FERROCENE-BASED CHIRAL CATALYST DESIGN FOR ENANTIOSELECTIVE CYCLOADDITIONS REACTIONS

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DOCTORAL THESIS
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Supervised by Prof. Antonio M. Echavarren

Institute of Chemical Research of Catalonia (ICIQ)

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UNIVERSITAT ROVIRA i VIRGILI

ICIQ
Institut Català d'Investigació Química

I STATE that the present study, entitled "Ferrocene-Based Chiral Catalyst Design for Enantioselective Cycloadditions Reactions", presented by Ulysse Caniparoli for the award of the degree of Doctor, has been carried out under my supervision at the Institut Català d'Investigació Química (ICIQ).

Tarragona, August 29th, 2021

Doctoral Thesis Supervisor

Prof. Antonio M. Echavarren

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Publications

At the time of writing this Doctoral Thesis the following manuscript has been published:

"New-Generation Ligand Design for the Gold-Catalyzed Assymetric Activation of Alkynes" Zuccarello, G.; Escofet, I.; Caniparoli, U.; Echavarren, A. M. *ChemPlusChem* **2021**, DOI:10.1002/cplu.202100232.

Results described in this Doctoral Thesis will be reported in the manuscript under preparation;

"Planar Chiral 1,3-Disubstituted Ferrocene-Based Ligands in Asymmetric Gold(I) Catalysis" Caniparoli, U.; Escofet, I; Echavarren, A. M.

Table of Contents

Prologue

This Doctoral Thesis manuscript is divided in a general introduction, three chapters describing the research results and a general conclusion. Each chapter contains an introduction on the topic, objectives, results and discussion, conclusion, and an experimental section. The compounds and references are numbered continuously throughout the thesis.

The **General Introduction** provides an overview on homogeneous gold(I) catalysis and introduces the most successful and established approaches to enantioselective gold(I) catalysis as well as last development.

Chapter I describes the design, synthesis and optimization of the synthetic route toward a new class of planar chiral 1-(2-phosphinylaryl)-3-aryl ferrocene ligands and their related gold(I) complexes.

Chapter II presents the application of the new class of planar chiral gold(I) complexes to enantioselective formal [4+2] cycloaddition of 1,6-arylenynes and computational studies on the working mode of the new chiral gold(I) catalyst. The computational work has been performed by Dr. Imma Escofet.

Chapter III describes the gold(I)-catalyzed enantioselective cyclization of 2-alkynylaryl metallocenes to planar chiral 1,2-disubstituted metallocenes. This work was performed in collaboration with Dr. Giuseppe Zuccarello and Dr. Leonardo Nannini.

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

List of Abbreviations and Acronyms

In this Doctoral Thesis abbreviations and acronyms 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
dba	Dibenzylvinylacetone
1,2-DCE	1,2-Dichloroethane
DIPP	2,6-Diisopropylphenyl
dppf	1,1'-Bis(diphenylphosphino)ferrocene
ee	Enantiomeric Excess
er	Enantiomeric Ratio
ESI	Electrospray Ionization
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
$i\text{Pr}^F$	Perfluoroisopropyl
JohnPhos	(2-Biphenyl)di-*tert*-butylphosphine
LDA	Lithium *N,N*-diisopropylamide
m-CPBA	*meta*-Chloroperbenzoic acid
Men	Menthyl
2-MeTHF	2-Methyltetrahydrofuran
morph	morpholine

*n*BuLi	*n*-Butyllithium
NHC	N-Heterocyclic carbene
NTf_2	Bis(trifluoromethyl)imidate
Ns	2-Nitrobenzene-1-sulfonyl
p-Tol	*para*-Tolyl
*t*BuLi	*tert*-Butyllithium
TFAA	Trifluoroacetic anhydride
TMP	2,2,4,4-Tetramethylpiperidine
TRIS	Triisopropylphenylsulfonyl

Abstract

Gold(I)-catalysis emerged as a powerful synthetic tool for the chemoselective activation of alkynes leading, in a single step, to complex molecular structures under mild conditions with good atom economy. Despite a rapid increase of available gold(I)-catalyzed transformations, enantioselective versions of these catalytic methods experienced a slower development. The challenge of enantioselective gold(I)-catalysis arise from the linear dicoordination adopted by gold(I) and the outer-sphere mechanism in gold(I) catalysis. The spatial separation between the chiral information, located on the ligand, and the catalytic site, located on the opposite side of the metal center, render the transfer of chirality difficult.

To overcome this limitation, we introduced a new class of ligand designed as ferrocene analogues of dialkylbiphenyl ligands. The planar chiral ferrocene scaffold acts as the source of chirality and as spacer between the dialkylaryl phosphine and the catalytic site creating a chiral environment proximal to the latter. The modular synthesis of this new class of ligand gave access to a family of planar chiral phosphine-supported gold(I) complexes. A member of this family catalyzes the formal [4+2] cycloaddition of 1,6-arylenynes in high yields and good enantioselectivities.

The working mode of our chiral catalysts was studied computationally. An attractive non-covalent interaction between the ligand and the substrate was found to be crucial to achieve high enantioinduction.

Finally, we applied a phosphine-supported gold(I) complex containing a chiral remote C_2-symmetric 2,5-disubstituted pyrrolidine to the enantioselective synthesis of planar chiral ferrocenes by hydroarylation of 2-alkynylaryl ferrocenes.

General Objectives

The objectives of this Doctoral Thesis were the design and synthesis of a new class of chiral ferrocene-based ligand for enantioselective gold(I) catalysis and the enantioselective synthesis of planar chiral metallocenes.

- The design, synthesis and derivatization of a new class of planar chiral 1-(2'-dialkylarylphosphine)-3-aryl ferrocene ligands and their related gold(I) complexes.

- The application of the new gold(I) complexes to gold(I)-catalyzed formal [4+2] cycloaddition of 1,6-arylenynes and the study of the mode of action of the catalyst.

- The enantioselective synthesis of 1,2-disubstituted metallocene by gold(I)-catalyzed intramolecular hydroarylation of 2-alkynylaryl metallocenes.

A detailed description of the objectives is provided in each chapter.

General Introduction

Origin of the Chemical Elements

The diversity of chemical elements allowing complex chemistry and the emergence of life have different origins in the universe. Their diversity and abundance known to this day is the result of the aging of the universe, *ca.* $13.7 \cdot 10^9$ years old, and the succession of generations of stars that populate it (Figure 1).[1]

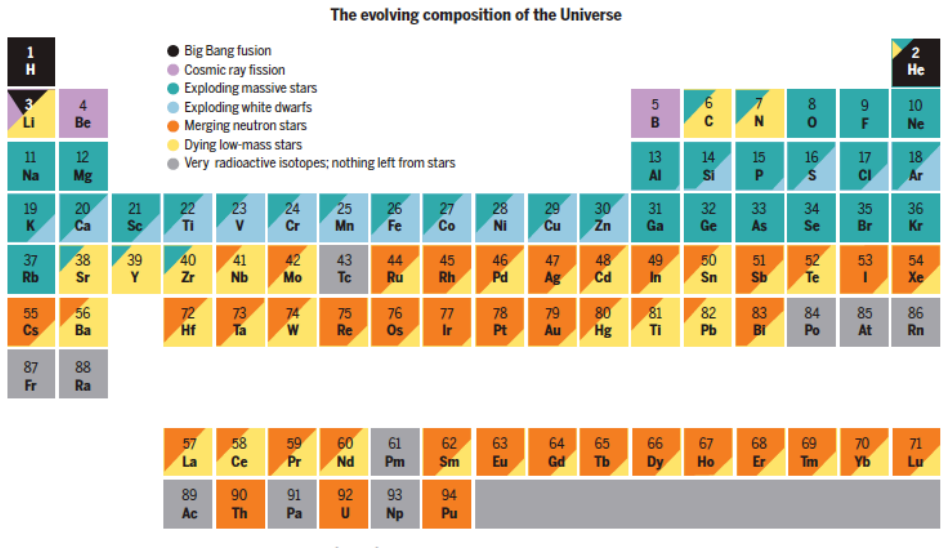

Figure 1. Origin of the elements in the universe (credit J. A. Johnson).[1]

After the Big Bang, the universe expanded resulting in its cooling and density decrease. After 10 s protons and neutrons were formed and the universe had a density of 10^4 g.cm^{-3} and a temperature of the order of 10^9 K.

During the Big Bang nucleosynthesis, roughly lasting from 10 s to 20 min after the Big Bang, the first nuclei were formed by combination of protons and neutrons. This primordial nucleosynthesis formed light nuclei of ^{2}H and ^{4}He. ^{3}He and very small amount of ^{7}Li were also formed. The nucleosynthesis stopped when

1 Johnson, J. A. *Science.* **2019**, *363*, 474–478.

temperature of the universe was too low for fusion reactions to occur. In few minutes ^{1}H and ^{4}He appeared to constitute 99 % of the know matter of the universe. The heavier elements were formed latter by the activity of stars.

The first stars appeared hundreds of millions of years after the Big Bang. The fusion of ^{1}H in the core of stars produces ^{4}He. This process occurs until depletion of the ^{1}H supply. Once exhausted, the equilibrium between the gravitational collapse and the pressure of the heated gas cannot be maintained and the core contract further until the ^{4}He burning is triggered and provides enough energy to support the star again. This cycle repeat itself, the core contract until the fusion of the product of the ending cycle is energetic enough to maintain a new equilibrium. ^{4}He fuses to C and O then stars evolve differently depending of their mass.

In low mass stars the nucleosynthesis stops at the after the fusion of He, sometime after production of Ne and Mg. Free neutrons produced by the fusion reactions can be captured by present nuclei thus producing heavier elements. At the end of their life low mass stars will slowly eject their stellar envelope containing new elements in the universe and turn into white dwarfs. In some cases of a binary system the companion object drops enough mass on the white dwarf to trigger the fusion of C and O to the iron peak in a cataclysmic event in which the whole body explodes.

In heavier mass stars the core can heat up sufficiently to trigger the fusion of C and O to form various nuclei. After exhaustion of the O supply the core cannot heat up sufficiently to trigger the fusion of Si. Massive star's life end in a supernovae event, a rapid contraction occurs and the falling material bounces back on the core then is expelled in the universe while creating a shock wave. Supernovae enrich the universe by spreading elements built up during the star's life into space. The extreme temperature and density caused by the shock wave

trigger additional nucleosyntheses and generate cosmic rays energetic enough to cause fission of some nuclei, source of a large fraction of Li, Be and B. This event can leave the collapsed core as a neutron star. During the merging of a double neutron stars or neutron start/black hole system, the tidal forces can tear apart the neutron stars generating neutrons available for captures by seed nuclei, thus synthesizing new elements, before the ejection of the material. Current models suggest these events can produce several Earth masses of gold.[2]

Although gold is one of the rarest stable elements in the universe,[3] the material in the region of the protoplanetary disk that formed the rocky planets was enriched in heavy elements as temperatures were too high for the condensation of light elements.[4] However, it is supposed that because of the differentiation that occurred on Earth, siderophilic elements such as gold sank with the molten iron phase to the core of the planet leaving the silica phase, the Earth's crust, depleted of noble metals.[5] A later surface enrichment process by meteoritic bombardment leading to the abundance of noble metals in the crust to their present level is hypothesized.

Despite its rarity gold appears to be among the first metal used by mankind.[6] Because of its resistance to oxidation, it can be found as native metal, pure or alloyed with silver, in its deposits. Hence it is collectable and usable without

2 Côté, B.; Fryer, C. L.; Belczynski, K.; Korobkin, O.; Chruslinska, M.; Vassh, N.; Mumpower, M. R.; Lippuner, J.; Sprouse, T. M.; Surman, R.; Wollaeger, R. *arXiv* **2017**, *99*.

3 Arlandini, C.; Kappeler, F.; Wisshak, K.; Gallino, R.; Lugaro, M.; Busso, M.; Straniero, O. S. *Astrophys. J.* **1999**, *525*, 886–900.

4 Davis A. M., Richter F. M. *Treatise Geochemistry Second Ed.* **2013**, *1*, 335–360.

5 Kimura, K.; Lewis, R. S.; Anders, E. *Geochim. Cosmochim. Acta* **1974**, *38*, 683–701.

6 Gopher, A.; Tsuk, T.; Shalev, S.; Gophna, R. *Curr. Anthropol.* **1990**, *31*, 436–443.

the requirement of chemical processes. However, it did not attract the same interest during the development of modern chemistry and its application remained sparse.

Homogeneous Gold(I) Catalysis

Despite few early reports,[7] gold was generally considered to be catalytically inert until the works reported by Ito and Hayashi on gold(I)-catalyzed asymmetric synthesis of chiral oxazolines[8] followed by the reports on the hydroxylation of alkynes described by Teles[9] and later Tanaka[10] marked the emergence of homogenous gold(I) catalysis. It is during the last two decades that this recent research field gained in importance revealing the powerful synthetic tools offered by gold(I)-catalyzed transformations.

Cationic gold(I) complexes own a unique reactivity because of their strong Lewis acidity and the ability to stabilize cationic reaction intermediates.[11] These properties are linked to their electronic structure whose characteristics are rooted in relativistic effects.

According to the special theory of relativity, as the velocity of a body approaches the velocity of light in vacuum its mass increases toward infinity. Hence, an increase of mass is observed for electrons orbiting a heavy nucleus at a

7 (a) Kharasch, M. S.; Isbell, H. S. *J. Am. Chem. Soc.* **1931**, *53*, 3053–3059. (b) Kharasch, M. S.; Beck, T. M. *J. Am. Chem. Soc.* **1934**, *56*, 2057–2060. (c) Meyer, L. U.; de Meijere, A. *Tetrahedron Lett.* **1976**, *17*, 497–500. (d) Hutchings, G. J. *J. Catal.* **1985**, *96*, 292–295.

