4. **HRMS** (ESI+) calculated for $[C_{40}H_{38}AuClF_{12}NP]^+$ 1024.1977 *m/z*; found [M + HCl]$^+$ 1024.1962 *m/z*.

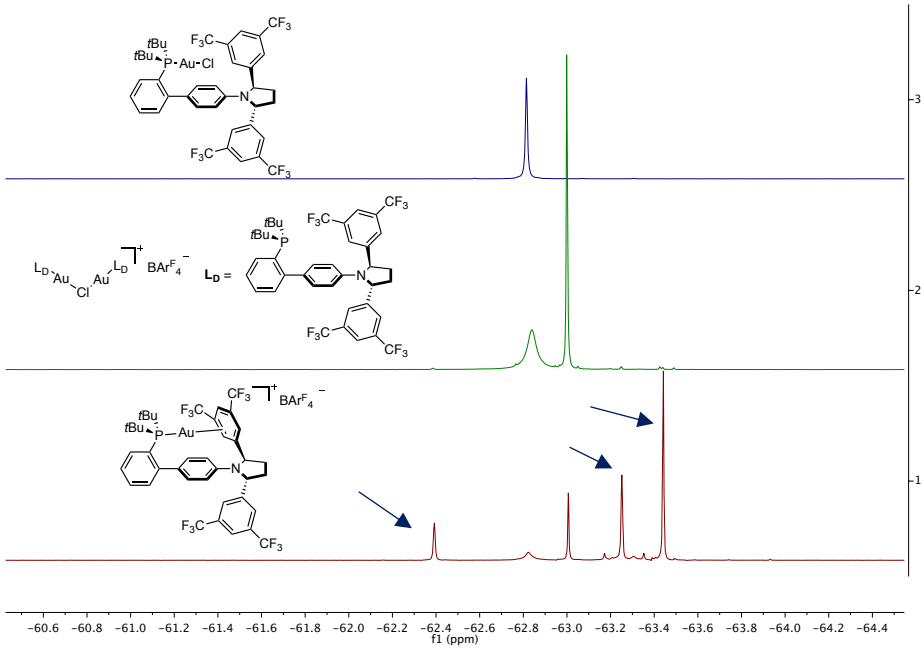
^{1}H NMR: 400 MHz, CD_2Cl_2, (*R*,*R*)-D, (*R*,*R*)-D_2-Cl and arene-gold(I) complex



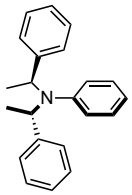
$^{31}P\{^{1}H\}$ NMR: 162 MHz,CD_2Cl_2, (*R*,*R*)-D, (*R*,*R*)-D_2-Cl and arene-gold(I) complex



$^{19}F\{^{1}H\}$ NMR: 376 MHz, (*R*,*R*)-D, (*R*,*R*)-D_2-Cl and arene-gold(I) complex



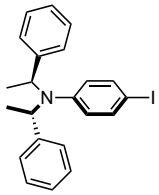
_N_,_N_-Bis((_S_)-1-phenylethyl)aniline



2-(Trimethylsilyl)phenyl trifluoromethanesulfonate (517 μL, 2.13 mmol, 1.2 equiv) was added dropwise to a solution of (*S*)-bis((*S*)-1-phenylethyl)amine (400 mg, 1.77 mmol, 1.0 equiv) and CsF (809 mg, 5.33 mmol, 3.0 equiv) in MeCN (7.0 mL) at 24 ºC. The solution was heated to 70 ºC for 14 h. The reaction mixture was cooled to 24, diluted with EtOAc (30 mL), washed with sat. $NaHCO_3$ (10 mL), brine (10 ml), dried over sodium sulfate and concentrated under reduced pressure. The crude was purified by flash column chromatography (pentane/CH_2Cl_2 5:1) to afford the title compound (460 mg, 1.75 mmol, 86%) as a colorless oil.

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.30 – 7.24 (m, 8H), 7.24 – 7.16 (m, 2H), 7.14 – 7.09 (m, 2H), 6.90 – 6.82 (m, 1H), 6.76 (dt, *J* = 7.9, 1.1 Hz, 2H), 4.70 (q, *J* = 6.9 Hz, 2H), 1.46 (d, *J* = 6.9 Hz, 6H). **^{13}C{^{1}H} NMR** (101 MHz, CD_2Cl_2) δ 146.6, 143.9, 128.4, 128.3, 128.1, 127.0, 123.4, 120.9, 56.9, 19.6. **HRMS** (EI+) calculated for $[C_{22}H_{24}N]^+$ 302.1903 *m/z*; found $[M + H]^+$ 302.1907 *m/z*. **α_D^{589}**($CHCl_3$, c 1.2, 298 K) = +31.0 deg.cm^2.g^{-1}.

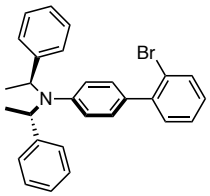
4-iodo-_N_,_N_-bis((_S_)-1-phenylethyl)aniline



To a solution of *N*,*N*-bis((*S*)-1-phenylethyl)aniline (428 mg, 1.42 mmol, 1.0 equiv) in 1,4-dioxane/pyridine (1:1, 7.0 mL) at 0 ºC was added iodine (1.08 g, 4.26 mmol, 3.0 equiv). The reaction was diluted with EtOAc (50 mL), washed with sat. Na_2SO_3, dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash column chromatography (pentane/CH_2Cl_2 5:1) to afford the title compound (540 mg, 1.26 mmol, 89%) as colorless oil.

^{1}H NMR (500 MHz, CD_2Cl_2) δ .41 – 7.35 (m, 1H), 7.29 – 7.24 (m, 4H),7.23 – 7.16 (m, 2H), 6.56 – 6.50 (m, 2H), 4.77 (q, *J* = 6.9 Hz, 2H), 1.52 (d, *J* = 6.9 Hz, 6H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 146.6, 143.9, 128.4, 128.3, 128.1, 127.0, 123.4, 120.9, 56.9, 19.6. **HRMS** (EI+) calculated for $[C_{22}H_{23}IN]^+$ 428.0870 *m/z*; found $[M + H]^+$ 428.0855 *m/z*. **α_D^{589}**($CHCl_3$, c 1.2, 298 K) = –8.5 deg.cm^2.g^{-1}.

2'-bromo-_N_,_N_-bis((_S_)-1-phenylethyl)-[1,1'-biphenyl]-4-amine

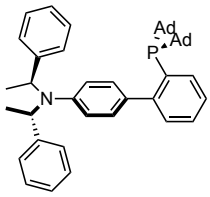


4-Iodo-*N*,*N*-bis((*R*)-1-phenylethyl)aniline (500 mg, 1.17 mmol, 1.0 equiv), (2-bromophenyl)boronic acid (470 mg, 2.34 mmol, 2.0 equiv), K_2CO_3 (485 mg, 3.51 mmol, 3.0 equiv) and $(PPh_3)_2PdCl_2$ (41.0 mg, 59.0 μmol, 5 mol%) were dissolved in DMF/H_2O (5:1, 6 mL), then the suspension was stirred at 55 ºC for 2 h. The reaction was cooled down to 24 ºC, diluted with EtOAc (40 mL), washed with sat. NH_4Cl, brine,

dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash column chromatography (pentane/CH_2Cl_2 5:1) affording the title compound (445 mg, 0.975 mmol, 83% yield) as a viscous oil.

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.65 (dt, *J* = 8.0, 0.9 Hz, 1H), 7.42 – 7.31 (m, 6H), 7.30 – 7.24 (m, 4H), 7.23 – 7.19 (m, 4H), 7.15 (ddd, *J* = 8.0, 6.1, 3.0 Hz, 1H), 6.84 – 6.76 (m, 2H), 4.89 (q, *J* = 6.9 Hz, 2H), 1.61 (d, *J* = 6.9 Hz, 6H). **^{13}C{^{1}H} NMR** (101 MHz, CD_2Cl_2) δ 146.4, 143.4, 142.8, 133.5, 131.8, 131.8, 129.7, 128.5, 128.4, 128.0, 127.8, 127.1, 122.9, 119.6, 56.2, 18.6. **HRMS** (ESI+) calculated for $[C_{28}H_{26}BrN]^+$ 456.1321 *m/z*; found $[M]^+$ 456.1329 *m/z*. α_D^{589}($CHCl_3$, c 1.1, 298 K) = –9.9 deg.cm^2.g^{-1}.

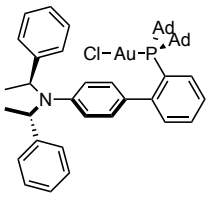
Ligand L$_I$

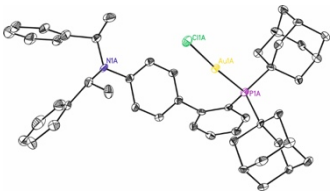


In a microwave vial 2'-bromo-*N*,*N*-bis((*S*)-1-phenylethyl)-[1,1'-biphenyl]-4-amine (150 mg, 0.329 mmol, 1.0 equiv), NaO*t*Bu (38.0 mg, 0.39 mmol, 1.2 equiv), (dppf)$PdCl_2$·CH_2Cl_2 (13.0 mg, 16.0 μmol, 5 mol%) were dissolved in toluene (3.0 mL). After stirring for 2 min di-(1-adamantyl)phosphine (109 mg, 0.362 mmol, 1.1 equiv) was added. The reaction was heated to 150 ºC for 7h under microwave radiation. The reaction was diluted with EtOAc (30 mL), washed with sat. NH_4Cl (10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated. The crude was purified by flash column chromatography (pentane/CH_2Cl_2 5:1 then pentane/Et_2O 20:1) to afford the title compound (150 mg, 221 μmol, 67%) as white foam.

M.p. = 109 – 111 °C (pentane/Et_2O). **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 7.92 (d, *J* = 7.6 Hz, 1H), 7.45 – 7.28 (m, 10H), 7.29 – 7.18 (m, 3H), 7.05 (d, *J* = 8.3 Hz, 2H), 6.76 (d, *J* = 8.5 Hz, 2H), 4.77 (q, *J* = 6.9 Hz, 2H), 2.05 – 1.84 (m, 18H), 1.70 (d, *J* = 12.8 Hz, 12H), 1.56 (d, *J* = 6.9 Hz, 6H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 152.3 (d, *J* = 32.5 Hz), 144.7, 143.8, 137.1 (d, *J* = 2.8 Hz), 136.7 (d, *J* = 7.1 Hz), 133.7 (d, *J* = 27.3 Hz), 131.2, 130.9 (d, *J* = 4.1 Hz), 128.5, 128.4, 128.2, 127.1, 125.4, 121.3, 56.8, 42.5 (d, *J* = 6.4 Hz), 42.3 (d, *J* = 6.3 Hz), 37.9, 37.4 (d, *J* = 4.0 Hz), 29.5 (d, *J* = 2.8 Hz), 29.5 (d, *J* = 3.0 Hz), 19.7. **^{31}P{^{1}H} NMR** (202 MHz, CD_2Cl_2) δ 24.3. **HRMS** (ESI+) calculated for $[C_{48}H_{57}NP]^+$ 678.4223 *m/z*; found $[M + H]^+$ 678.4256 *m/z*. α_D^{589}($CHCl_3$, c 1.1, 298 K) = –38.7 deg.cm^2.g^{-1}.

Complex (*S*,*S*)-I

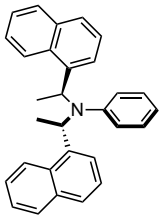




Ligand **L_I** (104 mg, 0.153 mmol, 1.0 equiv) and [Me_2SAuCl] (47.0 mg, 0.160 mmol, 1.1 equiv) were mixed in CH_2Cl_2 (3.0 mL) at 24 ºC. The solution was stirred for 2 h and then concentrated under reduced pressure. The crude was purified by flash column chromatography (cyclohexane/EtOAc 10:1) to yield the title compound (137 mg, 0.150 mmol, 98%) as white solid.

M.p. = >230 °C brown (decomposition; cyclohexane/EtOAc). **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 7.89 (td, *J* = 7.3, 1.7 Hz, 1H), 7.53 – 7.42 (m, 6H), 7.30 – 7.21 (m, 5H), 7.18 – 7.11 (m, 2H), 6.89 (td, *J* = 6.4, 3.2 Hz, 2H), 6.83 – 6.74 (m, 2H), 5.10 (q, *J* = 6.9 Hz, 2H), 2.28 – 2.10 (m, 10H), 2.01 (dq, *J* = 9.9, 3.1 Hz, 7H), 1.80 (d, *J* = 7.0 Hz, 6H), 1.70 (dd, *J* = 9.1, 3.0 Hz, 14H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 151.6 (d, *J* = 13.4 Hz), 147.4, 143.6, 135.0 (d, *J* = 2.5 Hz), 134.5 (d, *J* = 7.1 Hz), 131.2 (d, *J* = 6.6 Hz), 130.5 (d, *J* = 2.2 Hz), 128.2 (d, *J* = 2.7 Hz), 126.7, 126.1 (d, *J* = 6.5 Hz), 124.1, 116.6, 116.3, 55.1, 42.9 (d, *J* = 9.3 Hz), 42.8 (d, *J* = 9.6 Hz), 42.5 (t, *J* = 3.3 Hz), 36.7 (t, *J* = 2.2 Hz), 29.2, 29.2, 17.2. **^{31}P{^{1}H} NMR** (202 MHz, CD_2Cl_2) δ 65.1. **HRMS** (ESI+) calculated for $[C_{48}H_{57}AuClNP]^+$ 910.3577 *m/z*; found $[M + H]^+$ 910.3566 *m/z*. **α_D^{589}**($CHCl_3$, c 1.1, 298 K) = +21.6 deg.cm^2.g^{-1}.

***N*,*N*-Bis((*S*)-1-(naphthalen-1-yl)ethyl)aniline**



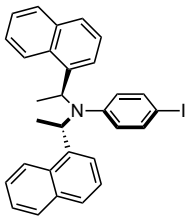
Bis[(*S*)-(+)-(1-naphthyl)ethyl]amine hydrochloride (400 mg, 1.11 mmol, 1.0 equiv) was suspended in CH_2Cl_2 (30 mL) in a separatory funnel and washed with KOH (20 mL, 2M). The organic phase was dried over Na_2SO_4 and concentrated.

The residue was dissolved in MeCN (5.5 mL), then cesium fluoride (504 mg, 3.32 mmol, 3.0 equiv) and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (0.349 mL, 1.437 mmol, 1.3 equiv) were added. The reaction was heated to 70 ºC for 14 h. Subsequently, the reaction was diluted with EtOAc (40 mL), washed with sat. NH_4Cl (10 mL), dried over Na_2SO_4 and concentrated. The crude was purified by flash column chromatography (pentane/CH_2Cl_2 5:1 yielding the title compound (385 mg, 0.959 mmol, 87%) as white foam.

M.p. = 48 – 50 °C (pentane/CH_2Cl_2). **^{1}H NMR** (400 MHz, CD_2Cl_2) δ 8.28 – 8.20 (m, 2H), 7.80 – 7.72 (m, 2H), 7.55 (d, *J* = 8.2 Hz, 2H), 7.53 – 7.39 (m, 4H), 7.31 (d, *J* = 7.3 Hz, 2H), 7.11 (dd, *J* = 8.2, 7.2 Hz, 2H), 7.02 (dd, *J* = 8.5, 7.3 Hz, 2H), 6.87 – 6.74 (m, 3H), 5.66 (q, *J* = 6.8 Hz, 2H), 1.68 (d, *J* = 6.8 Hz, 6H). **^{13}C{^{1}H} NMR** (101 MHz, CD_2Cl_2) δ 147.4, 140.0, 134.0, 132.0, 129.0, 128.0, 127.5, 126.0, 125.8, 125.5, 125.2, 124.9, 124.3, 121.8,

54.2, 18.5. **HRMS** (EI+) calculated for $[C_{30}H_{27}NNa]^+$ 424.2036 *m/z*; found $[M + H]^+$ 424.2044 *m/z*. α_D^{589}($CHCl_3$, c 1.1, 298 K) = +2665.11 deg.cm^2.g^{-1}.

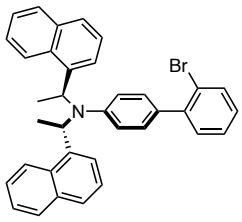
4-Iodo-*N*,*N*-bis((*S*)-1-(naphthalen-1-yl)ethyl)aniline



To a solution of *N*,*N*-bis((*S*)-1-(naphthalen-1-yl)ethyl)aniline (517 mg, 1.28 mmol, 1.0 equiv) in dioxane/pyridine (1:1, 6.5 mL) at 0 ºC, was added iodine (980 mg, 3.86 mmol, 3 equiv). The reaction was slowly warmed up to 24 ºC and stirred overnight. The mixture was diluted with EtOAc (50 mL), washed with sat. Na_2SO_3 (20 mL), dried over Na_2SO_4 and concentrated. The crude was purified by flash column chromatography (pentane/CH_2Cl_2 5:1) affording the title compound (651 mg, 1.23 mmol, 96%) as a white solid.

M.p. = 79 – 81 °C (pentane/CH_2Cl_2). **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 8.14 (dd, *J* = 8.6, 1.4 Hz, 2H), 7.78 – 7.68 (m, 2H), 7.52 (dd, *J* = 8.2, 1.2 Hz, 2H), 7.49 – 7.38 (m, 4H), 7.32 (d, *J* = 8.8 Hz, 2H), 7.25 (dt, *J* = 7.3, 1.0 Hz, 2H), 7.07 (dd, *J* = 8.2, 7.2 Hz, 2H), 6.61 – 6.55 (m, 2H), 5.65 (q, *J* = 6.8 Hz, 2H), 1.68 (d, *J* = 6.9 Hz, 6H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 147.5, 139.2, 137.1, 134.0, 131.9, 129.0, 127.7, 126.2, 125.7, 125.7, 125.6, 125.1, 124.2, 83.8, 54.0, 18.1. **HRMS** (APCI+) calculated for $[C_{30}H_{27}IN]^+$ 528.1183 *m/z*; found $[M + H]^+$ 528.1183 *m/z*. α_D^{589}($CHCl_3$, c 1.0, 298 K) = +2739.71 deg.cm^2.g^{-1}.

2'-Bromo-*N*,*N*-bis((*S*)-1-(naphthalen-1-yl)ethyl)-[1,1'-biphenyl]-4-amine

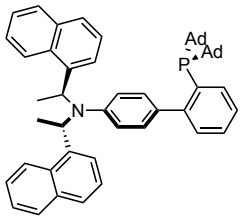


4-Iodo-*N*,*N*-bis((*S*)-1-(naphthalen-1-yl)ethyl)aniline (291 mg, 0.552 mmol, 1.0 equiv), (2-bromophenyl)boronic acid (222 mg, 1.10 mmol, 2.0 equiv), K_2CO_3 (229 mg, 1.65 mmol, 3.0 equiv) and $(PPh_3)_2PdCl_2$ (39.0 mg, 55.0 μmol, 5 mol%) were dissolved in in DMF:H_2O (5:1, 6.0 mL). The solution was stirred at 55 ºC for 2 h and then diluted with EtOAc (40 mL), washed with sat. NH_4Cl (10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated. The crude was purified by flash column chromatography (pentane/CH_2Cl_2 5:1) to afford the title compound (278 mg, 0.500 mmol, 91%) as white powder.

M.p. = 64 – 66 °C (pentane/CH_2Cl_2). **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 8.12 (d, *J* = 8.6 Hz, 2H), 7.77 – 7.70 (m, 2H), 7.66 (dt, *J* = 8.0, 0.9 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.48 – 7.38 (m, 4H), 7.38 – 7.27 (m, 4H), 7.26 – 7.19 (m, 2H), 7.16 (ddd, *J* = 8.0, 5.2, 3.9 Hz, 1H), 7.07 (dd, *J* = 8.2, 7.2 Hz, 2H), 6.99 – 6.92 (m, 2H), 5.72 (q, *J* = 6.9 Hz, 2H), 1.73 (d, *J* = 6.9 Hz, 6H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 147.1, 142.8, 139.3, 134.0, 133.5, 133.2, 131.9, 131.7, 129.5, 129.0, 128.6, 127.8, 127.5, 126.1, 125.8, 125.5, 125.1, 124.3, 123.0,

122.0, 18.6. **HRMS** (ESI+) calculated for $[C_{36}H_{31}BrN]^+$ 556.1634 *m/z*; found $[M + H]^+$ 556.1656 *m/z*. α_D^{589}($CHCl_3$, c 1.0, 298 K) = +2673.84 deg.cm^2.g^{-1}.

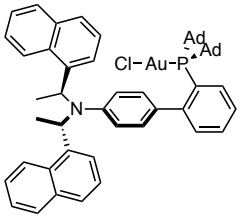
Ligand L$_J$



In a microwave vial 2'-bromo-*N*,*N*-bis((*S*)-1-(naphthalen-1-yl)ethyl)-[1,1'-biphenyl]-4-amine (150 mg, 0.270 mmol, 1.0 equiv), NaO*t*Bu (31.0 mg, 0.320 mmol, 1.2 equiv) and (dppf)$PdCl_2 \cdot CH_2Cl_2$ (11.0 mg, 13.0 µmol, 5 mol %) were dissolved in toluene (2.5 mL). After stirring for 2 min, di-(1-adamantyl)phosphine (90 mg, 0.30 mmol, 1.1 equiv) was added. The reaction was heated to 150 ºC for 4 h under microwave radiation. The reaction was diluted with EtOAc (30 mL), washed with sat. NH_4Cl (10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated. The crude was purified by flash column chromatography (pentane/CH_2Cl_2 5:1, then pentane/Et_2O 20:1) to afford the title compound (170 mg, 0.218 mmol, 81%) as white foam.

M.p. = 141 – 143 °C (pentane/Et_2O). **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 8.27 – 8.21 (m, 2H), 7.88 (d, *J* = 7.5 Hz, 1H), 7.82 – 7.77 (m, 2H), 7.60 (d, *J* = 8.1 Hz, 2H), 7.52 – 7.43 (m, 4H), 7.40 (d, *J* = 7.2 Hz, 2H), 7.37 – 7.26 (m, 2H), 7.23 (t, *J* = 7.6 Hz, 3H), 6.97 (d, *J* = 8.1 Hz, 2H), 6.76 (d, *J* = 8.2 Hz, 2H), 5.67 (q, *J* = 6.7 Hz, 2H), 1.99 – 1.81 (m, 20H), 1.77 – 1.64 (m, 20H). **^{13}C{^{1}H} NMR** (101 MHz, CD_2Cl_2) δ 152.2 (d, *J* = 32.4 Hz), 145.4, 140.1, 137.8 (d, *J* = 7.1 Hz), 137.1 (d, *J* = 2.6 Hz), 134.1, 134.0, 133.7, 132.2, 130.9 (d, *J* = 6.1 Hz), 130.7 (d, *J* = 4.4 Hz), 129.0, 128.5, 127.4, 126.0 (d, *J* = 3.5 Hz), 125.5, 125.4, 124.5, 123.7, 54.3, 42.5 (d, *J* = 7.1 Hz), 42.3 (d, *J* = 6.9 Hz), 37.8 (d, *J* = 4.1 Hz), 37.6 (d, *J* = 4.2 Hz), 37.5, 29.5 (d, *J* = 2.2 Hz), 29.5 (d, *J* = 2.4 Hz), 19.1. **^{31}P{^{1}H} NMR** (162 MHz, CD_2Cl_2) δ 24.2. **HRMS** (ESI+) calculated for $[C_{56}H_{61}PN]^+$ 778.4536 *m/z*; found $[M + H]^+$ 778.4569 *m/z*. α_D^{589}($CHCl_3$, c 1.1, 298 K) = +2471.09 deg.cm^2.g^{-1}.

Complex (*S*,*S*)-J

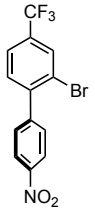


Ligand **L$_J$** (60.0 mg, 77.0 µmol, 1.0 equiv) and [Me_2SAuCl] (22.9 mg, 78.0 µmol, 1.0 equiv) were mixed in CH_2Cl_2 (1.0 mL) at 24 ºC. The solution was stirred for 2 h and then concentrated under reduced pressure. The crude e was purified by flash column chromatography (cyclohexane/EtOAc 10:1) to afford the title compound (64.0 mg, 63.0 µmol, 82%) as white solid.

M.p. = >230 °C brown (decomposition; cyclohexane/EtOAc). **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 8.02 (d, *J* = 8.6 Hz, 2H), 7.96 – 7.89 (m, 1H), 7.59 (d, *J* = 8.2 Hz, 2H), 7.55 – 7.51 (m, 1H), 7.51 – 7.47 (m, 3H), 7.44 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 2H), 7.19 (dd, *J* = 8.6,

2.4 Hz, 5H), 7.15 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.08 – 7.00 (m, 1H), 6.97 (dd, *J* = 8.2, 7.2 Hz, 2H), 5.79 (q, *J* = 6.9 Hz, 2H), 2.34 – 2.29 (m, 3H), 2.26 – 2.20 (m, 6H), 2.18 – 2.11 (m, 3H), 2.08 – 1.98 (m, 6H), 1.90 (d, *J* = 6.9 Hz, 6H), 1.80 – 1.66 (m, 12H). **$^{13}C\{^1H\}$ NMR** (126 MHz, CD_2Cl_2) δ 151.7 (d, *J* = 13.4 Hz), 147.3, 139.0, 135.1 (d, *J* = 2.5 Hz), 134.9 (d, *J* = 7.3 Hz), 133.6, 132.0 (d, *J* = 6.6 Hz), 131.6, 130.6 (d, *J* = 2.2 Hz), 130.3, 130.1, 128.6, 127.2, 126.2 (d, *J* = 6.5 Hz), 126.0, 125.9, 125.3, 124.9, 124.8, 124.2, 123.8, 118.2, 117.2, 53.6, 43.1 (d, *J* = 23.9 Hz), 42.8 (d, *J* = 2.6 Hz), 42.8 (d, *J* = 23.8 Hz), 42.4 (d, *J* = 2.6 Hz), 36.8 (d, *J* = 5.7 Hz), 29.3 (d, *J* = 9.8 Hz), 29.2 (d, *J* = 9.8 Hz), 18.2. **$^{31}P\{^1H\}$ NMR** (202 MHz, CD_2Cl_2) δ 65.1. **HRMS** (ESI+) calculated for $[C_{56}H_{61}AuClNP]^+$ 1010.3890 *m/z*; found $[M + H]^+$ 1010.3884 *m/z*. α_D^{589}($CHCl_3$, c 1.1, 298 K) = +2366.65 deg.cm^2.g^{-1}.

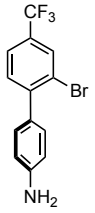
2-Bromo-4'-nitro-4-(trifluoromethyl)-1,1'-biphenyl



$(PPh_3)_2PdCl_2$ (51.0 mg, 73.0 μmol, 1.5 mol %), (4-nitrophenyl)boronic acid (890 mg, 5.33 mmol), 2-bromo-1-iodo-4-(trifluoromethyl)benzene (1.70 g, 4.84 mmol) and K_2CO_3 (1.67 g, 12.1 mmol) were dissolved in H_2O (2.47 mL) and DME (15 mL). The reaction mixture was degassed for 5 min with argon and then stirred at 80 ºC overnight. The reaction mixture was allowed to cool to 24 ºC and EtOAc was added. The layers were separated and the aqueous phase was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude was purified by flash column chromatography (cyclohexane/EtOAc 30:1) to yield the title compound (1.25 g, 3.61 mmol, 75%) as a white solid.

M.p. = 89–91 °C (cyclohexane/EtOAc). **^1H NMR** (400 MHz, CD_2Cl_2) δ 8.35 – 8.28 (m, 2H), 8.01 (d, *J* = 0.8 Hz, 1H), 7.70 (ddd, *J* = 8.0, 1.9, 0.8 Hz, 1H), 7.65 – 7.58 (m, 2H), 7.49 (d, *J* = 8.0 Hz, 1H). **$^{13}C\{^1H\}$ NMR** (101 MHz, CD_2Cl_2) δ 148.2, 146.5, 144.5, 132.2 (q, *J* = 33.0 Hz), 131.8, 130.8, 130.7 (q, *J* = 4.0 Hz), 125.0 (q, *J* = 3.7 Hz), 123.8, 123.5 (q, *J* = 273.3 Hz), 122.9. **$^{19}F\{^1H\}$ NMR** (376 MHz, CD_2Cl_2) δ –63.2. **HRMS** (APCI+) calculated for $[C_{13}H_7BrF_3NO_2]^+$ 344.9607 *m/z*; found $[M]^+$ 344.9596 *m/z*.

2'-Bromo-4'-(trifluoromethyl)-[1,1'-biphenyl]-4-amine

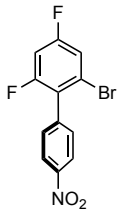


Iron powder (504 mg, 9.03 mmol, 2.5 equiv) was added to a solution of 2-bromo-4'-nitro-4-(trifluoromethyl)-1,1'-biphenyl (1.25 g, 3.61 mmol, 1.0 equiv) in AcOH (12 mL) and H_2O (0.61 mL) (20:1). The mixture was stirred at 50 ºC overnight, then allowed to cool to 24 ºC and filtered over Celite®. The filtrate was rinsed with AcOH and extracted with EtOAc (3x). The combined organic layers were washed with water, basified with Na_2CO_3, and then washed with $NaHCO_3$ and brine. The organic phase was dried over Na_2SO_4, filtered and concentrated.

The crude was purified by flash column chromatography (cyclohexane/EtOAc 10:1) to yield the title compound (853 mg, 2.70 mmol, 74%) as a brown gum.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 1.0 Hz, 1H), 7.57 (ddd, *J* = 8.0, 1.9, 0.8 Hz, 2H), 7.42 (d, *J* = 8.0, Hz, 2H), 7.25 – 7.20 (m, 2H), 6.78 – 6.71 (m, 2H), 3.79 (s, 2H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 146.7, 146.3, 131.7, 130.5, 130.3 (q, *J* = 4.0 Hz), 130.1, 130.0, 124.3 (q, *J* = 3.7 Hz), 123.5 (q, *J* = 272.6 Hz), 123.2, 114.6. **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) δ –62.6. **HRMS** (ESI+) calculated for $[C_{13}H_{10}BrF_3N]^+$ 315.9943 *m/z*; found $[M + H]^+$ 315.9947 *m/z*.

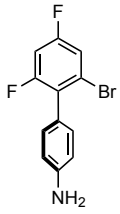
2-Bromo-4,6-difluoro-4'-nitro-1,1'-biphenyl



$(PPh_3)_2PdCl_2$ (56 mg, 0.015 mmol, 1.5 mol %), (4-nitrophenyl)boronic acid (979 mg, 5.86 mmol, 1.1 equiv), 1-bromo-3,5-difluoro-2-iodobenzene (1.7 g, 5.33 mmol, 1.0 equiv) and K_2CO_3 (1.84 g, 13.3 mmol, 2.5 equiv) were dissolved in Water (2.7 mL) and DME (16 mL). The reaction mixture was degassed for 5 min with argon and then stirred at 80 ºC for 24 h. The reaction mixture was allowed to cool to 24 ºC and EtOAc was added. The layers were separated and the aqueous phase was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude was purified by flash column chromatography (cyclohexane/EtOAc 30:1) to yield title compound (955 mg, 3.04 mmol, 57%) as a yellow gum.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 – 8.29f (m, 2H), 7.53 – 7.48 (m, 2H), 7.31 (ddd, *J* = 7.9, 2.5, 1.7 Hz, 1H), 6.96 (ddd, *J* = 9.3, 8.4, 2.5 Hz, 1H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 163.8 (d, *J* = 13.5 Hz), 161.2 (d, *J* = 13.2 Hz), 158.7 (d, *J* = 12.9 Hz), 148.0, 131.6, 125.4 (dd, *J* = 18.4, 4.4 Hz), 124.0 (dd, *J* = 11.6, 4.9 Hz), 123.7, 116.9 (dd, *J* = 24.5, 4.0 Hz), 104.1 (dd, *J* = 26.9, 25.2 Hz). **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) δ –106.1 (d, *J* = 7.3 Hz), –108.0 (d, *J* = 7.3 Hz). **HRMS** (APCI+) calculated for $[C_{12}H_7BrF_2NO_2]^+$ 313.9623 *m/z*; found $[M + H]^+$ 313.9624 *m/z*.