8 Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405–6406.

9 Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem. Int. Ed.* **1998**, *37*, 1415–1418.

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11 (a) Pyykkoe, P., *Angew. Chem. Int. Ed.* **2002**, *41*, 3573–3578. (b) Pyykkö, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 4412–4456. (c) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395–403.

significant fraction of the speeding of light. The increase in mass of an electron leads to the decrease of its Bohr radius as it is inversely proportional to its mass. This contraction applies to all *s* and *p* orbitals but is practically significant only for elements with filled orbital 4*f* and 5*d*. The contractions of orbitals *s* and *p* increase the shielding effect, thus electrons occupying orbitals *d* and *f* see a reduced nuclear attraction leading to the expansion of these orbitals. The electrons populating the expended orbitals are subjected to less electron-electron repulsion. This behavior reaches a maximum for gold, being accentuated by interactions between relativistic and shell structure effects, thus providing gold complexes particular reactivity.

Relativistic effects are also responsible of the high electronegativity of gold (2.4) and the aurophilic interaction. The strong Lewis acidity combined with the large size of Au(I) makes it more amenable for the activation of soft electrophiles such as π-systems.[11c]

The favored linear coordination adopted by gold(I) associated with its high oxidation potential ($E(Au^{III}/Au^{I}) = 1.41$ V) result in less nucleophilic metal species and strongly decrease their ability to undergo oxidative addition and reductive elimination,[11c,12] which are common in catalytic cycles of late transition metals. Therefore, the redox stability of gold(I) provides a distinct mode of reactivity with a high functional group tolerance by excluding redox transformations. Additionally, it makes gold(I) complexes generally tolerant toward oxygen thus potentially suppressing the requirement of inert atmosphere. Computational studies by DFT calculations show that the oxidative addition products have reasonable energy levels and therefore are thermodynamically allowed but are kinetically inaccessible. However, the use of bidentate hemilabile (P,N) ligands[13] or bipyridine

12 Livendahl, M.; Goehry, C.; Maseras, F.; Echavarren, A. M. *Chem. Commun.* **2014**, *50*, 1533–1536.

13 Zeineddine, A.; Estévez, L.; Mallet-Ladeira, S.; Miqueu, K.; Amgoune, A.; Bourissou, D. *Nat. Commun.* **2017**, *8*, 1–8

ligands[14] gave access to Au(I)/Au(III) mediated cross coupling under stoichiometric conditions by enhancing gold backdonation. The use of strong external oxidants[15] or photocatalysts[16] can promote the Au(I)/Au(III) turn-over thus achieving gold-catalyzed coupling reactions.

Electronic properties of ancillary ligand L affect the reaction intermediates such as gold(I) carbenes stated in several gold(I)-catalyzed transformations due to a strengthened Au–L bond, result of the contraction of the orbital 6*s*. According to the model described by Toste and Goddard[17] the ligand–Au–carbene bond forms a linear three-center four-electron σ-hyperbond (Scheme 1). In addition, the gold center can form two π-bonds by back-donation of its electrons in the 5*d* orbitals to the empty π-orbitals of the ligand and the carbene. Consequently, σ-donating ligands will favor carbene like intermediates while π-acidic ligands induce stronger

14 (a) Harper, M. J.; Arthur, C. J.; Crosby, J.; Emmett, E. J.; Falconer, R. L.; Fensham-Smith, A. J.; Gates, P. J.; Leman, T.; McGrady, J. E.; Bower, J. F.; Russell, C. A. *J. Am. Chem. Soc.* **2018**, *140*, 4440–4445. (b) Cadge, J. A.; Sparkes, H. A.; Bower, J. F.; Russell, C. A. *Angew. Chem. Int. Ed.* **2020**, *59*, 6617–6621.

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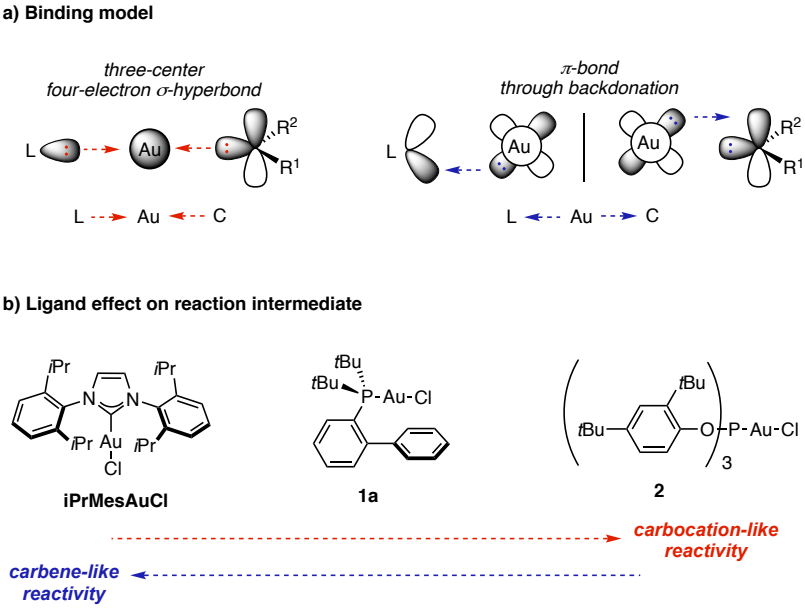
17 Benitez, D.; Shapiro, N. D.; Tkatchouk, E.; Wang, Y.; Goddard, W. A.; Toste, F. D. A *Nat. Chem.* **2009**, *1*, 482–486.

gold-to-ligand backdonation resulting in the elongation of the gold-carbene bond leading to a more cationic character of the intermediate.[18]



Scheme 1. Binding model and ligand effects.

Catalytically active cationic gold(I) complexes are generally prepared *in situ* from neutral precursors by protolysis of [LAuMe] with a strong acid or by chloride abstraction of a gold(I) chloride complex [LAuCl], mainly using silver salts AgX or $NaBAr^F_4$. The upstream preparation of storable cationic complex [LAu(NCR)]X is possible and advantageous when silver is undesired.[19] The use of silver(I) salts in gold(I) catalysis can be non-innocent[20] since it can impact the

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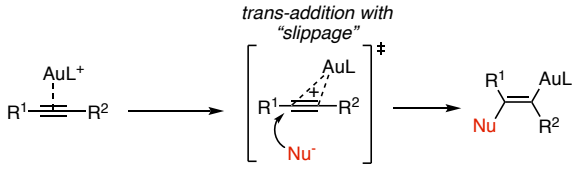
selectivity of the reaction[21] and lead to the formation of less active chloride-bridged digold complexes.[22] However, few reports describe chloride-scavenger free gold(I)-catalyzed transformations.[23,24]

Gold(I)-catalyzed transformations take place upon π-activation through an outer-sphere mechanism. The nucleophile adds trans to the gold atom inducing a slippage of the metal center along the activated C–C multiple bond forming an alkenyl-gold complex (Scheme 2). A wide array of heteronucleophiles such as water, alcohols, amines, imines, thiols, sulfoxides and *N*-oxides as well as carbonucleophiles such as arenes were used in gold(I)-catalyzed transformations performed inter- or intramolecularly.



Scheme 2. Nucleophile addition to (η^2-alkyne)gold(I) complexes.

Because its versatility, atom economical nature, and the display of an excellent chemoselectivity and functional group tolerance, homogeneous gold(I) catalysis became over the past two decades a recognized and powerful tool for

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24 Franchino, A.; Montesinos-Magraner, M.; Echavarren, A. M. *Bull Chem. Soc. Jpn.* **2021**, *94*, 1099–1117.

selective π-activation of C–C multiple bonds (alkenes, alkynes and allenes) suitable to access complex molecular structures. Gold(I) catalyzes a variety of transformations,[25] among which some were applied to natural product total synthesis.[26] Noteworthy, cycloisomerizations of 1,*n*-enynes are among the most recognized gold(I)-catalyzed transformations.

Cycloisomerization of 1,*n*-Enynes

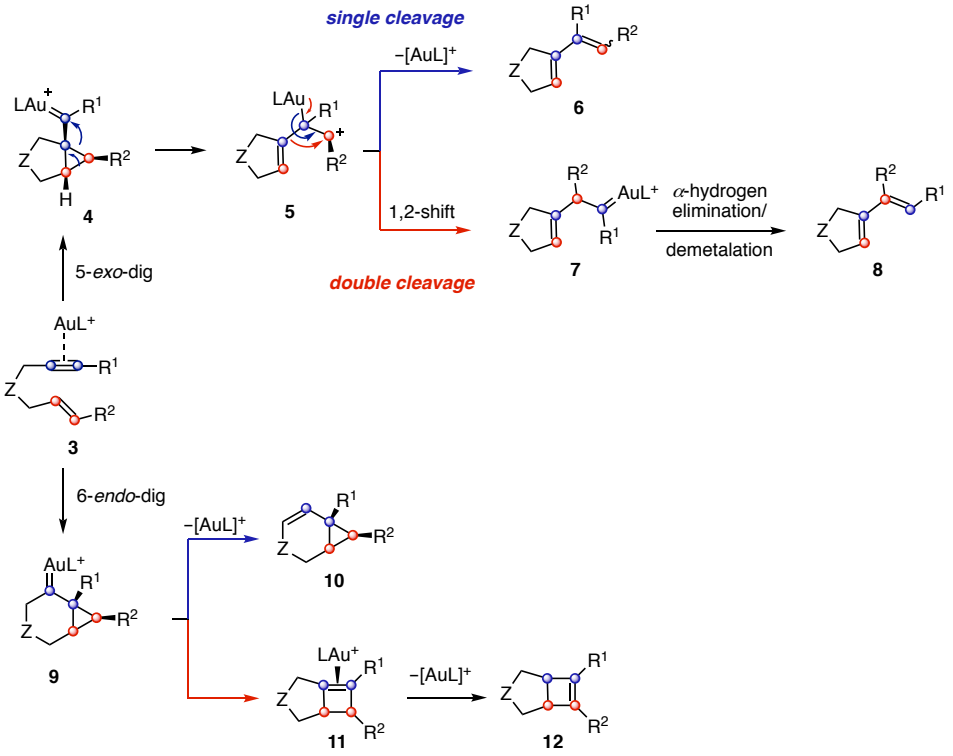
The emergence of gold(I)-catalyzed cycloisomerization of 1,*n*-enynes greatly impacted the field and provided a very powerful tool for such transformations. These reactions lead, in a single synthetic step, to a significant increase of the molecular complexity under mild conditions with excellent atom economy.

The outcome of gold(I)-catalyzed cycloisomerization of 1,6-enynes is influenced by different factors such as the ancillary ligand, the respective

25 (a) Stephen, A.; Hashmi, K. *Gold Bull.* **2003**, *36*, 3–9. (c) Hashmi, A. S. K. *Gold Bull.* **2004**, *37*, 51–65. (d) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180–3211. (e) Fürstner, A.; Davies, P. W. *Angew. Chem. Int. Ed.* **2007**, *46*, 3410-3449 (f) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326–3350. (g) Fürstner, A. *Chem. Soc. Rev.* **2009**, *38*, 3208–3221. (h) Shapiro, N. D.; Toste, F. D. *Synlett.* **2010**, *5*, 675–691. (h) Obradors, C.; Echavarren, A. M. *Acc. Chem. Res.* **2014**, *47*, 902–912. (i) Fensterbank, L.; Malacria, M. *Acc. Chem. Res.* **2014**, *47*, 953–965. (j) Dorel, R.; Echavarren, A. M. *Chem. Rev.* **2015**, *115*, 9028–9072. (k) Boyle, J. W.; Zhao, Y.; Chan, P. W. H. *Synth.* **2018**, *50*, 1402–1416. (l) Mato, M.; Franchino, A.; García-Morales, C.; Echavarren, A. M. **2020**. https://doi.org/10.1021/acs.chemrev.0c00697.

26 (a) Hashmi, A. S. K.; Rudolph, M. *Chem. Soc. Rev.* **2008**, *37*, 1766–1775. (b) Rudolph, M.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2012**, *41*, 2448–2462. (c) Pflästerer, D.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2016**, *45*, 1331–1367. (d) Mayans, J. G.; Armengol-Relats, H.; Calleja, P.; Echavarren, A. M. *Isr. J. Chem.* **2018**, *58*, 639–658.

substitution of the alkene and the alkyne, as well as the presence of a nucleophile in the reaction medium (Scheme 3).[21,25h,27]

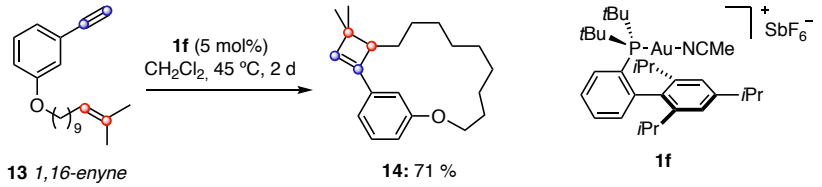


Scheme 3. Reaction pathways of the cycloisomerizations of 1,6-enynes.

In absence of a nucleophile, skeletal rearrangements can form different products by intramolecular reactions proceeding through single or double cleavage mechanisms. The (η^2-alkyne)gold(I) complex **3** can undergo 5-*exo*-dig cyclization yielding the intermediate **4** or 6-*endo*-dig cyclization yielding the intermediate **9**. In the first case, the intermediate **4** leads to the formation of the gold(I)-stabilized carbocation **5** by skeletal rearrangement, which can evolve to the diene product **6** (single cleavage) by protodemetalation, or undergo 1,2-shift leading to the gold(I)

27 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.

carbene **7** that yields the diene **8** (double cleavage) upon formal proton elimination and subsequent demetalation. Similarly, carbene **9** can form product **10** by protodemetalation or undergo a ring expansion forming the intermediate **11**, followed by double bond isomerization yielding product **12**. Importantly, the species represented as cyclopropyl gold(I) carbene have a highly distorted structure,[28] intermediate between a cyclopropyl gold carbene and a homoallylic stabilized carbocation.[25f,29] 1,*n*-Enynes with a longer spacer ($n > 6$) allow the construction of medium-sized rings and macrocycles through formal [2+2] cycloaddition reactions (Scheme 4).[21,27,30]



Scheme 4. Cyclization of 1,16-enynes.

Asymmetric Gold(I) Catalysis

The synthetic power of gold(I)-catalyzed reactions for the formation of C–C bonds renders asymmetric gold(I)-catalyzed transformations highly desirable. Despite the "Gold Rush" that has seen a fast development of gold(I)-catalyzed transformations, the development of enantioselective gold(I) catalysis proceeded

28 Nieto-Oberhuber, C.; López, S.; Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Eur. J.* **2006**, *12*, 5916–5923.

29 Jiménez-Núñez, E.; Claverie, C. K.; Bour, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2008**, *47*, 7892–7895.

30 (a) Obradors, C.; Leboeuf, D.; Aydin, J.; Echavarren, A. M. *Org. Lett.* **2013**, *15*, 1576–1579. (b) Ranieri, B.; Obradors, C.; Mato, M.; Echavarren, A. M. *Org. Lett.* **2016**, *18*, 1614–1617.

at a slower rate.[31] The inherent challenge for asymmetric transformations is set by the characteristics of gold(I).

Because of the preferred linear dicoordination of gold(I) complexes, the chiral information, located on the ligand, and the catalytic site, are on opposite sides of the metal center. The outer-sphere mechanism of gold(I)-catalyzed transformations additionally increases the distance between the ligand and the nucleophilic reagent. The resulting spatial separation between the chiral source and the substrate limits the chirality transfer, thus leading to poor enantioinduction. Moreover, the easy rotations of L–Au and Au–substrate bonds increase the difficulty of fixation of the substrate in a well-defined chiral environment (Figure 2).

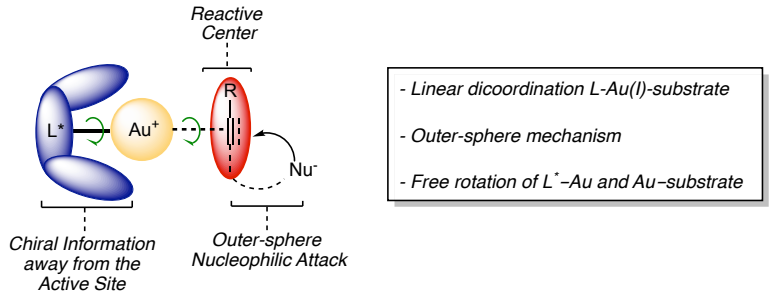


Figure 2. Limitations associated with enantioselective gold(I) catalysis.

Although the report by Ito and Hayashi in 1986 described the enantioselective synthesis of chiral oxazolines by aldol-type addition of isocyanate on aldehyde using a mono-gold bifunctional complex,[8] it was not until 2005 that our group reported the second example of an asymmetric gold(I)-catalyzed

31 (a) Widenhoefer, R. A. *Chem. Eur. J.* **2008**, *14*, 5382–5391. (b) Sengupta, S.; Shi, X. *ChemCatChem* **2010**, *2*, 609–619. (c) Wang, Y. M.; Lackner, A. D.; Toste, F. D. *Acc. Chem. Res.* **2014**, *47*, 889–901. (d) Zi, W.; Toste D. F. *Chem. Soc. Rev.* **2016**, *45*, 4567–4589. (e) Li, Y.; Li, W.; Zhang, J. *Chem. Eur. J.* **2017**, *23*, 467–512.

transformation.[32] The asymmetric alkoxycyclization of enynes catalyzed by digold(I) complexes of axially-chiral biarylbisphosphines has a marked substrates dependence, yet this report set a milestone in asymmetric gold(I) enantioselective catalysis. To this day, digold(I) complexes supported by axially-chiral bisphosphines remain common tools in enantioselective gold(I)-catalyzed transformations along with newly developed enantioselective catalytic systems.

Three main approaches have been developed to achieve asymmetric gold(I)-catalyzed transformations: digold(I) complexes of axially-chiral bisphosphines, chiral phosphoramidite ligands, and chiral counter anions (Figure 3).[33]

Axially-chiral bisphosphines digold(I) complexes are the first developed and the most studied systems. They have been applied to various inter- and intramolecular transformations, in addition to the cycloisomerization of 1,*n*-enynes,[31,34] such as cyclopropanation of alkenes,[35] hydro-functionalization of

32 Paz Muñoz, M.; Adrio, J.; Carretero, J. C.; Echavarren, A. M. *Organometallics* **2005**, *24*, 1293–1300.

33 Zuccarello, G.; Escofet, I.; Caniparoli, U.; Echavarren, A. M. *ChemPlusChem* **2021**, DOI: 10.1002/cplu.202100232.

34 (a) Chao, C. M.; Beltrami, D.; Toullec, P. Y.; Michelet, V. *Chem. Commun.* **2009**, *45*, 6988–6990. (b) Chao, C. M.; Vitale, M. R.; Toullec, P. Y.; Genêt, J. P.; Michelet, V. *Chem. Eur. J.* **2009**, *15*, 1319–1323. (c) Gawade, S. A.; Bhunia, S.; Liu, R. S. *Angew. Chem. Int. Ed.* **2012**, *51*, 7835–7838.

35 (a) Johansson, M. J.; Gorin, D. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 18002–18003. (b) Watson, I. D. G.; Ritter, S.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 2056–2057. (c) Briones, J. F.; Davies, H. M. L. *J. Am. Chem. Soc.* **2012**, *134*, 11916–11919.

alkenes[36] and allenes,[37] and other reactions.[38] Similarly, related axially-chiral acyclic diaminocarbenes,[39] spirocyclic bisphosphines[40] and axially-chiral 1,2,3-triazole[41] digold(I) complexes have been applied to enantioselective catalysis. Albeit the exact cause of the high enantioinduction has not been studied in detail in most cases, it has been postulated that aurophilic interactions might play an important role.[42]

36 (a) Zhang, Z.; Lee, S. D.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2009**, *131*, 5372–5373. (b) Mukherjee, P.; Widenhoefer, R. A. *Angew. Chem. Int. Ed.* **2012**, *51*, 1405–1407. (c) Bandini, M.; Bottoni, A.; Chiarucci, M.; Cera, G.; Miscione, G. Pietro. *J. Am. Chem. Soc.* **2012**, *134*, 20690–20700. (d) Lee, S. D.; Timmerman, J. C.; Widenhoefer, R. A. *Adv. Synth. Catal.* **2014**, *356*, 3187–3192. (e) Fang, W.; Presset, M.; Guérinot, A.; Bour, C.; Bezzenine-Lafollée, S.; Gandon, V. *Org. Chem. Front.* **2014**, *1*, 608–613.

37 Miles, D. H.; Veguillas, M.; Toste, F. D. *Chem. Sci.* **2013**, *4*, 3427–3431.

38 (a) Melhado, A. D.; Luparia, M.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 12638–12639. (b) Luzung, M. R.; Mauleón, P.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 12402–12403. (c) Liu, F.; Qian, D.; Li, L.; Zhao, X.; Zhang, J. *Angew. Chem. Int. Ed.* **2010**, *49*, 6669–6672. (d) Zhou, G.; Liu, F.; Zhang, J. *Chem. Eur. J.* **2011**, *17*, 3101–3104. (e) Huang, L.; Yang, H. Bin; Zhang, D. H.; Zhang, Z.; Tang, X. Y.; Xu, Q.; Shi, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 6767–6771. (f) Guo, R.; Li, K. N.; Liu, B.; Zhu, H. J.; Fan, Y. M.; Gong, L. Z. *Chem. Commun.* **2014**, *50*, 5451–5454. (g) Sota, Y.; Yamamoto, M.; Murai, M.; Uenishi, J.; Uemura, M. *Chem. Eur. J.* **2015**, *21*, 4398–4404. (h) Zi, W.; Wu, H.; Toste, F. D. *J. Am. Chem. Soc.* **2015**, *137*, 3225–3228.

39 (a) Bartolomé, C.; García-Cuadrado, D.; Ramiro, Z.; Espinet, P. *Inorg. Chem.* **2010**, *49*, 9758–9764. (b) Wang, Y. M.; Kuzniewski, C. N.; Rauniyar, V.; Hoong, C.; Toste, F. D. *J. Am. Chem. Soc.* **2011**, *133*, 12972–12975. (c) Niemeyer, Z. L.; Pindi, S.; Khrakovsky, D. A.; Kuzniewski, C. N.; Hong, C. M.; Joyce, L. A.; Sigman, M. S.; Toste, F. D. *J. Am. Chem. Soc.* **2017**, *139*, 12943–12946.

40 Cao, Z. Y.; Wang, X.; Tan, C.; Zhao, X. L.; Zhou, J.; Ding, K. *J. Am. Chem. Soc.* **2013**, *135*, 8197–8200.

41 Huang, W.; Zhang, Y. C.; Jin, R.; Chen, B. L.; Chen, Z. *Organometallics* **2018**, *37*, 3196–3209.

42 Zhang, Z. M.; Chen, P.; Li, W.; Niu, Y.; Zhao, X. L.; Zhang, J. *Angew. Chem. Int. Ed.* **2014**, *53*, 4350–4354.

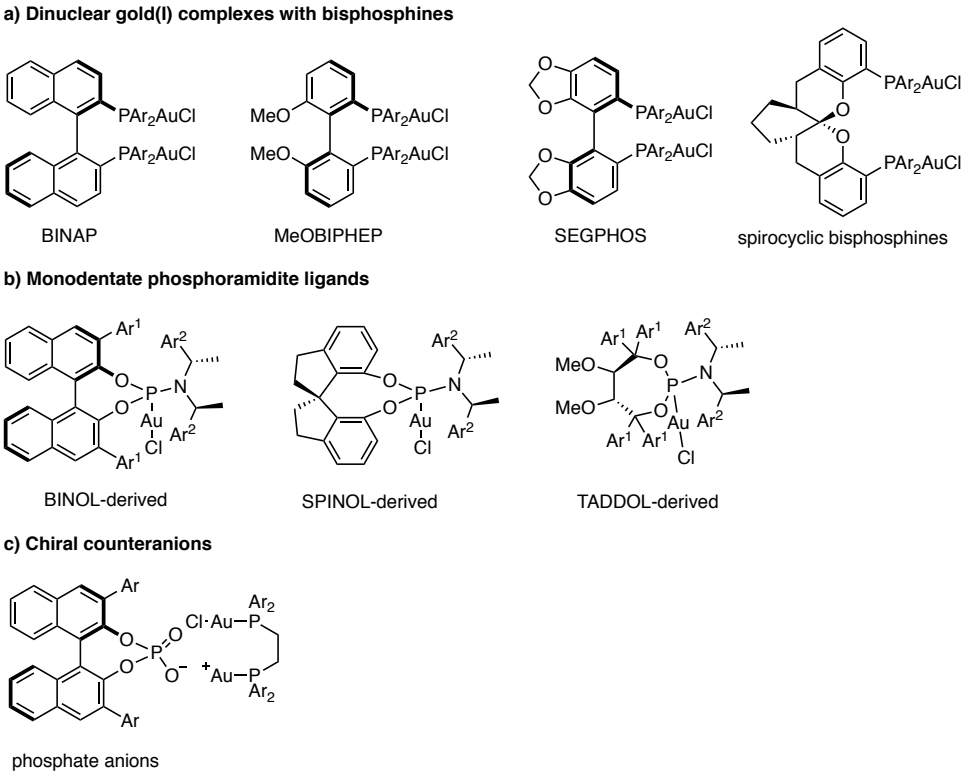


Figure 3. Three main designs for enantioselective gold(I) catalysis.

The groups of Mascareñas,[43] Toste[44] and Fürstner[45] contributed to the emergence of another approach based on the use of one-point-binding chiral phosphoramidites readily available from BINOL, SPINOL or TADDOL scaffolds with extended groups to wall the reactive site in a chiral environment with the participation of the bulky substituents of the amine moiety. This modular design

43 Alonso, I.; Trillo, B.; López, F.; Montserrat, S.; Ujaque, G.; Castedo, L.; Lledós, A.; Mascareñas, J. L. *J. Am. Chem. Soc.* **2009**, *131*, 13020–13030.

44 González, A. Z.; Benitez, D.; Tkatchouk, E.; Goddard, W. A.; Toste, F. D. *J. Am. Chem. Soc.* **2011**, *133*, 5500–5507.