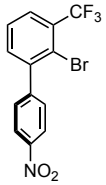
2'-Bromo-4',6'-difluoro-[1,1'-biphenyl]-4-amine



Iron powder (693 mg, 12.4 mmol, 2.5 equiv) was added to a solution of 2-bromo-4,6-difluoro-4'-nitro-1,1'-biphenyl (1.56 g, 4.97 mmol, 1.0 equiv) in AcOH (17 mL)/H_2O (0.85 mL) (20:1). The mixture was stirred at 50 ºC overnight, then allowed to cool to 24 ºC and filtered over Celite®. The filtrate was rinsed with AcOH and extracted with EtOAc (3x). The combined organic layers were washed with water, basified with Na_2CO_3, and then washed with $NaHCO_3$ and brine. The organic phase was dried over Na_2SO_4, filtered and concentrated. The crude was purified by flash column chromatography (cyclohexane/EtOAc 10:1) to afford the title compound (920 mg, 3.24 mmol, 65%) as a pale yellow solid.

M.p. = 107–109 °C (cyclohexane/EtOAc). **^{1}H NMR** (400 MHz, CD_2Cl_2) δ 7.24 (ddd, *J* = 8.1, 2.6, 1.7 Hz, 1H), 7.12 – 7.06 (m, 2H), 6.92 – 6.83 (m, 1H), 6.78 – 6.72 (m, 2H), 3.79 (s, 2H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 161.9 (dd, *J* = 126.8, 13.3 Hz), 159.9 (dd, *J* = 126.1, 13.2 Hz), 146.7, 131.3, 127.6 (d, *J* = 23.1 Hz), 125.2 (dd, *J* = 11.7, 4.5 Hz), 123.6, 116.2 (dd, *J* = 24.1, 4.1 Hz), 114.8, 104.1 – 103.2 (m). **^{19}F{^{1}H} NMR** (376 MHz, CD_2Cl_2) δ –106.2 (d, *J* = 6.4 Hz), –111.3 (d, *J* = 6.4 Hz). **HRMS** (ESI+) calculated for $[C_{12}H_9BrF_2N]^+$ 283.9881 *m/z*; found $[M + H]^+$ 283.9875 *m/z*.

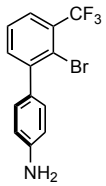
2-Bromo-4'-nitro-3-(trifluoromethyl)-1,1'-biphenyl



$(PPh_3)_2PdCl_2$ (49 mg, 69.0 μmol, 1.5 mol %), (4-nitrophenyl)boronic acid (848 mg, 5.08 mmol, 1.1 equiv), 2-bromo-1-iodo-4-(trifluoromethyl)benzene (1.62 g, 4.62 mmol, 1.0 equiv) and K_2CO_3 (1.59 g, 11.54 mmol, 2.5 equiv) were dissolved in water (2.4 mL) and DME (14 mL). The reaction mixture was degassed for 5 min with argon and then stirred at 80 ºC overnight. The reaction mixture was allowed to cool to 24 ºC and EtOAc was added. The layers were separated and the aqueous phase was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude was purified by flash column chromatography (cyclohexane/Et_2O 50:1) to afford the title compound (937 mg, 2.70 mmol, 59%) as a white solid.

M.p. = 106–108 °C (cyclohexane/Et_2O). **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 8.34 – 8.28 (m, 2H), 7.80 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.59 – 7.54 (m, 3H), 7.51 (dd, *J* = 8.0, 1.6 Hz, 1H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 148.1, 147.4, 143.9, 134.5, 131.5 (q, *J* = 30.6 Hz), 131.0, 128.3 (q, *J* = 5.6 Hz), 128.1, 123.8, 123.5 (q, *J* = 273.4 Hz), 120.3. **^{19}F{^{1}H} NMR** (471 MHz, CD_2Cl_2) δ –62.6. **HRMS** (APCI+) calculated for $[C_{13}H_8BrF_3NO_2]^+$ 345.9685 *m/z*; found $[M + H]^+$ 345.9677 *m/z*.

2'-Bromo-3'-(trifluoromethyl)-[1,1'-biphenyl]-4-amine

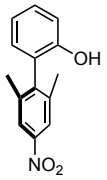


Iron powder (371 mg, 6.65 mmol, 2.5 equiv) was added to a solution of 2-bromo-4'-nitro-3-(trifluoromethyl)-1,1'-biphenyl (920 mg, 2.66 mmol, 1.0 equiv) in AcOH (9.0 mL)/H_2O (0.45 mL) (20:1). The mixture was stirred at 50 ºC overnight. The reaction progress was monitored by GC-MS. Another portion of iron powder (3.14 mg, 2.66 mmol, 1.0 equiv) was added and the reaction mixture was stirred for other 8 h. The reaction was allowed to cool to 24 ºC and filtered over Celite®. The filtrate was rinsed with AcOH and extracted with EtOAc (3x). The combined organic layers were washed with water, basified with Na_2CO_3, and then washed with $NaHCO_3$ and brine. The organic phase was dried over Na_2SO_4, filtered and concentrated. The crude was purified by flash column chromatography

(cyclohexane/EtOAc 4:1) to yield the title compound (686 mg, 2.17 mmol, 82%) as a brown oil.

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.66 (dd, *J* = 7.4, 2.1 Hz, 1H), 7.52 – 7.40 (m, 2H), 7.19 – 7.11 (m, 2H), 6.78 – 6.70 (m, 2H), 3.86 (s, 2H). **^{13}C{^{1}H} NMR** (101 MHz, CD_2Cl_2) δ 147.2, 146.1, 135.1, 131.3 (q, *J* = 21.0 Hz), 130.9, 126.7 (q, *J* = 5.8 Hz), 123.8 (q, *J* = 273.3 Hz), 121.1 (d, *J* = 1.6 Hz), 114.6. **^{19}F{^{1}H} NMR** (376 MHz, CD_2Cl_2) δ –62.4. **HRMS** (ESI+) calculated for $[C_{13}H_{10}BrF_3N]^+$ 315.9943 *m/z*; found $[M + H]^+$ 315.9938 *m/z*.

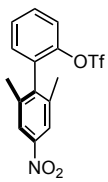
2',6'-Dimethyl-4'-nitro-[1,1'-biphenyl]-2-ol[182]



2,6-Dimethyl-4-nitrophenyl trifluoromethanesulfonate[183] (200 mg, 670 μmol, 1.0 equiv), 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (0.14 mL, 700 μmol, 1.1 equiv), LiOH (38.0 mg, 1.60 mmol, 2.4 equiv), $Pd(OAc)_2$ (3.00 mg, 13 μmol, 2 mol %), and CyJohnPhos (5.62 mg, 16.0 μmol, 2.4 mol %) were placed in a flask, and then evacuated and backfilled with argon. THF (0.53 mL) and water (0.13 mL) were added, and the reaction mixture was stirred at 24 ºC overnight. After adding aq. HCl (5.0 mL, 10%), the product was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude was purified by flash column chromatography (cyclohexane/EtOAc 10:1) to yield the title compound (128 mg, 0.52 mmol, 79%) as a brown solid.

M.p. =123 – 125 °C (cyclohexane/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02 (t, *J* = 0.7 Hz, 2H), 7.33 (ddd, *J* = 8.1, 7.3, 1.8 Hz, 1H), 7.05 (td, *J* = 7.4, 1.1 Hz, 1H), 7.02 – 6.95 (m, 2H), 4.46 (s, 1H), 2.16 (t, *J* = 0.7 Hz, 6H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 151.9, 147.5, 143.2, 139.9, 130.0, 129.4, 125.0, 122.5, 121.5, 116.1, 20.7. **HRMS** (ESI–) calculated for $[C_{14}H_{12}NO_3]^-$ 242.0823 *m/z*; found $[M – H]^-$ 242.0819 *m/z*.

2',6'-Dimethyl-4'-nitro-[1,1'-biphenyl]-2-yl trifluoromethanesulfonate



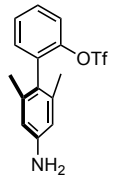
A solution of 2',6'-dimethyl-4'-nitro-[1,1'-biphenyl]-2-ol (748 mg, 3.07 mmol, 1.0 equiv) in CH_2C_2 (24 mL) was cooled to 0 °C and *N*-ethyl-*N*-isopropylpropan-2-amine (1.33 mL, 7.69 mmol, 2.5 equiv) was added followed by $(Tf)_2O$ (1.09 mL, 6.46 mmol, 2.1 equiv). The cooling bath was removed, and the mixture was stirred at 24 ºC for 12 h. The mixture was washed with aq. HCl (10%), sat. $NaHCO_3$, and brine. The organic phase was dried over Na_2SO_4, filtered and concentrated. The crude was purified by flash column chromatography

182. The title compound was synthesized according to a modified procedure: Ishikawa, S.; Manab, K. *Chem. Commun.* **2006**, 2589–2591.
183. Gantenbein, M.; Hellstern, M.; Le Pleux, L.; Neuburger, M.; Mayor, M. *Chem. Mater.* **2015**, *27*, 1772–1779.

(cyclohexane/CH_2Cl_2 10/1) to yield the title compound (728 mg, 1.94 mmol, 63%) as an orange solid.

M.p. = 109 – 111 °C (cyclohexane/ CH_2Cl_2). **^{1}H NMR** (400 MHz, CD_2Cl_2) δ 8.03 – 7.98 (m, 2H), 7.60 – 7.51 (m, 2H), 7.47 – 7.43 (m, 1H), 7.33 – 7.27 (m, 1H), 2.15 (s, 6H). **^{13}C{^{1}H} NMR** (101 MHz, CD_2Cl_2) δ 148.1, 146.7, 141.7, 139.6, 132.8, 132.0, 130.8, 129.4, 122.6, 122.5, 120.3, 117.1, 20.7. **^{19}F{^{1}H} NMR** (376 MHz, CD_2Cl_2) δ –74.5. **HRMS** (ESI+) calculated for $[C_{15}H_{12}F_3NNaO_5S]^+$ 398.0280 *m/z*; found $[M + Na]^+$ 398.0288 *m/z*.

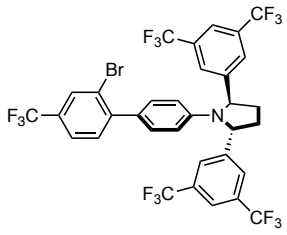
4'-Amino-2',6'-dimethyl-[1,1'-biphenyl]-2-yl trifluoromethanesulfonate



Iron powder (379 mg, 6.79 mmol, 3.5 equiv) was added to a solution of 2',6'-dimethyl-4'-nitro-[1,1'-biphenyl]-2-yl trifluoromethanesulfonate (728 mg, 1.94 mmol, 1.0 equiv) in AcOH (6.6 mL)/Water (0.33 mL). The mixture was stirred at 50 ºC overnight, then allowed to cool to 24 ºC and filtered over Celite®. The filtrate was rinsed with AcOH and extracted with EtOAc (3x). The combined organic layers were washed with water, basified with $NaCO_3$, and then washed with sat. $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated. The crude was purified by flash column chromatography (cyclohexane/EtOAc 10:1) to afford the title compound (506 mg, 1.47 mmol, 76% yield) as a white solid.

M.p. = 81 – 83 °C (cyclohexane/ EtOAc). **^{1}H NMR** (400 MHz, CD_2Cl_2) δ 7.48 – 7.41 (m, 2H), 7.38 – 7.33 (m, 1H), 7.30 (dd, *J* = 6.0, 3.4 Hz, 1H), 6.47 (s, 2H), 3.70 (s, 2H), 1.95 (s, 6H). **^{13}C{^{1}H} NMR** (101 MHz, CD_2Cl_2) δ 148.3, 147.1, 138.2, 135.2, 133.8, 129.3, 128.8, 125.0, 121.8, 118.8 (q, *J* = 319.0 Hz), 114.3, 20.5. **^{19}F{^{1}H} NMR** (376 MHz, CD_2Cl_2) δ –74.1. **HRMS** (ESI+) calculated for $[C_{15}H_{15}F_3NO_3S]^+$ 346.0719 *m/z*; found $[M + H]^+$ 346.0724 *m/z*

(2*R*)-2,5-Bis(3,5-bis(trifluoromethyl)phenyl)-1-(2'-bromo-4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)pyrrolidine

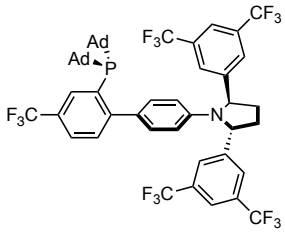


To a solution of (1*S*,4*S*)-1,4-bis(3,5-bis(trifluoromethyl) phenyl)butane-1,4-diol (290 g, 560 μmol, 1.0 equiv) in CH_2Cl_2 (5.6 mL) at –20 °C were added NEt_3 (240 μL, 1.70 mmol, 3.0 equiv) and methanesulfonyl chloride (110 μL, 1.50 mmol, 2.6 equiv) under an atmosphere of argon. The mixture was stirred for 2.5 h at –20 °C. Then, a solution of 2'-bromo-4'-(trifluoromethyl)-[1,1'-biphenyl]-4-amine (873 mg, 2.70 mmol, 4.9 equiv) in CH_2Cl_2 (1.0 mL) was added and the resulting mixture was stirred at 24 ºC overnight. The volatile products were removed under reduced pressure and the organic materials were extracted

with EtOAc. The combined organic phases were washed with brine and sat. $NaHCO_3$, dried over Na_2SO_4 and concentrated. The crude was purified by flash column chromatography (cyclohexane/EtOAc 30:1) to afford the title compound (325 mg, 410 μmol, 73%) as a white solid.

M.p. = 160 – 162 °C (cyclohexane/ EtOAc). **^{1}H NMR** (400 MHz, CD_2Cl_2) δ 7.87 (s, 1H), 7.84 (s, 2H), 7.73 (s, 4H), 7.54 (ddd, *J* = 8.0, 1.9, 0.8 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.18 – 7.10 (m, 2H), 6.43 – 6.36 (m, 2H), 5.48 (d, *J* = 6.9 Hz, 2H), 2.71 – 2.53 (m, 2H), 2.02 – 1.87 (m, 2H). **^{13}C{^{1}H} NMR** (101 MHz, CD_2Cl_2) δ 146.6, 146.4, 143.9, 132.3 (q, *J* = 32.9 Hz), 132.0, 130.6, 130.2, 130.5 – 130.3 (m), 129.3, 126.9 (d, *J* = 4.0 Hz), 124.6 (q, *J* = 3.7 Hz), 123.8 (q, *J* = 271.7 Hz), 123.3, 121.8 (p, *J* = 3.9 Hz), 114.1, 63.2, 32.5. **^{19}F{^{1}H} NMR** (376 MHz, CD_2Cl_2) δ –63.0, –63.3. **HRMS** (ESI+) calculated for $[C_{33}H_{20}BrF_{15}]^+$ 794.0534 *m/z*; found $[M + H]^+$ 794.0541 *m/z*. α_D^{589} = +29.5 deg.cm^2.g^{-1} ($CHCl_3$, c 1.0, 300 K).

Ligand L$_K$

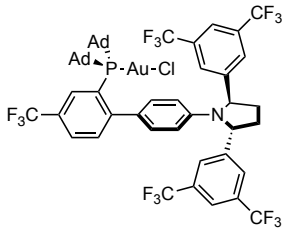


A flame-dried 10 mL Schlenk flask was charged with (2*R*)-2,5-bis(3,5-bis(trifluoromethyl)phenyl)-1-(2'-bromo-4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)pyrrolidine (220 mg, 250 μmol, 1.0 equiv), $Pd(OAc)_2$ (2.83 mg, 13.0 μmol, 5 mol %), dppf (8.40 mg, 15.0 μmol, 6 mol %), NaO*t*Bu (29.0 mg, 300 μmol, 1.2 equiv) and toluene (1.3 mL) and the resulting suspension was stirred for 15 min at 24 ºC. Di(1-adamantyl)phosphine (84 mg, 0.28 mmol, 1.1 equiv) was added and the reaction mixture was stirred at 120 ºC for 16 h. Then, the reaction was allowed to cool to 24 ºC and the crude was purified by flash column chromatography (cyclohexane/CH_2Cl_2 40:1 then 4:1) to yield ligand **L$_K$** (208 mg, 200 μmol, 81%) as a white solid.

M.p. = >160 °C (decomposition; cyclohexane/CH_2Cl_2). **^{1}H NMR** (400 MHz, CD_2Cl_2) δ 8.09 (s, 1H), 7.83 (s, 2H), 7.74 (s, 4H), 7.54 (d, *J* = 8.1 Hz, 1H), 7.30 (dd, *J* = 8.2, 3.9 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 2H), 6.35 – 6.26 (m, 2H), 5.49 (d, *J* = 6.4 Hz, 2H), 2.69 – 2.52 (m, 2H), 1.99 – 1.81 (m, 11H), 1.78 (s, 3H), 1.74 – 1.64 (m, , 12H), 1.64 – 1.49 (m, 6H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 154.8 (d, *J* = 31.1 Hz), 146.4, 142.3, 134.8, 134.5, 133.3 – 133.0 (m), 131.8 (q, *J* = 33.2 Hz), 131.7 (d, *J* = 5.1 Hz), 131.5 (d, *J* = 6.4 Hz), 131.1 (d, *J* = 5.3 Hz), 126.5 (t, *J* = 3.9 Hz), 124.62 (q, *J* = 3.7 Hz), 124.58 (q, *J* = 273.8 Hz), 122.9 (q, *J* = 272.3 Hz), 121.2 (p, *J* = 4.0 Hz), 112.8, 62.6, 42.0 (d, *J* = 13.3 Hz), 41.4 (d, *J* = 13.1 Hz), 37.5 (d, *J* = 26.5 Hz), 37.2 (d, *J* = 27.1 Hz), 36.8, 36.69, 32.0, 29.0 (d, *J* = 8.6 Hz), 28.8 (d, *J* = 8.6 Hz). **^{31}P{^{1}H} NMR** (162 MHz, CD_2Cl_2) δ 23.7. **^{19}F{^{1}H} NMR** (376 MHz, CD_2Cl_2) δ –62.8 (d, *J* = 2.2 Hz), –63.2. **HRMS** (ESI+) calculated for

$[C_{53}H_{50}F_{15}NP]^+$1016.3436 *m/z*; found $[M + H]^+$ 1016.3475 *m/z*. α_D^{589} = –1.4 deg.cm^2.g^{-1} ($CHCl_3$, c 1.0, 300 K).

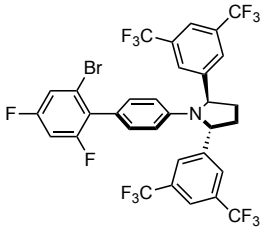
Complex (*R*,*R*)-K



$[Me_2SAuCl]$ (18.7 mg, 64.0 µmol, 1.0 equiv) and ligand $\mathbf{L_K}$ (64.6 mg, 64.0 µmol, 1.0 equiv) were dissolved in CH_2Cl_2 (1.4 mL) under an atmosphere of argon. The reaction mixture was stirred at 24 ºC for 30 min. The mixture was filtered through a syringe filter and concentrated. The crude was purified by flash column chromatography (cyclohexane/Et_2O 40:1) to yield complex (*R*,*R*)-**K** (63.4 mg, 51.0 µmol, 80%) as a white solid.

M.p. = >250 °C (decomposition; cyclohexane/ Et_2O). **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 8.08 (d, *J* = 6.9 Hz, 1H), 7.91 (s, 4H), 7.82 (s, 2H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.41 (dd, *J* = 8.1, 3.9 Hz, 1H), 6.91 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.74 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.31 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.25 (dd, *J* = 8.5, 2.7 Hz, 1H), 5.50 (d, *J* = 6.9 Hz, 2H), 2.66 – 2.55 (m, 2H), 2.27 – 2.14 (m, 6H), 2.01 (s, 3H), 1.98 – 1.88 (m, 9H), 1.88 – 1.81 (m, 2H), 1.71 (s, 6H), 1.60 (q, *J* = 12.3 Hz, 6H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 154.7 (d, *J* = 11.9 Hz), 146.9, 144.3, 134.6 (d, *J* = 6.5 Hz), 132.1 (q, *J* = 33.1 Hz), 131.6 (q, *J* = 3.4 Hz), 130.0, 129.71, 129.6 (d, *J* = 6.1 Hz), 127.3 (d, *J* = 3.9 Hz), 126.0, 125.6, 123.90 (q, *J* = 272.6 Hz), 123.93 (q, *J* = 272.3 Hz), 121.5 (p, *J* = 4.0 Hz), 116.2, 114.0, 63.6, 43.5 (d, *J* = 22.5 Hz), 43.1 (d, *J* = 2.7 Hz), 42.7 (d, *J* = 22.3 Hz), 41.9 (d, *J* = 2.6 Hz), 36.6, 36.5, 29.3 (d, *J* = 9.8 Hz), 29.0 (d, *J* = 9.9 Hz). **^{31}P{^{1}H} NMR** (202 MHz, CD_2Cl_2) δ 65.4. **^{19}F{^{1}H} NMR** (471 MHz, CD_2Cl_2) δ –62.81, –63.10. **HRMS** (ESI+) calculated for $[C_{53}H_{49}AuClF_{15}NNaP]^+$ 1270.2610 *m/z*; found $[M + Na]^+$ 1270.2591 *m/z*. α_D^{589} = +35.2 deg.cm^2.g^{-1} ($CHCl_3$, c 1.0, 300 K).

(2*R*)-2,5-Bis(3,5-bis(trifluoromethyl)phenyl)-1-(2'-bromo-4',6'-difluoro-[1,1'-biphenyl]-4-yl)pyrrolidine

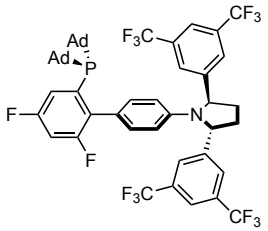


To a solution of (1*S*,4*S*)-1,4-bis(3,5-bis(trifluoromethyl) phenyl)butane-1,4-diol (330 mg, 0.64 mmol, 1.0 equiv) in CH_2Cl_2 (6.4 mL) at –20 °C were added NEt_3 (0.27 mL, 1.90 mmol, 3.0 equiv) and methanesulfonyl chloride (0.13 mL, 1.70 mmol, 2.6 equiv) under an atmosphere of argon. The mixture was stirred for 2.5 h at –20 °C. Then, a solution of 2'-Bromo-4',6'-difluoro-[1,1'-biphenyl]-4-amine (893 mg, 3.10 mmol, 4.9 equiv) in CH_2Cl_2 (1.0 mL) was added and the resulting mixture was stirred at 24 ºC overnight. The volatile products were removed under reduced pressure and the organic materials were extracted with EtOAc. The combined organic phases were washed with brine and sat. $NaHCO_3$, dried

over Na_2SO_4 and concentrated. The crude was purified by flash column chromatography (cyclohexane/EtOAc 30:1) to yield the title compound (202 mg, 0.260 mmol, 41%) as a white solid.

M.p. = 126 – 128 °C (cyclohexane/ EtOAc). **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 7.84 (s, 2H), 7.72 (s, 4H), 7.21 (ddd, *J* = 8.2, 2.5, 1.7 Hz, 1H), 6.99 (d, *J* = 8.9 Hz, 2H), 6.85 (td, *J* = 9.0, 2.6 Hz, 1H), 6.40 (d, *J* = 8.9 Hz, 2H), 5.47 (d, *J* = 7.2 Hz, 2H), 2.68 – 2.54 (m, 2H), 2.01-1.85 (m, 2H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 162.8 (d, *J* = 13.5 Hz), 161.6 (d, *J* = 13.1 Hz), 160.8 (d, *J* = 13.7 Hz), 159.6 (d, *J* = 13.0 Hz), 146.6, 143.9, 132.3 (q, *J* = 33.2 Hz), 131.4, 126.9 (d, *J* = 3.8 Hz), 123.8 (q, *J* = 272.8 Hz), 123.1, 121.8 (p, *J* = 3.8 Hz), 116.4 (dd, *J* = 24.2, 3.9 Hz), 114.2, 103.8 (dd, *J* = 28.0, 25.1 Hz), 63.2, 32.5. **^{19}F{^{1}H} NMR** (471 MHz, CD_2Cl_2) δ –63.3, –107.1 (d, *J* = 6.7 Hz), –112.0 (d, *J* = 6.2 Hz). **HRMS** (ESI+) calculated for $[C_{32}H_{19}BrF_{14}N]^+$ 762.0472 *m/z*; found $[M + H]^+$ 762.0454 *m/z*. α_D^{589} = +22.6 deg.cm^2.g^{-1} ($CHCl_3$, c 1.0, 300 K).

Ligand L$_L$

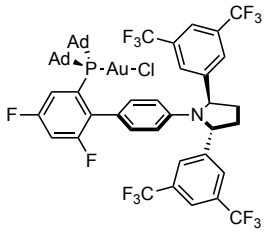


A flame-dried 10 mL Schlenk flask was charged with (2*R*)-2,5-bis(3,5-bis(trifluoromethyl)phenyl)-1-(2'-bromo-4',6'-difluoro-[1,1'-biphenyl]-4-yl)pyrrolidine (132 mg, 0.170 mmol, 1.0 equiv), $Pd(OAc)_2$ (1.94 mg, 8.66 µmol, 5 mol %), dppf (5.76 mg, 10.4 µmol, 6 mol %), NaO*t*Bu (20 mg, 0.21 mmol, 1.2 equiv) and toluene (0.90 mL) and the resulting suspension was stirred for 15 min at 24 ºC. Di(1-adamantyl)phosphine (58.0 mg, 0.190 mmol, 1.1 equiv) was added and the reaction mixture was stirred at 120 ºC for 16 h. Then, the reaction was allowed to cool to 24 ºC and the crude was purified by flash column chromatography (cyclohexane/CH_2Cl_2 40:1 then 4:1) to afford ligand **L$_L$** (125 mg, 0.12 mmol, 73%) as a white solid.

M.p. = 149 – 151 °C (decomposition; cyclohexane/EtOAc). **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 7.83 (s, 2H), 7.75 (s, 4H), 7.38 (d, *J* = 12.2 Hz, 1H), 6.91 – 6.72 (m, 3H), 6.32 (d, *J* = 8.2 Hz, 2H), 5.48 (d, *J* = 7.0 Hz, 2H), 2.73 – 2.51 (m, 2H), 1.97 – 1.91 (m, 2H), 1.91 – 1-84 (m, 6H), 1.84 – 1.76 (m, 6H), 1.76 – 1.70 (m, 3H), 1.67 (s, 9H), 1.63 – 1.52 (m, 6H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 160.7 (dt, *J* = 246.4, 11.4 Hz), 160.1 (ddd, *J* = 248.8, 12.4, 1.9 Hz), 146.9, 142.9, 139.7 (dd, *J* = 33.5, 5.2 Hz), 134.8 (ddd, *J* = 34.4, 14.0, 3.7 Hz), 132.7, 132.2 (q, *J* = 33.1 Hz), 127.0 (q, *J* = 3.6 Hz), 124.94, 124.88, 123.9 (q, *J* = 272.8 Hz), 121.6 (p, *J* = 3.9 Hz), 118.6 (dt, *J* = 18.7, 3.1 Hz), 113.4, 104.3 (dd, *J* = 28.1, 25.2 Hz), 63.1, 42.2 (d, *J* = 13.6 Hz), 41.8 (d, *J* = 13.4 Hz), 37.9 (d, *J* = 12.0 Hz), 37.7 (d, *J* = 12.5 Hz), 32.5, 29.4 (d, *J* = 8.6 Hz), 29.3 (d, *J* = 8.6 Hz). **^{31}P{^{1}H} NMR** (203 MHz, CD_2Cl_2) δ 24.11 (d, *J* = 11.4 Hz). **^{19}F{^{1}H} NMR** (471 MHz, CD_2Cl_2) δ –63.05, –108.52 (dd, *J* = 11.7, 6.8 Hz), –114.28 (d, *J* = 5.8 Hz). **HRMS** (ESI+) calculated for $[C_{52}H_{49}F_{14}NP]^+$

984.3374 *m/z*; found $[M + H]^+$ 984.3365 *m/z*. α_D^{589} = +24.5 deg.cm^2.g^{-1} ($CHCl_3$, c 1.0, 300 K).

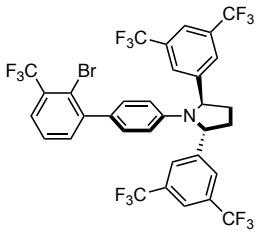
Complex (*R*,*R*)-L



[Me_2SAuCl] (17.9 mg, 61 μmol, 1.0 equiv) and ligand $\mathbf{L_L}$ (60.0 mg, 61.0 μmol, 1.0 equiv) were dissolved in CH_2Cl_2 (1.4 mL) under an atmosphere of argon. The reaction mixture was stirred at 24 ºC for 30 min. The mixture was filtered through a syringe filter and concentrated. The crude was purified by flash column chromatography (cyclohexane/ CH_2Cl_2 3:1) to afford complex (*R*,*R*)-**L** (69.5 mg, 57.0 μmol, 94%) as a white solid.

M.p. = 222 – 227 °C (cyclohexane/CH_2Cl_2). **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 7.92 (s, 4H), 7.82 (s, 2H), 7.40 (t, *J* = 7.7 Hz, 1H), 7.03 (td, *J* = 8.4, 2.4 Hz, 1H), 6.82 (dd, *J* = 8.5, 2.1 Hz, 1H), 6.69 (dd, *J* = 8.6, 2.1 Hz, 1H), 6.34 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.28 (dd, *J* = 8.4, 2.6 Hz, 1H), 5.50 (d, *J* = 6.5 Hz, 2H), 2.67 – 2.54 (m, 2H), 2.25 – 2.12 (m, 6H), 2.01 – 1.91 (m, 12H), 1.90 – 1.80 (m, 2H), 1.71 (s, 6H), 1.66 – 1.58 (m, 6H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 162.4 (dt, *J* = 247.3, 12.4 Hz), 160.5 (dt, *J* = 249.8, 12.4 Hz), 146.9, 144.8, 134.7 – 134.6 (m), 132.1 (q, *J* = 33.2 Hz), 130.9 (d, *J* = 5.5 Hz), 129.16 – 128.17 (m), 127.3 (d, *J* = 3.7 Hz), 124.3 (q, *J* = 273.8 Hz), 121.9 (d, *J* = 6.6 Hz), 121.4 (p, *J* = 4.0 Hz), 117.3 (dt, *J* = 21.6, 3.6 Hz), 116.7, 114.1, 107.0 (dd, *J* = 28.8, 24.6 Hz), 63.7, 43.7 (d, *J* = 22.2 Hz), 42.9 (d, *J* = 2.9 Hz), 42.7 (d, *J* = 22.2 Hz), 42.0 (d, *J* = 2.7 Hz), 36.6 (d, *J* = 21.6 Hz), 32.6, 29.3 (d, *J* = 9.9 Hz), 29.0 (d, *J* = 10.2 Hz). **^{31}P{^{1}H} NMR** (203 MHz, CD_2Cl_2) δ 64.7 (d, *J* = 9.2 Hz). **^{19}F{^{1}H} NMR** (471 MHz, CD_2Cl_2) δ –62.7, –102.2 (t, *J* = 8.9 Hz), –111.3 (d, *J* = 8.4 Hz). **HRMS** (ESI+) calculated for $[C_{52}H_{48}AuClF_{14}NNaP]^+$ 1238.2547 *m/z*; found [M + Na]$^+$ 1238,2502 *m/z*. α_D^{589} = 48.7 deg.cm^2.g^{-1} ($CHCl_3$, c 1.0, 298 K).

(2*R*)-2,5-bis(3,5-bis(trifluoromethyl)phenyl)-1-(2'-bromo-3'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)pyrrolidine

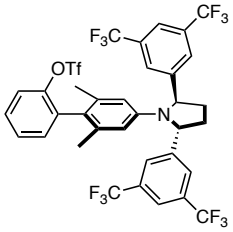


To a solution of (1*S*,4*S*)-1,4-bis(3,5-bis(trifluoromethyl) phenyl)butane-1,4-diol (215 mg, 0.420 mmol, 1.0 equiv) in CH_2Cl_2 (4.2 mL) at –20 °C were added NEt_3 (0.18 mL, 1.25 mmol, 3.0 equiv) and methanesulfonyl chloride (85.0 μL, 1.09 mmol, 2.6 equiv) under an atmosphere of argon. The mixture was stirred for 2.5 h at –20 °C. Then, a solution of 2'-bromo-3'-(trifluoromethyl)-[1,1'-biphenyl]-4-amine (648 mg, 2.05 mmol, 4.9 equiv) in CH_2Cl_2 (1.0 mL) was added and the resulting mixture was stirred at 24 ºC overnight. The volatile products were removed under reduced pressure and the organic materials were

extracted with EtOAc. The combined organic phases were washed with brine and sat. $NaHCO_3$, dried over Na_2SO_4 and concentrated. The crude was purified by flash column chromatography (cyclohexane/EtOAc 30:1) to yield the title compound (220 mg, 0.27 mmol, 66%) as a white solid.

M.p. =101 – 103 °C (Et_2O). **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 7.84 (s, 2H), 7.73 (s, 4H), 7.62 (dd, *J* = 7.1, 2.5 Hz, 1H), 7.44 – 7.35 (m, 2H), 7.09 – 7.03 (m, 2H), 6.43 – 6.36 (m, 2H), 5.49 (d, *J* = 7.0 Hz, 2H), 2.69 – 2.54 (m, 2H), 2.02 – 1.90 (m, 2H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 146.6, 145.9, 143.7, 135.0, 132.3 (q, *J* = 33.2 Hz), 130.8, 130.3, 127.5, 127.0 (d, *J* = 3.9 Hz), 126.7 (q, *J* = 5.7 Hz), 123.88 (q, *J* = 272.3 Hz), 123.80 (q, *J* = 273.7 Hz), 121.8 (dt, *J* = 7.9, 3.8 Hz), 114.1, 63.2, 32.5. **^{19}F{^{1}H} NMR** (471 MHz, CD_2Cl_2) δ -62.5, -63.3. **HRMS** (ESI+) calculated for $[C_{33}H_{20}BrF_{15}N]^+$ 794.0534 *m/z*; found $[M + H]^+$ 794.0520 *m/z*. **α_D^{589}** = +22.8 deg.cm^2.g^{-1} ($CHCl_3$, c 1.0, 300 K).

4'-((2*R*,5*R*)-2,5-Bis(3,5-bis(trifluoromethyl)phenyl)pyrrolidin-1-yl)-2',6'-dimethyl-[1,1'-biphenyl]-2-yl trifluoromethanesulfonate

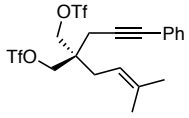


To a solution of (1*S*,4*S*)-1,4-bis(3,5-bis(trifluoromethyl)phenyl) butane-1,4-diol (145 mg, 0.280 mmol, 1.0 equiv) in CH_2Cl_2 (2.8 mL) at –20 °C were added NEt_3 (0.12 mL, 0.850 mmol, 3.0 equiv) and methanesulfonyl chloride (57.0 μL, 0.73 mmol, 2.6 equiv) under an atmosphere of argon. The mixture was stirred for 2.5 h at –20 °C. Then, a solution of 4'-Amino-2',6'-dimethyl-[1,1'-biphenyl]-2-yl trifluoromethanesulfonate (477 mg, 1.40 mmol, 4.9 equiv) in CH_2Cl_2 (1.0 mL) was added and the resulting mixture was stirred at 24 ºC overnight. The volatile products were removed under reduced pressure and the organic materials were extracted with EtOAc. The combined organic phases were washed with brine and sat. $NaHCO_3$, dried over Na_2SO_4 and concentrated. The crude was purified by flash column chromatography (cyclohexane/EtOAc 40:1) to yield the title compound (157 mg, 0.190 mmol, 68%) as a white solid.

M.p. = 184 – 186 °C (cyclohexane/ EtOAc). **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 7.82 (s, 2H), 7.72 (s, 4H), 7.43 – 7.35 (m, 2H), 7.34 – 7.28 (m, 1H), 7.26 – 7.21 (m, 1H), 6.15 – 6.07 (m, 2H), 5.47 (d, *J* = 7.3 Hz, 2H), 2.62 – 2.49 (m, 2H), 1.94 – 1.85 (m, 2H), 1.80 (s, 3H), 1.79 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 147.8, 147.1, 143.7, 138.2 (d, *J* = 2.2 Hz), 134.6, 133.6, 132.2 (q, *J* = 33.2 Hz), 129.2, 128.7, 126.8 (d, *J* = 3.9 Hz), 124.3, 123.9 (q, *J* = 273.1 Hz), 122.1, 121.7 (q, *J* = 3.7 Hz), 118.6 (q, *J* = 319.1 Hz), 113.7, 113.4, 62.8, 32.4, 20.8. **^{19}F{^{1}H} NMR** (471 MHz, CD_2Cl_2) δ –63.3, –75.8. **HRMS** (ESI+) calculated for $[C_{35}H_{24}F_{15}NNaO_3S]^+$ 846.1130 *m/z*; found $[M + Na]^+$ 846.1171 *m/z*. **α_D^{589}** = –5.2 deg.cm^2.g^{-1} ($CHCl_3$, c 0.84, 296 K).

Synthesis of 1,6-Enynes for Mechanistic Studies

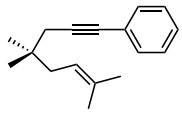
2-(3-Methylbut-2-en-1-yl)-2-(3-phenylprop-2-yn-1-yl)propane-1,3-diyl bis(trifluoromethanesulfonate)



2-(3-Methylbut-2-en-1-yl)-2-(3-phenylprop-2-yn-1-yl)propane-1,3-diol[133] (154 mg, 0.59 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (6 mL) in a flame and dried 25 mL two necked flask and pyridine (1.2 mL, 14.9 mmol, 25 equiv) was added. The reaction mixture was cooled to –78 ºC and $(Tf)_2O$ (0.28 mL, 1.7 mmol, 2.8 equiv) was added dropwise. The reaction was allowed to warm up to 24 ºC overnight. Water was added to the reaction and the organic layer was separated. The aqueous phase was extracted from CH_2Cl_2 (3x) and the combined organic layers were washed with HCl (0.1 M). The organic layers were dried over Na_2SO_4, filtered and concentrated. The crude was purified by flash column chromatography (40:1, CH:EtOAc) to yield the title compound (246 mg, 0.47 mmol, 79 %) as a pale yellow oil.

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.47 – 7.39 (m, 2H), 7.37 – 7.28 (m, 3H), 5.18 – 5.10 (m, 1H), 4.60 – 4.46 (m, 4H), 2.58 (s, 2H), 2.32 (d, *J* = 7.9 Hz, 2H), 1.79 (d, *J* = 1.4 Hz, 3H), 1.71 (d, *J* = 1.4 Hz, 3H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 139.4, 132.0, 128.9, 128.81, 123.0, 119.1 (q, *J* = 319.4 Hz), 115.0, 85.2, 82.5, 76.60 43.2, 29.2, 26.3, 22.3, 18.2. **^{19}F{^{1}H} NMR** (376 MHz, CD_2Cl_2) δ –74.6. **HRMS** (ESI+) calculated for $[C_{19}H_{20}F_6NaO_6S_2]^+$ 545.0498 *m/z*; found $[M + Na]^+$ 545.0517 *m/z* .

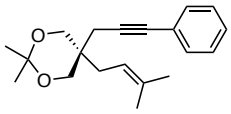
(4,4,7-Trimethyloct-6-en-1-yn-1-yl)benzene



2-(3-Methylbut-2-en-1-yl)-2-(3-phenylprop-2-yn-1-yl)propane-1,3-diyl bis(trifluoromethanesulfonate) (441 mg, 0.84 mmol, 1.0 equiv) was dissolved in anhydrous THF (17 mL) and cooled to –78 ºC. To this, a solution of L-selectride (4.22 ml, 4.22 mmol, 5.0 equiv, 1 M) was added in one portion and the reaction mixture was allowed to warm to 25 ºC. The reaction was stirred for additional 30 min and the volatiles were removed under vacuum. The crude was purified by flash column chromatography (hexane) to afford the title compound (160 mg, 0.700 mmol, 84%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.36 (m, 2H), 7.32 – 7.25 (m, 3H), 5.27 – 5.15 (m, 1H), 2.27 (s, 2H), 2.05 (d, *J* = 7.7 Hz, 1H), 1.74 (d, *J* = 1.3 Hz, 3H), 1.64 (s, 3H), 1.01 (s, 6H).

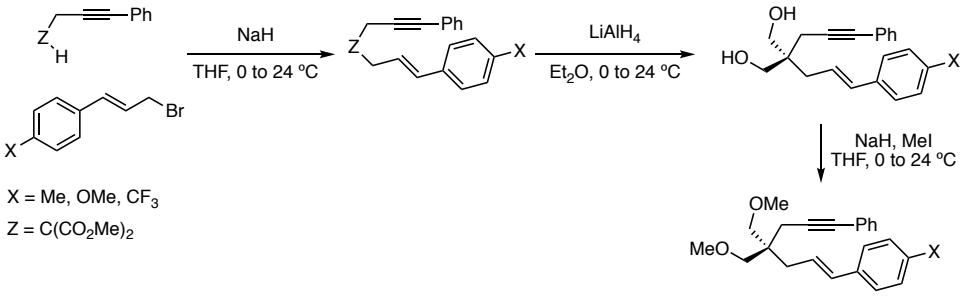
2,2-Dimethyl-5-(3-methylbut-2-en-1-yl)-5-(3-phenylprop-2-yn-1-yl)-1,3-dioxane



2-(3-Methylbut-2-en-1-yl)-2-(3-phenylprop-2-yn-1-yl)propane-1,3-diol[133] (100 mg, 0.380 mmol, 1.0 equiv) was dissolved in acetone (3.9 mL) and 2,2-dimethoxypropane (52.0 μL, 0.430 mmol, 1.1 euiv) and 4-methylbenzenesulfonic acid hydrate (74.0 mg, 0.390 mmol, 1.0 equiv) were sequentially added at 24 ºC. The reaction mixture was stirred at the same temperature for 2 h and then quenched with sat. $NaHCO_3$. The aqueous phase was extracted with EtOAc (3x) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude was purified by flash column chromatography to afford the title compound (110 mg, 0.370 mmol, 95%) as a colorless gum.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.36 (m, 2H), 7.28 (dt, *J* = 4.6, 2.9 Hz, 3H), 5.15 (tt, *J* = 7.9, 1.4 Hz, 1H), 3.78 – 3.67 (m, 4H), 2.57 (s, 2H), 2.18 (d, *J* = 7.9 Hz, 2H), 1.74 (d, *J* = 1.4 Hz, 3H), 1.68 (d, *J* = 1.4 Hz, 3H), 1.44 (s, 6H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 135.6, 131.7, 128.4, 127.8, 118.1, 98.2, 87.0, 83.1, 67.1, 36.9, 31.3, 26.3, 23.5, 22.4, 18.1.

Synthesis of 1,6-enynes 2.75a-c

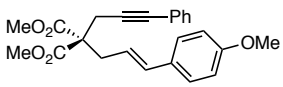


General Procedure A: allylation

A two-necked round bottom flask was charged with NaH (1.1 equiv, 60% in mineral oil) and THF was added. The suspension was cooled to 0 ºC and a solution of dimethyl 2-(3-phenylprop-2-yn-1-yl)malonate[184] (1.0 equiv) in THF (0.15 M total concentration) was added dropwise at the same temperature. The reaction mixture was stirred for 10 min and a solution the allylbromide (1.2 equiv) in THF was added. The reaction was stirred at 24 ºC for the given time. The reaction was quenched with sat. NH_4Cl and extracted from EtOAc (3x). The organic layers were separated, dried over Na_2SO_4, filtered and concentrated. The crude was purified by flash column chromatography to yield the desired 1,6-enyne.

184. Gasperini, D.; Maggi, L.; Dupuy, S.; Veenboer, R. M. P.; Cordes, D. B.; Slawin, A. M. Z.; Nolan, S. P. *Adv. Synth. Catal.* **2016**, *358*, 3857–3862.

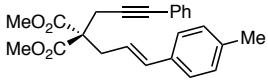
Dimethyl (*E*)-2-(3-(4-methoxyphenyl)allyl)-2-(3-phenylprop-2-yn-1-yl)malonate



The title compound (colorless gum, 275 mg, 0.700 mmol, 86%) was synthesized following general procedure **A** using dimethyl 2-(3-phenylprop-2-yn-1-yl)malonate (200 mg, 0.810 mmol) and (*E*)-1-(3-bromoprop-1-en-1-yl)-4-methoxybenzene[185] (221 mg, 1.00 mmol) whereby the reaction was stirred overnight. Purification was performed by flash column chromatography (cyclohexane/EtOAc 10:1).

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.42 – 7.37 (m, 2H), 7.33 – 7.26 (m, 5H), 6.88 – 6.77 (m, 2H), 6.49 (d, *J* = 15.6 Hz, 1H), 5.93 (dt, *J* = 15.6, 7.7 Hz, 1H), 3.78 (s, 3H), 3.76 (s, 6H), 3.04 (s, 2H), 2.97 (d, *J* = 7.6 Hz, 2H). **^{13}C{^{1}H} NMR** (101 MHz, CD_2Cl_2) δ 170.7, 159.7, 134.3, 132.0, 130.2, 128.7, 128.5, 127.8, 123.6, 121.4, 114.3, 85.0, 83.8, 58.0, 55.6, 36.5, 24.1. **HRMS** (ESI+) calculated for $[C_{24}H_{24}NaO_5]^+$ 415.1516 *m/z*; found $[M + Na]^+$ 415.1508 *m/z*.

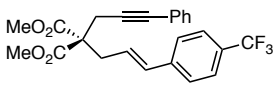
Dimethyl (*E*)-2-(3-phenylprop-2-yn-1-yl)-2-(3-(*p*-tolyl)allyl)malonate



The title compound (colorless gum, 305 mg, 0.81 mmol, 99%) was synthesized following general procedure **A** using dimethyl 2-(3-phenylprop-2-yn-1-yl)malonate (200 mg, 0.812 mmol) and (*E*)-1-(3-bromoprop-1-en-1-yl)-4-methylbenzene[185] (206 mg, 0.975 mmol) whereby the reaction was stirred for 3 h. Purification was performed by flash column chromatography (cyclohexane/EtOAc 20:1).

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.42 – 7.35 (m, 2H), 7.35 – 7.28 (m, 3H), 7.26 – 7.19 (m, 2H), 7.15 – 7.08 (m, 2H), 6.51 (d, *J* = 15.7 Hz, 1H), 6.02 (dt, *J* = 15.5, 7.6 Hz, 1H), 3.76 (s, 6H), 3.04 (s, 2H), 2.99 (d, *J* = 7.7 Hz, 2H), 2.32 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, CD_2Cl_2) δ 170.7, 137.9, 134.8, 134.7, 132.0, 129.6, 128.7, 128.5, 126.5, 123.6, 122.7, 84.9, 83.9, 58.0, 53.1, 36.5, 24.2, 21.3. **HRMS** (ESI+) calculated for $[C_{24}H_{24}NaO_4]^+$ 399.1567 *m/z*; found $[M + Na]^+$ 399.1573 *m/z*.

Dimethyl (*E*)-2-(3-phenylprop-2-yn-1-yl)-2-(3-(4-(trifluoromethyl)phenyl) allyl)-malonate



The title compound (colorless gum, 404 mg, 0.930 mmol, 78%) was synthesized following general procedure **A** using dimethyl 2-(3-phenylprop-2-yn-1-yl)malonate (296 mg, 1.20 mmol) and (*E*)-1-(3-bromoprop-1-en-1-yl)-4-(trifluoromethyl)benzene[185] (382 mg, 1.44

185. He, J.; Jia, Z.; Tan, H.; Luo, X.; Qiu, D.; Shi, J.; Xu, H.; Li, Y. *Angew. Chem. Int. Ed.* **2019**, *58*, 18513–18518.

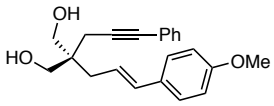
mmol) whereby the reaction was stirred overnight. Purification was performed by flash column chromatography (cyclohexane/EtOAc 30:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.1 Hz, 2H), 7.42 (d, *J* = 8.2 Hz, 2H), 7.40 – 7.35 (m, 2H), 7.33 – 7.27 (m, 3H), 6.57 (d, *J* = 15.7 Hz, 1H), 6.20 (dt, *J* = 15.5, 7.6 Hz, 1H), 3.78 (s, 6H), 3.07 (s, 2H), 3.04 (dd, *J* = 7.7, 1.3 Hz, 2H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 170.45, 140.6, 133.4, 131.8, 129.5 (q, *J* = 32.5 Hz), 128.4, 128.3, 126.6, 126.6, 125.6 (q, *J* = 3.8 Hz), 123.2, 84.2, 84.1, 57.7, 53.0, 36.5, 24.3. **^{19}F{^{1}H} NMR** (471 MHz, $CDCl_3$) δ –62.6. **HRMS** (ESI+) calculated for $[C_{24}H_{21}F_3NaO_4]^+$ 453.1284 *m/z*; found $[M + Na]^+$ 453.1279 *m/z*.

General Procedure B: reduction

A solution of the corresponding 1,6-enynes (1.0 equiv) in Et_2O (0.1 M) was added dropwise to a suspension of $LiAlH_4$ (3.0 equiv) in Et_2O (2 mL) at 0 ºC. The reaction was stirred for 1 h and after consumption of the starting material the reaction was quenched with HCl (0.5 M). After stirring for 30 min the mixture was filtered over Celite® and the organic phase was separated. The aqueous phase was extracted with Et_2O (3x) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude was purified by flash column chromatography to yield the the desired diols.

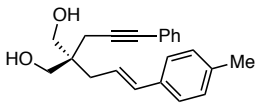
(*E*)-2-(3-(4-Methoxyphenyl)allyl)-2-(3-phenylprop-2-yn-1-yl)propane-1,3-diol



The title compound (white solid, 176 mg, 0.523 mmol, 90%) was synthesized following general procedure **B** using dimethyl (*E*)-2-(3-(4-methoxyphenyl)allyl)-2-(3-phenylprop-2-yn-1-yl)malonate (227 mg, 0.578 mmol). Purification was performed by flash column chromatography (cyclohexane/EtOAc 3:1, then 1:1).

M.p. = 76–78 °C (cyclohexane/ EtOAc). **^{1}H NMR** (400 MHz, CD_2Cl_2) δ 7.45 – 7.37 (m, 2H), 7.35 – 7.25 (m, 5H), 6.87 – 6.79 (m, 2H), 6.46 (d, *J* = 15.7 Hz, 1H), 6.16 (dt, *J* = 15.6, 7.7 Hz, 1H), 3.79 (s, 3H), 3.78 – 3.67 (m, 4H), 2.51 (s, 2H), 2.35 (dd, *J* = 7.7, 1.3 Hz, 2H), 2.28 (brs, 2H). **^{13}C{^{1}H} NMR** (101 MHz, CD_2Cl_2) δ 159.5, 133.1, 131.9, 130.6, 128.7, 128.2, 127.6, 124.1, 123.4, 114.3, 87.1, 83.3, 67.9, 55.6, 43.7, 35.9, 22.9. **HRMS** (ESI+) calculated for $[C_{22}H_{24}NaO_3]^+$ 359.1618 *m/z*; found $[M + Na]^+$ 359.1606 *m/z*.

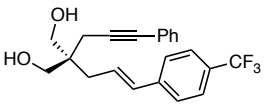
(*E*)-2-(3-Phenylprop-2-yn-1-yl)-2-(3-(*p*-tolyl)allyl)propane-1,3-diol



The title compound (white solid, 165 mg, 0.514 mmol, 73%) was synthesized following general procedure **B** using dimethyl (*E*)-2-(3-phenylprop-2-yn-1-yl)-2-(3-(*p*-tolyl)allyl)malonate (264 mg, 0.701 mmol). Purification was performed by flash column chromatography (cyclohexane/EtOAc 2:1).

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.45 – 7.39 (m, 2H), 7.35 – 7.29 (m, 3H), 7.28 – 7.23 (m, 2H), 7.11 (d, *J* = 6.2 Hz, 2H), 6.49 (d, *J* = 15.7 Hz, 1H), 6.25 (dt, *J* = 15.5, 7.7 Hz, 1H), 3.79 – 3.62 (m, 4H), 2.51 (s, 2H), 2.36 (dd, *J* = 7.7, 1.3 Hz, 2H), 2.32 (brs, 5H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 137.5, 135.1, 133.6, 131.9, 129.6, 128.7, 128.2, 126.4, 124.6, 124.1, 87.1, 83.3, 67.9, 43.7, 35.9, 22.9, 21.3. **HRMS** (ESI+) calculated for $[C_{22}H_{24}NaO_2]^+$ 343.1669 *m/z*; found $[M + Na]^+$ 343.1658 *m/z*.

(*E*)-2-(3-Phenylprop-2-yn-1-yl)-2-(3-(4-(trifluoromethyl)phenyl)allyl)propane-1,3-diol



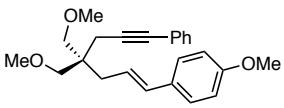
The title compound (white solid, 308 mg, 0.823 mmol, 92%) was synthesized following general procedure **B** using dimethyl (*E*)-2-(3-phenylprop-2-yn-1-yl)-2-(3-(4-(trifluoromethyl) phenyl)allyl)-malonate (386 mg, 897 μmol). Purification was performed by flash column chromatography (cyclohexane/EtOAc 2:1).

M.p. = 93–95 °C (cyclohexane/ EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.2 Hz, 2H), 7.48 – 7.36 (m, 4H), 7.33 – 7.27 (m, 3H), 6.55 (d, *J* = 15.8 Hz, 1H), 6.41 (dt, *J* = 15.5, 7.6 Hz, 1H), 3.77 (q, *J* = 10.9 Hz, 4H), 2.51 (s, 2H), 2.50 (brs, 2H), 2.43 (s, 1H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 140.9, 132.5, 131.7, 129.2 (q, *J* = 32.3 Hz), 128.5, 128.3, 128.1, 126.4, 125.6 (q, *J* = 3.9 Hz), 124.4 (q, *J* = 271.4 Hz), 123.5, 86.3, 83.6, 67.8 (d, *J* = 6.7 Hz), 43.5, 35.7 (d, *J* = 2.6 Hz), 22.9. **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) δ –62.5. **HRMS** (ESI+) calculated for $[C_{22}H_{21}F_3NaO_2]^+$ 397.1386 *m/z*; found $[M + Na]^+$ 397.1396 *m/z*.

General Procedure C: methylation

A solution of the corresponding diol (1.0 equiv) in THF (0.1 M) was added to a suspension of NaH (2.4 equiv, 60% in mineral oil) in THF at 0 ºC. After stirring the mixture for 10 min MeI (3.0 equiv) was added slowly. The reaction was stirred at 24 ºC for 1 h and then quenched with sat. NH_4Cl. The aqueous phase was extracted with EtOAc (3x) and the combined organic phases were dried over Na_2SO_4, filtered and concentrated. The crude was purified by flash column chromatography to afford the corresponding 1,6-enynes.

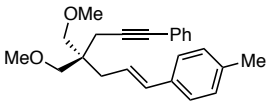
(*E*)-1-(4,4-Bis(methoxymethyl)-7-phenylhept-1-en-6-yn-1-yl)-4-methoxybenzene



The title compound (colorless gum, 165 mg, 0.373 mmol, 94%) was synthesized following general procedure **C** using (*E*)-2-(3-(4-methoxyphenyl)allyl)-2-(3-phenylprop-2-yn-1-yl)propane-1,3-diol (133 mg, 395 μmol). Purification was performed by flash column chromatography (cyclohexane/EtOAc 60:1, then 20:1).

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.44 – 7.37 (m, 2H), 7.34 – 7.26 (m, 5H), 6.86 – 6.79 (m, 2H), 6.42 (d, *J* = 15.7 Hz, 1H), 6.14 (dt, *J* = 15.5, 8.0 Hz, 1H), 3.79 (s, 3H), 3.35 (s, 6H), 3.37 – 3.30 (m, 6H), 2.45 (s, 2H), 2.35 (d, *J* = 7.6 Hz, 1H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 159.4, 132.7, 131.9, 131.0, 128.7, 128.0, 127.5, 124.5, 124.1, 114.3, 87.7, 82.8, 75.0, 59.5, 55.7, 43.4, 36.2, 23.6. **HRMS** (ESI+) calculated for $[C_{24}H_{28}NaO_3]^+$ 387.1931 *m/z*; found $[M + Na]^+$ 387.1928 *m/z*.

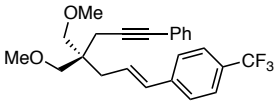
(*E*)-1-(4,4-Bis(methoxymethyl)-7-phenylhept-1-en-6-yn-1-yl)-4-methylbenzene



The title compound (colorless gum, 142 mg, 0.407 mmol, 86%) was synthesized following general procedure **C** using (*E*)-2-(3-phenylprop-2-yn-1-yl)-2-(3-(*p*-tolyl)allyl)propane-1,3-diol (151 mg, 0.471 mmol). Purification was performed by flash column chromatography (cyclohexane/EtOAc 60:1, then 40:1).

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.44 – 7.37 (m, 2H), 7.33 – 7.28 (m, 3H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 7.9 Hz, 2H), 6.44 (d, *J* = 15.7 Hz, 1H), 6.28 – 6.19 (m, 1H), 3.37 – 3.31 (m, 10H), 2.45 (s, 2H), 2.35 (d, *J* = 7.7 Hz, 2H), 2.32 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 137.3, 135.4, 133.2, 131.9, 129.5, 128.7, 128.0, 126.3, 125.3, 124.5, 87.7, 82.9, 75.0, 59.5, 43.4, 36.2, 23.6, 21.2. **HRMS** (ESI+) calculated for $[C_{24}H_{28}NaO_2]^+$ 371.1982 *m/z*; found $[M + Na]^+$ 371.1974 *m/z*.

(*E*)-1-(4,4-Bis(methoxymethyl)-7-phenylhept-1-en-6-yn-1-yl)-4-(trifluoromethyl)benzene



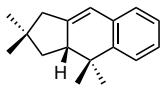
The title compound (colorless gum, 275 mg, 0.683 mmol, 93%) was synthesized following general procedure **C** using (*E*)-2-(3-phenylprop-2-yn-1-yl)-2-(3-(4-(trifluoromethyl) phenyl)allyl)propane-1,3-diol (275 mg, 0.735 mmol). Purification was performed by flash column chromatography (cyclohexane/EtOAc 60:1, then 40:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.3 Hz, 2H), 7.48 – 7.36 (m, 4H), 7.33 – 7.27 (m, 3H), 6.52 (d, *J* = 15.8 Hz, 1H), 6.47 – 6.35 (m, 1H), 3.41 – 3.32 (m, 10H), 2.51 – 2.47 (m, 2H), 2.42 (dd, *J* = 8.5, 2.9 Hz, 2H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 141.3, 131.9, 131.7, 129.3, 129.0 (q, *J* = 32.2 Hz), 128.4, 127.8, 126.4, 125.6 (q, *J* = 3.8 Hz), 124.4 (q, *J* = 271.5 Hz), 124.1, 87.0, 83.0, 74.9, 59.6, 43.2, 36.2, 23.5. **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) δ –62.5. **HRMS** (ESI+) calculated for $[C_{24}H_{25}F_3NaO_2]^+$ 425.1699 *m/z*; found $[M + Na]^+$ 4251691*m/z*.

General procedure D: enantioselective formal [4+2] cycloaddition

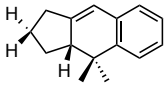
The 1,6-enyne (1.0 equiv) and (*R*,*R*)-**E** (4 mol %) were dissolved in 1,2-dichloroethane and a solution of $AgPF_6$ (4 mol %) in 1,2-dichloroethane (total concentration 0.05M) was added dropwise. The reaction was stirred for the given time at 24 ºC in the dark, quenched by addition of 3 drops of NEt_3 and concentrated. The crude was purified by flash column chromatography or preparative TLC.

(*R*)-2,2,4,4-Tetramethyl-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*b*]naphthalene



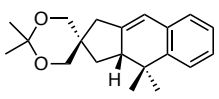
The title compound (colorless oil, 18.1 mg, 80.0 µmol, 61%, 76:24 *er*) was synthesized following general procedure **D** using (4,4,7-Trimethyloct-6-en-1-yn-1-yl)benzene (30.0 mg, 0.130 mmol) whereby the reaction was stirred for 18 h. Purification was performed by preparative TLC (pentane).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 1H), 7.18 – 7.09 (m, 2H), 7.04 – 6.97 (m, 1H), 6.27 (q, *J* = 2.5 Hz, 1H), 2.79 – 2.68 (m, 1H), 2.35 (dq, *J* = 17.4, 1.7 Hz, 1H), 2.24 (dt, *J* = 17.4, 3.1 Hz, 1H), 1.59 (ddd, *J* = 12.1, 7.6, 1.7 Hz, 1H), 1.48 (t, *J* = 12.0 Hz, 1H), 1.38 (s, 3H), 1.17 (s, 3H), 0.97 (s, 3H), 0.90 (s, 3H). **UPC^2** Chiralpak OJ (150 × 4.6mm, 3µm) at 35 ºC, flow 2 mL/min, isocratic CO_2/MeOH 95:5, ABRP pressure 2000 psi, 267 nm, t_R (minor) 1.5; t_R (major) 1.7.

(*R*)-4,4-Dimethyl-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*b*]naphthalene



The title compound (colorless oil, 10.5 mg, 50.0 µmol, 31%, 67:33 *er*) was synthesized following general procedure **D** using (7-methyloct-6-en-1-yn-1-yl)benzene[61] (33.0 mg, 0.170 mmol) whereby the reaction was stirred for 18 h. Purification was performed by preparative TLC (pentane). The spectral data were fully consistent with those previously reported.[61] **UPC^2** Chiralpak OJ (150 × 4.6mm, 3µm) at 35 ºC, flow 2 mL/min, isocratic CO_2/MeOH 85:15, ABRP pressure 2000 psi, 266 nm, t_R (minor) 1.8; t_R (major) 2.3.

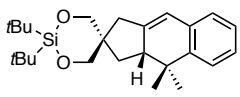
(*R*)-2',2',4,4-Tetramethyl-1,3,3a,4-tetrahydrospiro[cyclopenta[*b*]naphthalene-2,5'-[1,3]dioxane]



The title compound (colorless oil, 25.0 mg, 84.0 µmol, 83%, 75:25 *er*) was synthesized following general procedure **D** using 2,2-dimethyl-5-(3-methylbut-2-en-1-yl)-5-(3-phenylprop-2-yn-1-yl)-1,3-dioxane (30.0 mg, 0.100 mmol) whereby the reaction was stirred for 18 h. Purification was performed by preparative TLC (cyclohexane/EtOAc 30:1).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 1H), 7.19 – 7.10 (m, 2H), 7.04 – 6.97 (m, 1H), 6.31 (q, *J* = 2.5 Hz, 1H), 3.80 – 3.71 (m, 2H), 3.70 – 3.56 (m, 2H), 2.74 – 2.66 (m,

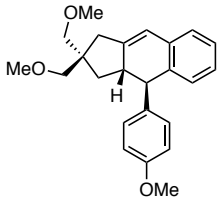
1H), 2.66 – 2.57 (m, 1H), 2.28 (dt, *J* = 18.1, 2.9 Hz, 1H), 2.11 – 2.00 (m, 1H), 1.46 (d, *J* = 2.9 Hz, 6H), 1.40 (s, 3H). **$^{13}C^{13}C\{^1H\}$ NMR** (101 MHz, $CDCl_3$) δ 145.2, 144.4, 134.4, 126.9, 126.3, 126.2, 123.7, 119.7, 98.2, 69.8, 68.0, 48.0, 40.9, 38.8, 36.7, 32.9, 25.8, 24.2, 23.8, 22.1. **UPC²** Chiralpak IA (150 × 4.6mm, 3µm) at 35 ºC, flow 3 mL/min, isocratic CO_2/MeOH 95:5, ABRP pressure 1500 psi, 266 nm, t_R (major) 1.3; t_R (minor) 1.5.

(*R*)-2',2'-Di-*tert*-butyl-4,4-dimethyl-1,3,3a,4-tetrahydrospiro[cyclopenta[*b*]naphthalene-2,5'-[1,3,2]dioxasilinane]



The title compound (34%, 68:32 *er*) was synthesized following general procedure **D** using 2,2-di-*tert*-butyl-5-(3-methylbut-2-en-1-yl)-5-(3-phenylprop-2-yn-1-yl)-1,3,2-dioxasilinane[133] (22.3 mg, 0.056 mmol) whereby the reaction was stirred for 48 h. The reaction was quenched by addition of NEt_3 and the yield was determined by ^{1}HNMR using 1,3,5-tribromobenzene as internal standard. The spectral data were fully consistent with those previously reported.[133] **UPC²** Chiralpak IB (150 × 4.6mm, 3µm) at 35 ºC, flow 3 mL/min, isocratic CO_2/MeOH 98:2, ABRP pressure 1500 psi, 216 nm, t_R (minor) 2.1; t_R (major) 2.3.

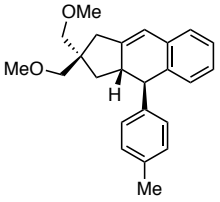
(3a*S*,4*R*)-2,2-Bis(methoxymethyl)-4-(4-methoxyphenyl)-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*b*]naphthalene



The title compound (colorless oil, 12.6 mg, 34.5 µmol, 63%, 84:16 *er*) was synthesized following general procedure **D** using (*E*)-1-(4,4-bis(methoxymethyl)-7-phenylhept-1-en-6-yn-1-yl)-4-methoxybenzene (20.0 mg, 55.0 µmmol) whereby the reaction was stirred for 3 weeks. Purification was performed by preparative TLC (toluene/CH_2Cl_2 4:1).