45 Teller, H.; Corbet, M.; Mantilli, L.; Gopakumar, G.; Goddard, R.; Thiel, W.; Fürstner, A. *J. Am. Chem. Soc.* **2012**, *134*, 15331–15342.

has proven its efficiency especially in cycloaddition of allenes.[46] A related design was reported by our group using chiral phosphite ligands for the enantioselective [4+2] cycloaddition of 1,6-aryleneynes.[47] Recently, the group of Alcarazo introduced a chiral α-cationic phosphonite ligands based on a TADDOL scaffold in the context of enantioselective gold(I)-mediated synthesis of chiral helicenes[48] and other axially chiral molecules.[49]

Finally, the combination of gold(I) complexes with chiral counter anions constitutes another successful approach.[50] This concept was introduced by Toste in gold(I)-catalyzed intramolecular hydroamination and hydrocarboxylation of allenes using chiral BINOL-phosphate anion.[51] Chiral counter anions can be used in the presence of chiral or achiral gold(I) complexes. This approach relies on the ion pair interaction to keep the chiral information close to the catalytic site, overcoming the limitations imposed by the linear coordination of gold(I). However, the basicity of phosphates is sufficiently high to abstract the alkyne

46 (a) Li, G. H.; Zhou, W.; Li, X. X.; Bi, Q. W.; Wang, Z.; Zhao, Z. G.; Hu, W. X.; Chen, Z. *Chem. Commun.* **2013**, *49*, 4770–4772. (b) Suárez-Pantiga, S.; Hernández-Díaz, C.; Rubio, E.; González, J. M. *Angew. Chem. Int. Ed.* **2012**, *51*, 11552–11555. (c) Wang, Y.; Zhang, P.; Liu, Y.; Xia, F.; Zhang, J. *Chem. Sci.* **2015**, *6*, 5564–5570. (d) Wang, Y.; Zhang, P.; Qian, D.; Zhang, J. *Angew. Chem. Int. Ed.* **2015**, *54*, 14849–14852. (e) Shen, Z. Q.; Li, X. X.; Shi, J. W.; Chen, B. L.; Chen, Z. *Tetrahedron Lett.* **2015**, *56*, 4080–4083.

47 Delpont, N.; Escofet, I.; Pérez-Galán, P.; Spiegl, D.; Raducan, M.; Bour, C.; Sinisi, R.; Echavarren, A. *Catal. Sci. Technol.* **2013**, *3*, 3007–3012.

48 (a) Nicholls, L. D. M.; Marx, M.; Hartung, T.; González-Fernández, E.; Golz, C.; Alcarazo, M. *ACS Catal.* **2018**, *8*, 6079–6085. (b) Hartung, T.; Machleid, R.; Simon, M.; Golz, C.; Alcarazo, M. *Angew. Chem. Int. Ed.* **2020**, *59*, 5660–5664.

49 Hartung, T.; Machleid, R.; Simon, M.; Golz, C.; Alcarazo, M. *Angew. Chem. Int. Ed.* **2020**, *59*, 5660–5664.

50 Inamdar, S. M.; Konala, A.; Patil, N. T. *Chem. Commun.* **2014**, *50*, 15124–15135.

51 Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, F. D. *Science.* **2007**, *317*, 496–499.

proton leading to the formation of catalytically inert gold(I) acetylides[52] making this system incompatible with activation of terminal alkynes.[53]

These three approaches are well established and proved to be efficient for several transformations. However, they have limitations and none of these systems provides a broad scope of applications thus driving the emergence of new designs.

In 2014 Zhang introduced Mingphos[54] **17** and later Xiangphos[55] **19** which represent a new class of chiral sulfinamide monophosphine ligands, highly tunable and readily accessible from commercial sources (Scheme 5). This design was based on the observation that monocationic digold complexes [LAu_2ClX] can give better enantioselectivity than dicationic [LAu_2X_2] complexes indicating that the second metallic site might interact with the substrate or has a steric influence. The second gold site was substituted by a chiral sulfinamide to achieve similar effects. The Mingphos ligand **17a** is a suitable ligand for the enantioselective cycloaddition of nitrone **16** with 2-(1-alkynyl)-2-alken-1-one **15**. The same group later introduced PCPhos ligand **20**,[56] analogue of Mingphos on a Xanthphos backbone, for the cyclization of *N*-allenamides, where the non-covalent hydrogen bonding with the substrate is key to achieve good enantioinduction. The sulfonamide group in **20** plays a crucial role, when Ns protecting group is used instead of TRIS lower enantioinduction was obtained. The use of a Xanthphos scaffold increases the space

52 Ferrer, S.; Echavarren, A. M. *Organometallics* **2018**, *37*, 781–786.

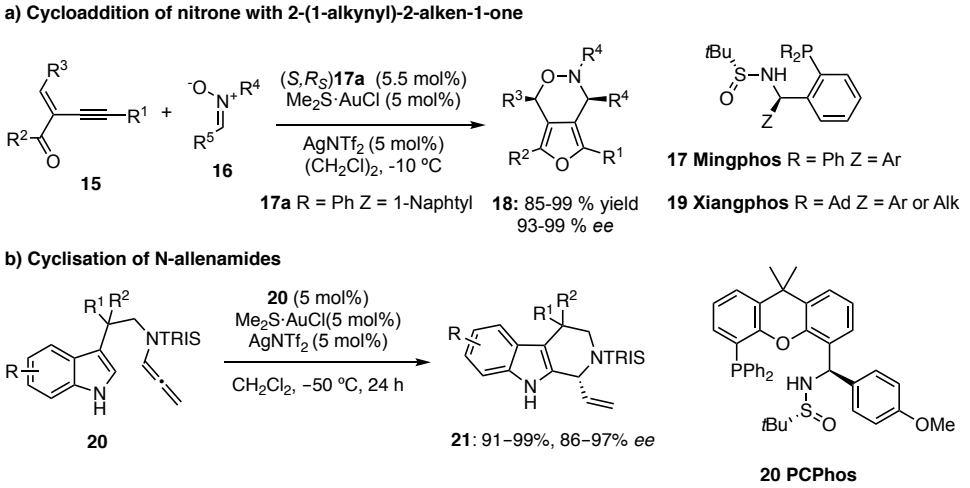
53 Raducan, M.; Moreno, M.; Bour, C.; Echavarren, A. M. *Chem. Commun.* **2012**, *48*, 52–54

54 Zhang, Z. M.; Chen, P.; Li, W.; Niu, Y.; Zhao, X. L.; Zhang, J. *Angew. Chem. Int. Ed.* **2014**, *53*, 4350–4354.

55 Hu, H.; Wang, Y.; Qian, D.; Zhang, Z. M.; Liu, L.; Zhang, J. *Org. Chem. Front.* **2016**, *3*, 759–763.

56 Wang, Y.; Zhang, P.; Di, X.; Dai, Q.; Zhang, Z. M.; Zhang, J. *Angew. Chem. Int. Ed.* **2017**, *56*, 15905–15909.

between the coordinating phosphine and the chiral source, thus moving it closer from the catalytic site taking account the linear coordination adopted by gold(I).



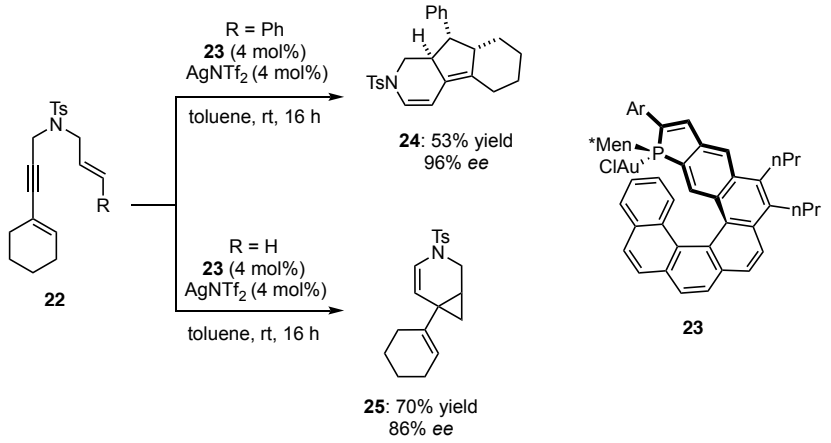
Scheme 5. Chiral sulfinamide monophosphine ligands for gold(I) catalysis.

Fensterbank and Sollogoup reported the encapsulation of the metal center using a NHC-capped-*β*-cyclodextrin[57] ligand providing high enantioselectivity in the alkoxycyclization reaction of 1,6-enynes. Additionally, Marinetti and Voituriez introduced chiral helicenes gold(I) complexes[58] with an embedded phosphole in

57 (a) 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. (b) 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. (c) Kaya, Z.; Andna, L.; Matt, D.; Bentouhami, E.; Djukic, J. P.; Armspach, D. *Chem. Eur. J.* **2018**, *24*, 17921–17926. (d) Tugny, C.; Del Rio, N.; Koohgard, M.; Vanthuyne, N.; Lesage, D.; Bijouard, K.; Zhang, P.; Meijide Suárez, J.; Roland, S.; Derat, E.; Bistri-Aslanoff, O.; Sollogoub, M.; Fensterbank, L.; Mouriès-Mansuy, V. *ACS Catal.* **2020**, *10*, 5964–5972.

58 (a) Yavari, K.; Aillard, P.; Zhang, Y.; Nuter, F.; Retailleau, P.; Voituriez, A.; Marinetti, A. *Angew. Chem.* **2014**, *126*, 880–884. (b) Aillard, P.; Voituriez, A.; Dova, D.; Cauteruccio, S.; Licandro, E.; Marinetti, A. *Chem. Eur. J.* **2014**, *20*, 12373–12376.

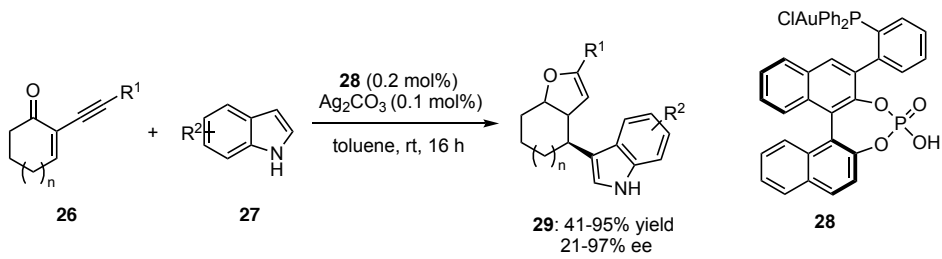
the inner ring catalyzing the cyclization of the *N*-tethered 1,6-enynes **22** to give products **24** and **25** (Scheme 6) in good yield and high enantiomeric excess. This design was later applied to other asymmetric transformations.[59]



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

In 2020 Marinetti and Guinchard reported a bifunctional ligand combining a phosphate counter anion tethered to a monophosphine with an axially chiral BINOL (Scheme 7).[23c] The related gold(I) complex **28** catalyzes the cycloisomerization/nucleophilic additions of 2-alkynyl-enones **26** yielding the adduct **29** with high enantioselectivity. This is the result of the cationic intermediate being stabilized by the phosphate counter anion in a well-defined spatial arrangement created by the binaphtyl scaffold.

59 (a) Aillard, P.; Retailleau, P.; Voituriez, A.; Marinetti, A. *Chem. Eur. J.* **2015**, *21*, 11989–11993. (b) Aillard, P.; Dova, D.; Magné, V.; Retailleau, P.; Cauteruccio, S.; Licandro, E.; Voituriez, A.; Marinetti, A. *Chem. Commun.* **2016**, *52*, 10984–10987.



Scheme 7. Application of phosphate tethered gold(I) complex.

Most of these new approaches share a design based on a mononuclear gold(I) complex with a spacer to keep the chiral information close to the reaction site.

Biarylaryl Phosphines Ligands in Gold(I) Catalysis

In 1998 Buchwald introduced bulky dialkylbiaryl phosphines ligands applied to form highly active catalysts for palladium-catalyzed Suzuki-Miyaura cross-coupling and amination of aryl chlorides.[60] The electron rich phosphine facilitates oxidative additions to palladium(0) and the bulkiness of ligands promote reductive eliminations. In addition, their synthetic accessibility and tunability[61] as well as their resistance toward oxidation[62] render this class of ligand very attractive. Hence, dialkylbiaryl phosphines were applied to various palladium-catalyzed C–X

60 (a) David, W. O.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722–9723. (b) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **1999**, *38*, 2413–2416.

61 Tomori, H.; Fox, J. M.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 5334–5341.

62 Barder, T. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 5096–5101.

bonds formation (X = C[63], N[64], O[65], F[66]) and employed with other transition metals such as Ru,[67] Cu,[68] Rh,[69] and Ag.[70] In this context, our group reported in 2005 the first application of dialkylbiaryl phosphine ligands in the field of homogeneous gold(I) catalysis introducing a family of highly electrophilic gold(I) complexes **1a-d** active in various transformations upon in situ chloride abstraction (Figure 4).[71] This work was followed shortly after by the preparation of the bench stable preactivated cationic gold(I) complexes **1e-g**, obtained by reaction of their gold(I) chloride precursors with $AgSbF_6$ in MeCN.[21]

1a: R = *t*Bu, $R^1 = R^2 = H$
1b: R = Cy, $R^1 = R^2 = H$
1c: R = Cy, $R^1 = R^2 = i$Pr
1d: R = Cy, R^1 = OMe, $R^2 = H$

1e: R = *t*Bu, $R^1 = H$
1f: R = *t*Bu, $R^1 = i$Pr
1g: R = Cy, $R^1 = H$

Figure 4. Dialkylbiaryl phosphine gold(I) complexes.

63 (a) Billingsley, K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3358–3366. (b) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461–1473.

64 (a) Surry, D. S.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 6338–6361. (b) Dorel, R.; Grugel, C. P.; Haydl, A. M. *Angew. Chem. Int. Ed.* **2019**, *58*, 17118–17129. (c) Ingoglia, B. T.; Wagen, C. C.; Buchwald, S. L. *Tetrahedron* **2019**, *75*, 4199–4211.