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.27 – 7.23 (m, 2H), 7.16 – 7.10 (m, 1H), 7.08 – 7.03 (m, 1H), 7.01 – 6.93 (m, 3H), 6.58 (d, *J* = 7.7 Hz, 1H), 6.39 – 6.34 (m, 1H), 3.86 (s, 3H), 3.69 (d, *J* = 15.1 Hz, 1H), 3.34 (d, *J* = 1.7 Hz, 3H), 3.33 – 3.31 (m, 2H), 3.30 (d, *J* = 1.5 Hz, 3H), 3.24 – 3.21 (m, , 2H), 3.15 – 3.02 (m, 1H), 2.53 (s, 2H), 1.72 – 1.63 (m, 1H), 1.36 – 1.25 (m, 1H). **$^{13}C\{^1H\}$ NMR** (101 MHz, CD_2Cl_2) δ 158.9, 149.1, 139.1, 136.3, 134.8, 127.1, 126.8, 126.3, 125.5, 119.3, 114.3, 77.4, 76.3, 59.4, 59.4, 55.6, 52.6, 47.4, 45.5, 38.2, 37.6. **HRMS** (ESI+) calculated for $[C_{24}H_{28}NaO_3]$+ 387.1931 m/z; found $[M + Na]^+$ 387.1937 m/z. **α_D^{589}** = –140.5 deg.cm^2.g^{-1} ($CHCl_3$, c 0.6, 296 K). **SFC** Chiralpak OJ (100 × 4.3 mm, 3 µm) at 35 ºC, flow 1.8 mL/min, isocratic CO_2/MeOH 98:2, ABRP pressure 150 bar, 280 nm, t_R (minor) 1.76; t_R (major) 1.95.

(3a*S*,4*R*)-2,2-Bis(methoxymethyl)-4-(*p*-tolyl)-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*b*]naphthalene



The title compound (colorless oil, 13.4 mg, 38.4 μmol, 70%, 84:16 *er*) was synthesized following general procedure **D** using (*E*)-1-(4,4-bis(methoxymethyl)-7-phenylhept-1-en-6-yn-1-yl)-4-methylbenzene (19.2 mg, 55 μmol) whereby the reaction was stirred for 3 weeks. Purification was performed by preparative TLC (toluene/CH_2Cl_2 4:1).

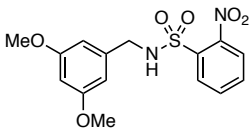
^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.20 (q, *J* = 7.8 Hz, 4H), 7.12 – 7.06 (m, 1H), 7.03 (d, *J* = 7.3 Hz, 1H), 6.93 (t, *J* = 7.5 Hz, 1H), 6.53 (d, *J* = 7.6 Hz, 1H), 6.34 (s, 1H), 3.67 (d, *J* = 15.1 Hz, 1H), 3.30 (d, *J* = 1.0 Hz, 3H), 3.28 (d, *J* = 1.8 Hz, 2H), 3.26 (d, *J* = 1.0 Hz, 3H), 3.19 (s, 2H), 3.15 – 2.99 (m, 1H), 2.49 (s, 2H), 2.38 (s, 3H), 1.62 (dd, *J* = 12.9, 8.1 Hz, 1H), 1.32 – 1.22 (m, 1H). **^{13}C{^{1}H} NMR** (101 MHz, CD_2Cl_2) δ 149.1, 139.8, 138.9, 136.7, 136.3, 129.6, 127.2, 126.8, 126.3, 125.5, 119.3, 77.4, 76.3, 59.4, 59.4, 53.0, 47.4, 45.4, 38.2, 37.6, 21.2. **HRMS** (ESI+) calculated for $[C_{24}H_{28}NaO_2]$+ 371.1982 m/z; found $[M + Na]^+$ 371.1988 m/z. **α_D^{589}** = –241.9 deg.cm^2.g^{-1} ($CHCl_3$, c 0.65, 296 K). **SFC** Chiralpak IG (100 × 4.3 mm, 3 μm) at 35 ºC, flow 1.2 mL/min, isocratic CO_2/MeOH 95:5, ABRP pressure 150 bar, 230 nm, t_R (major) 1.7; t_R (minor) 1.9.

Enantioselective Cascade Cyclization of 1-Bromo-1,5-enynes

General procedure E: preparation of sulfonamides

To a solution of (3,5-dimethoxyphenyl)methanamine (1.0 equiv) in CH_2Cl_2 was added NEt_3 at 0 ºC and the mixture was stirred for 10 min at the same temperature. The corresponding sulfonyl chloride (1.2 equiv) was added dropwise and the reaction mixture was allowed to warm up to 24 ºC and stirred overnight. The reaction was quenched with water and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude was purified by flash column chromatography (cyclohexane/EtOAc 3:1 to 2:1).

***N*-(3,5-dimethoxybenzyl)-2-nitrobenzenesulfonamide**

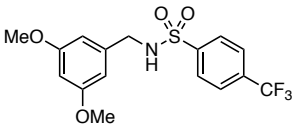


The title compound (white solid, 88%) was synthesized according to general procedure **E** using 2-nitrobenzenesulfonyl chloride.

M.p. = 85 – 87 °C (cyclohexane/ EtOAc). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.04 – 7.99 (m, 1H), 7.85 – 7.80 (m, 1H), 7.72 – 7.62 (m, 2H), 6.34 (dd, *J* = 2.3, 0.6 Hz, 2H), 6.27 (t, *J* = 2.3 Hz, 1H), 5.72 (t, *J* = 6.3 Hz, 1H), 4.25 (d, *J* = 6.3 Hz, 2H), 3.70 (s, 6H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 161.0, 147.8, 137.9, 134.0, 133.4, 132.7,

131.0, 125.2, 105.6, 100.0, 55.3, 48.0. **HRMS** (ESI+) calculated for $[C_{15}H_{16}N_2NaO_6S]^+$ 375.0621 *m/z*; found $[M + Na]^+$ 375.0613 *m/z*.

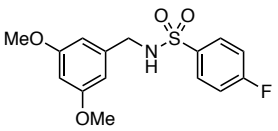
***N*-(3,5-Dimethoxybenzyl)-4-(trifluoromethyl)benzenesulfonamide**



The title compound (white solid, 89%) was synthesized according to general procedure **E** using 4-(trifluoromethyl)benzenesulfonyl chloride.

M.p. = 95 – 97 °C (cyclohexane/ EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.1 Hz, 2H), 7.75 (d, *J* = 7.9 Hz, 2H), 6.31 (t, *J* = 2.3 Hz, 1H), 6.27 (d, *J* = 2.3 Hz, 2H), 4.91 (s, 1H), 4.13 (d, *J* = 6.0 Hz, 2H), 3.71 (s, 6H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 161.1, 143.8, 137.9, 127.6, 126.2 (q, *J* = 7.6 Hz), 105.7, 99.8, 55.3, 47.5. **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) δ –63.3. **HRMS** (ESI–) calculated for $[C_{16}H_{15}F_3NO_4S]^-$ 374.0679 *m/z*; found $[M – H]^-$ 374.0666 *m/z*.

***N*-(3,5-Dimethoxybenzyl)-4-fluorobenzenesulfonamide**



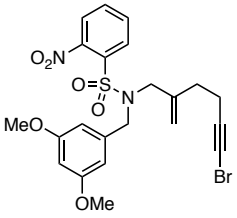
The title compound (white solid, 93%) was synthesized according to general procedure **E** using 4-fluorobenzenesulfonyl chloride.

M.p. = 93 – 95 °C (cyclohexane/ EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.01 – 7.71 (m, 2H), 7.17 (td, *J* = 7.9, 7.1, 1.3 Hz, 2H), 6.37 – 6.24 (m, 3H), 4.83 (brs, 1H), 4.08 (d, *J* = 6.2 Hz, 2H), 3.72 (s, 6H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 165.2 (d, *J* = 254.9 Hz), 161.2, 138.4, 136.2 (d, *J* = 3.3 Hz), 130.0, 129.9, 116.4 (d, *J* = 3.0 Hz), 105.8, 100.0, 55.5, 47.5. **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) δ –105.3. **HRMS** (ESI–) calculated for $[C_{15}H_{15}FNO_4S]^-$ 324.0711 *m/z*; found $[M – H]^-$ 324.0709 *m/z*.

General procedure F: synthesis of 1,5-enynes

To a solution of the corresponding sulfonamides (1.2 equiv.) and 6-bromo-2-(chloromethyl)hex-1-en-5-yne[121] (1.0 equiv) in acetone was added K_2CO_3 (1.2 equiv) and KI (0.12 equiv) at 24 °C. The mixture was set to reflux for 24 h before the solvent was evaporated. The residue was taken up in Et_2O and washed sequentially with water and brine, dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude was purified by flash column chromatography (cyclohexane/EtOAc 3:1) to give target compounds.

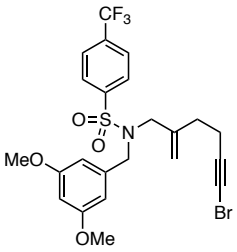
***N*-(6-Bromo-2-methylenehex-5-yn-1-yl)-*N*-(3,5-dimethoxybenzyl)-2-nitrobenzenesulfonamide**



The title compound (white solid, 86%) was synthesized according to general procedure **F** using *N*-(3,5-dimethoxybenzyl)-2-nitrobenzenesulfonamide.

M.p. = 104 – 106 °C (cyclohexane/ EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.71 – 7.61 (m, 3H), 6.31 (t, *J* = 2.3 Hz, 1H), 6.28 (d, *J* = 2.2 Hz, 2H), 4.95 (d, *J* = 15.8 Hz, 2H), 4.45 (s, 2H), 3.91 (s, 2H), 3.68 (s, 6H), 2.25 (td, *J* = 7.2, 0.7 Hz, 2H), 2.09 (t, *J* = 7.2 Hz, 2H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 161.0, 147.7, 140.9, 137.6, 134.2, 133.5, 131.8, 131.2, 124.2, 115.4, 105.9, 100.0, 79.2, 55.3, 51.7, 50.3, 38.7, 31.4, 18.1. **HRMS** (ESI+) calculated for $[C_{22}H_{24}BrN_2O_6S]^+$ 523.0533 *m/z*; found $[M + H]^+$ 523.0508 *m/z*.

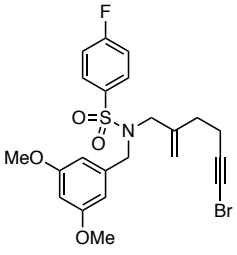
***N*-(6-Bromo-2-methylenehex-5-yn-1-yl)-*N*-(3,5-dimethoxybenzyl)-4-(trifluoromethyl)benzenesulfonamide**



The title compound (white solid, 80%) was synthesized according to general procedure **F** using *N*-(3,5-dimethoxybenzyl)-4-(trifluoromethyl)benzenesulfonamide.

M.p. = 91 – 93 °C (cyclohexane/ EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.9 Hz, 2H), 7.76 (d, *J* = 8.8 Hz, 2H), 6.32 (t, *J* = 2.3 Hz, 1H), 6.20 (d, *J* = 2.3 Hz, 2H), 4.97 (s, 1H), 4.89 (s, 1H), 4.31 (s, 2H), 3.81 (s, 2H), 3.68 (s, 6H), 2.29 (td, *J* = 7.2, 0.8 Hz, 2H), 2.13 (t, *J* = 7.2 Hz, 2H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 161.0, 144.3, 141.3, 137.5, 134.4 (d, *J* = 33.0 Hz), 127.7, 126.4 (q, *J* = 3.6 Hz), 115.8, 106.6, 99.9, 79.3, 55.4, 52.3, 50.9, 38.9, 31.6, 18.2. **HRMS** (ESI+) calculated for $[C_{23}H_{23}BrF_3NNaO_4S]^+$ 568.0375 *m/z*; found $[M + Na]^+$ 568.0365 *m/z*.

***N*-(6-Bromo-2-methylenehex-5-yn-1-yl)-*N*-(3,5-dimethoxybenzyl)-4-fluorobenzenesulfonamide**



The title compound (colorless oil, 89%) was synthesized according to general procedure **F** using *N*-(3,5-dimethoxybenzyl)-4-fluorobenzenesulfonamide.

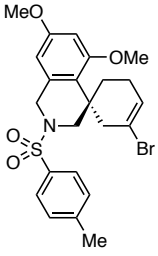
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 7.7 Hz, 2H), 6.33 (s, 2H), 4.92 (d, *J* = 1.4 Hz, 1H), 4.86 (d, *J* = 1.3 Hz, 1H), 4.27 (s, 2H), 3.81 (s, 3H), 3.73 (s, 6H), 3.72 (s, 2H), 2.43 (s, 3H), 2.22 (td, *J* = 7.5, 1.0 Hz, 2H), 2.10 (t, *J* = 7.3 Hz, 2H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 161.0, 141.6, 138.0, 136.7, 130.0, 129.9, 116.5, 116.3,

115.5, 106.6, 100.0, 79.4, 55.4, 52.2, 51.0, 38.8, 31.6, 18.2. **HRMS** (ESI+) calculated for $[C_{22}H_{23}BrFNNaO_4S]^+$ 518.0407 *m/z*; found $[M + Na]^+$ 518.0426 *m/z*.

General procedure G: enantioselective catalytic spiro cyclization

A 5 mL microwave vial was charged with $AgSbF_6$ (5 mol %) cooled to –40 ºC and a solution of the corresponding enyne (1.0 equiv) and (*R*,*R*)-**K** in chlorobenzene (0.05M) was added. The reaction was stirred for 7 d at the same temperature and then quenched by addition of 3 drops of NEt_3. The volatiles were removed under reduced pressure and the crude was purified by preparative TLC to give the target copound.

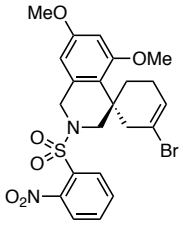
3-bromo-5',7'-dimethoxy-2'-tosyl-2',3'-dihydro-1'*H*-spiro[cyclohexane-1,4'-isoquinolin]-3-ene



The title compound (colorless gum, 21.9 mg, 44.0 μmol, 61%, 71% brsm 92:8 *er*) was synthesized following general procedure **G** using *N*-(6-bromo-2-methylenehex-5-yn-1-yl)-*N*-(3,5-dimethoxybenzyl)-4-fluorobenzenesulfonamide[121] (35.9 mg, 73 μmol). Purification was performed by preparative TLC (cyclohexane/EtOAc 4:1).

M.p. = 81 – 83°C (Et_2O). α_D^{589} = –257.5 deg.cm^2.g^{-1} ($CHCl_3$, c 1.0, 296 K). **HPLC** Chiralpak IA (250 × 4.6mm, 5μm) at 25 ºC, flow 1.0 mL/min, isocratic hexane/iPrOH 90:10, 280 nm, t_R (major) 13.2; t_R (minor) 23.4. The spectral data were fully consistent with those previously reported.[121]

3-Bromo-5',7'-dimethoxy-2'-((2-nitrophenyl)sulfonyl)-2',3'-dihydro-1'*H*-spiro[cyclohexane-1,4'-isoquinolin]-3-ene

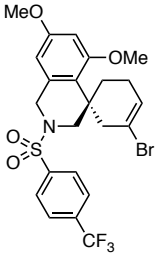


The title compound (white solid, 6.80 mg, 13.0 μmol, 18%, 69% brsm 90:10 *er*) was synthesized following general procedure **G** using *N*-(6-bromo-2-methylenehex-5-yn-1-yl)-*N*-(3,5-dimethoxybenzyl)-2-nitrobenzenesulfonamide (39.9 mg, 73 μmol). Purification was performed by preparative TLC (cyclohexane/EtOAc 2:1).

M.p. = 62 – 64 °C (CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.06 – 8.01 (m, 1H), 7.76 – 7.71 (m, 2H), 7.65 – 7.61 (m, 1H), 6.35 (d, *J* = 2.5 Hz, 1H), 6.22 (d, *J* = 2.5 Hz, 1H), 6.11 – 6.07 (m, 1H), 4.47 (d, *J* = 15.2 Hz, 1H), 4.37 (d, *J* = 15.2 Hz, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.45 (d, *J* = 12.7 Hz, 1H), 3.37 (s, 2H), 3.34 (d, *J* = 7.3 Hz, 1H), 2.68 (ddd, *J* = 13.6, 11.7, 6.5 Hz, 1H), 2.34 – 2.06 (m, 4H), 1.51 (dd, *J* = 13.8, 5.9 Hz, 1H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 159.7, 159.3, 134.4, 134.0, 131.9, 131.4, 131.2, 127.2, 124.3, 120.8, 120.7, 102.2, 98.9, 55.5, 55.4, 52.3, 49.4, 41.4, 39.6, 26.5, 24.2. **HRMS** (ESI+) calculated for $[C_{22}H_{24}BrN_2O_6S]^+$ 523.0533 m/z; found [M + H]+ 523.0535 m/z.

α_D^{589} = +289.8 deg.cm^2.g^{-1} ($CHCl_3$, c 0.35, 296 K). **HPLC** Chiralpak IB (250 × 4.6mm, 5μm) at 25 ºC, flow 1.0 mL/min, isocratic hrxane/iPrOH 80:20, 280 nm, t_R (major) 12.1; t_R (minor) 14.1.

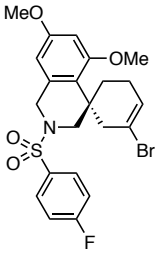
3-Bromo-5',7'-dimethoxy-2'-((4-(trifluoromethyl)phenyl)sulfonyl)-2',3'-dihydro-1'*H*-spiro[cyclohexane-1,4'-isoquinolin]-3-ene



The title compound (white solid, 18.6 mg, 34.0 μmol, 47%, 68% brsm 92:8 *er*) was synthesized following general procedure **G** using *N*-(6-bromo-2-methylenehex-5-yn-1-yl)-*N*-(3,5-dimethoxybenzyl)-4-(trifluoromethyl)benzenesulfonamide (39.9 mg, 73 μmol). Purification was performed by preparative TLC (cyclohexane/EtOAc 5:1).

M.p. = 92 – 94 °C (Et_2O). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.2 Hz, 2H), 7.84 (d, *J* = 8.9 Hz, 2H), 6.34 (d, *J* = 2.5 Hz, 1H), 6.16 (d, *J* = 2.5 Hz, 1H), 6.13 – 6.08 (m, 1H), 4.23 – 4.10 (m, 2H), 3.79 (s, 3H), 3.76 (s, 3H), 3.52 – 3.43 (m, 1H), 3.23 (d, *J* = 12.0 Hz, 1H), 3.06 (d, *J* = 12.0 Hz, 1H), 2.66 – 2.56 (m, 1H), 2.32 – 2.22 (m, 1H), 2.22 – 2.09 (m, 2H), 1.56 (dd, *J* = 13.7, 5.9 Hz, 1H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 159.6, 159.3, 140.2, 135.3 – 134.3 (m), 134.0, 128.4, 127.1, 126.6 (q, *J* = 3.7 Hz), 123.4 (q, *J* = 272.7 Hz), 121.0, 120.7, 102.3, 98.8, 55.44, 55.37, 52.2, 49.7, 41.4, 39.7, 26.5, 24.1. **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) δ –62.5. **HRMS** (ESI+) calculated for $[C_{23}H_{23}BrF_3NNaO_4S]^+$ 568.0375 m/z; found [M + Na]+ 568.0373 m/z. α_D^{589} = –182.1 deg.cm^2.g^{-1} ($CHCl_3$, c 1.0, 296 K). **HPLC** Chiralpak IA (250 × 4.6mm, 5μm) at 25 ºC, flow 1.0 mL/min, isocratic hexane/iPrOH 90:10, 280 nm, t_R (major) 10.1; t_R (minor) 16.9.

3-Bromo-2'-((4-fluorophenyl)sulfonyl)-5',7'-dimethoxy-2',3'-dihydro-1'*H*-spiro[cyclohexane-1,4'-isoquinolin]-3-ene



The title compound (white solid, 18.7 mg, 38.0 μmol, 51%, 80% brsm 92:8 *er*) was synthesized following general procedure **G** using *N*-(6-bromo-2-methylenehex-5-yn-1-yl)-*N*-(3,5-dimethoxybenzyl)-4-(trifluoromethyl)benzenesulfonamide (36.2 mg, 73 μmol). Purification was performed by preparative TLC (cyclohexane/Et_2O 5:1).

M.p. = 75 – 77 °C (CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.94 – 7.82 (m, 2H), 7.30 – 7.20 (m, 2H), 6.34 (d, *J* = 2.5 Hz, 1H), 6.16 (d, *J* = 2.4 Hz, 1H), 6.12 – 6.05 (m, 1H), 4.21 – 4.04 (m, 2H), 3.79 (s, 3H), 3.75 (s, 3H), 3.53 – 3.41 (m, 1H), 3.21 (d, *J* = 11.9 Hz, 1H), 2.99 (d, *J* = 12.0 Hz, 1H), 2.64 – 2.52 (m, 1H), 2.32 – 2.04 (m, 3H), 1.56 (dd, *J* = 13.5, 5.8 Hz, 1H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 165.47 (d, *J* = 255.3 Hz), 159.4 (d, *J* = 38.0 Hz), 134.3, 132.5 (d, *J* = 3.4 Hz), 130.6 (d, *J* = 9.2 Hz), 127.1, 121.1, 120.8, 116.8, 116.6, 102.4, 98.7, 55.4, 55.4, 52.3, 49.8, 41.5, 39.8, 26.5,

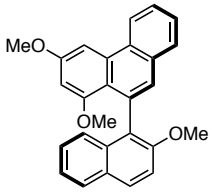
24.1. **$^{19}F\{^{1}H\}$ NMR** (376 MHz, $CDCl_3$) δ –104.8. **HRMS** (ESI+) calculated for $[C_{22}H_{24}BrFNO_4S]^+$ 496.0588 *m/z*; found $[M + H]^+$ 496.0589 *m/z*. α_D^{589} = –227.5 deg.cm^2.g^{-1} ($CHCl_3$, c 1.0, 296 K). **HPLC** Chiralpak IA (250 × 4.6mm, 5μm) at 25 ºC, flow 1.0 mL/min, isocratic hrxane/iPrOH 90:10, 220 nm, t_R (major) 11.3; t_R (minor) 20.4.

Synthesis of Axially-Chiral Biaryls

General procedure H: atroposelective synthesis of biaryls

The 1,2-diarylalkyne (1.0 equiv) and (*R*,*R*)-**K** (5 mol %) were dissolved in CH_2Cl_2 and a solution of $AgSbF_6$ (5 mol %) in CH_2Cl_2 (total concentration 0.05M) was added dropwise at respectively –40 ºC or –30 ºC. The reaction was stirred for 2 d at the same temperature, quenched by addition of 3 drops of NEt_3 and concentrated. The crude was purified by flash column chromatography or preparative TLC.

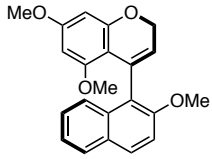
1,3-dimethoxy-10-(2-methoxynaphthalen-1-yl)phenanthrene



The title compound (wite solid, 88%, 96:4 *er*) was synthesized following general procedure **H** using 1-((3',5'-dimethoxy-[1,1'-biphenyl]-2-yl)ethynyl)-2-methoxynaphthalene[175] (20.0 mg, 57 μmol). Purification was performed by flash column chromatography (cyclohexane/EtOAc 100:1).

M.p. = °C (CH_2Cl_2). α_D^{589} = deg.cm^2.g^{-1} ($CHCl_3$, c 1.0, 296 K). **SFC** Chiralpak IC (100 × 4.3 mm, 3 μm) at 35 ºC, flow 1.2 mL/min, isocratic CO_2/MeOH 75:25, ABRP pressure 150 bar, 230 nm, t_R (minor) 1.4; t_R (major) 1.8. The spectral data were fully consistent with those previously reported.[175]

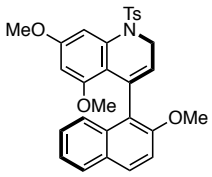
5,7-Dimethoxy-4-(2-methoxynaphthalen-1-yl)-2*H*-chromene



The title compound (100% conversion, 56:44 *er*) was synthesized following general procedure **H** using 1-(3-(3,5-dimethoxyphenoxy)prop-1-yn-1-yl)-2-methoxynaphthalene (20.0 mg, 57 μmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.74 (m, 2H), 7.70 – 7.65 (m, 1H), 7.33 – 7.27 (m, 3H), 6.23 (d, *J* = 2.4 Hz, 1H), 5.88 (d, *J* = 2.4 Hz, 1H), 5.61 (t, *J* = 4.2 Hz, 1H), 4.84 (d, *J* = 4.2 Hz, 2H), 3.85 (s, 3H), 3.78 (s, 3H), 2.95 (s, 3H). **HPLC** Chiralpak AD (250 × 4.6mm, 5μm) at 25 ºC, flow 1.0 mL/min, isocratic hexane/iPrOH 90:10, 280 nm, t_R (minor) 6.3; t_R (mjor) 8.2.

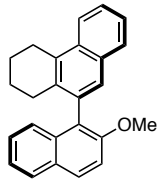
5,7-Dimethoxy-4-(2-methoxynaphthalen-1-yl)-1-tosyl-1,2-dihydroquinoline



The title compound (100% conversion, 70:30 *er*) was synthesized following general procedure **H** using *N*-(3,5-dimethoxyphenyl)-*N*-(3-(2-methoxynaphthalen-1-yl)prop-2-yn-1-yl)-4-methylbenzene sulfonamide (20.0 mg, 57 μmol).

HPLC Chiralpak AD (250 × 4.6mm, 5μm) at 25 ºC, flow 1.0 mL/min, isocratic hexane/iPrOH 90:10, 280 nm, t_R (major) 10.1; t_R (minor) 16.9.

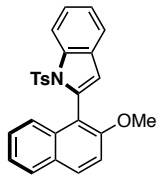
10-(2-Methoxynaphthalen-1-yl)-1,2,3,4-tetrahydrophenanthrene



The title compound (100% conversion, 93:7 *er*) was synthesized following general procedure **H** using 2-methoxy-1-((2',3',4',5'-tetrahydro-[1,1'-biphenyl]-2-yl)ethynyl)naphthalene[175] (20.0 mg, 57 μmol). Purification was performed by flash column chromatography (cyclohexane/EtOAc 100:1).

M.p. = °C (CH_2Cl_2). $\boldsymbol{\alpha_D^{589}}$ = deg.cm^2.g^{-1} ($CHCl_3$, c 1.0, 296 K). **SFC** Chiralpak IC (100 × 4.3 mm, 3 μm) at 35 ºC, flow 1.2 mL/min, isocratic CO_2/MeOH 75:25, ABRP pressure 150 bar, 230 nm, t_R (minor) 1.4; t_R (major) 1.8. The spectral data were fully consistent with those previously reported.[175]

2-(2-Methoxynaphthalen-1-yl)-1-tosyl-1*H*-indole



The title compound (100% conversion, 50:50 *er*) was synthesized following general procedure **H** using *N*-(2-((2-methoxynaphthalen-1-yl)ethynyl)phenyl)-4-methylbenzenesulfonamide (30.0 mg, 70.0 μmol). The crude ^{1}H NMR was analyzed.

M.p. = °C (CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.36 (dd, *J* = 8.4, 0.9 Hz, 1H), 8.00 (d, *J* = 9.0 Hz, 1H), 7.83 (d, *J* = 8.5 Hz, 1H), 7.60 (d, *J* = 7.7 Hz, 1H), 7.44 – 7.35 (m, 2H), 7.35 – 7.29 (m, 2H), 7.28 – 7.21 (m, 3H), 7.16 (ddd, *J* = 8.4, 6.7, 1.3 Hz, 1H), 6.92 (d, *J* = 7.7 Hz, 2H), 6.66 (d, *J* = 0.8 Hz, 1H), 3.88 (s, 3H), 2.28 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 156.5, 144.2, 137.2, 136.1, 134.6, 134.5, 131.2, 129.8, 129.1, 128.4, 127.8, 127.0, 126.5, 124.8, 124.3, 123.2, 120.7, 115.1, 114.7, 112.7, 56.2, 21.4. **HPLC** Chiralpak IA (250 × 4.6mm, 5μm) at 25 ºC, flow 1.0 mL/min, isocratic hexane/iPrOH 90:10, 280 nm, t_R (major) 11.5; t_R (minor) 13.0.

Kinetic Investigations

Order of Reagents

To determine the reaction order of enyne **1.2a**, the reaction progress was monitored during the first 10 min reaction time in 1 min intervals assuming that the initial concentrations do not change significantly (Figure 2.7).

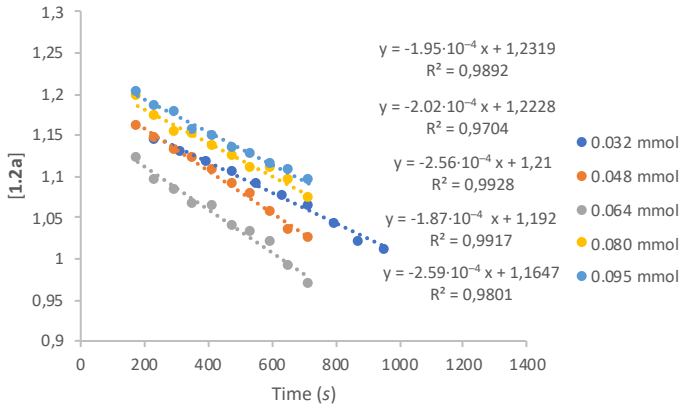


Figure 2.7. Kinetic profiles of formal [4+2] cycloaddition modifying substrate concentration.

The kinetic experiments were repeated keeping the concentration of enyne **1.2a** constant and changing the amounts of (*R*,*R*)-**D**/$AgSbF_6$ in CD_2Cl_2 (Figure 2.8).

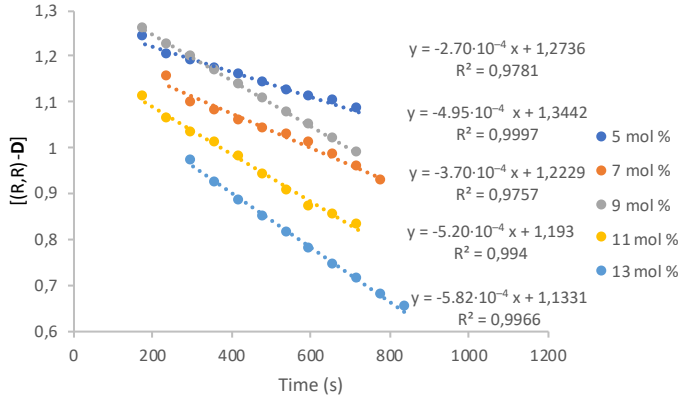


Figure 2.8. Kinetic profiles of formal [4+2] cycloaddition with variating catalyst concentration.

The obtained initial rates (Table 2.14) were plotted against the initial concentrations on a logarithmic scale (Figure 2.9).

Table 2.14. Initial rates.

1.2a (*mmol*)	***k* (s^{-1})**	**Cat.[a] (μ*mol*)**	***k* (s^{-1})**
0.032	$1.87 \cdot 10^{-4}$	3.18	$2.70 \cdot 10^{-4}$
0.048	$2.56 \cdot 10^{-4}$	4.56	$3.70 \cdot 10^{-4}$
0.064	$2.59 \cdot 10^{-4}$	5.86	$4.95 \cdot 10^{-4}$
0.080	$2.02 \cdot 10^{-4}$	7.17	$5.20 \cdot 10^{-4}$
0.095	$1.95 \cdot 10^{-4}$	8.27	$5.82 \cdot 10^{-4}$

[a]Cat. = 1:1 mixture of (*R*,*R*)-**D** and $AgSbF_6$.

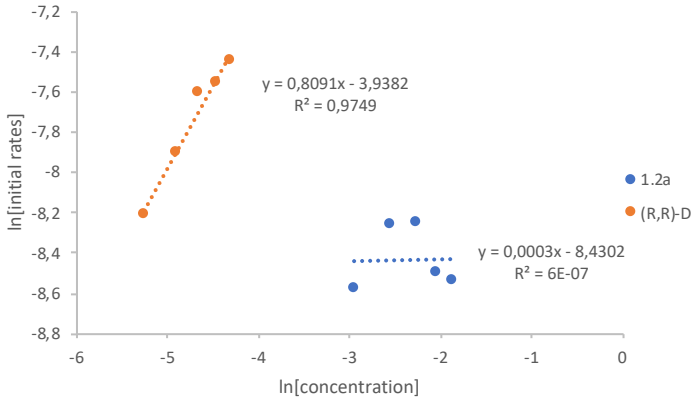


Figure 2.9. Order of enyne **1.2a** and catalyst (*R*,*R*)-**D**/$AgSbF_6$.