65 Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4369–4378.

66 Sather, A. C.; Buchwald, S. L. *Acc. Chem. Res.* **2016**, *49*, 2146–2157.

67 Faller, J. W.; D'Alliessi, D. G. *Organometallics* **2003**, *22*, 2749–2757.

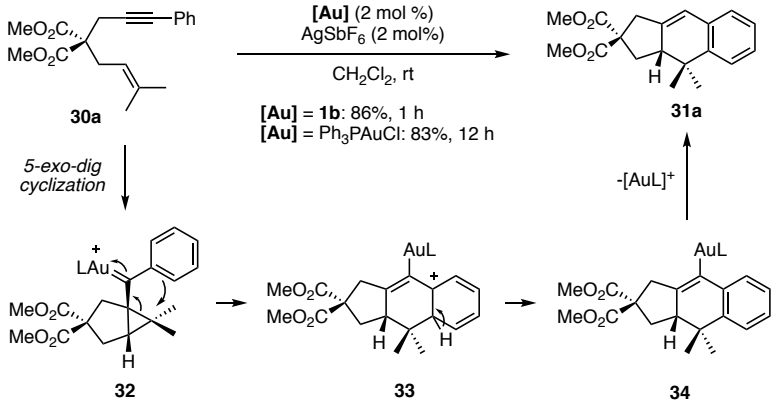
68 Haider, J.; Kunz, K.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 717–722.

69 (a) Dhondi, P. K.; Chisholm, J. D. *Org. Lett.* **2006**, *8*, 67–69. Dhondi, P. K.; Carberry, P.; Choi, L. B.; Chisholm, J. D. *J. Org. Chem.* **2007**, *72*, 9590–9596.

70 Porcel, S.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 2672–2676.

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

Although internal enynes are known to be reluctant to undergo cycloisomerization reactions, especially arylalkynes, the complex **1b** catalyzed the formal [4+2] cycloaddition of internal 1,6-enyne **30a** delivering product **31a** in good yield and short reaction time compared to PPh_3AuCl (Scheme 8). Higher activity is also displayed in the alkoxycyclization of 1,6-enynes. Experiments and theoretical studies suggested that the formation of cyclopenta[*b*]naphthalene **31a** involves a 5-*exo*-dig cyclization forming the *anti*-cyclopropyl gold(I) carbene **32**, followed by a Friedel-Craft-type reaction to form the Wheland intermediate **33** that gives the product **31a** by a proton loss and protodeauration.[72]



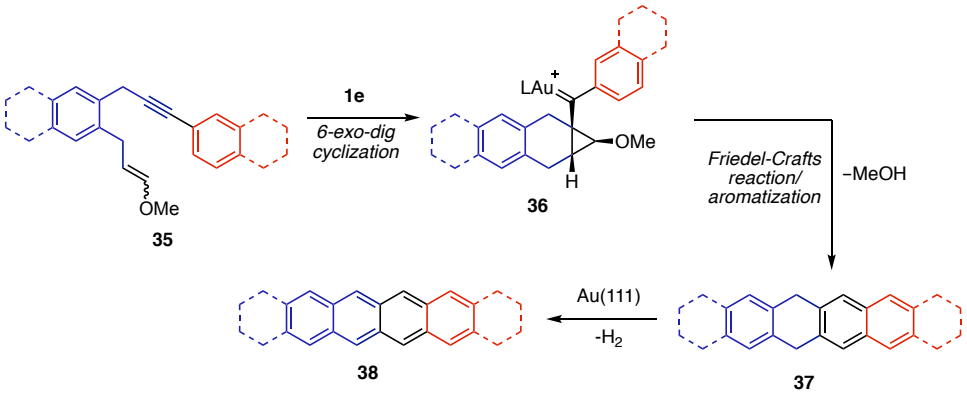
Scheme 8. Formal [4+2] cycloaddition of 1,6-arylenynes **30a.**

Our group applied the formal [4+2] cycloaddition to 1,7-enyne **35**, in which the alkene is replaced by an enol ether, to obtain the dihydroacenes **37** (Scheme 9).[73] These compounds are of particular interest as they are stable

72 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.

73 (a) Dorel, R.; McGonigal, P. R.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2016**, *55*, 11120–11123. (b) Zuzak, R.; Dorel, R.; Krawiec, M.; Such, B.; Kolmer, M.; Szymonski, M.; Echavarren, A. M.; Godlewski, S. *ACS Nano* **2017**, *11*, 9321–9329. (c) Zuzak, R.; Dorel, R.; Krawiec, M.; Such, B.; Kolmer, M.; Szymonski, M.; Echavarren, A. M.; Godlewski, S. *ACS Nano* **2017**, *11*, 9321–9329. (d) Zuzak,

precursors of long acenes, a class of polycyclic aromatic molecules appealing for their properties as semiconductors.[74] The corresponding acenes **38** were synthesized on Au(111) surface from the dihydroacenes **37** by dehydrogenation upon heating. For this application, complex **1e** proved to be a superior catalyst over NHC- and phosphite gold(I) complexes. This reaction proceeds with the formation of gold carbene **36** via 6-*exo*-dig cyclization of **35** followed by aromatization and loss of methanol to form the dihydroacenes **37**.



Scheme 9. Preparation of acenes via gold(I)-catalyzed 1,7-enyne cyclization.

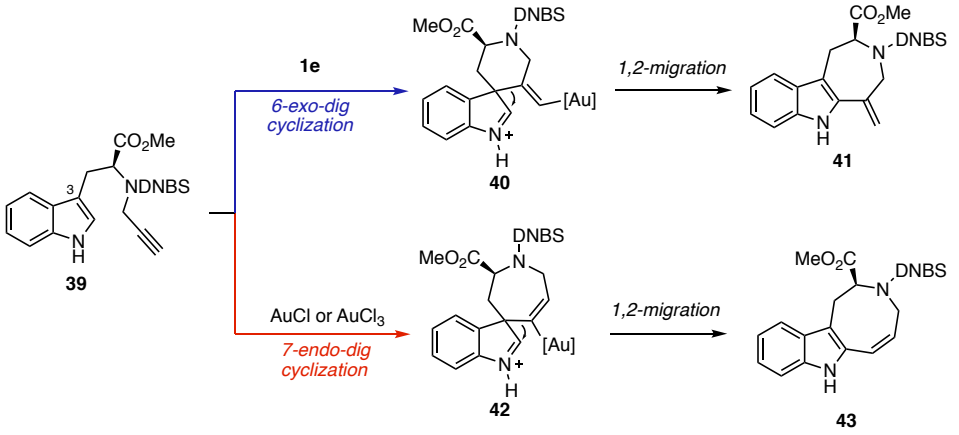
The outcome of gold(I)-catalyzed transformations can be dependent of the ligand employed. When using alkynyl-indoles **39** as substrates of gold(I)-catalyzed intramolecular hydroarylation, cationic complex **1e** leads to the exclusive formation of **41**, while **43** was selectively formed in presence of AuCl or $AuCl_3$ salts (scheme 10).[75] The products are the results of a 6-*exo*-dig and a 7-*endo*-dig

R.; Stoica, O.; Blieck, R.; Echavarren, A. M.; Godlewski, S. *ACS Nano* **2021**, *15*, 1548–1554.

74 Anthony, J. E. *Chem. Rev.* **2006**, *106*, 5028–5048.

75 (a) Ferrer, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 1105–1109. (b) Ferrer, C.; Amijs, C. H. M.; Echavarren, A. M. *Chem. Eur. J.* **2007**, *13*, 1358–1373 (c) Zhang, L.; Chang, L.; Hu, H.; Wang, H.; Yao, Z. J.; Wang, S. *Chem. Eur. J.* **2014**, *20*, 2925–2932.

cyclizations by electrophilic aromatic substitution, respectively, followed by a 1,2-alkyl migration.[76]

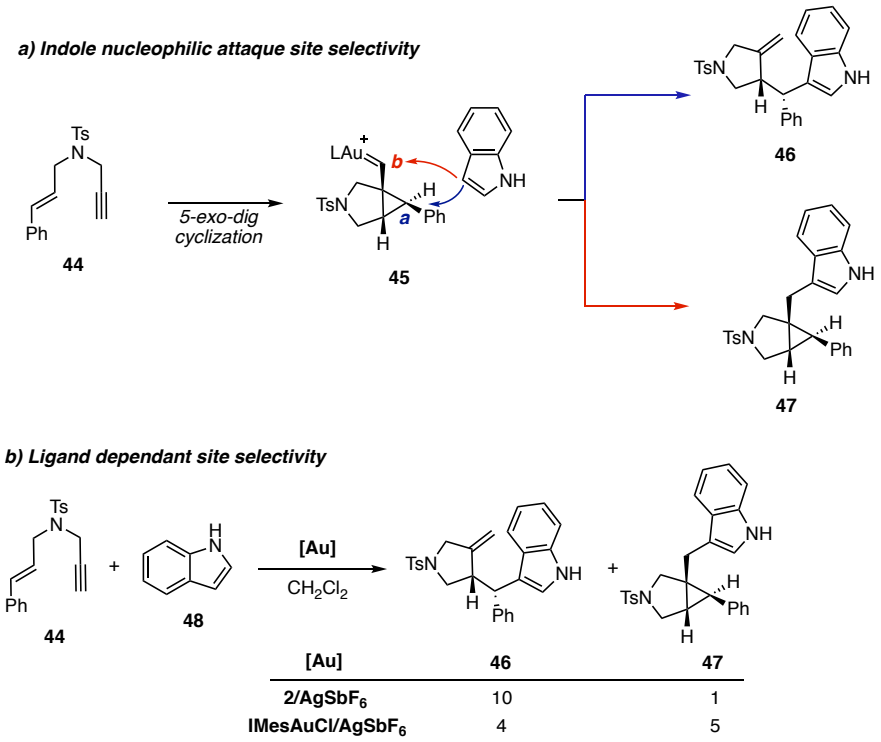


Scheme 10. Catalyst dependent regioselectivity of the hydroarylation of **39**.

In the case of the gold(I)-catalyzed cycloisomerization of *N*-tethered 1,6-enyne **44** in the presence of nucleophiles such as indole, the choice of catalyst can influence the regioselectivity of the nucleophilic attack (Scheme 11). Both **2** and IMesAuCl gold(I) complexes induce a 5-*exo*-dig cyclization. Whereas the catalytic system **2**/$AgSbF_6$ favors the attack at the cyclopropane carbon ***a*** yielding a mixture of **46** and **47** in a 10:1 ratio, the use of σ-donating NHC-supported complex IMesAuCl/$AgSbF_6$ slightly favors the formation of **47** (5:4 ratio) by preferential nucleophilic attack at carbon ***b*** of the carbene like intermediate.[77]

76 (a) Jackson, A. H.; Smith, A. E. *Tetrahedron* **1968**, *24*, 403–413. (b) Genosan, A.; Heathcock, C. H. *Tetrahedron Lett.* **1993**, *34*, 439–440.

77 Amijs, C. H. M.; Ferrer, C.; Echavarren, A. M. *Chem. Commun.* **2007**, *7*, 698–700.



Scheme 11. Catalyst-dependent regioselectivity in the cycloisomerization/nucleophilic attack of **44**.

Because of their robustness, high activity and unique reactivity, dialkylbiaryl phosphine gold(I) complexes have been among the most often used catalysts in homogenous gold(I) catalysis. In the case of cationic complex **1e**, it was demonstrated that the M-arene interaction is not significant, in contrast to that found in palladium systems.[78] Presumably, the efficiency of these bulky electron-donating biaryl phosphine ligands is related to their ability to stabilize carbene or carbocation like intermediates.[79]

78 Pérez-Galán, P.; Delpont, N.; Herrero-Gómez, E.; Maseras, F.; Echavarren, A. M. *Chem. Eur. J.* **2010**, *16*, 5324–5332.

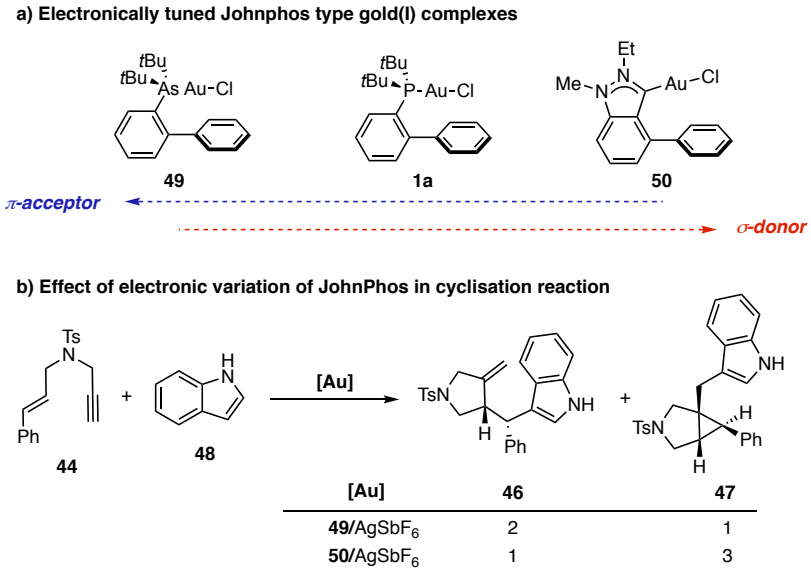
79 Brooner, R. E. M.; Widenhoefer, R. A. *Angew. Chem. Int. Ed.* **2013**, *52*, 11714–11724.

Dialkylbiaryl phosphine ligands provide an interesting architecture adapted to gold(I) linear dicoordination. Therefore, taking advantage on the tunability of this class of ligands, several modifications where explored.