Eyring Analysis

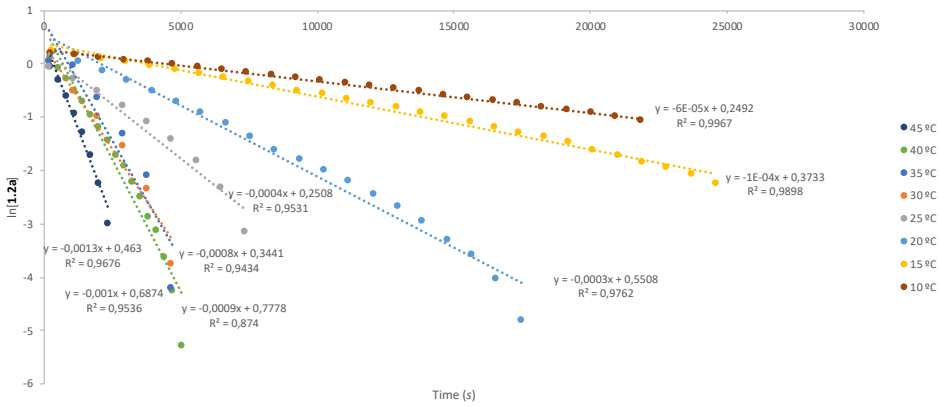


Figure 2.10. Kinetic profiles of formal [4+2] reaction at different temperatures.

According to the Eyring equation (equation 2.1), $\ln(k \cdot T^{-1})$ was plotted versus T^{-1} (Figure 2.11).

$$\ln\left(\frac{k}{T}\right) = \ln\left(\frac{k_B}{T}\right) - \frac{\Delta H^{\ddagger}}{RT} + \frac{\Delta S^{\ddagger}}{R} \qquad \textbf{(eq. 2.1.)}$$

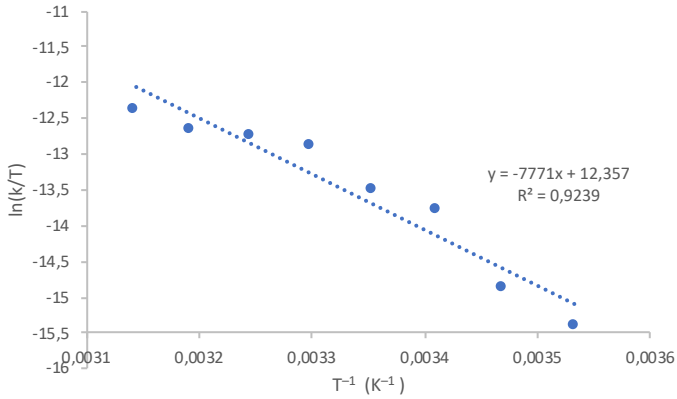
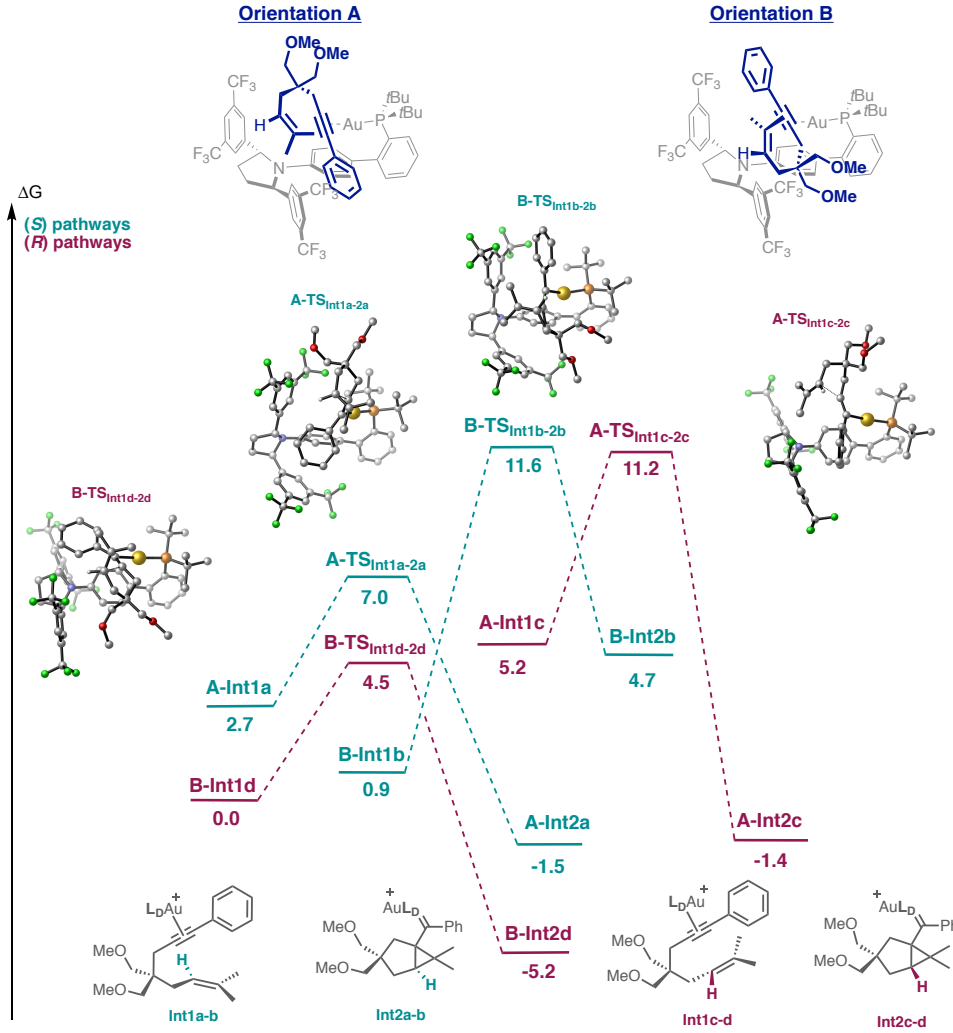
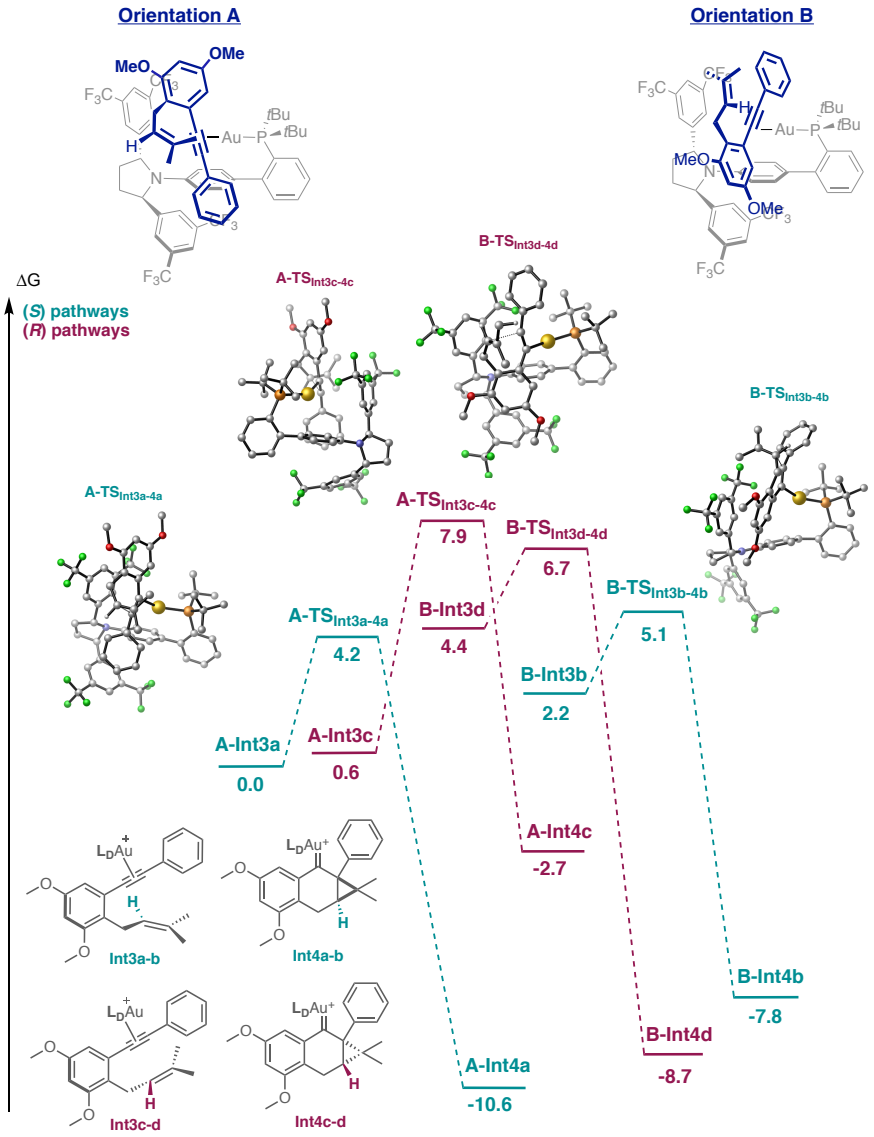


Figure 2.11. Eyring plot of the gold(I)-catalyzed formal [4+2] with (*R*,*R*)-**D**.

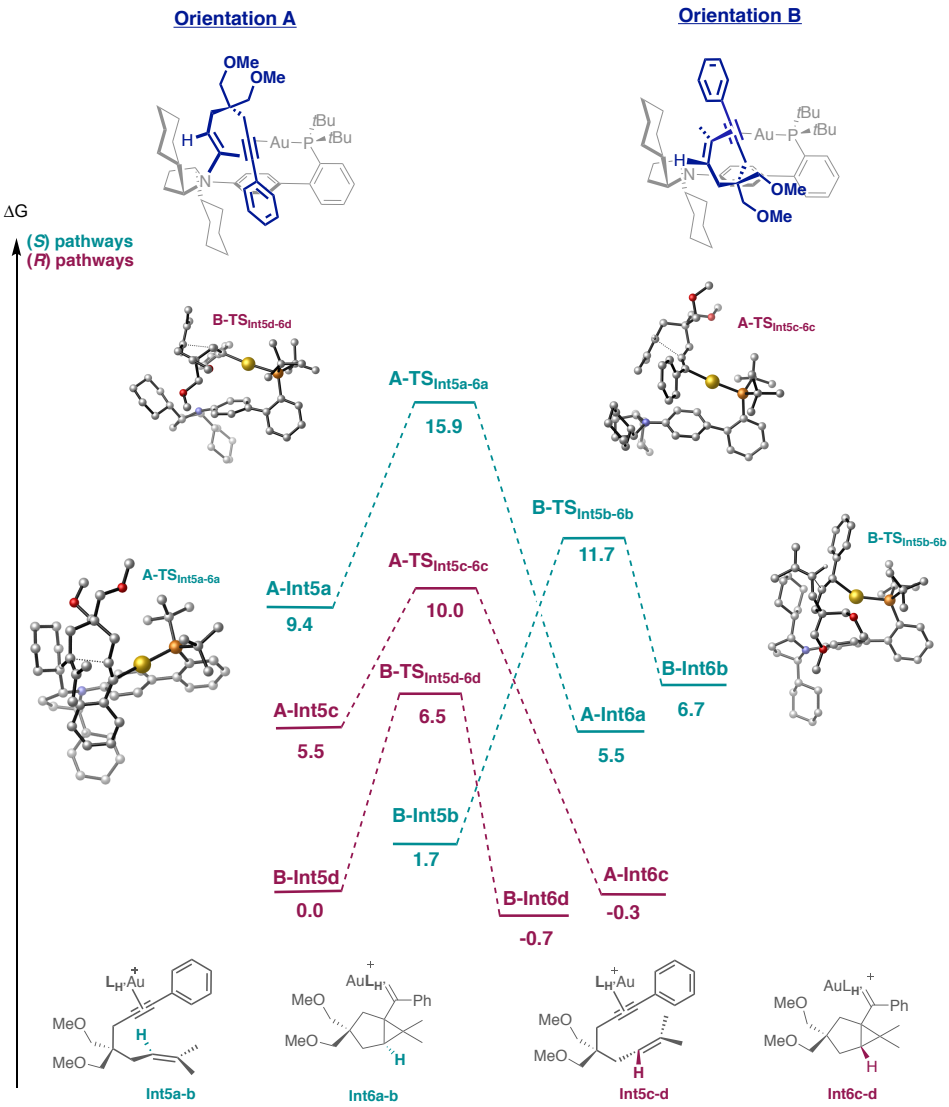
Calculated Energy Diagrams



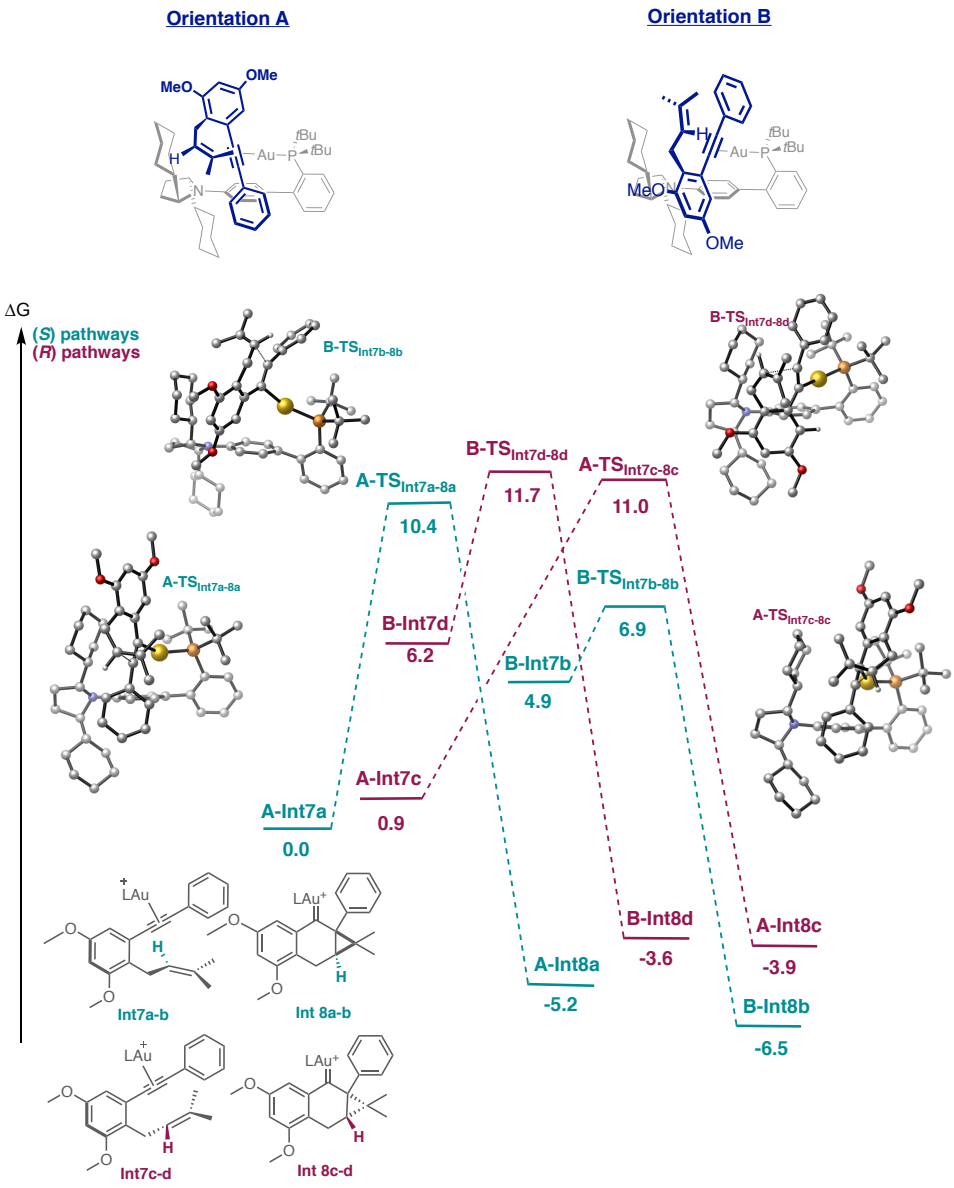
Free energy profiles for the enantioselective 5-*exo*-dig cyclization reaction of 1,6-enynes **1.2b** with (*R*,*R*)-**D**. (*S*) pathway is depicted in green and (*R*) pathway in purple. The energy values are given in kcal·mol^{-1} and represent the relative free energies. Hydrogen atoms have been omitted for clarity.



Free energy profiles for the enantioselective 6-*endo*-dig cyclization reaction of 1,6-enynes **1.93k** with (*R*,*R*)-**D**. (*S*) pathway is depicted in green and (*R*) pathway in purple. The energy values are given in kcal·mol^{-1} and represent the relative free energies. Hydrogen atoms have been omitted for clarity.



Free energy profiles for the enantioselective 5-*exo*-dig cyclization reaction of 1,6-enynes **1.2b** with (*R*,*R*)-**H'**. (*S*) pathway is depicted in green and (*R*) pathway in purple. The energy values are given in kcal·mol^{-1} and represent the relative free energies. Hydrogen atoms have been omitted for clarity.



Free energy profiles for the enantioselective 6-*endo*-dig cyclization reaction of 1,6-enynes **1.93k** with (*R*,*R*)-**H'**. (*S*) pathway is depicted in green and (*R*) pathway in purple. The energy values are given in kcal·mol^{-1} and represent the relative free energies. Hydrogen atoms have been omitted for clarity.

Chapter 3.

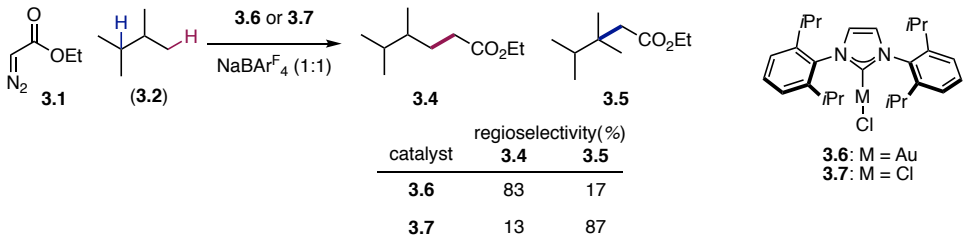
Synthesis of 1,2-Dihydronaphthalenes via Intramolecular C(sp^3)–H Insertion of Gold(I) Carbenes

Introduction

Gold(I)-Catalyzed C(sp3)–H Insertion Reactions

The direct functionalization of aliphatic C(sp^3)–H bonds via metal carbene insertion has attracted significant interest as it represents an atom economic and straight forward strategy for the build up of molecular complexity.[186] Despite the low reactivity of C(sp^3)–H bonds[186c] and the difficulty in controlling regioselectivity, several Rh-, Ru- and Cu-catalyzed processes have been reported. The versatility of these transformations has been demonstrated in the synthesis of numerous natural products.[187] In contrast, gold(I) catalyzed C(sp^3)–H functionalization reactions remain scarce.[188]

The first gold(I)-catalyzed C(sp^3)–H insertion with simple alkanes was reported by the group of Pérez generating the corresponding metal carbenes from ethyl diazoacetate **3.1** (Scheme 3.1).[189] Key for these transformations was the use of σ-donating IPr ligand.[190] Interestingly, in the functionalization of 2,3-dimethylbutane (**3.2**), primary C(sp^3)–H bonds were selectively functionalized in the presence of a gold(I) catalyst, whereas the use of copper-based complexes was more selective for the functionalization of tertiary C(sp^3)–H bonds.

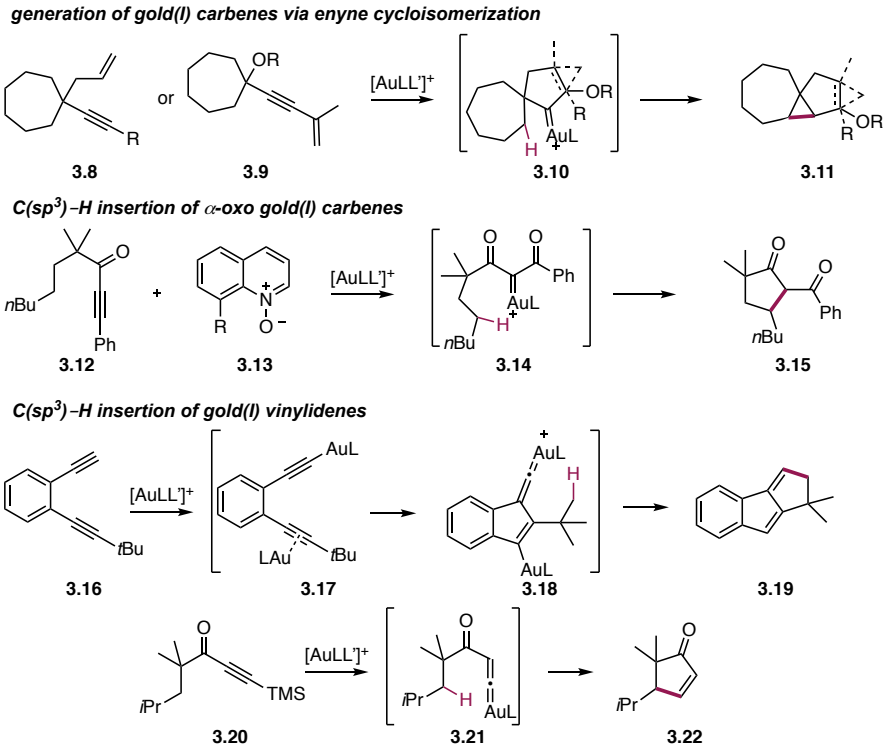


catalyst	regioselectivity(%) 3.4	3.5
3.6	83	17
3.7	13	87

Scheme 3.1. Gold(I)-catalyzed C(sp^3)–H insertion with simple alkanes.

186. (a) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861–2903. (b) Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev.* **2010**, *110*, 704–724. (c) Caballero, A.; Díaz-Requejo, M. M.; Fructos, M. R.; Olmos, A.; Urbano, J.; Pérez, P. J. *Dalt. Trans.* **2015**, *44*, 20295–20307.
187. (a) Taber, D. F.; Stiriba, S. E. *Chem. Eur. J.* **1998**, *4*, 990–992. (b) Davies, H. M. L.; Denton, J. R. *Chem. Soc. Rev.* **2009**, *38*, 3061–3071. (c) Egger, J.; Carreira, E. M. *Nat. Prod. Rep.* **2014**, *31*, 449–455.
188. (a) Xie, J.; Pan, C.; Abdukader, A.; Zhu, C. *Chem. Soc. Rev.* **2014**, *43*, 5245–5256. (b) Skouta, R.; Li, C. J. *Tetrahedron* **2008**, *64*, 4917–4938.
189. Fructos, M. R.; De Frémont, P.; Nolan, S. P.; Mar Díaz-Requejo, M.; Pérez, P. J. *Organometallics* **2006**, *25*, 2237–2241.
190. Fructos, M. R.; Belderrain, T. R.; De Frémont, P.; Scott, N. M.; Nolan, S. P.; Díaz-Requejo, M. M.; Pérez, P. J. *Angew. Chem. Int. Ed.* **2005**, *44*, 5284–5288.

Other C(sp^3)–H functionalizations through insertion of gold(I) carbenes derived from diazo compounds have been reported.[191] Insertion of gold(I) carbenes into non-activated C(sp^3)–H bonds have proved to be a powerful method for the synthesis of different complex polycyclic structures. Thereby, distinct approaches for the generation of the metal carbene were selected. The groups of Toste[192] and Malacria[193] reported the insertion reaction of gold(I) carbenes **3.10** generated from cycloisomerizations of enynes **3.8** or **3.9** giving highly fused ring systems such as **3.11** (Scheme 3.2).



Scheme 3.2. Examples of gold(I)-catalyzed C(sp^3)–H bond insertions.

α-Oxo gold carbenes[194] such as **3.14** generated via oxidation of alkynes **3.12** with pyridine *N*-oxides **3.13** undergo insertion into C(sp^3)–H bonds to give synthetically useful

191. (a) Ma, B.; Wu, Z.; Huang, B.; Liu, L.; Zhang, J. *Chem. Commun.* **2016**, *52*, 9351–9354. (b) Ma, B.; Wu, J.; Liu, L.; Zhang, J. *Chem. Commun.* **2017**, *53*, 10164–10167. (c) Ren, Y. Y.; Chen, M.; Li, K.; Zhu, S. F. *Chem. Asian J.* **2018**, *13*, 2606–2610.
192. Horino, Y.; Yamamoto, T.; Ueda, K.; Kuroda, S.; Toste, D. F. *J. Am. Chem. Soc.* **2009**, *131*, 2809–2811.
193. Lemière, G.; Gandon, V.; Cariou, K.; Hours, A.; Fukuyama, T.; Dhimane, A. L.; Fensterbank, L.; Malacria, M. *J. Am. Chem. Soc.* **2009**, *131*, 2993–3006.
194. Bhunia, S.; Ghorpade, S.; Huple, D. B.; Liu, R. S.. *Angew. Chem. Int. Ed.* **2012**, *51*, 2939–2942.

cyclopentanones **3.15** (Scheme 3.2).[195] Similarly, gold(I) vinylidenes have been found to undergo insertion in aliphatic C(sp^3)–H bonds. The groups of Hashmi[196] and Zhang[197] have reported several examples on the "dual activation" of diynes **3.16** in which one molecule of gold(I) catalyst activates one triple bond by π-coordination and a second gold(I) catalyst forms gold(I) acetylides **3.17** with a terminal alkyne. The resulting gold(I) vinylidene intermediate **3.18** undergoes C(sp^3)–H insertion to give fulvene derivatives **3.19**. Complementary work has been reported by Zhang generating gold(I) vinylidenes **3.21** from TMS-alkynes **3.20** to obtain cyclopentenones **3.22**.[198] Different precursors of gold(I) carbenes undergoing C(sp^3)–H insertion have also been studied.[199]

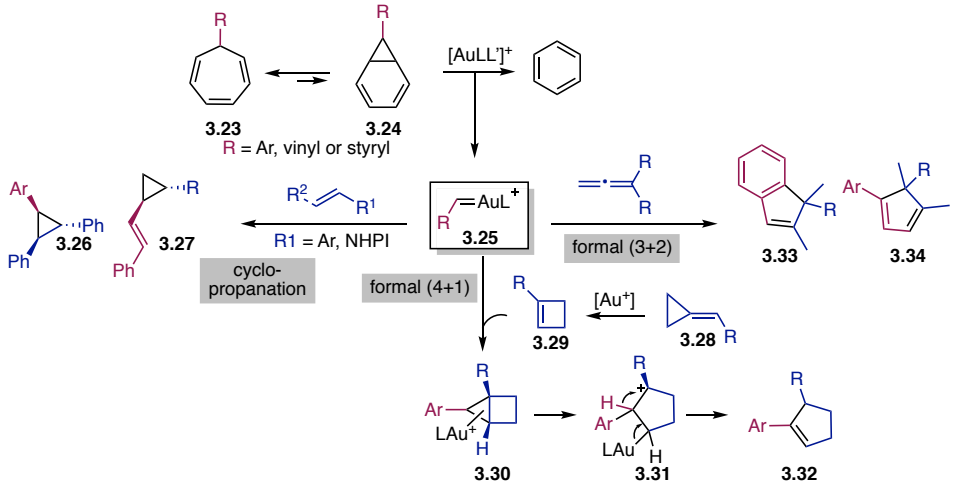
Generation of Gold(I) Carbenes via Retro-Buchner Reaction

The field of homogeneous gold(I) catalysis has been marked by the constant development of new methods for the generation of the corresponding metal carbenes.[200] In this context, our group has discovered the formation of gold(I) carbenes by retro-Buchner reaction of 7-substituted-1,3,5-cycloheptatrienes **3.23** (Scheme 3.3).[201]

Cycloheptatriene **3.23** is in equilibrium with its norcaradiene tautomer **3.24**[202] from which gold(I) carbene **3.25** is generated together with a molecule of benzene via a stepwise retro-cyclopropanation,[203] resulting in an overall retro-Buchner (decarbenation) reaction (Scheme 3.3). Compared to the most commonly employed diazo compounds as carbene precursors, this process stands out for being safer since cycloheptatrienes are stable compounds that can be stored under ordinary conditions. In addition, the starting materials are easily accessible by reaction of the corresponding organolithium or Grignard reagent to commercial tropylium tetrafluoroborate or, alternatively, via Julia-Kocienski olefination.[204]

195. Wang, Y.; Zheng, Z.; Zhang, L. *J. Am. Chem. Soc.* **2015**, *137*, 5316–5319.
196. (a) Hashmi, A. S. K.; Wieteck, M.; Braun, I.; Rudolph, M.; Rominger, F. *Angew. Chem. Int. Ed.* **2012**, *51*, 10633–10637. (b) Tšupova, S.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *Chem. Eur. J.* **2017**, *23*, 12259–12263. (c) Klein, J. E. M. N.; Knizia, G.; Nunes dos Santos Comprido, L.; Kästner, J.; Hashmi, A. S. K. *Chem. Eur. J.* **2017**, *23*, 16097–16103. (d) Hashmi, A. S. K.; Braun, I.; Nösel, P.; Schädlich, J.; Wieteck, M.; Rudolph, M.; Rominger, F. *Angew. Chem. Int. Ed.* **2012**, *51*, 4456–4460.
197. Ye, L.; Wang, Y.; Aue, D. H.; Zhang, L. *J. Am. Chem. Soc.* **2012**, *134*, 31–34.
198. Wang, Y.; Zarca, M.; Gong, L. Z.; Zhang, L. *J. Am. Chem. Soc.* **2016**, *138*, 7516–7519.
199. (a) Li, D. Y.; Fang, W.; Wei, Y.; Shi, M. *Chem. Eur. J.* **2016**, *22*, 18080–18084. (b) Archambeau, A.; Miege, F.; Meyer, C.; Cossy, J. *Acc. Chem. Res.* **2015**, *48*, 1021–1031.
200. Harris, R. J.; Widenhoefer, R. A. *Chem. Soc. Rev.* **2016**, *45*, 4533–4551.
201. Mato, M.; García-Morales, C.; Echavarren, A. M. *ChemCatChem* **2019**, *11*, 53–72.
202. (a) McNamara, O. A.; Maguire, A. R.. *Tetrahedron* **2011**, *67*, 9–40. (b) Hoffmann, R. *Tetrahedron Lett.* **1970**, *11*, 2907–2909.
203. Batiste, L.; Fedorov, A.; Chen, P. *Chem. Commun.* **2010**, *46*, 3899–3901.
204. (a) Herlé, B.; Holstein, P. M.; Echavarren, A. M. *ACS Catal.* **2017**, *7*, 3668–3675.

Gold(I) carbenes **3.25** engage in numerous cyclopropanation reactions of alkenes leading to a broad scope of di- and tri-aryl- and vinyl cyclopropanes **3.26** and **3.27** (Scheme 3.3).[204a,205] In the formation of highly substituted cyclopentenes **3.32** from 1,3-diene equivalents such as methylenecyclopropanes **3.28** or cyclobutenes **3.29**, gold(I) is involved in three catalytic steps.[206] In addition to generating carbene **3.25**, gold(I) also promotes the isomerization of **3.28** into **3.29** and the subsequent cyclopropanation to give bicyclo[2.1.0]pentanes **3.30**. Cleavage of the internal C–C bond and 1,2-hydrogen shift in **3.31** affords **3.32** in a formal (4+1) cycloaddition. The reaction of aryl and styryl gold(I) carbenes **3.25** with allenes gives indenes **3.33** and cyclopentadienes **3.34**, respectively through formal (3+2) cycloaddition.[207] Examples of intramolecular transformations in which the gold(I) carbenes generated by retro-Buchner undergo Friedel-Crafts-type annulation have also been reported.[205b]



Scheme 3.3. Synthetic versatility of gold(I)-carbenes generated by retro-Buchner reaction.