Functionalized Biaryls Ligands

The well-defined spatial arrangement of bulky biaryl phosphines ligands and their tunability makes them a privileged scaffold in gold(I) homogenous catalysis.

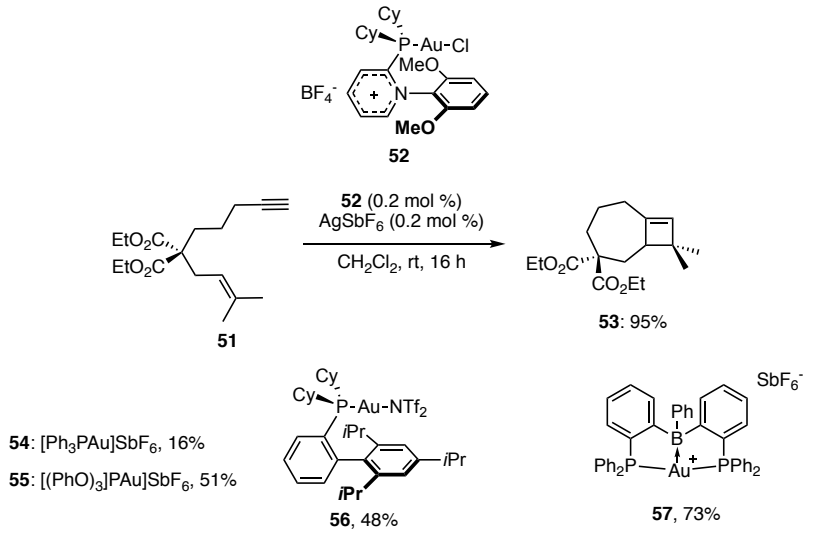
Our group reported the synthesis and catalytic activity of electronically modified JohnPhos-type complexes with the arsine ligand of **49** featuring an enhanced π-acceptor character, while the 4-arylindazole-incorporated biaryl ligand in complex **50** showed enhanced σ-donor properties (Scheme 12). The catalytic performances of gold(I) complexes **49** and **50** were evaluated in the cycloisomerization reaction of enyne **44** in presence of indole as external nucleophile. As expect **49** favored the formation of **46**, while **50** favored the formation of bicyclic compound **47**.[18b]



Scheme 12. Electronically tuned JohnPhos-type gold(I) complexes.

The group of Alcarazo reported a series of gold(I) complexes using strong π-acceptor cationic *N*-arylpyridinophosphine as ligand.[80] The cationic nature of the ligand allows activation of substrates displaying a low reactivity while the bottom ring provide stability to the complex preventing the catalyst decomposition. These ligands were the most efficient catalysts for the [2+2] cyclization of 1,8-enyne **51** yielding bicyclo[5.2.0]non-7-ene **53** in excellent yields (Scheme 13).

80 (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.

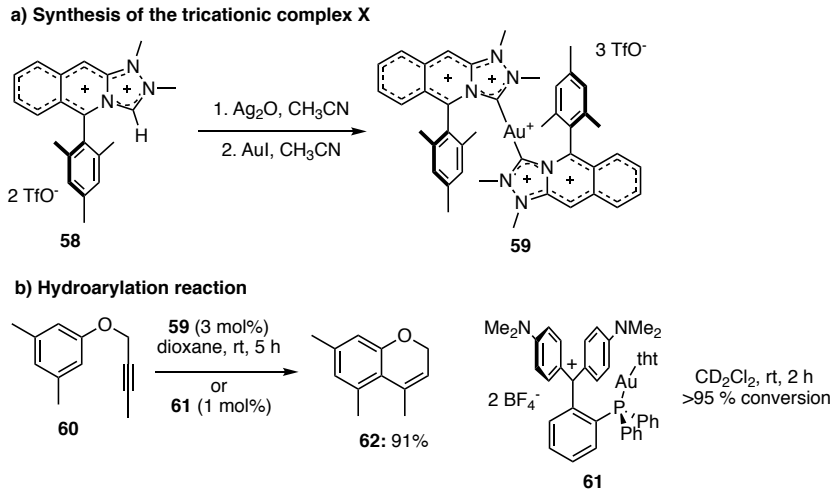


Scheme 13. Cationic *N*-arylpyridinophosphine ligand for gold(I)-catalyzed 1,8-enyne cyclization.

The groups of Lassaletta and Fernández introduced NHC ligands with a biaryl motif with a triazoquinoline core to enhance the π-acidity of the associated metal complex (Scheme 14).[81] The tricationic gold(I) complex **59**, accessed from the dicationic azolium precursor **58**, was reported to be an efficient catalyst for the intramolecular hydroarylation of **60**, while traditional NHC gold(I) complexes like IMesAuCl performed poorly. Recently, Gabbaï reported the cationic complex **62** as a catalyst for the same reaction.[82]

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

82 Litle, E. D.; Wilkins, L. C.; Gabbaï, F. P.. *Chem. Sci.* **2021**. https://doi.org/10.1039/d0sc05777k.

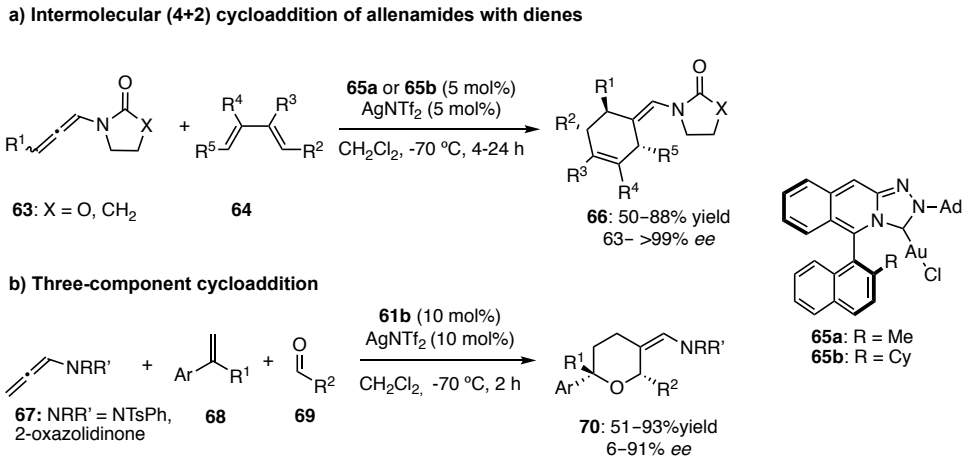


Scheme 14. Cationic ligands for gold(I)-catalyzed hydroarylation of **60**.

Previously, the group of Lassaletta reported axially-chiral NHC ligands containing a similar neutral triazoquinoline motif for asymmetric catalysis.[83] The application of the corresponding gold(I) complexes **65** for the intramolecular [4+2] cycloaddition of allenamides **63** with dienes **64** afforded enantioenriched cyclohexenes **66** (Scheme 15a). Gold(I) complex **65b** provided enantioinduction in the three-component [2+2+2] cycloaddition reaction of allenamides **67**, styrenes **68** and aldehydes **69** yielding chiral pyranes **70** (Scheme 15b). Zhang reported an NHC biaryl ligand with a related structure for enantioselective gold(I)-catalyzed transformation.[84] These reports showcase the potential of biaryl scaffolds to achieve asymmetric gold(I) catalysis.

83 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.

84 Zhang, J. Q.; Liu, Y.; Wang, X. W.; Zhang, L. *Organometallics* **2019**, *38*, 3931–3938.



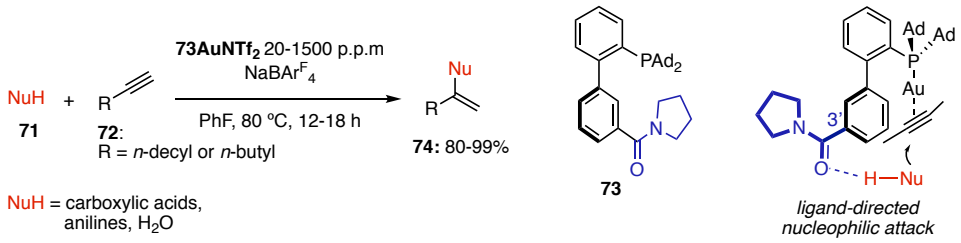
Scheme 15. Axially-chiral triazoquinoline-biaryl-based ligands and their application in gold(I) catalysis.

Ligand-Assisted Gold(I) Catalysis

The group of Liming Zhang pioneered in the development of ligand-assisted gold(I) catalysis for the *anti*-nucleophilic addition of carboxylic acids, aniline or water to alkynes (Scheme 16).[85] This reaction is assisted by a biaryl ligand whose phenyl ring is functionalized in position 3' with a hydrogen bond acceptor such as an amine or amide group. The amphoteric character of the hydrogen bond acceptor group is the key point of this design. The distal group first acts as a base pre-orienting the incoming nucleophile, giving partially intramolecular character to the intermolecular process facilitating the addition. Once protonated, the functional group acts as a general acid favoring rapid intramolecular protodeauration. This leads to an enhancement of the reaction rate and overall efficiency, allowing to use of low catalyst loadings to obtain the final

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

products in excellent yields, outperforming JohnPhos and NHC ligands for this particular transformation.



Scheme 16. Ligand-directed nucleophile addition to alkynes by bifunctionnal biaryl phosphine.

The concept of "soft deprotonation" was successfully extended to other gold(I)-catalyzed intramolecular transformations such as the isomerization of alkynes 7**6**,[86] ynamides, allenamides,[87] propargylic esters[88] and allyl ynoates (Scheme 17).[89] Additionally, the intermolecular hydroalkenylation of propargyl alcohols **79** and alkenyltrifluoroborates **78** give rise to dienols **81**[90] and the propargylation of aldehydes with alkynyl silanes **82** to form **86** were reported.[91] According to theoretical studies, the interaction between the basic site and propargylic alcohol by hydrogen bond increases the nucleophilicity of the oxygen atom.[92]

86 Wang, Z.; Wang, Y.; Zhang, L. *J. Am. Chem. Soc.* **2014**, *136*, 8887–8890.

87 Li, X.; Wang, Z.; Ma, X.; Liu, P. N.; Zhang, L. *Org. Lett.* **2017**, *19*, 5744–5747.

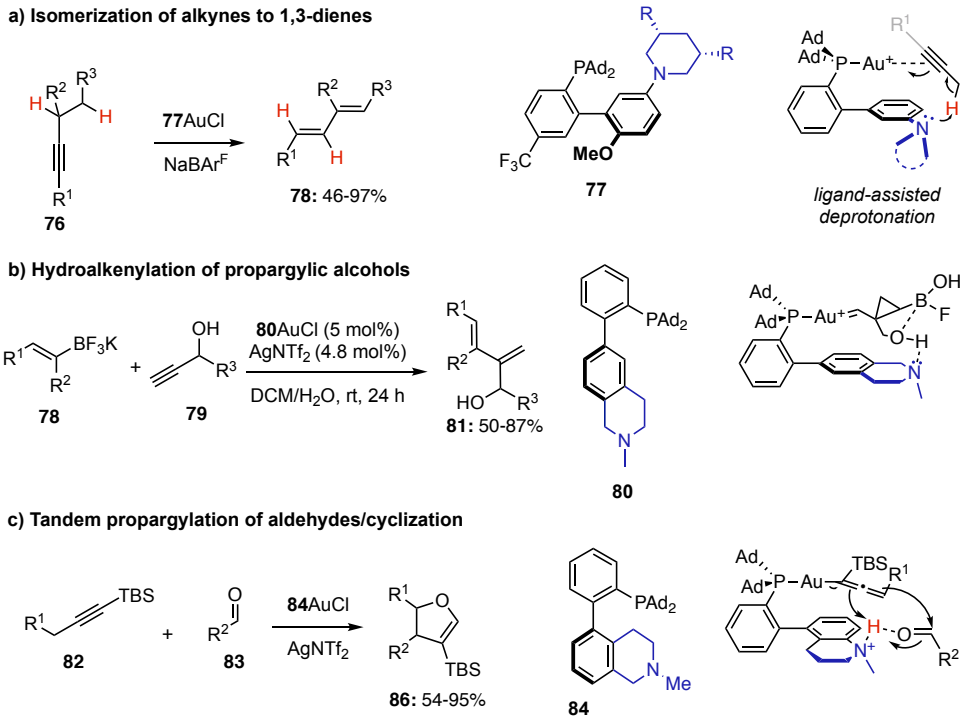
88 Wang, Z.; Ying, A.; Fan, Z.; Hervieu, C.; Zhang, L. *ACS Catal.* **2017**, *7*, 3676–3680.