Despite being a powerful method, the generation of gold(I) carbenes via retro-Buchner reaction requires elevated temperatures (75-120 ºC) which results in moderate stereocontrol and functional group tolerance. To overcome this limitation, our group has introduced a 2nd generation of 7-styryl-1,3,5-trimethyl-cycloheptatrienes **3.35** (Scheme 3.4). The electron-donating methyl substituents stabilize Wheland intermediate **3.37**, formed upon the first

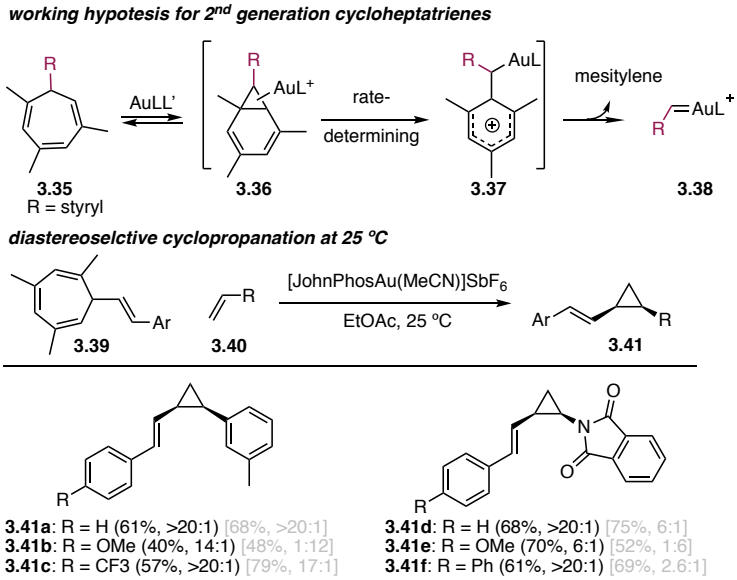
(b) Mato, M.; Herlé, B.; Echavarren, A. M. *Org. Lett.* **2018**, *20*, 4341–4345.

205. (a) Solorio-Alvarado, C. R.; Wang, Y.; Echavarren, A. M. *J. Am. Chem. Soc.* **2011**, *133*, 11952–11955. (b) Wang, Y.; McGonigal, P. R.; Herlé, B.; Besora, M.; Echavarren, A. M. *J. Am. Chem. Soc.* **2014**, *136*, 801–809.

206. Wang, Y.; Muratore, M. E.; Rong, Z.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2014**, *53*, 14022–14026.

207. Yin, X.; Mato, M.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2017**, *56*, 14591–14595.

C–C bond cleavage in norcaradiene **3.36**, which was found to be the rate-determining step.[204a,205a] Finally, gold(I) carbene **3.38** is formed with the concomitant generation of one molecule of mesitylene.

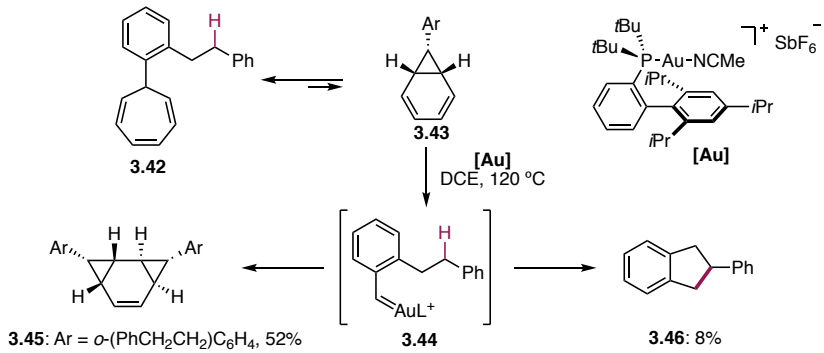


Scheme 3.4. 2nd Generation of cycloheptatrienes and application in diastereoselective cyclopropanation under mild conditions. In grey: results obtained with 1st generation of cycloheptatrienes.

Compared to the 1st generation of cycloheptatrienes, under gold(I)-catalyzed conditions compounds **3.39** react with a broad scope of alkenes **3.40** at 25 ºC affording vinyl cyclopropanes **3.41** with improved *cis*-diastereoselectivity.[204b] Importantly, the 2nd generation of cycloheptatriene undergoes retro-Buchner reaction also in presence of zinc- and rhodium-based catalysts.[208]

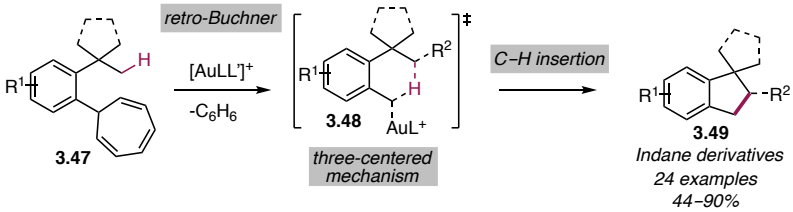
Among the useful transformations, the C(sp^3)–H isertion of gold(I) carbenes generated by retro-Buchner reaction was found to be more challenging. Indeed, cycloheptatriene **3.42** undergoes retro-Buchner/C–H insertion forming indane **3.46**, albeit in low yields (Scheme 3.5). Biscyclopropane **3.45** was found to be the major product formed upon cyclopropanation of norcaradiene tautomer **3.43** with carbene **3.44**.[205a]

208. Mato, M.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2019**, *58*, 2088–2092.



Scheme 3.5. First C(sp^3)–H insertion reactivity.

Our group addressed this limitation introducing a quaternary carbon center adjacent to the reacting C–H bond in substrate **3.47** (Scheme 3.6). Thus, the target C–H bond is placed closer to the gold(I) carbene **3.48** and the activation barrier for the cyclization is lowered as the proportion of reactive conformers increases. This strategy proved successful resulting in the broad scope synthesis of substituted indanes **3.49**. Mechanistic studies were consistent with a three-centered concerted mechanism.[209]

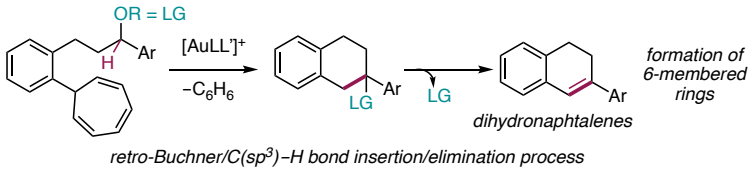


Scheme 3.6. Synthesis of indanes via C(sp^3)–H insertion.

209. Yin, X.; Zuccarello, G.; García-Morales, C.; Echavarren, A. M. *Chem. Eur. J.* **2019**, *25*, 9485–9490.

Objectives

Encouraged by the efficient synthesis of indanes via C(sp^3)–H isertion we aimed at extending this reaction to the analogous but less favored formation of 6-membered rings. We targeted weaker benzylic C–H bonds activated by an α-OR group. Elimination of the OR-group would lead to the formation of substituted dihydronaphthalenes.

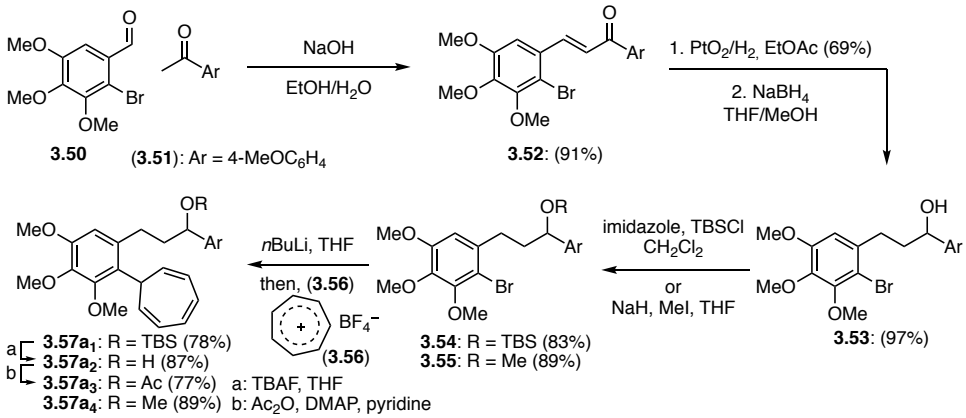


Scheme 3.7. Gold(I)-catalyzed synthesis of dihydronaphthalenes.

Results and Discussion

Reaction Development

Our first studies focused on identifying the most suitable leaving group in substrates such as **3.57a$_1$-a$_4$** (Scheme 3.8). Their synthesis was accomplished in 5-7 high yielding steps (44-91%) from commercially available benzaldehyde **3.50** and 1-(4-methoxyphenyl)ethan-1-one (**3.51**). Chalcone **3.52** was synthesized via aldol condensation and then converted into **3.54**/**3.55** following a 3-steps sequence including reductions with Adams' precatalyst and $NaBH_4$ followed by TBS- or Me-protection. The cycloheptatriene moiety was introduced through formation of the corresponding organolithium compound and addition to tropylium tetrafluoroborate **3.56** affording **3.57a$_1$,a$_4$** in good yields. Silyl-deprotection of **3.57a$_1$** and functional group interconversion afforded **3.57a$_2$-xa$_3$**.



Scheme 3.8. Synthesis of **3.57a$_1$-a$_4$**.

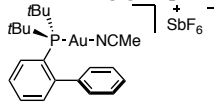
We tested the obtained substrates using cationic complex **A** at 100 ºC in 1,2-dichloroethane. Gratifyingly, TBS-protected secondary alcohol **3.57a$_1$** afforded dihydronaphthalene **3.58a** in 30% yield via benzylic C–H insertion/elimination pathway (Table 3.1, entry 1). Substrates **3.57a$_1$,a$_2$** containing hydroxy or acetate as the leaving group did not give the desired product **3.58a** as only decomposition of starting material was observed (Table 3.1, entries 2 and 3). Methylether **3.57a$_4$** gave **3.58a** in 71% yield and established methoxy as the best leaving group.

Table 3.1. Substrate optimization for formation.

3.57a$_1$-a$_4$: Ar = 4-MeOC$_6$H$_4$ **3.58a**

entry	3.57	LG	t (*h*)	yield (%)[a]
1	**3.57a$_1$**	TBS	18	30
2	**3.57a$_2$**	OH	18	n.d.[b]
3	**3.57a$_3$**	OAc	18	n.d.[b]
4	**3.57a$_4$**	OMe	2.5	71

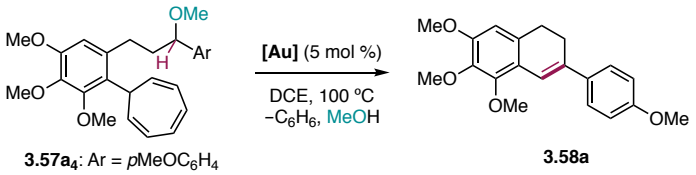
[a]Yields determined by ^{1}H NMR using 3,5-dimethylpyrazol as internal standard. LG = leaving group. [b]n.d. = not detected.



A

Catalyst optimization identified IPr-gold(I) complex **F** as the best one giving 1,2-dihydronaphthalene **3.58a** as a single double bond isomer in 89% isolated yield (Table 3.2, entry 6). Catalysts **B-D** also afforded the desired product however in lower yields (26-48%) (Table 3.2, entries 2-4). The remaning catalysts, including gold(III) complex **I** and AuCl **J**, failed to give the desired product **3.58a**, presumably due to their lack of stability at the high temperatures required for the retro-Buchner reaction.

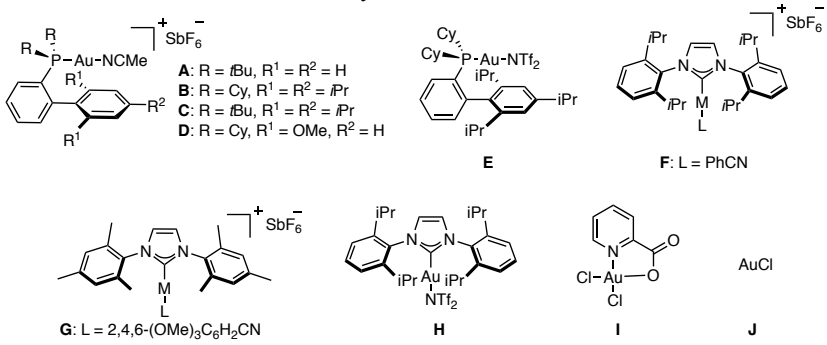
Table 3.2. Catalyst screening for formation of **3.58a**.



3.57a$_4$: Ar = *p*MeOC$_6$H$_4$ **3.58a**

entry	[Au]	T (*h*)	yield (%)[a]
1	**A**	2.5	71
2	**B**	16	26
3	**C**	5	31
4	**D**	6	48
5	**E**	16	n.d.[b]
6	**F**	0.5	89[c]
7	**G**	16	n.d.[b]
8	**H**	16	n.d.[b]
9	**I**	16	n.d.[b]
10	**J**	16	n.d.[b]

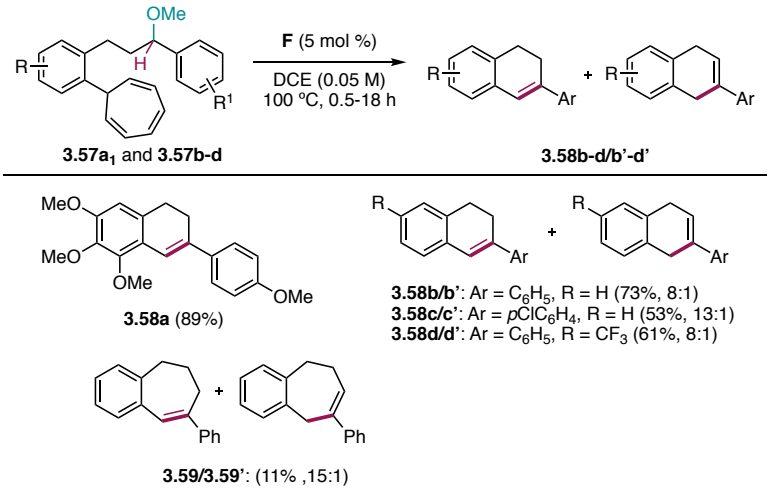
[a]Yields determined by 1H NMR using 1,3,5-tribromobenzene as internal standard. [b] n.d. = non detected. [c]Isolated yield.



Synthesis of Dihydronaphthalenes

The scope of the reaction was examined under the optimized reaction conditions. (Table 3.3). Cycloheptatrienes **3.57b-d** were converted into the corresponding 1,2-dihydronaphthalenes **3.58b-d** in good yields (53-73%) along with minor amounts of their double bond isomers **3.58b'-d'**.

Table 3.3. Synthesis of dihydronaphthalenes: scope.



We also attempted the synthesis of the 7-membered ring product **3.59**. However, this compound was isolated in only poor 11% yield together with isomer **3.59'**, as a 15:1 mixture.

The reaction scope was found to be limited to the activation of benzylic C–H bonds. Figure 3.1 shows substrates that failed to deliver the desired products.

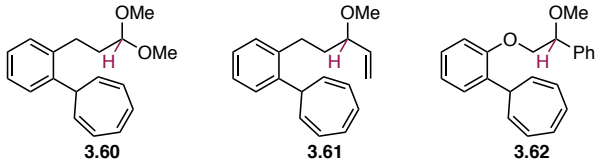
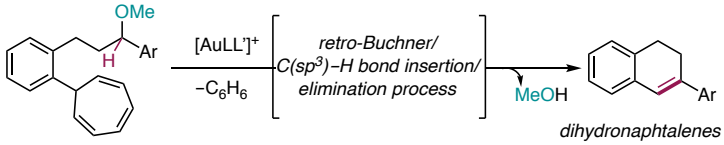


Figure 3.1. Unsuccessful substrates.

Conclusions

We have found that substituted 1,2-dihydronaphthalenes can be synthesized following a retro-Buchner/C(sp^3)–H insertion/elimination reaction sequence. Key for this transformation is the additional activation of a benzylic C–H with an α-MeO group which subsequently undergoes elimination.



Scheme 3.9. Synthesis of 1,2-dihydronaphthalenes via gold(I)-catalyzed C(sp^3)–H insertion.

Experimental Section

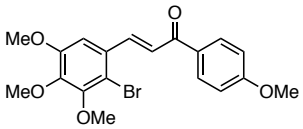
General Information

The general information is provided in the Experimental Section of **Chapter 1**. All gold complexes were prepared according to a previously reported procedure by our group.[161b] Complexes **A** and **C** were purchased from Sigma Aldrich and used as such.

Synthetic Procedures and Characterization of Compounds

Synthesis of Starting Materials

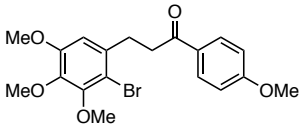
(*E*)-3-(2-Bromo-3,4,5-trimethoxyphenyl)-1-(4-methoxyphenyl)prop-2-en-1-one



In a 100 mL one-necked flask NaOH (309 mg, 7.72 mmol, 1.25 equiv) was dissolved in water (1.6 mL) and ethanol (13.0 mL). The solution was cooled to 0 ºC and 1-(4-methoxyphenyl)ethan-1-one (928 mg, 6.2 mmol, 1.0 equiv) was added in one portion followed by 2-bromo-3,4,5-trimethoxybenzaldehyde[210] (1.70 g, 6.20 mmol, 1.0 equiv.). Stirring was continued at 24 ºC for 1 h. The reaction mixture was cooled to 0 ºC to allow the product to precipitate. The mixture was filtered and the filtrate was washed with cold ethanol to yield the title compound (2.30 g, 5.60 mmol, 91%) as a pale yellow solid.

M.p. = 77 – 79 °C (CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 15.7 Hz, 1H), 8.04 – 7.99 (m, 2H), 7.29 (d, *J* = 15.6 Hz, 1H), 7.04 (s, 1H), 7.01 – 6.95 (m, 2H), 3.93 (2s, 6H), 3.90 (s, 3H), 3.89 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 189.1, 163.6, 153.0, 151.4, 145.1, 142.9, 131.1, 131.0, 130.8, 124.6, 114.0, 113.5, 106.5, 61.4, 61.1, 56.5, 55.6. **HRMS** (ESI+) calculated for $[C_{19}H_{19}BrNaO_5]^+$ 429.0308 *m/z*; found $[M+Na]^+$ 429.0312 *m/z*.

3-(2-Bromo-3,4,5-trimethoxyphenyl)-1-(4-methoxyphenyl)propan-1-one



(*E*)-3-(2-Bromo-3,4,5-trimethoxyphenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (1.28 g, 3.14 mmol, 1.0 equiv.) was dissolved in a EtOAc (23 mL). The solution was degassed with argon for 15 min and PtO_2 (36.0 mg, 0.157 mmol, 5 mol %) was added. The reaction was stirred at 23 ºC under 1 atm of H_2 for 2.5 h. After consumption of the starting material (TLC cyclohexane/EtOAc 3:1) the reaction mixture

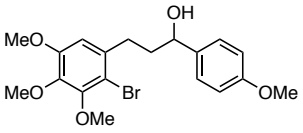
210. Molander, G. A.; George, K. M.; Monovich, L. G. *J. Org. Chem.* **2003**, *68*, 9533–9540.

was degassed with argon and filtered over Celite®. The filtrate was concentrated and the crude was purified by flash column chromatography (cyclohexane/EtOAc 4:1) to yield the title compound (890 mg, 2.17 mmol, 69 %) as a yellow gum.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 – 7.72 (m, 2H), 7.05 – 6.85 (m, 2H), 6.71 (s, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.88 (s, 3H), 3.85 (s, 3H), 3.32 – 3.21 (m, 2H), 3.21 – 3.11 (m, 2H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 197.9, 163.7, 152.7, 151.1, 141.7, 136.5, 130.5, 130.1, 113.9, 110.5, 109.7, 61.2, 61.1, 56.3, 55.6, 38.5, 31.6. **HRMS** (ESI+) calculated for $[C_{19}H_{22}BrO_5]^+$ 409.0645 *m/z*; found $[M+H]^+$ 409.0646 *m/z*.

3-(2-Bromo-3,4,5-trimethoxyphenyl)-1-(4-methoxyphenyl)propan-1-ol

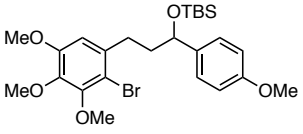


3-(2-Bromo-3,4,5-trimethoxyphenyl)-1-(4-methoxyphenyl) propan-1-one (1.50 g, 3.67 mmol, 1.0 equiv) was dissolved in a mixture of THF:MeOH (4:1) (28.2 mL, 0.13M) and $NaBH_4$ (180 mg, 4.76 mmol, 1.3 equiv) was added to the reaction mixture. The reaction was stirred at 24 ºC. After consumption of the starting material (TLC cyclohexane/EtOAc 2:1), the reaction was quenched with sat. NH_4Cl solution and extracted with Et_2O (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude was purified by flash column chromatography (cyclohexane/EtOAc 3:1) to yield the title compound (1.46 g, 3.54 mmol, 97%) as a colorless gum.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.32 – 7.28 (m, 2H), 6.91 – 6.87 (m, 2H), 6.58 (s, 1H), 4.69 (ddd, *J* = 8.1, 5.3, 3.1 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.83 (s, 3H), 3.81 (s, 3H), 2.89 – 2.81 (m, 1H), 2.77 – 2.68 (m, 1H), 2.13 – 1.96 (m, 1H), 1.85 (d, *J* = 3.3 Hz, 1H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ = 159.3, 152.7, 151.1, 141.5, 137.0, 136.7, 127.3, 114.1, 110.7, 109.2, 73.8, 61.2, 61.1, 56.3, 55.5, 40.0, 33.2. **HRMS** (ESI+) calculated for $[C_{19}H_{23}BrNaO_2]^+$ 433.0621 *m/z*; found $[M+Na]^+$ 433.0626 *m/z*.

(3-(2-Bromo-3,4,5-trimethoxyphenyl)-1-(4-methoxyphenyl)propoxy)(*tert*-butyl)dimethylsilane

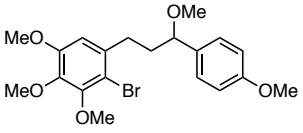


To a solution of 3-(2-bromo-3,4,5-trimethoxyphenyl)-1-(4-methoxyphenyl)propan-1-ol (613 mg, 1.49 mmol, 1.0 equiv) in CH_2Cl_2 (30 mL) were added imidazole (609 mg, 8.94 mmol, 6.0 equiv) and TBSCl (539 mg, 3.58 mmol, 2.4 equiv) and the reaction mixture was stirred overnight at 24 ºC. After full conversion of the starting material (TLC, cyclohexane/EtOAc, 3:1), the reaction was quenched with sat. NH_4Cl solution and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude was purified by flash column chromatography

(cyclohexane/EtOAc 20:1) to yield the title compound (653 mg, 1.24 mmol, 83%) as a yellow gum.

^{1}H NMR (400 MHz, CD_2Cl_2) 7.30 – 7.22 (m, 2H), 6.89 – 6.81 (m, 2H), 6.53 (s, 1H), 4.72 (dd, *J* = 7.1, 5.0 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.79 (s, 3H), 3.79 (s, 3H), 2.77 (ddd, *J* = 13.6, 11.4, 5.3 Hz, 1H), 2.63 (ddd, *J* = 13.7, 11.2, 5.3 Hz, 1H), 2.06 – 1.78 (m, 2H), 0.91 (s, 9H), 0.08 (s, 3H), –0.12 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, CD_2Cl_2) δ 159.3, 153.2, 151.4, 141.9, 138.0, 127.6, 113.9, 110.8, 109.5, 74.9, 61.4, 61.3, 56.6, 55.7, 41.4, 33.4, 26.2, 18.7, –4.3, –4.6. **HRMS** (ESI+) calculated for $[C_{25}H_{37}BrNaO_5Si]^+$ 547.1486 *m/z*; found $[M+Na]^+$ 547.1482 *m/z*.

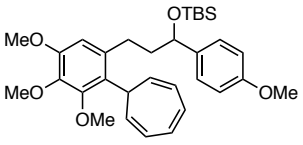
2-Bromo-3,4,5-trimethoxy-1-(3-methoxy-3-(4-methoxyphenyl)propyl)benzene



NaH (73.0 mg, 1.82 mmol, 2.0 equiv) was provided in a 10 mL flask under argon. A solution of 3-(2-bromo-3,4,5-trimethoxyphenyl)-1-(4-methoxyphenyl)propan-1-ol (374 mg, 0.91 mmol, 1.0 equiv) in THF (3.7 mL) was added at 0 ºC. Then, MeI (0.170 mL, 2.73 mmol, 3.0 equiv) was added and the reaction was stirred at 24 ºC overnight. The reaction was monitored by TLC (cyclohexane/EtOAc 2:1). After full conversion of the starting material the reaction was quenched with sat. NH_4Cl and extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude was purified by flash column chromatography (cyclohexane/Et_2O 3:1) to yield the title compound (344 mg, 0.809 mmol, 89%) as a colorless gum.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.25 – 7.20 (m, 2H), 6.92 – 6.87 (m, 2H), 6.56 (s, 1H), 4.08 (dd, *J* = 8.0, 5.2 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.82 (s, 3H), 3.81 (s, 3H), 3.22 (s, 3H), 2.89 – 2.77 (m, 1H), 2.76 – 2.66 (m, 1H), 2.11 – 2.00 (m, 1H), 2.00 – 1.88 (m, 1H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ = 159.3, 152.6, 151.0, 141.4, 137.1, 134.1, 128.1, 113.9, 110.7, 109.2, 82.9, 61.2, 61.0, 56.5, 56.2, 55.4, 38.1, 33.2. **HRMS** (ESI+) calculated for $[C_{20}H_{25}BrNaO_5]^+$ 447.0778 *m/z*; $[M+Na]^+$ found 447.0785 *m/z*.

***tert*-Butyl(3-(2-(cyclohepta-2,4,6-trien-1-yl)-3,4,5-trimethoxyphenyl)-1-(4-methoxyphenyl)propoxy)dimethylsilane**

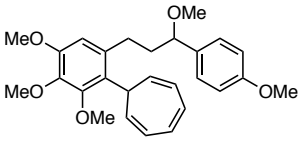


*n*BuLi (0.357 mL, 0.891 mmol, 2.5M, 1.3 equiv) was added dropwise to a solution of (3-(2-bromo-3,4,5-trimethoxyphenyl)-1-(4-methoxyphenyl)propoxy)(*tert*-butyl)dimethylsilane (0.432 g, 0.823 mmol, 1.2 equiv) in dry THF (5.7 mL) at –78 ºC under argon. The mixture was stirred for 30 min at the same temperature and tropylium tetrafluoroborate (122 mg, 0.686 mmol, 1.0 equiv) was added in one portion. The cooling bath was removed and the reaction was stirred at 24 ºC for 12 h. The reaction was quenched with water. The aqueous phase was extracted with Et_2O, the

combined organic layers were dried over Na_2SO_4, and the solvent was evaporated. The crude was purified by flash column chromatography (cyclohexane/Et_2O 10:1) to yield the title compound (288 mg, 0.537 mmol, 78%) as a yellow oil.

^{1}H NMR (500 MHz, CD_2Cl_2) 7.18 – 7.12 (m, 2H), 6.84 – 6.79 (m, 2H), 6.70 – 6.61 (m, 2H), 6.42 (s, 1H), 6.19 – 6.10 (m, 2H), 5.34 – 5.26 (m, 2H), 4.54 (dd, *J* = 7.2, 5.1 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 3.80 (s, 3H), 3.03 (t, *J* = 5.3 Hz, 1H), 2.63 – 2.52 (m, 1H), 2.40 – 2.30 (m, 1H), 1.78 (s, 1H), 1.74 – 1.66 (m, 1H), 0.85 (s, 9H), 0.07 (s, 3H), -0.02 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 153.0, 152.1, 140.8, 137.6, 136.6, 130.9, 130.9, 129.6 (d, *J* = 1.3 Hz), 127.4, 127.1, 123.8, 123.7, 113.6, 108.4, 74.6, 60.8 (d, *J* = 19.1 Hz), 56.1, 55.4, 42.8, 39.5, 31.0, 26.0, 18.4, -4.6 (d, *J* = 39.9 Hz). **HRMS** (ESI+) calculated for $[C_{32}H_{44}NaO_5Si]^+$ 559.2850 *m/z*; found $[M+Na]^+$ 559.2856 *m/z*.

7-(2,3,4-Trimethoxy-6-(3-methoxy-3-(4-methoxyphenyl)propyl)phenyl)cyclohepta-1,3,5-triene



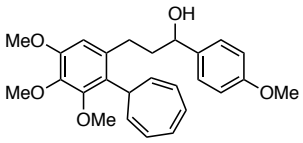
*n*BuLi (1.34 mL, 3.36 mmol, 2.5M, 1.3 equiv) was added dropwise to a solution of 2-bromo-3,4,5-trimethoxy-1-(3-methoxy-3-(4-methoxyphenyl)propyl)benzene (1.32 g, 3.10 mmol, 1.2 equiv) in dry THF (21.5 mL) at –78 ºC under argon. The mixture was stirred for 30 min at the same temperature, and then tropylium tetrafluoroborate (460 mg 2.59 mmol, 1.0 equiv) was added in one portion. The cooling bath was removed and the reaction was stirred at 24 ºC for 12 h. The reaction was quenched by addition of water. The aqueous phase was extracted with Et_2O (x3) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude was purified by flash column chromatography (cyclohexane/Et_2O 5:1) to yield the title compound (500 mg, 1.15 mmol, 44%) as a white solid.

M.p. 92–94 ºC (cyclohexane/Et_2O). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.16 – 7.11 (m, 2H), 6.88 – 6.84 (m, 2H), 6.68 – 6.61 (m, 2H), 6.47 (s, 1H), 6.18 – 6.10 (m, 2H), 5.35 – 5.25 (m, 2H), 3.95 (dd, *J* = 7.7, 5.6 Hz, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.81 (s, 3H), 3.15 (s, 3H), 2.98 (tt, *J* = 5.3, 1.6 Hz, 1H), 2.58 – 2.50 (m, 1H), 2.48 – 2.40 (m, 1H), 1.95 – 1.85 (m, 1H), 1.73 – 1.63 (m, 1H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ = 159.2, 153.0, 152.1, 140.8, 136.2, 134.1, 130.8 (d, *J* = 6.9 Hz), 129.6 (d, *J* = 9.4 Hz), 128.0, 127.4, 123.7, 113.9, 108.7, 82.9, 60.9, 60.7, 56.5, 56.1, 55.4, 39.7, 39.6, 30.9. **HRMS** (ESI+) calculated for $[C_{27}H_{32}NaO_5]^+$ 459.2142 *m/z*; found $[M + Na]^+$ 459.2146 *m/z*.

General procedure A

TBAF (1M in THF, 1.2 equiv) was added dropwise to a solution of the corresponding silyl-protected secondary alcohol (1.0 equiv.) in dry THF (0.4 M) at 0 °C under argon. The cooling bath was removed and the reaction was stirred at 24 °C for 6 h. The reaction was quenched by addition of water. The aqueous phase was extracted with Et_2O, the combined organic extracts were dried over $MgSO_4$ and the solvent was evaporated. The crude reaction mixture was purified by flash column chromatography (cyclohexane/EtOAc) to yield the targed secondary alcohol.

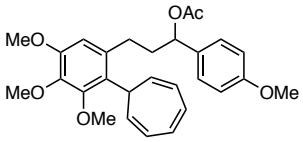
3-(2-(Cyclohepta-2,4,6-trien-1-yl)-3,4,5-trimethoxyphenyl)-1-(4-methoxyphenyl)-propan-1-ol



The title compound (yellow gum, 82 mg, yield 87%) was synthesized fllowing general procedure **B** using *tert*-butyl (3-(2-(cyclohepta-2,4,6-trien-1-yl)-3,4,5-trimethoxyphenyl)-1-(4-methoxyphenyl)propoxy) dimethylsilane (120 mg, 0.224 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 – 7.17 (m, 2H), 6.88 – 6.83 (m, 2H), 6.69 – 6.63 (m, 2H), 6.48 (s, 1H), 6.19 – 6.11 (m, 2H), 5.33 (td, *J* = 8.6, 5.3 Hz, 2H), 4.54 (t, *J* = 6.4 Hz, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 3.80 (s, 3H), 3.04 – 2.98 (m, 1H), 2.62 – 2.53 (m, 1H), 2.52 – 2.42 (m, 1H), 1.95 – 1.85 (m, 1H), 1.83 – 1.73 (m, 1H), 1.68 (s, 1H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 159.2, 153.1, 152.2, 140.9, 136.7, 136.0, 131.0, 130.8, 129.7, 129.6, 127.4, 127.2, 123.8, 123.7, 114.0, 108.6, 73.6, 60.9, 60.7, 56.1, 55.4, 40.7, 39.7, 30.9. **HRMS** (ESI+) calculated for $[C_{26}H_{29}O_4]^+$ 405.2060 *m/z*; found $[M–OH]^+$ 405.2067 *m/z*.

3-(2-(Cyclohepta-2,4,6-trien-1-yl)-3,4,5-trimethoxyphenyl)-1-(4-methoxyphenyl)-propyl acetate



Acetic anhydride (22.0 µL, 0.237 mmol, 5.0 equiv) was added to a stirring solution of 3-(2-(cyclohepta-2,4,6-trien-1-yl)-3,4,5-trimethoxyphenyl)-1-(4-methoxyphenyl)-propan-1-ol (20.0 mg, 0.047 mmol, 1.0 equiv) and DMAP (0.578 mg, 4.73 µmol, 10 mol %) in pyridine (0.2 mL). The reaction mixture was stirred at 24 ºC for 2 h. After full conversion of the starting material, the reaction was diluted with Et_2O and quenched with sat. NH_4Cl solution. The aqueous phase was extracted with Et_2O (3x) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude was purified by flash column chromatography

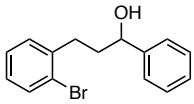
(cyclohexane/EtOAc 10:1) to yield the title compound (16.9 mg, 36.0 μmol, 77%) as a yellow gum.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.71 – 6.61 (m, 2H), 6.43 (s, 1H), 6.21 – 6.11 (m, 2H), 5.68 – 5.58 (m, 1H), 5.31 (td, *J* = 9.6, 5.2 Hz, 2H), 3.89 (s, 3H), 3.85 (s, 3H), 3.85 (s, 3H), 3.80 (s, 3H), 2.97 (t, *J* = 5.1 Hz, 1H), 2.55 – 2.44 (m, 1H), 2.44 – 2.32 (m, 1H), 2.01 (s, 4H), 1.91 – 1.79 (m, 1H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 170.5, 159.4, 153.1, 152.2, 141.0, 135.4, 132.4, 130.9, 130.8, 129.51, 129.49, 128.1, 127.3, 123.78, 123.76, 114.0, 108.6, 75.4, 60.9, 60.7, 56.1, 55.4, 39.6, 37.9, 30.8, 21.5. **HRMS** (ESI+) calculated for $[C_{28}H_{32}NaO_6]^+$ 487.2091 *m/z*; found $[M+Na]^+$ 487.2094 *m/z*.

General procedure B: Grignard addition

A flame-dried two-necked flask was charged with the corresponding aryl-Grignard solution (1.1 equiv) and diluted with dry Et_2O (total concentration 0.1 M). The solution was cooled to –78 ºC and a solution of 3-(2-bromophenyl)propanal or 3-(2-bromo-5-(trifluoromethyl)phenyl)propanal (1.0 equiv) in dry Et_2O was added dropwise. The mixture was stirred 30 min at the same temperature and 30 min at 24 ºC. The reaction was quenched with sat. NH_4Cl and extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude was purified by flash column chromatography to afford the corresponding secondary benzylic alcohol.

3-(2-bromophenyl)-1-phenylpropan-1-ol

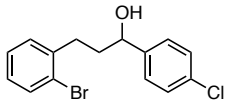


The title compound (yellow gum, 436 mg, 1.50 mmol, 63%) was synthesized following general procedure **B** from 3-(2-bromophenyl)propanal[211] (505 mg, 2.37 mmol) using phenylmagnesium bromide (2.49 mL, 2.49 mmol, 1 M in THF). The crude was purified by flash column chromatography (cyclohexane/EtOAc 10:1) and further purified by second column chromatography on silica gel (toluene 100%).

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.53 (d, *J* = 7.8 Hz, 1H), 7.42 – 7.33 (m, 4H), 7.32 – 7.27 (m, 1H), 7.26 – 7.23 (m, 2H), 7.11 – 7.03 (m, 1H), 4.76 – 4.68 (m, 1H), 2.89 (ddd, *J* = 13.7, 9.7, 6.0 Hz, 1H), 2.76 (ddd, *J* = 13.7, 9.6, 6.8 Hz, 1H), 2.13 – 2.09 (m, 1H), 2.08 – 1.97 (m, 2H). **^{13}C{^{1}H} NMR** (101 MHz, CD_2Cl_2) δ 143.8, 141.7, 133.5, 133.3, 131.0, 129.0, 128.3, 128.1, 128.0, 124.8, 73.6, 39.6, 32.9. **HRMS** (APCI+) calculated for $[C_{15}H_{14}BrO]^+$ 289.0223 *m/z*; found $[M–H]^+$ 289.0220 *m/z*.

211. Schuster, C. H.; Coombs, J. R.; Kasun, Z. A.; Morken, J. P. *Org. Lett.* **2014**, *16*, 4420–4423.

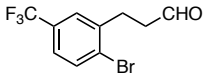
3-(2-bromophenyl)-1-(4-chlorophenyl)propan-1-ol



The title compound (pale yellow gum, 619 mg, 1.90 mmol, 80%) was synthesized following general procedure **B** from 3-(2-bromophenyl)propanal[211] (505 mg, 2.37 mmol) using 4-chlorophenylmagnesium bromide (2.49 mL, 2.49 mmol, 1 M in THF). The crude was purified by flash column chromatography (cyclohexane/EtOAc 10:1) and further purified by second column chromatography on silica gel (toluene 100%).

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.52 (d, *J* = 8.0 Hz, 1H), 7.33 (s, 4H), 7.28 – 7.21 (m, 2H), 7.11 – 7.02 (m, 1H), 4.72 (ddd, *J* = 7.4, 5.5, 3.7 Hz, 1H), 2.87 (ddd, *J* = 13.7, 9.7, 6.0 Hz, 1H), 2.75 (ddd, *J* = 13.7, 9.5, 6.8 Hz, 1H), 2.11 – 2.02 (m, *J* = 4.1 Hz, 1H), 2.05 – 1.92 (m, 2H). **^{13}C{^{1}H} NMR** (101 MHz, CD_2Cl_2) δ 145.3, 141.9, 133.3, 131.0, 129.0, 128.2, 128.1, 128.1, 126.5, 124.9, 74.3, 39.6, 33.1. **HRMS** (APCI+) calculated for $[C_{15}H_{13}BrClO]^+$ 322.9833 *m/z*; $[M–H]^+$ found 322.9826 *m/z*.

3-(2-Bromo-5-(trifluoromethyl)phenyl)propanal



A 25 mL Schlenk flask was flame-dried and charged with 1-bromo-2-iodo-4-(trifluoromethyl)benzene (0.691 mL, 4.27 mmol, 1.0 equiv), $Pd(OAc)_2$ (19.0 mg, 85.0 μmol, 2 mol %), $NaHCO_3$ (898 mg, 10.69 mmol, 2.5 equiv), *n*Bu_4NCl (1.23 g, 4.27 mmol, 1.0 equiv), allylic alcohol (0.436 ml, 6.41 mmol, 1.5 equiv) and DMF (4.8 mL). The reaction mixture was stirred at 40 ºC for 24 h. The reaction was diluted with Et_2O and filtered over Celite®. The crude was purified by flash column chromatography (cyclohexane/EtOAc 10:1) to yield the title compound (700 mg, 2.49 mmol, 58%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 (t, *J* = 1.0 Hz, 1H), 7.67 (d, *J* = 8.3 Hz, 1H), 7.51 (d, *J* = 2.0 Hz, 1H), 7.34 (dd, *J* = 8.3, 2.0 Hz, 1H), 3.12 (t, *J* = 7.5 Hz, 2H), 2.88 – 2.81 (m, 2H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 200.3, 141.0, 133.6, 130.3 (q, *J* = 32.8 Hz), 128.3 (d, *J* = 1.5 Hz), 127.3 (q, *J* = 3.7 Hz), 124.9 (q, *J* = 3.7 Hz), 123.8 (q, *J* = 272.6 Hz), 43.4, 28.7. **^{19}F NMR** (376 MHz, $CDCl_3$) δ –62.8.

3-(2-bromo-5-(trifluoromethyl)phenyl)-1-phenylpropan-1-ol

The title compound (colorless gum, 611 mg, 1.70 mmol, 82%) was synthesized following general procedure **B** from 3-(2-bromo-5-(trifluoromethyl)phenyl)propanal (585 mg, 2.08 mmol) using phenylmagnesium bromide (2.19 mL, 2.19 mmol, 1 M in THF). The crude was purified by flash column chromatography (cyclohexane/EtOAc 10:1).

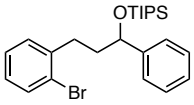
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.3 Hz, 1H), 7.47 (d, *J* = 1.8 Hz, 1H), 7.41 – 7.34 (m, 4H), 7.34 – 7.27 (m, 2H), 4.79 – 4.71 (m, 1H), 3.03 – 2.91 (m, 1H), 2.89 – 2.77 (m, 1H), 2.19 – 1.99 (m, 2H), 1.94 (s, 1H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 144.2,

142.4, 133.5, 130.1 (q, J = 32.6 Hz), 128.8, 128.4 (d, J = 1.6 Hz), 128.0, 127.1 (q, J = 3.7 Hz), 126.0, 124.4 (q, J = 3.8 Hz), 124.0 (q, J = 271.6 Hz), 74.0, 38.6, 32.7. **^{19}F NMR** (376 MHz, $CDCl_3$) δ –62.7. **HRMS** (ESI+) calculated for $[C_{16}H_{13}BrF_3O]^+$ 357.0096 *m/z*; found $[M–H]^+$ 357.0100 *m/z*.

General procedure C: TIPS protection

To a solution of the corresponding secondary benzylic alcohol (1.0 equiv.) in anhydrous CH_2Cl_2 (0.1 M) at 0 ºC was added 2,6-lutidine (3.0 equiv.) dropwise followed by TIPSOTf (2.0 equiv.). The mixture was stirred at 24 ºC for 6 h. The reaction was quenched with sat. NH_4Cl at 0 ºC, followed by water and extracted with CH_2Cl_2 (x3). The combined organic layers were washed with brine and dried over $MgSO_4$. The crude reaction mixture was purified by column chromatography on silica gel (cyclohexane, 100%) otherwise stated.

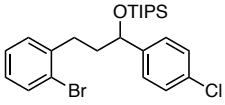
(3-(2-Bromophenyl)-1-phenylpropoxy)triisopropylsilane



The title compound (colorless oil, 709 mg, 1.58 mmol, 89%) was synthesized following general procedure **C** from 3-(2-bromophenyl)-1-phenylpropan-1-ol (517 mg, 1.78 mmol), 2,6-lutidine (0.62 mL, 5.33 mmol) and TIPSOTf (0.96 mL, 3.55 mmol).

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.52 (dd, J = 8.0, 1.3 Hz, 1H), 7.46 – 7.42 (m, 2H), 7.41 – 7.35 (m, 2H), 7.32 – 7.27 (m, 1H), 7.24 (td, J = 7.4, 1.3 Hz, 1H), 7.17 (dd, J = 7.7, 1.9 Hz, 1H), 7.06 (ddd, J = 7.9, 7.2, 1.9 Hz, 1H), 4.97 (t, J = 5.7 Hz, 1H), 2.69 (m, 2H), 2.18 – 1.98 (m, 2H), 1.16 – 1.06 (m, 12H), 1.06 – 1.01 (m, 9H). **^{13}C{^{1}H} NMR** (101 MHz, CD_2Cl_2) δ 145.6, 142.4, 133.2, 130.7, 128.5, 128.0, 128.0, 127.6, 126.9, 124.9, 75.3, 41.4, 32.2, 18.4 (d, J = 7.3 Hz), 13.0. **HRMS** (APCI+) calculated for $[C_{24}H_{34}BrOSi]^+$ 445.1557 *m/z*; found $[M]^+$ 445.1557 *m/z*.

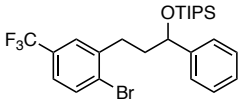
(3-(2-Bromophenyl)-1-(4-chlorophenyl)propoxy)triisopropylsilane



The title compound (colorless oil, 750 mg, 1.56 mmol, 83%) was synthesized following general procedure **C** from 3-(2-bromophenyl)-1-(4-chlorophenyl)propan-1-ol (609 mg, 1.70 mmol), 2,6-lutidine (0.65 mL, 5.6 mmol) and TIPSOTf (1.0 mL, 3.7 mmol).

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.48 (dd, J = 8.0, 1.2 Hz, 1H), 7.38 – 7.29 (m, 4H), 7.20 (td, J = 7.4, 1.3 Hz, 1H), 7.13 (dd, J = 7.6, 1.8 Hz, 1H), 7.03 (td, J = 7.7, 1.8 Hz, 1H), 4.95 – 4.90 (m, 1H), 2.63 (dd, J = 9.0, 7.9 Hz, 2H), 2.11 – 1.93 (m, 2H), 1.10 – 1.03 (m, 12H), 1.02 – 0.97 (m, 9H). **^{13}C{^{1}H} NMR** (101 MHz, CD_2Cl_2) 144.3, 142.2, 133.2, 133.0, 130.7, 128.7, 128.3, 128.1, 128.1, 124.8, 74.6, 41.2, 31.9, 18.4 (d, J = 5.7 Hz), 12.9. **HRMS** (ESI+) calculated for $[C_{24}H_{33}BrClOSi]^+$ 479.1167 *m/z*; found $[M–H]^+$ 479.1157 *m/z*.

(3-(2-Bromo-5-(trifluoromethyl)phenyl)-1-phenylpropoxy)triisopropylsilane



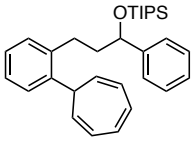
The title compound (colorless oil, 809 mg, 1.57 mmol, 96%) was prepared according to tgeneral procedure **C** from 3-(2-bromo-5-(trifluoromethyl)phenyl)-1-phenylpropan-1-ol (588 mg, 1.64 mmol), 2,6-lutidine (570 μL, 4.90 mmol) and TIPSOTf (890 μL, 3.3 mmol).

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.63 (d, *J* = 8.3 Hz, 1H), 7.43 – 7.32 (m, 5H), 7.32 – 7.23 (m, 2H), 4.96 (t, *J* = 5.7 Hz, 1H), 2.81 – 2.67 (m, 2H), 2.17 – 1.97 (m, 2H), 1.10 – 1.03 (m, 12H), 1.03 – 0.97 (m, *J* = 6.2 Hz, 9H). **^{13}C{^{1}H} NMR** (101 MHz, CD_2Cl_2) δ 145.3, 143.6, 133.9, 130.2 (q, *J* = 32.4 Hz), 128.9 (d, *J* = 1.5 Hz), 128.6, 127.7, 127.3 (q, *J* = 3.7 Hz), 126.8, 124.6 (q, *J* = 3.7 Hz), 124.59 (q, *J* = 271.3 Hz), 75.1, 40.9, 32.2, 18.5, 18.4, 13.0. **^{19}F NMR** (376 MHz, $CDCl_3$) δ –62.8. **HRMS** (APCI+) calculated for $[C_{22}H_{27}BrF_3OSi]^+$ 471.0961 *m/z*; found $[M–C_3H_7]^+$ 471.0967 *m/z*.

General procedure D: synthesis of arylcycloheptatrienes

*n*BuLi (2.5 M in hexanes, 1.0 equiv.) was added dropwise to a solution of the corresponding aryl bromide (1.0 equiv.) in dry THF (0.4 M) at −78 °C under argon. The mixture was stirred for 30 min at −78 °C, and then tropylium tetrafluoroborate (1.2 equiv.) was added in one portion. The cooling bath was removed and the reaction was stirred at 24 °C for 12 h. The reaction was quenched by addition of water. The aqueous phase was extracted with Et_2O, the combined organic extracts were dried over $MgSO_4$, and the solvent was evaporated. The crude reaction mixture was purified by flash column chromatography (cyclohexane/EtOAc) unless otherwise stated.

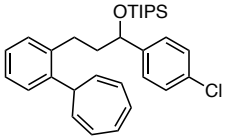
(3-(2-(Cyclohepta-2,4,6-trien-1-yl)phenyl)-1-phenylpropoxy)triisopropylsilane



The title compound (colorless oil, 608 mg, 1,32 mmol, 83%) was synthesized following general procedure **D** from (3-(2-bromophenyl)-1-phenylpropoxy)triisopropylsilane (714 mg, 1.59 mmol), *n*BuLi (2.5 M, 0.766 mL, 1.91 mmol) and tropylium tetrafluoroborate (369 mg, 2.07 mmol).

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.46 (d, *J* = 7.7 Hz, 1H), 7.29 (q, *J* = 4.2, 3.5 Hz, 4H), 7.27 – 7.21 (m, 2H), 7.16 (t, *J* = 7.4 Hz, 1H), 7.09 (d, *J* = 7.6 Hz, 1H), 6.73 – 6.67 (m, 2H), 6.25 – 6.16 (m, 2H), 5.26 (dd, *J* = 9.1, 5.4 Hz, 2H), 4.80 (t, *J* = 5.7 Hz, 1H), 2.79 (t, *J* = 5.2 Hz, 1H), 2.48 – 2.34 (m, 2H), 1.96 – 1.80 (m, 2H), 1.05 – 0.99 (m, 12H), 0.98 – 0.93 (d, 9H). **^{13}C{^{1}H} NMR** (101 MHz, CD_2Cl_2) δ 145.6, 142.7, 141.1, 131.3, 130.0, 128.5, 127.8, 127.4, 127.2, 127.1, 127.0, 126.8, 125.0, 75.4, 43.1, 41.5, 29.1, 18.4 (d, *J* = 9.3 Hz), 12.9. **HRMS** (APCI+) calculated for $[C_{31}H_{43}OSi]^+$ $[M+H]^+$ 459.3078 *m/z*; found $[M+H]^+$ 459.3080 *m/z*.

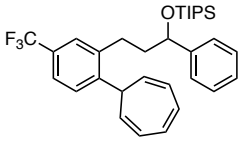
(1-(4-Chlorophenyl)-3-(2-(cyclohepta-2,4,6-trien-1-yl)phenyl)propoxy)-triisopropylsilane



The title compound (yellow oil, 618 mg, 1.22 mmol, 85%) was synthesized following general procedure **D** from (3-(2-bromophenyl)-1-(4-chlorophenyl)propoxy)triisopropyls (709 mg, 1.47 mmol), *n*BuLi (2.5 M, 706 μL, 1.76 mmol) and tropylium tetrafluoroborate (340 g, 1.91 mmol).

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.45 (dt, *J* = 7.8, 1.7 Hz, 1H), 7.31 – 7.20 (m, 5H), 7.16 (tt, *J* = 7.4, 1.7 Hz, 1H), 7.08 (dt, *J* = 7.6, 1.9 Hz, 1H), 6.72 – 6.64 (m, 2H), 6.24 – 6.13 (m, 2H), 5.24 (ddd, *J* = 8.6, 5.4, 1.9 Hz, 2H), 4.80 (td, *J* = 5.8, 2.0 Hz, 1H), 2.72 – 2.62 (m, 1H), 2.38 (ddd, *J* = 10.8, 6.4, 2.4 Hz, 2H), 1.90 – 1.78 (m, 2H), 1.10 – 0.93 (m, 21H). **^{13}C{^{1}H} NMR** (101 MHz, CD_2Cl_2) δ 144.3, 142.6, 140.8, 132.9, 131.3, 130.0, 128.7, 128.2, 127.8, 127.1, 127.1, 127.0, 127.0, 125.0, 74.6, 43.0, 41.4, 28.6, 18.4 (d, *J* = 7.3 Hz), 12.9. **HRMS** (ESI+) calculated for $[C_{31}H_{41}ClNaSi]^+$ 515.2528 *m/z*; found $[M+Na]^+$ 515.2507 *m/z*.

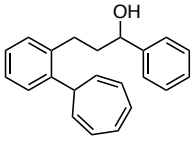
(3-(2-(Cyclohepta-2,4,6-trien-1-yl)-5-(trifluoromethyl)phenyl)-1-phenylpropoxy)-triisopropylsilane



The title compound (yellow gumm, 640 mg, 1.21 mmol, 84%) was synthesized following general procedure **D** from (3-(2-bromo-5-(trifluoromethyl)phenyl)-1-phenylpropoxy)triisopropylsilane (745 mg, 1.45 mmol), *n*BuLi (2.5 M, 0.694 mL, 1.73 mmol) and tropylium tetrafluoroborate (334 g, 1.88 mmol).

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.60 (d, *J* = 8.1 Hz, 1H), 7.50 (d, *J* = 8.7 Hz, 1H), 7.35 (s, 1H), 7.33 – 7.20 (m, 5H), 6.76 – 6.68 (m, 2H), 6.28 – 6.19 (m, 2H), 5.23 (dd, *J* = 9.1, 5.4 Hz, 2H), 4.81 (t, *J* = 5.7 Hz, 1H), 2.86 (t, *J* = 5.3 Hz, 1H), 2.56 – 2.39 (m, 2H), 1.98 – 1.81 (m, 2H), 1.05 – 0.98 (m, 12H), 0.95 (d, *J* = 6.3 Hz, 9H). **^{13}C{^{1}H} NMR** (101 MHz, CD_2Cl_2) δ 146.3 (d, *J* = 1.1 Hz), 144.8, 141.5, 131.0 – 130.6 (m), 128.0, 127.8, 127.0, 126.1, 126.0 (q, *J* = 3.8 Hz), 125.4, 124.90, 124.89, 124.4 (q, *J* = 272.0 Hz), 123.2 (q, *J* = 3.8 Hz), 74.6, 42.0, 40.8, 28.4, 17.8 (d, *J* = 10.0 Hz), 12.3. **^{19}F NMR** (376 MHz, CD_2Cl_2) δ –62.8. **HRMS (APCI**+) calculated for $[C_{23}H_{20}F_3]^+$ 353.1512 *m/z*; found $[M–OTIPS]^+$ 353.1516 *m/z*.

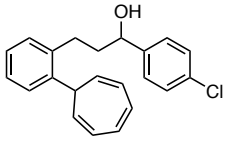
3-(2-(Cyclohepta-2,4,6-trien-1-yl)phenyl)-1-phenylpropan-1-ol



The title compound (white solid, 230 mg, 0.76 mmol, 93%) was synthesized following general procedure **A** from (3-(2-(cyclohepta-2,4,6-trien-1-yl)phenyl)-1-phenylpropoxy)triisopropylsilane (377 mg, 0.822 mmol) and TBAF (1M, 0.986 mL, 0.986 mmol).

M.p. = 74-76 °C (CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.4 Hz, 1H), 7.36 – 7.23 (m, 6H), 7.23 – 7.18 (m, 2H), 6.79 – 6.70 (m, 2H), 6.29 – 6.19 (m, 2H), 5.34 (dd, *J* = 8.9, 5.4 Hz, 2H), 4.60 (t, *J* = 6.3 Hz, 1H), 2.92 (t, *J* = 5.4 Hz, 1H), 2.71 – 2.50 (m, 2H), 2.02 – 1.80 (m, 2H), 1.78 (s, 1H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 144.5, 142.3, 140.0, 131.0, 130.9, 129.9, 128.6, 127.7, 127.6, 127.09, 127.08, 127.0, 126.7, 126.0, 124.7, 124.6, 74.0, 41.1, 40.6, 29.6. **HRMS** (APCI+) calculated for $[C_{22}H_{21}]^+$ 285.1638 *m/z*; found $[M–OH]^+$ 285.1640 *m/z*.

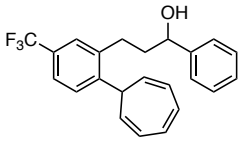
1-(4-Chlorophenyl)-3-(2-(cyclohepta-2,4,6-trien-1-yl)phenyl)propan-1-ol



The title compound (yellow gum, 250 mg, 0.74 mmol, 97%) was synthesized following general procedure **A** from (1-(4-chlorophenyl)-3-(2-(cyclohepta-2,4,6-trien-1-yl)phenyl)propoxy)-triisopropylsilane (378 mg, 0.76 mmol) and TBAF (1 M, 920 μL, 0.92 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.6 Hz, 1H), 7.33 – 7.27 (m, 3H), 7.24 – 7.16 (m, 4H), 6.79 – 6.70 (m, 2H), 6.30 – 6.18 (m, 2H), 5.32 (dd, *J* = 8.8, 5.4 Hz, 2H), 4.62 – 4.56 (m, 1H), 2.84 (t, *J* = 5.4 Hz, 1H), 2.66 – 2.46 (m, 2H), 1.97 – 1.77 (m, 2H), 1.77 – 1.72 (m, 1H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 143.0, 142.2, 139.7, 133.3, 131.0, 130.9, 129.8, 128.8, 127.6, 127.4, 127.1, 126.98, 126.96, 126.7, 124.7, 124.7, 73.3, 41.1, 40.7, 29.3. **HRMS (ESI+)** calculated for $[C_{22}H_{20}Cl]^+$ 319.1248 *m/z*; found $[M–OH]^+$ 319.1256 *m/z*.

3-(2-(cyclohepta-2,4,6-trien-1-yl)-5-(trifluoromethyl)phenyl)-1-phenylpropan-1-ol



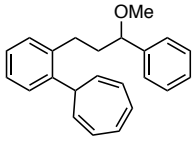
The title compound (yellow gum, 384 mg, 1.04 mmol, 91%) was synthesized following general procedure **A** from (3-(2-(cyclohepta-2,4,6-trien-1-yl)-5-(trifluoromethyl)phenyl)-1-phenylpropoxy)-triisopropylsilane (600 mg, 1.14 mmol) and TBAF (1M, 1.37 mL, 1.37 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.1 Hz, 1H), 7.54 (d, *J* = 8.2 Hz, 1H), 7.44 (s, 1H), 7.38 – 7.31 (m, 2H), 7.31 – 7.26 (m, 3H), 6.81 – 6.71 (m, 2H), 6.34 – 6.22 (m, 2H), 5.28 (dd, *J* = 9.0, 5.6 Hz, 2H), 4.65 – 4.56 (m, 1H), 2.96 (t, *J* = 5.4 Hz, 1H), 2.77 – 2.53 (m, 2H), 2.05 – 1.83 (m, 2H), 1.82 – 1.76 (m, 1H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ. 146.3 (d, *J* = 1.2 Hz), 144.3, 140.9, 131.1, 131.0, 128.9 (q, *J* = 32.6 Hz) ,128.7, 128.0, 127.8, 126.5 (q, *J* = 3.7 Hz), 125.9, 125.8, 125.2, 125.1, 124.4 (q, *J* = 271.7 Hz), 123.7 (q, *J* = 3.8 Hz), 73.8, 41.1, 40.2, 29.5. **^{19}F NMR** (376 MHz, CD_2Cl_2) δ –62.4. **HRMS (APCI+)** calculated for $[C_{23}H_{20}F_3]^+$ 353.1512 *m/z*; found $[M–OH]^+$ 353.1512 *m/z*.

General procedure E: methylation

A two-necked flame-dried flask was charged with NaH (1.5 equiv, 60% in mineral oil) and THF (total concentration 0.2 M) was added. The suspension was cooled to 0 ºC and a solution of the corresponding secondary benzylic alcohol (1.0 equiv.) in THF was added dropwise. The reaction mixture was stirred at the same temperature for 15 min and MeI (1.5 equiv) was added. The reaction was allowed to warm up to 23 ºC and stirred until full conversion of the starting material (TLC: cyclohexane/EtOAc). The reaction was quenched with sat. NH_4Cl and extracted from Et_2O (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude was purified by flash column chromatography.

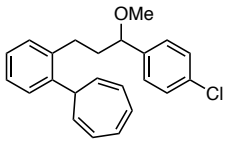
7-(2-(3-Methoxy-3-phenylpropyl)phenyl)cyclohepta-1,3,5-triene



The title compound (colorless oil, 187 mg, 0.59 mmol, 89%) was following general procedure **E** from 3-(2-(cyclohepta-2,4,6-trien-1-yl)phenyl)-1-phenylpropan-1-ol (200 mg, 0.661 mmol), NaH (40.0 mg, 0.99 mmol) and MeI (0.062 mL, 99 μmol). The reaction was stirred overnight and the crude was purified by flash column chromatography (cyclohexane/CH_2Cl_2 40:1).

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.52 – 7.46 (m, 1H), 7.35 – 7.23 (m, 4H), 7.23 – 7.15 (m, 4H), 6.73 (dt, *J* = 4.1, 1.7 Hz, 2H), 6.28 – 6.17 (m, 2H), 5.34 – 5.25 (m, 2H), 4.00 (dd, *J* = 7.7, 5.5 Hz, 1H), 3.14 (s, 3H), 2.87 (t, *J* = 5.4 Hz, 1H), 2.63 – 2.53 (m, 1H), 2.52 – 2.41 (m, 1H), 1.96 – 1.82 (m, 1H), 1.78 – 1.64 (m, 1H). **^{13}C{^{1}H} NMR** (101 MHz, CD_2Cl_2) δ 142.79, 142.77, 140.7, 131.3, 131.3, 130.3, 128.9, 127.9, 127.4, 127.2, 127.0, 125.0, 125.0, 83.6, 56.9, 41.6, 40.1, 29.9. **HRMS** (APCI+) calculated for $[C_{22}H_{21}]^+$ 2851638 *m/z*; found $[M–CH_3O]^+$ 285.1640 *m/z*.

7-(2-(3-(4-Chlorophenyl)-3-methoxypropyl)phenyl)cyclohepta-1,3,5-triene

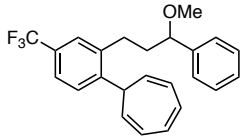


The title compound (yellow oil, 325 mg, 0.92 mmol, 92%) was synthesized following general procedure **E** from 1-(4-chlorophenyl)-3-(2-(cyclohepta-2,4,6-trien-1-yl)phenyl)propan-1-ol (338 mg, 1.00 mmol), NaH (60.0 mg, 1.50 mmol) and MeI (94.0 μL, 1.50 mmol). The reaction was stirred for 3 h and the crude was purified by flash column chromatography (cyclohexane/CH_2Cl_2 40:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.6 Hz, 1H), 7.32 – 7.26 (m, 3H), 7.24 – 7.12 (m, 4H), 6.78 – 6.68 (m, 2H), 6.29 – 6.17 (m, 2H), 5.30 (td, *J* = 9.4, 5.4 Hz, 2H), 4.02 – 3.96 (m, 1H), 3.16 (s, 3H), 2.82 (t, *J* = 5.3 Hz, 1H), 2.62 – 2.44 (m, 2H), 1.98 – 1.82 (m, 1H), 1.78 – 1.66 (m, 1H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 142.3, 140.7, 139.9, 133.2,

130.9, 130.9, 129.9, 128.7, 128.1, 127.5, 126.97, 126.95, 126.9, 126.6, 124.6, 124.6, 82.5, 56.7, 41.0, 39.5, 29.2. **HRMS (APCI+)** calculated for $[C_{22}H_{20}Cl]^+$ 319.1248 *m/z*; found $[M-CH_3O]^+$ 319.1248 *m/z*.

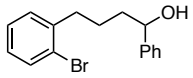
7-(2-(3-Methoxy-3-phenylpropyl)-4-(trifluoromethyl)phenyl)cyclohepta-1,3,5-triene



The title compound (colorless oil, 312 mg, 0.81 mmol, 89%) was synthesized following general procedure **E** from 3-(2-(cyclohepta-2,4,6-trien-1-yl)-5-(trifluoromethyl)phenyl)-1-phenylpropan-1-ol (338 mg, 1.00 mmol), NaH (55.0 mg, 1.37 mmol) and MeI (0.085 mL, 1.37 mmol). The reaction was stirred for 2 h and the crude was purified by flash column chromatography (cyclohexane/EtOAc 20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.1 Hz, 1H), 7.58 – 7.52 (m, 1H), 7.45 (s, 1H), 7.37 – 7.31 (m, 2H), 7.31 – 7.26 (m, 1H), 7.24 – 7.19 (m, 2H), 6.80 – 6.70 (m, 2H), 6.33 – 6.22 (m, 2H), 5.34 – 5.21 (m, 2H), 3.98 (dd, *J* = 7.9, 5.2 Hz, 1H), 3.18 (s, 3H), 2.95 (t, *J* = 5.4 Hz, 1H), 2.72 – 2.55 (m, 2H), 2.02 – 1.90 (m, 1H), 1.84 – 1.71 (m, 1H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 146.3 (d, *J* = 1.1 Hz), 141.9, 141.0, 131.1, 131.0, 128.9 (q, *J* = 32.3 Hz), 128.6, 128.0, 127.7, 126.7, 125.9, 125.8, 125.1 (d, *J* = 0.9 Hz), 124.4 (q, *J* = 271.1 Hz), 123.6 (q, *J* = 3.7 Hz), 82.9, 56.7, 41.0, 39.2, 29.5. **^{19}F NMR** (376 MHz, CD_2Cl_2) δ – 62.4. **HRMS (APCI+)** calculated for $[C_{23}H_{20}F_3]^+$ 353.1512 *m/z*; found $[M - OCH_3]^+$ 353.1510 *m/z*.