89 Wang, H.; Li, T.; Zheng, Z.; Zhang, L. *ACS Catal.* **2019**, *9*, 10339–10342.

90 Liao, S.; Porta, A.; Cheng, X.; Ma, X.; Zanoni, G.; Zhang, L. *Angew. Chem. Int. Ed.* **2018**, *57*, 8250–8254.

91 Li, T.; Zhang, L. *J. Am. Chem. Soc.* **2018**, *140*, 17439–17443.

92 Liao, S.; Porta, A.; Cheng, X.; Ma, X.; Zanoni, G.; Zhang, L. *Angew. Chem. Int. Ed.* **2018**, *57*, 8250–8254.



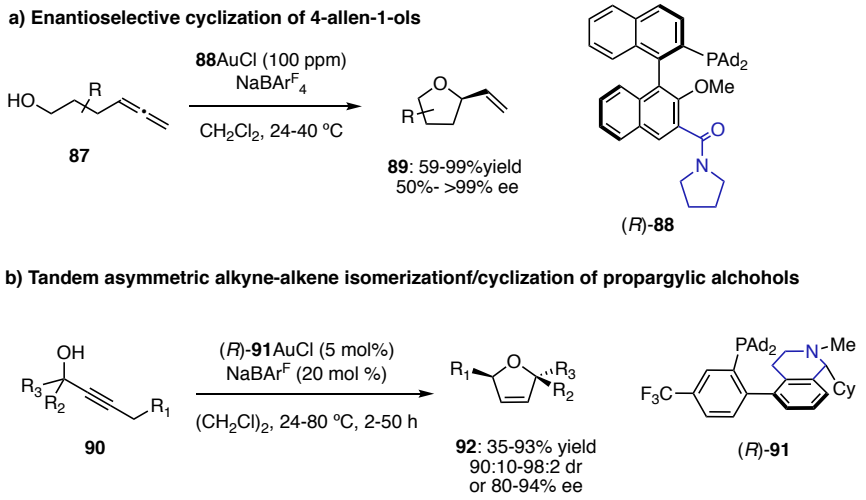
Scheme 17. Bifunctional biaryl phosphine for cooperative gold(I) catalysis.

As the proton shuttle is key for these reactions, the well-defined orientation of the basic site relative to the gold center can induce enantioselectivity in the transformation. Exploiting this aspect, the same group reported the axially chiral binaphtyl phosphine ligand **88** functionalized with a remote amide as basic site (Scheme 18a).[93] The corresponding gold complex leads to high level of enantioselectivity at low catalyst loading in the cyclization of 4-allene-1-ols **87** giving 2-vinyltetrahydrofurans **89** due to the preorientation of the substrate by hydrogen-bonding with the ligand.[94] Using a similar design, the group of Zhang reported a tandem asymmetric alkyne-alkene isomerization/cyclization of

93 Cheng, X.; Wang, Z.; Quintanilla, C. D.; Zhang, L. *J. Am. Chem. Soc.* **2019**, *141*, 3787–3791.

94 Wang, Z.; Nicolini, C.; Hervieu, C.; Wong, Y. F.; Zanoni, G.; Zhang, L. *J. Am. Chem. Soc.* **2017**, *139*, 16064–16067.

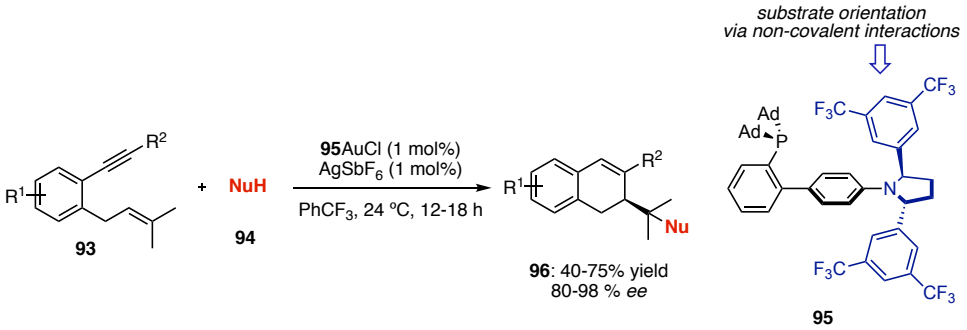
propargylic alcohols **90** affording enantioenriched 2,5-dihydrofurans **92** with good enantioinduction (Scheme 18b).



Scheme 18. Axially-chiral bifunctional biaryl phosphine for cooperative asymmetric gold(I) catalysis.

Recently, our group reported a biaryl monophosphine gold(I) catalyst with a remote C_2-chiral element consisting in a 2,5-disubstituted pyrrolidine, which gives high enandioinduction in the formal [4+2] cycloaddition of 1,6-enyne **93** (Scheme 19).[95] Gold(I) complex of **95** folds the substrate by non-covalent interactions between the substrate and the aryl substituent of the pyrrolidine proximal to the catalytic site.

95 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.



Scheme 19. Chiral JohnPhos-type ligand for asymmetric gold(I) catalysis.

The success of bulky dialkylbiarylphosphine gold(I) complexes in homogenous gold(I) catalysis is mainly due to their robustness and high activity. The tunability of the biaryl scaffold allowed modifications leading to new reactivities in asymmetric gold(I) catalysis. These reports demonstrate that introduction of less conventional aromatic systems can bring new reactivities. However, this design has never been exploited with a ferrocene moiety. Therefore, we decided to investigate the possibility of synthesizing chiral ferrocene-based JohnPhos-type ligands suitable for gold(I) asymmetric catalysis.

Chapter I

Design and Synthesis of Planar Chiral Mononuclear Gold(I) Complexes

Introduction

Synthesis and Application of 1,2-Disubstituted Ferrocenes

Ferrocene was discovered in the early 1950's independently by Pauson and Miller.[96] Since, it has been a subject of interest in all fields of chemistry because of its unique structure and properties and has found a vast number of applications with a notable contribution in ligand design.[97] The first and most representative ferrocene-derived ligand is the achiral 1,1'-bis(diphenylphosphino)ferrocene (dppf) introduced in 1965,[98] but the main contribution of ferrocene is in the field of asymmetric catalysis. Ferrocene has characteristics appealing for its use as ligand scaffold such as rigidity, bulkiness, stability, availability and the possibility to create planar chirality. The planar chirality of ferrocene derivatives was demonstrated in 1959 by Thomson.[99] The functionalization of one cyclopentadiene ring by at least two distinct groups breaks the symmetry of the plane thus generating chirality (Figure 1.1). Although some chiral ferrocene ligands are not planar chiral, most of the designs involve the planar chirality of the scaffold.

96 (a) Kealy T. J.; Pauson P. L. *Nature*, **1951**, *168*, 1039–1040. (b) Miller S. A.; Tebboth J. F.; Tremaine, K. F. *J. Chem. Soc*. **1952**, 632–635.

97 (a) Cunningham, L.; Benson, A.; Guiry, P. J. *Org. Biomol. Chem.* **2020**, *18*, 9329–9370. (b) Toma, Š.; Csizmadiová, J.; Mečiarová, M.; Šebesta, R. *Dalt. Trans.* **2014**, *43*, 16557–16579. (c) Gómez Arrayás, R.; Adrio, J.; Carretero, J. C. *Angew. Chem. Int. Ed.* **2006**, *45*, 7674–7715.

98 Sollot G. P.; Snead J. L.; Portnoy S.; Peterson Jr. W. R.; Mertow H. E. *Chem. Abstr.* **1965**, *63*, 18147b

99 Thomson J. B.; *Tetrahedron Lett.* **1959**, *1*, 26–27.

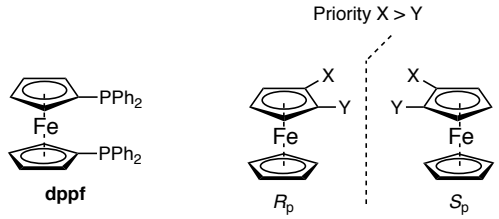


Figure 1.1. Structure of dppf and ferrocene chirality.

In 1970 Ugi disclosed in pioneering works the synthesis of chiral *N,N*-dimethyl-(*S*)-ferrocenylethylamine[100] **(*S*)-1.4** and its enantiomer **(*R*)-1.4** (Scheme 1.1a) and their ability to undergo diastereoselective lithiation. Since then, other chiral ferrocenes were used for diastereoselective metalation such as the chiral ferrocenyl sulfoxide[101] **1.11** and acetal[102] **1.7** (Scheme 1.1b-c) reported by Kagan and the chiral ferrocenyl oxazolines **1.12** (Scheme 1.1d) disclosed almost simultaneously by Sammakia[103], Uemura[104] and Richards.[105] These reports were the cornerstone for the development of planar chiral ferrocene-based ligands.

100 Marquarding D.; Klusacek H.; Gokel G.; P. Hoffmann, Ugi I. *J. Am. Chem. Soc.* **1970**, *92*, 5389–5393.

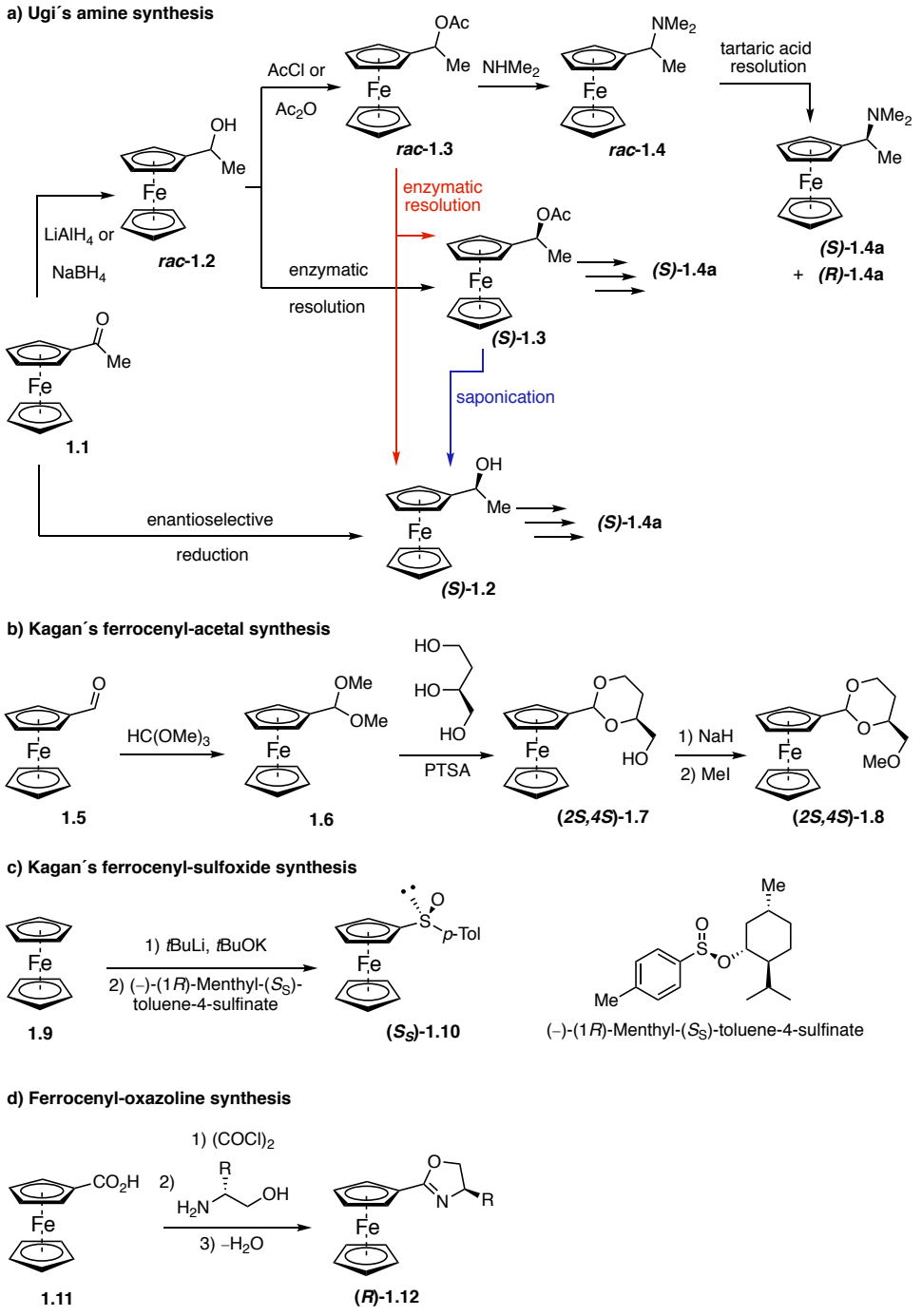
101 (a) Guillaneux D.; Kagan H. B. *J. Org. Chem.* **1995**, *60*, 2502–2505. (b) Rebière, F.; Riant, O.; Ricard, L.; Kagan, H. B. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 568–570. (c) Rebière F.; Samuel O.; Kagan H. B. *Tetrahedron Lett.* **1990**, *31*, 3121-3124.

102 (a) Riant, O.; Samuel, O.; Kagan, H. B. *J. Am. Chem. Soc.* **1993**, *115*, 5835–5836. (b) Riant O.; Samuel O.; Flessner T.; Taudien S.; Kagan H. B. *J. Org. Chem.* **1997**, *62*, 6733–6745.