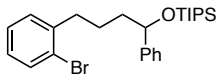
4-(2-Bromophenyl)-1-phenylbutan-1-ol



The title compound (colorless gum, 587 mg, 1.92 mmol, 60%) was synthesized following general procedure **B** from 4-(2-bromophenyl)butanal (733 mg, 3.23 mmol) using phenylmagnesium bromide (3.39 mL, 3.39 mmol, 1 M in THF). The crude was purified by flash column chromatography (cyclohexane/EtOAc 10:1).

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.52 (d, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 4.4 Hz, 4H), 7.30 – 7.24 (m, 1H), 7.24 – 7.17 (m, 2H), 7.09 – 7.01 (m, 1H), 4.74 – 4.64 (m, 1H), 2.76 (t, *J* = 7.5 Hz, 2H), 1.92 (d, *J* = 2.6 Hz, 1H), 1.87 – 1.68 (m, 3H), 1.67 – 1.55 (m, 1H). **^{13}C NMR** (101 MHz, CD_2Cl_2) δ 145.6, 142.3, 133.2, 131.0, 128.9, 128.1, 128.0, 128.0, 126.4, 124.9, 74.8, 39.3, 36.4, 26.7. **HRMS** (ESI+) calculated for $[C_{16}H_{16}BrO]^+$ *m/z*; found $[M - H]^+$ 303.0388 *m/z*.

(4-(2-Bromophenyl)-1-phenylbutoxy)triisopropylsilane

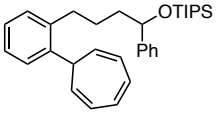


The title compound (colorless oil, 811 mg, 1.76 mmol, 94%) was synthesized following general procedure **C** from 4-(2-

bromophenyl)-1-phenylbutan-1-ol (573 mg, 1.88 mmol), 2,6-lutidine (660 μL, 5.60 mmol) and TIPSOTf (1.02 mL, 3.80 mmol). The crude was purified by flash column chromatography (pentane/Et_2O 100:1).

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.52 – 7.46 (m, 1H), 7.37 – 7.26 (m, 4H), 7.26 – 7.17 (m, 2H), 7.16 – 7.11 (m, 1H), 7.07 – 6.99 (m, 1H), 4.89 – 4.80 (m, 1H), 2.67 (dt, *J* = 7.8, 4.0 Hz, 2H), 1.94 – 1.74 (m, 2H), 1.62 – 1.47 (m, 2H), 1.06 – 0.99 (m, 12H), 0.99 – 0.94 (m, 9H). **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 146.0, 142.4, 133.2, 130.9, 128.4, 128.0, 127.9, 127.4, 126.8, 124.9, 75.4, 40.9, 36.6, 25.4, 18.4 (d, *J* = 7.8 Hz), 13.0. **HRMS** (APCI+) calculated for $[C_{25}H_{36}BrOSi]^+$ 459.1713 *m/z*; found $[M - H]^+$ 459.1700 *m/z*.

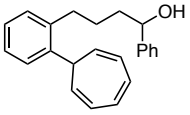
(4-(2-(Cyclohepta-2,4,6-trien-1-yl)phenyl)-1-phenylbutoxy)triisopropylsilane



The title compound (colorless gum, 664 mg, 1.39 mmol, 84%) was synthesized following general procedure **D** from (4-(2-bromophenyl)-1-phenylbutoxy)triisopropylsilane (770 mg, 1.67 mmol), *n*BuLi (2.5 M, 800 μL, 2.00 mmol) and tropylium tetrafluoroborate (386 g, 2.17 mmol).

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.46 (d, *J* = 7.7 Hz, 1H), 7.30 – 7.14 (m, 7H), 7.10 (d, *J* = 7.6 Hz, 1H), 6.72 – 6.68 (m, 2H), 6.23 – 6.14 (m, 2H), 5.32 – 5.24 (m, 2H), 4.73 (t, *J* = 5.9 Hz, 1H), 2.86 (t, *J* = 5.3 Hz, 1H), 2.49 – 2.41 (m, 2H), 1.81 – 1.64 (m, 2H), 1.37 (p, *J* = 8.0 Hz, 2H), 1.02 – 0.97 (m, 12H), 0.95 (d, *J* = 6.0 Hz, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.5, 142.2, 140.6, 130.9, 130.9, 129.7, 128.0, 127.4, 127.2, 126.9, 126.7, 126.5, 126.3, 124.5, 75.0, 41.2, 40.78, 33.4, 26.4, 18.2 (d, *J* = 8.5 Hz), 12.4. **HRMS** (APCI+) calculated for $[C_{32}H_{45}OSi]^+$ 473.3234 *m/z*; found $[M + H]^+$ 473.3238 *m/z*.

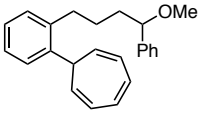
4-(2-(Cyclohepta-2,4,6-trien-1-yl)phenyl)-1-phenylbutan-1-ol



The title compound (colorless gum, 330 mg,1.04 mmol, 94%) was synthesized following general procedure **A** from (4-(2-(cyclohepta-2,4,6-trien-1-yl)phenyl)-1-phenylbutoxy)triisopropylsilane (522 mg, 1.10 mmol) and TBAF (1M, 1.33 mL, 1.33 mmol).

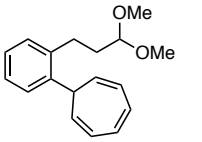
^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.48 (d, *J* = 7.7 Hz, 1H), 7.36 – 7.23 (m, 6H), 7.22 – 7.14 (m, 2H), 6.78 – 6.68 (m, 2H), 6.28 – 6.15 (m, 2H), 5.32 – 5.25 (m, 2H), 4.63 – 4.57 (m, 1H), 2.89 (t, *J* = 5.3 Hz, 1H), 2.52 (t, *J* = 7.8 Hz, 2H), 1.89 – 1.80 (m, 1H), 1.78 – 1.69 (m, 1H), 1.68 – 1.61 (m, 1H), 1.60 – 1.49 (m, 1H), 1.47 – 1.37 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ. 144.4, 142.1, 140.4, 130.9, 129.8, 128.6, 127.7, 127.5, 127.2, 126.8, 126.6, 126.1, 124.6, 74.5, 41.2, 38.83 33.1, 27.6. **HRMS** (ESI+) calculated for $[C_{23}H_{23}]^+$ 299.1794 *m/z*; found $[M - OH]^+$ 299.1793 *m/z*.

7-(2-(4-Methoxy-4-phenylbutyl)phenyl)cyclohepta-1,3,5-triene



The title compound (colorless oil, 267 mg, 0.810 mmol, 86%) was synthesized following general procedure **E** from 4-(2-(cyclohepta-2,4,6-trien-1-yl)phenyl)-1-phenylbutan-1-ol (269 mg, 0.940 mmol), NaH (56.0 mg, 1.40 mmol) and MeI (0.085 mL, 1.37 mmol). The reaction was stirred for 5 h and the crude was purified by flash column chromatography (cyclohexane/EtOAc 40:1). **^{1}H NMR** (400 MHz, CD_2Cl_2) δ 7.47 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.37 – 7.30 (m, 2H), 7.30 – 7.20 (m, 4H), 7.20 – 4.12 (m, 2H), 6.76 – 6.72 (m, 2H), 6.25 – 6.17 (m, 2H), 5.31 – 5.25 (m, 2H), 4.06 – 3.99 (m, 1H), 3.13 (s, 1H), 2.93 – 2.85 (m, 1H), 2.50 (t, *J* = 7.6 Hz, 2H), 1.81 – 1.67 (m, 1H), 1.63 – 1.47 (m, 2H), 1.45 – 1.33 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.1, 142.6, 141.1, 131.3, 131.3, 130.2, 128.8, 127.89, 127.89, 127.4, 127.3, 127.1, 126.9, 125.0, 84.2, 56.9, 41.6, 38.4, 33.6, 28.2. **HRMS** (APCI+) calculated for $[C_{23}H_{23}]^+$ 299.1794 *m/z*; found $[M - OCH_3]^+$ 299.1801 *m/z*.

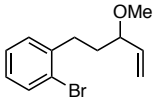
7-(2-(3,3-Dimethoxypropyl)phenyl)cyclohepta-1,3,5-triene



*n*BuLi (0.906 ml, 2.65 mmol, 2.5 M, 1.3 equiv) was added dropwise a solution of 1-bromo-2-(3,3-dimethoxypropyl)benzene[62] (0.451 g, 1.74 mmol, 1.2 equiv) in dry THF (15 mL) at –78 ºC under argon. The mixture was stirred for 30 min at –78 ºC, and then tropylium tetrafluoroborate (0.310 g 1.74 mmol, 1.0 equiv) was added in one portion. The cooling bath was removed and the reaction was stirred at 24 ºC for 12 h. The reaction was quenched by addition of water. The aqueous phase was extracted with Et_2O, the combined organic layers were dried over Na_2SO_4, and concentrated. The crude was purified by flash column chromatography (cyclohexane/Et_2O 5:1) to yield the title compound (230 mg, 0.851 mmol, 49 %) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ =7.54 – 7.48 (m, 1H), 7.32 – 7.28 (m, 1H), 7.24 – 7.18 (m, 2H), 6.74 (dd, *J* = 3.7, 2.7 Hz, 2H), 6.26 (dddd, *J* = 8.9, 3.9, 2.6, 1.5 Hz, 2H), 5.35 (dd, *J* = 9.1, 5.4 Hz, 2H), 4.28 (t, *J* = 5.7 Hz, 1H), 3.27 (s, 6H), 2.96 (tt, *J* = 5.4, 1.6 Hz, 1H), 2.61 – 2.53 (m, 2H), 1.78 – 1.71 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 42.3, 139.8, 131.0, 129.9, 127.6, 127.1, 127.0, 126.7, 124.7, 103.9 52.8, 41.1, 34.1, 28.3.

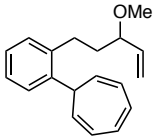
1-Bromo-2-(3-methoxypent-4-en-1-yl)benzene



The title compound (colorless oil, 283 mg, 1.11 mmol, 79%) was following general procedure **E** from 5-(2-bromophenyl)pent-1-en-3-ol[211] (397 mg, 2.80 mmol), NaH (84.0 mg, 2.09 mmol) and MeI (0.174 mL, 2.80 mmol). The reaction was stirred overnight and the crude was purified by flash column column chromatography (cyclohexane/CH_2Cl_2 40:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.9 Hz, 1H), 7.25 – 7.19 (m, 2H), 7.10 – 6.99 (m, 1H), 5.79 – 5.63 (m, 1H), 5.26 (s, 1H), 5.24 – 5.18 (m, 1H), 3.55 (q, *J* = 7.0 Hz, 1H), 3.31 (s, 3H), 2.92 – 2.67 (m, 2H), 1.99 – 1.70 (m, 2H).

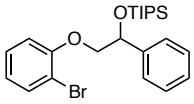
5-(2-(Cyclohepta-2,4,6-trien-1-yl)phenyl)pent-1-en-3-ol



The title compound (colorless gum, 235 mg, 0.88 mmol, 79%) was synthesized following general procedure **D** from 1-bromo-2-(3-methoxypent-4-en-1-yl)benzene (283 mg, 1.11 mmol), *n*BuLi (2.5 M, 0.57 mL, 1.43 mmol) and tropylium tetrafluoroborate (197 mg, 1.11 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.31 – 7.27 (m, 1H), 7.23 – 7.17 (m, 2H), 6.78 – 6.71 (m, 2H), 6.30 – 6.21 (m, 2H), 5.65 – 5.54 (m, 1H), 5.39 – 5.30 (m, 2H), 5.20 – 5.10 (m, 2H), 3.48 – 3.40 (m, 1H), 3.23 (s, 3H), 2.94 (td, *J* = 5.4, 2.7 Hz, 1H), 2.56 (dd, *J* = 9.0, 7.0 Hz, 2H), 1.78 – 1.69 (m, 1H), 1.64 – 1.55 (m, 1H).

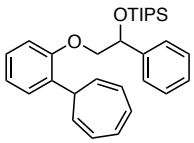
(2-(2-Bromophenoxy)-1-phenylethoxy)triisopropylsilane



The title compound (colorless oil, 896 mg, 1.99 mmol, 89%) was synthesized following general procedure **C** from 2-(2-bromophenoxy)-1-phenylethan-1-ol[212] (659 mg, 2.25 mmol), 2,6-lutidine (0.780 mL, 6.74 mmol) and TIPSOTf (1.22 mL, 4.50 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.7 Hz, 3H), 7.35 (t, *J* = 7.3 Hz, 2H), 7.31 – 7.26 (m, 1H), 7.23 – 7.16 (m, 1H), 6.86 – 6.76 (m, 2H), 5.22 (t, *J* = 5.7 Hz, 1H), 4.25 – 4.17 (m, 1H), 3.96 – 3.89 (m, 1H), 1.19 – 1.08 (m, 3H), 1.04 (d, *J* = 7.7 Hz, 9H), 1.00 (d, *J* = 7.2 Hz, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.5, 142.4, 133.6, 128.4, 128.3, 127.9, 126.81, 122.0, 113.4, 112.3, 75.3, 73.8, 18.2 (d, *J* = 7.0 Hz), 12.5. **HRMS** (APCI+) calculated for $[C_{23}H_{33}BrNaO_2Si]^+$ 471.1325 *m/z*; found $[M + Na]^+$ 471.1321 *m/z*.

(2-(2-(Cyclohepta-2,4,6-trien-1-yl)phenoxy)-1-phenylethoxy)triisopropylsilane



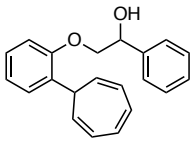
The title compound (pale yellow oil, 776 mg, 1.68 mmol, 87%) was synthesized following general procedure **D** from (2-(2-bromophenoxy)-1-phenylethoxy)triisopropylsilane (874 mg, 1.94 mmol), *n*BuLi (2.5 M, 0.77 mL, 1.94 mmol) and tropylium tetrafluoroborate (415 g, 2.33 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 3H), 7.29 – 7.16 (m, 4H), 6.96 (td, *J* = 7.5, 1.0 Hz, 1H), 6.86 (dd, *J* = 8.2, 0.9 Hz, 1H), 6.74 (dd, *J* = 3.6, 2.5 Hz, 2H), 6.26 – 6.16 (m, 2H), 5.35 – 5.25 (m, 2H), 5.03 (t, *J* = 5.8 Hz, 1H), 4.17 (dd, *J* = 9.0, 5.5 Hz, 1H), 3.89 (dd,

212. Naidu, A. B.; Ganapathy, D.; Sekar, G. *Synthesis* **2010**, 20, 3509–3519.

J = 9.0, 6.3 Hz, 1H), 3.17 (t, *J* = 5.5 Hz, 1H), 1.08 – 1.02 (m, 3H), 1.00 (d, *J* = 6.6 Hz, 9H), 0.96 (d, *J* = 6.7 Hz, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.6, 142.7, 132.2, 130.83, 130.82, 128.8, 128.1, 127.7, 127.6, 127.5, 127.3, 126.9, 124.2, 124.2, 121.0, 111.8, 74.4, 73.7, 39.8, 18.1 (d, *J* = 7.3 Hz), 12.41.**HRMS** (ESI+) calculated for $[C_{30}H_{40}NaO_2Si]^+$ 483.2690 *m/z*; found $[M+Na]^+$ 483.2695 *m/z*.

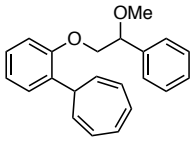
2-(2-(Cyclohepta-2,4,6-trien-1-yl)phenoxy)-1-phenylethan-1-ol



The title compound (colorless gum, 403 mg, 1.32 mmol, 81%) was synthesized following general procedure **A** from (2-(2-(cyclohepta-2,4,6-trien-1-yl)phenoxy)-1-phenylethoxy)triisopropylsilane (751 mg, 1.63 mmol) and TBAF (1M, 2.00 mL, 2.00 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) 7.44 – 7.30 (m, 6H), 7.29 – 7.23 (m, 1H), 7.03 (td, *J* = 7.5, 1.1 Hz, 1H), 6.89 (dd, *J* = 8.2, 1.1 Hz, 1H), 6.81 – 6.73 (m, 2H), 6.34 – 6.23 (m, 2H), 5.49 (ddd, *J* = 27.6, 9.4, 5.6 Hz, 2H), 5.05 (dt, *J* = 8.2, 3.2 Hz, 1H), 4.17 (dd, *J* = 9.3, 3.4 Hz, 1H), 4.03 – 3.95 (m, 1H), 3.10 (t, *J* = 5.6 Hz, 1H), 2.84 (d, *J* = 3.0 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.3, 139.7, 131.6, 131.13, 131.10, 128.6, 128.5, 128.2, 128.0, 126.9, 126.4, 124.7, 124.4, 121.5, 112.2, 73.5, 72.6, 40.7. **HRMS** (APCI) calculated for $[C_{21}H_{19}O]^+$ 287.1430 *m/z*; found $[M–OH]^+$ 287.1430 *m/z*.

7-(2-(2-Methoxy-2-phenylethoxy)phenyl)cyclohepta-1,3,5-triene



The title compound (colorless oil, 379 mg, 1.19 mmol, 96%) was following general procedure **E** from 2-(2-(cyclohepta-2,4,6-trien-1-yl)phenoxy)-1-phenylethan-1-ol (379 mg, 1.25 mmol), NaH (75.0 mg, 1.87 mmol) and MeI (0.12 mL, 1.87 mmol). The reaction was stirred overnight and the crude was purified by flash column column chromatography (cyclohexane/CH_2Cl_2 30:1).

^{1}H NMR (500 MHz, $CDCl_3$) 7.37 – 7.28 (m, 6H), 7.24 – 7.19 (m, 1H), 7.00 – 6.94 (m, 1H), 6.90 – 6.84 (m, 1H), 6.76 – 6.70 (m, 2H), 6.24 – 6.17 (m, 2H), 5.46 – 5.32 (m, 2H), 4.52 – 4.45 (m, 1H), 4.23 – 4.14 (m, 1H), 4.05 – 3.96 (m, 1H), 3.34 – 3.28 (m, 3H), 3.14 – 3.07 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.7, 139.0, 132.1, 130.8, 128.9, 128.6, 128.2, 127.8, 127.3, 127.2, 124.10, 124.09, 121.2, 112.2, 82.3, 72.7, 57.5, 40.7. **HRMS** (APCI+) calculated for $[C_{21}H_{19}O]^+$ 287.1430 *m/z*; found $[M–OMe]^+$ 287.1432 *m/z*.

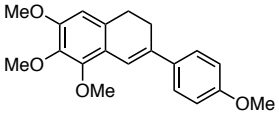
Synthesis of Dihydronaphthalenes

General procedure F: gold(I) catalyzed C(sp^3)–H insertion

A 2-5 mL microwave vial was charged with the corresponding cycloheptatriene (1.0 equiv.), catalyst **F** (5 mol %) and 1,2-dichloroethane (0.05M) was added. The reaction

mixture was stirred at 100 ºC until full conversion of the starting material (TLC: cyclohexane/CH_2Cl_2 1:1). The reaction was quenched by addition of triethylamine (3 drops) and concentrated. The crude was purified by chromatography.

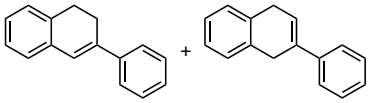
5,6,7-Trimethoxy-3-(4-methoxyphenyl)-1,2-dihydronaphthalene



The title compound (white solid, 29 mg, 8.9 μmol, 89%) was synthesized following general procedure **F** from 7-(2,3,4-trimethoxy-6-(3-methoxy-3-(4-methoxyphenyl)propyl) phenyl)cyclohepta-1,3,5-triene (44.0 mg, 10.0 μmol), and catalyst **F** (4.63 mg, 4.63 μmol). The reaction was stirred for 30 min at 100 ºC and the crude was purified by column chromatography on silica gel (cyclohexane/CH_2Cl_2 5:1) and further purified by preparative TLC (CH_2Cl_2).

M.p. = 112 – 114 °C (cyclohexane/CH_2Cl_2/Et_2O). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.54 – 7.48 (m, 2H), 7.04 – 7.01 (m, 1H), 6.94 – 6.89 (m, 2H), 6.53 (s, 1H), 3.90 (s, 3H), 3.88 (s, 6H), 3.84 (s, 3H), 2.90 – 2.82 (m, 2H), 2.72 – 2.64 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.0, 152.1, 149.8, 140.7, 135.8, 134.2, 130.9, 126.4, 121.8, 116.5, 114.0, 107.2, 61.6, 61.1, 56.3, 55.5, 28.8, 26.4. **HRMS (APCI**+) calculated for $[C_{20}H_{23}O_4]^+$ 327.1591 *m/z*; found $[M+H]^+$ 327.1592 *m/z*.

3-Phenyl-1,2-dihydronaphthalene and 2-phenyl-1,4-dihydronaphthalene

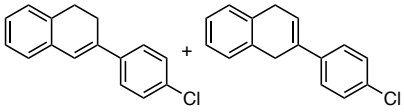


The title compounds (white solids, 12.8 mg, 6.2 μmol, 73%) were obtained as a mixture (8:1) of double bond isomers and synthesized following general procedure **F** from 7-(2-(3-methoxy-3-phenylpropyl)phenyl)cyclohepta-1,3,5-triene (26.9 mg, 10.0 μmol), and catalyst **F** (4.00 mg, 4.74 μmol). The reaction was stirred for 3 h and the crude was purified by column chromatography (cyclohexane/CH_2Cl_2 5:1) and further purified by preparative TLC (cyclohexane/CH_2Cl_2 10:1). Characteristic protons of the minor isomer could be assigned.

M.p. = 56 – 58°C (cyclohexane/CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ δ 7.62 – 7.57 (m, 2H), 7.55 – 7.50 (m, minor3H), 7.45 – 7.38 (m, 2H), 7.35 – 7.29 (m, 1H), 7.25 – 7.14 (m, 4H), 6.89 (s, 1H), 6.35 (tt, *J* = 3.8, 1.7 Hz, minor1H), 3.84 (td, *J* = 4.9, 1.5 Hz, minor2H), 3.65 (q, *J* = 4.8 Hz, minor2H), 3.00 (t, *J* = 8.1 Hz, 2H), 2.84 – 2.76 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.3, 138.8, 134.9, 134.9, 128.6, 127.5, 127.4, 127.1, 126.7, 125.3, 124.5, 28.3, 26.5. HRMS information is reported in the literature.[213]

213. Scheiper, B.; Bonnekessel, M.; Krause, H.; Fürstner, A. *J. Org. Chem.* **2004**, *69*, 3943–3949.

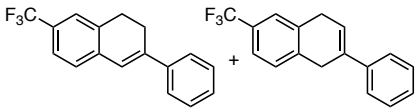
3-(4-chlorophenyl)-1,2-dihydronaphthalene and 2-(4-chlorophenyl)-1,4-dihydronaphthalene



The title compounds (white solids, 10.1 mg, 4.2 μmol, 53%) were obtained as a mixture (13:1) of double bond isomers and synthesized following general procedure **F** from 7-(2-(3-(4-chlorophenyl)-3-methoxypropyl)phenyl)cyclohepta-1,3,5-triene (28.0 mg, 11.6 μmol), and catalyst **F** (3.80 mg, 4.74 μmol). The reaction was stirred for 1 h and the crude was purified by column chromatography on silica gel (cyclohexane/CH_2Cl_2 5:1) and further purified by preparative TLC (cyclohexane/CH_2Cl_2 10:1). Characteristic protons of the minor isomer could be assigned.

M.p. = 95 – 97 °C (CH_2Cl_2). **^{1}H NMR** (400 MHz, CD_2Cl_2) 7.55 – 7.47 (m, 2H), 7.45 (d, *J* = 8.8 Hz, minor2H), 7.38 – 7.32 (m, 2H), 7.21 – 7.11 (m, 4H), 6.86 (s, 1H), 6.34 (tt, *J* = 3.8, 1.6 Hz, minor1H), 3.75 (t, *J* = 3.1 Hz, minor2H), 3.60 (q, *J* = 4.8 Hz, minor2H), 2.95 (t, *J* = 8.1 Hz, 2H), 2.79 – 2.62 (m, 2H). **^{13}C NMR** (101 MHz, CD_2Cl_2) δ 140.2, 138.0, 135.5, 135.0, 133.4, 129.1, 127.8, 127.2, 127.2, 127.0, 125.2, 28.6, 26.8. **HRMS** (APCI+) calculated for $[C_{16}H_{14}Cl]^+$ 241.0779 *m/z*; found $[M+H]^+$ 241.0777 *m/z*.

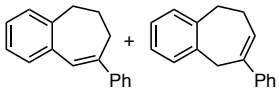
3-Phenyl-7-(trifluoromethyl)-1,2-dihydronaphthalene and 2-phenyl-6-(trifluoromethyl)-1,4-dihydronaphthalene



The title compounds (white solids, 11.7 mg, 4.2 μmol, 61%) were obtained as a mixture (8:1) of double bond isomers and synthesized following general procedure **F** from compound 7-(2-(3-methoxy-3-phenylpropyl)-4-(trifluoromethyl)phenyl)cyclohepta-1,3,5-triene (29 mg, 7.5 μmol), and catalyst **F** (4.80 mg, 5.20 μmol). The reaction was stirred for 24 h and the crude was purified by preparative TLC (cyclohexane/CH_2Cl_2 10:1). Characteristic protons of the minor isomer could be assigned.

M.p. = 89 – 91°C (cyclohexane/CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.59 – 7.54 (m, 2H), 7.51 – 7.47 (m, minor2H), 7.47 – 7.37 (m, 4H), 7.35 – 7.29 (m, 1H), 7.21 (d, *J* = 7.8 Hz, 1H), 6.88 (s, 1H), 6.32 (tt, *J* = 3.8, 1.7 Hz, minor1H), 3.84 (t, *J* = 5.3 Hz, minor2H), 3.65 (q, *J* = 4.7 Hz, minor2H), 3.01 (t, *J* = 8.1 Hz, 2H), 2.87 – 2.72 (m, 2H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 141.6, 140.6, 135.4, 128.7, 128.1, 126.6, 125.4, 124.5 (q, *J* = 271.7 Hz), 124.1 (q, *J* = 3.7 Hz), 123.8 (q, *J* = 4.0 Hz), 123.4, 28.1, 26.3. **^{19}F NMR** (376 MHz, CD_2Cl_2) (major and minor peaks overlap) δ –62.4. **HRMS** (APCI+) calculated for $[C_{17}H_{14}F_3]^+$ 275.1042 *m/z*; found $[M+H]^+$ 275.1040 *m/z*.

8-phenyl-6,7-dihydro-5*H*-benzo[7]annulene and 8-phenyl-6,9-dihydro-5*H*-benzo[7]annulene



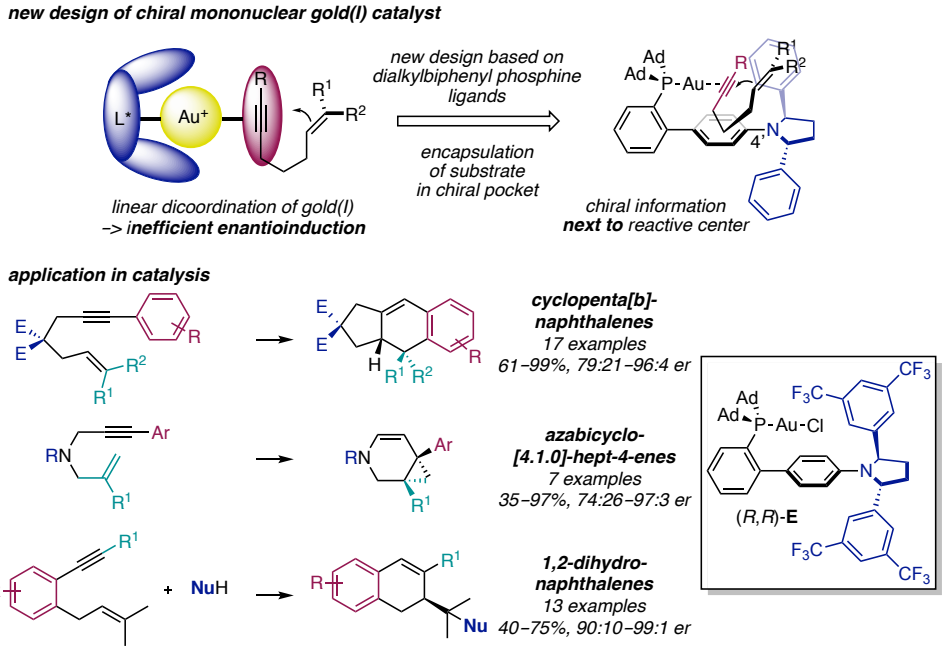
The title compounds (colorless gumm, 2.50 mg, 1.1 μmol, 11%) were obtained as a mixture (15:1) of double bond isomers and synthesized following general procedure **F** from compound 7-(2-(4-methoxy-4-phenylbutyl)phenyl)cyclohepta-1,3,5-triene (35.0 mg, 0.106 mmol), and catalyst **F** (4.90 mg, 5.30 μmol). The reaction was stirred for 24 h and the crude was purified by preparative TLC (cyclohexane/CH_2Cl_2 10:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 – 7.49 (m, 2H), 7.40 – 7.34 (m, 2H), 7.31 – 7.26 (m, 1H), 7.22 – 7.12 (m, 4H), 6.80 (s, 1H), 2.85 – 2.79 (m, 2H), 2.68 – 2.63 (m, 2H), 2.26 – 2.19 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.4, 143.1, 141.4, 137.6, 130.5, 129.2, 128.8, 128.5, 127.2, 126.8, 126.4, 126.1, 34.5, 32.8, 30.9. **HRMS** (APCI+) calculated for $[C_{17}H_{17}]^+$ 221.1325 *m/z*; found $[M+H]^+$ 221.1332 *m/z*.

General Conclusions

This Doctoral Thesis presents the design and synthesis of a new family of chiral mononuclear gold(I) complexes and their application in catalysis. The mode of action and enantioinduction of the chiral catalysts has been studied experimentally and computationally. Furthermore, the synthesis of 1,2-dihydronaphthalenes through gold(I)-catalyzed C(sp^3)–H insertion has been developed.

Our ligand design is based on the privileged dialkylbiaryl phosphine ligands. The strategic functionalization at the 4' position with C_2-symmetric *trans*-2,5-disubstituted pyrrolidines resulted key to overcome the limitations in asymmetric gold(I) catalysis arising from the linear dicoordination of gold(I) and the outer-sphere nucleophilic additions to coordinated alkynes. In this new class of ligands, the rigid biphenyl scaffold and the chiral information enclose the coordinated substrate in a chiral pocket. Enantioenriched products of formal [4+2] cycloaddition, azabicyclo[4.1.0]hept-4-enes and substituted 1,2-dihydronaphthalenes were obtained from the corresponding 1,6-arylenynes. The enantioselective preparation of 1,2-dihydronaphthalenes has been applied in the first asymmetric total synthesis of three members of the carexane family of natural products.

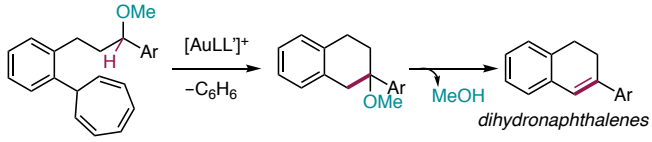


The simple design of our mononuclear complexes containing a single source of chirality allowed for the systematic investigation of their mode of action. Attractive non-covalent interactions between stereodirecting components of the 1,6-enynes and the aromatic substituents of the chiral pyrrolidine induce a defined binding orientation and

enantioselective folding inside the chiral pocket. The elucidation of the mode of action and enantioinduction led to the synthesis of a 2nd generation of chiral catalysts and in the development of new asymmetric transformations including the atroposelective synthesis of biaryls and the enantioselective cascade cyclization of 1-bromo-1,5-enyne.

Kinetic investigations showed that the pyrrolidinyl-biphenyl phosphine ligands have an important impact on the rate-determining step of the formal [4+2] cycloaddition. A positive entropy of activation $\Delta S^{\ddagger} = +24.5 \pm 6.0$ cal·mol^{-1}·K^{-1} was found by Eyring analysis. Additionally, the temperature-sensitive Eyring analysis suggests two competing rate-determining steps being the formation of the cyclopropyl gold(I) carbene and the ligand exchange.

Finally, a novel synthesis of 1,2-dihydronaphthalenes by C(sp^3)–H insertion of gold(I) carbenes generated by retro-Buchner reaction has also been developed. The α-OMe group has a dual role, providing additional activation to a benzylic C–H bond in the first place and acting as a leaving group after the C–H insertion event.



retro-Buchner/C(sp^3)–H bond insertion/elimination process

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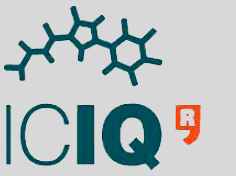

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