103 Sammakia T.; Latham H. A.; Schaad D. R. *J. Org. Chem.* **1995**, *60*, 10–11.

104 Nishibayashi Y.; Uemura; *Synlett*, **1995**, 78–81

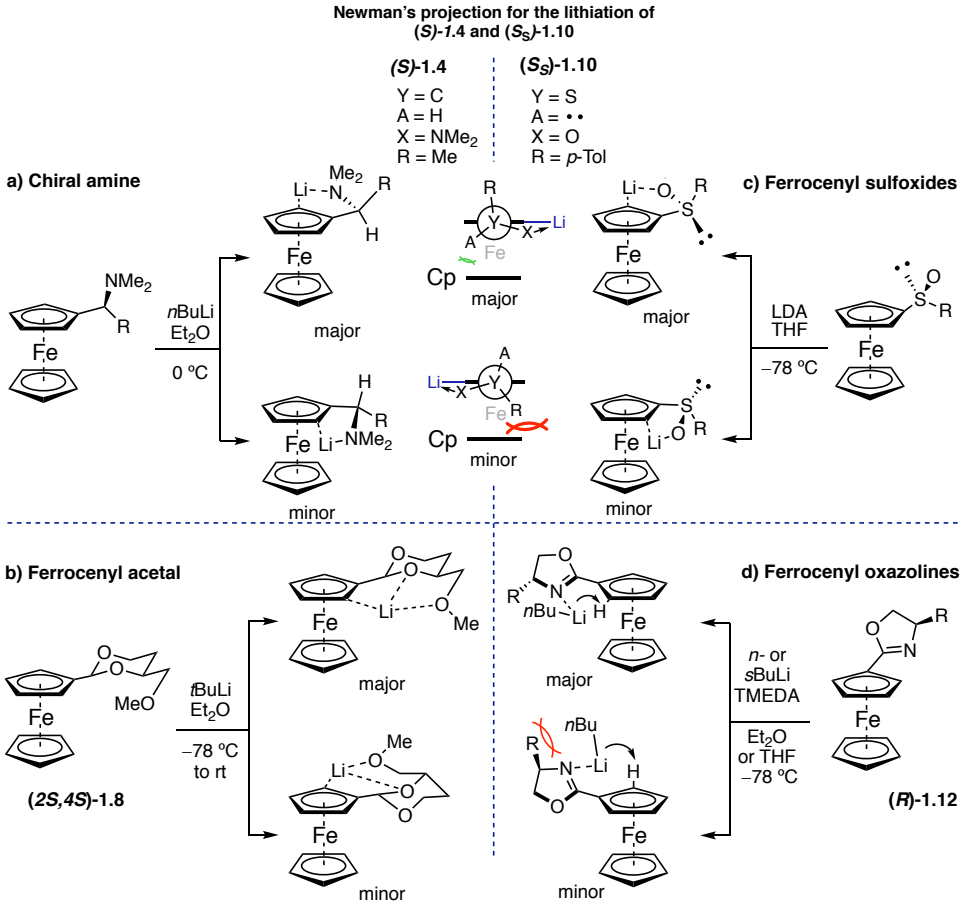
105 Richards C. J.; Damalidis T., Hibbs D. E.; Hurtshouse M. B. *Synlett.* **1995**, *1*, 74–76.



Scheme 1.1. Synthesis of chiral ferrocenes for diastereoselective metalation.

To this day, the majority of reports on planar chiral ligands are based on 1,2-disubstituted ferrocenes. Those scaffolds are mainly prepared by diastereoselective metalation of a ferrocene functionalized by a chiral *ortho*-metalation directing group and further derivatization. The *ortho*-lithiation of ferrocenes functionalized with a chiral directing group occurs diastereoselectively due to steric interactions. In the case of chiral amines **1.4**,[100] sulfoxides **1.11**[101] and acetal **1.8**[102] directing group (Scheme 1.2a-c), the favored diastereomer is formed in order to minimize steric repulsion between the bottom cyclopentadienyl ring and the substituent R of the directing group, thus substituent R will point above the plane of the top cyclopentadienyl ring. In the case of lithiation of ferrocenyl oxazoline **1.12**, the favored diastereomer is formed to minimize the steric repulsion between the R side chain of the oxazoline and the incoming alkyl-lithium (Scheme1.2d).[103,106]

106 Sammakia, T.; Latham, H. A. *J. Org. Chem.* **1995**, *60*, 6002–6003.



Scheme 1.2. Diastereoselective directed lithiation of chiral ferrocenes.

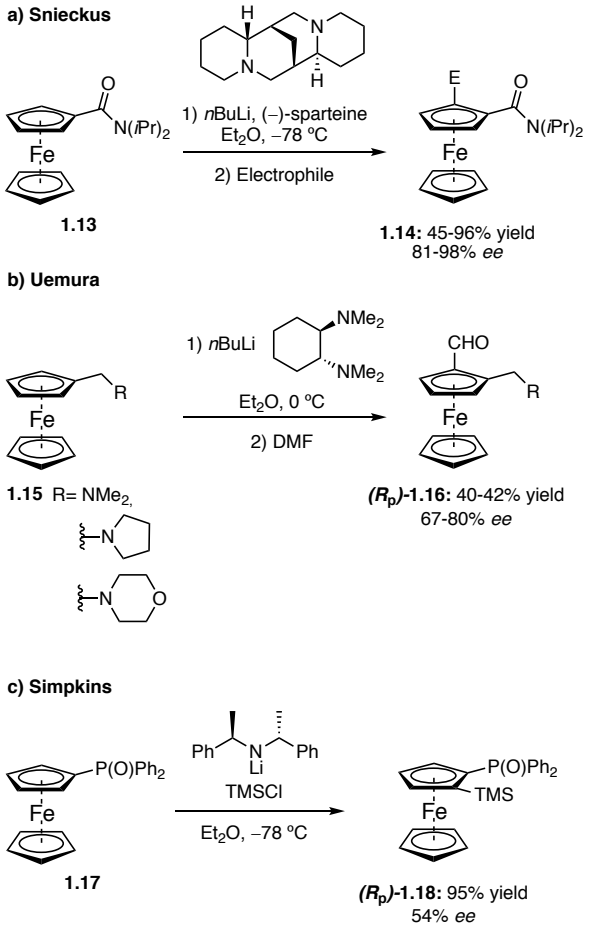
In a similar manner, Snieckus reported the use of (−)-sparteine as chiral ligand in combination with alkyl-lithium for the enantioselective lithiation of ferrocene functionalized with an achiral directing group (Scheme 1.3a).[107] Simpkins[108] and Uemura[109] reported similar examples using respectively chiral

107 (a) Tsukazaki, M.; Tinkl, M.; Roglans, A.; Chapell, B. J.; Taylor, N. J.; Snieckus, V. *J. Am. Chem. Soc.* **1996**, *118*, 685–686. (b) Metallinos, C.; Snieckus, V. *Org. Lett.* **2002**, *4*, 1935–1938.

108 Price, D.; Simpkins, N. S. *Tetrahedron Lett.* **1995**, *36*, 6135–6136.

109 Nishibayashi, Y.; Arikawa, Y.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1996**, *61*, 1172–1174.

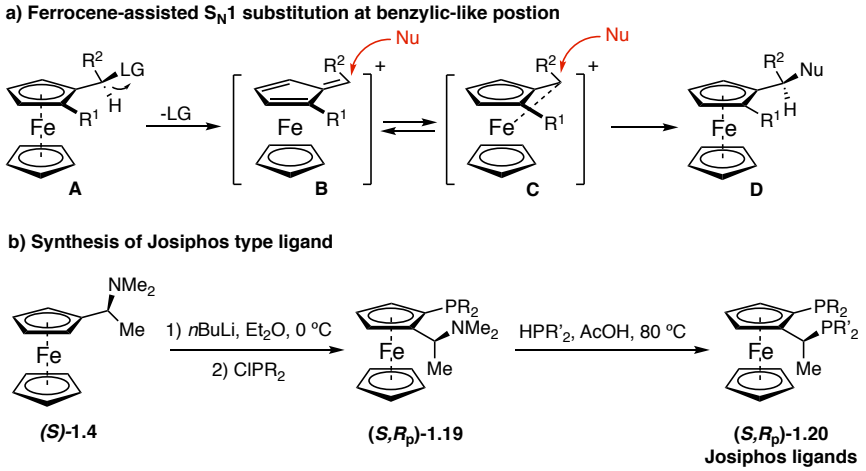
amine ligand and amide base, but achieved lower enantioselectivity (Scheme 1.3b-c).



Scheme 1.3. Enantioselective directed lithiation of ferrocenes.

An additional interesting property of the ferrocene scaffold is its ability to stabilize carbocations at the benzylic-like position by interaction with the iron atom. In this manner, stereospecific nucleophilic substitution reactions take place at the benzylic-like position with retention of configuration through a S_N1

mechanism (Scheme 1.4a).[110] In 1994, the group of Togni, in a seminal report, synthesized the bisphosphine ligands Josiphos by stereospecific S_N1 reaction of the dimethylamino group of Ugi´s amine-derived ligands **1.19** with secondary phosphines (Scheme 1.4b).[111] Numerous ligands have been prepared by substitution of the dimethylamino moiety of Ugi's amine with different nucleophiles such as phosphines, amines or pyrazole. This stabilization of benzylic carbocations has also been used more recently for the enantioselective synthesis of Ugi´s amine and analogues thus avoiding the need of resolution of the racemate by co-crystallization with optically pure tartaric acid.[112]



Scheme 1.4. Synthesis of Josiphos-type ligands.

110 Schuecker, R.; Weissensteiner, W.; Mereiter, K.; Lotz, M.; Spindler, F. *Organometallics* **2010**, *29*, 6443–6458.

111 Togni, A.; Breutel, C.; Schnyder, A.; Spindler, F.; Landert, H.; Tijani, A. *J. Am. Chem. Soc.* **1994**, *116,* 4062–4066.

112 (a) Boaz, N. W. *Tetrahedron Lett.* **1989**, *30*, 2061–2064. (b) Izumi, T.; Aratani, S. *J. Chem. Tech. Biotechnol.* **1995**, *63*, 25–32. (c) Kloetzing, R. J.; Lotz, M.; Knochel, P. *Tetrahedron Asymmetry* **2003**, *14*, 255–264. (d) Wright, J.; Frambes, L.; Reeves, P. **1994**, *476*, 215–217.

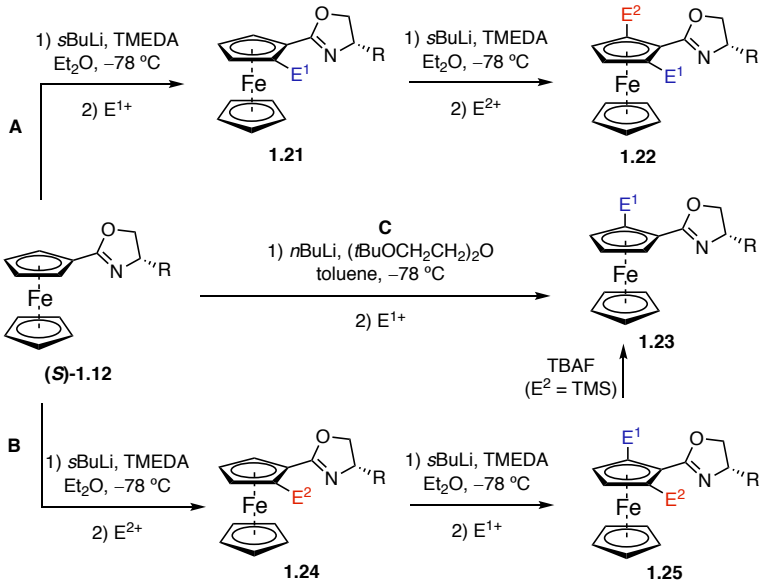
A wide variety of chiral ferrocene-based ligands has been synthesized by *ortho*-metalation of chiral ferrocenes. Ferrocene-based ligands often display an element of chirality in addition to the planar chirality. However, the contribution of each element of chirality to the enantioselectivity of the reaction often remains unclear. In in some cases, the planar chirality of ferrocene is crucial to achieve high level of enantioselectivity, while it has a negligible impact in other reactions.[113] Interestingly, the use of a chiral *ortho*-metalation directing group often allows the synthesis of the different diastereomer of a ligand by various strategies. Thus, diastereomers of ferrocene **1.22** (Scheme 1.5A) can be synthesized by protection of the favored metalated position,[105,114] inversion of the order of functionalization (Scheme 1.5B)[115] or by the use of an achiral ligand for the lithiation[116] (Scheme 1.5C).

113 (a) Dai L. X.; Tu T.; You S. L.; Deng W. P.; Hou X. L. *Acc. Chem. Res.* **2003**, *36*, 659–667. (b) Deng W. P.; You S. L.; Hou X. L.; L. X. Dai, Y. H. Yu, W. Xia, J. Sun, *J. Am. Chem. Soc.* **2001**, *123*, 6508–6519.

114 Arthurs, R. A.; Richards, C. J. *Org. Lett.* **2017**, *19*, 702–705.

115 Almássy, A.; Rakovský, E.; Malastová, A.; Sorádová, Z.; Šebesta, R. *J. Organomet. Chem.* **2016**, *805*, 130–138.

116 Herbert S. A.; Castell D. C.; Clayden J.; Arnott G. E. *Org. Lett*. **2013**, *15*, 3334-337



Scheme 1.5. Strategy of synthesis of different diastereoemeric chiral ferrocenes.

Overview of Bidentate Ferrocene-Based Chiral Ligands

Ferrocene is an attractive scaffold and from its high tunability results the diversity of ferrocene-based ligands synthesized including notable examples such as the *P,N*-ligand Fc-Phox,[117] and *P,P*-ligands Taniaphos and Josiphos (Figure 1.2), the latter being applied industrially in the synthesis sitagliptin[118] and metolachlor.[119] Despite recent reports,[120] the development of ferrocene based-organocatalysts has been rather slow and ligand synthesis remains the major application of chiral ferrocenes.

117 Sutcliffe O. B.; Bryce M. R. *Tetrahedron Asymmetry* **2003**, *14*, 2297–2325.

118 Hansen K. B.; Hsiao Y.; Xu F.; Rivera N.; Clausen A.; Kubryk M.; Krska S.; Rosner T.; Simmons B.; Balsells J. *J. Am. Chem. Soc.* **2009**, *131*, 8798–8804.

119 Blaser H. U.; Brieden W.; Pugin B.; Spindler F.; Studer M.; Togni A. *Top. Catal.* **2002**, *19*, 3–16.

120 Zhu, J. C.; Cui, D. X.; Li, Y. D.; Jiang, R.; Chen, W. P.; Wang, P. A. *ChemCatChem* **2018**, *10*, 907–919.

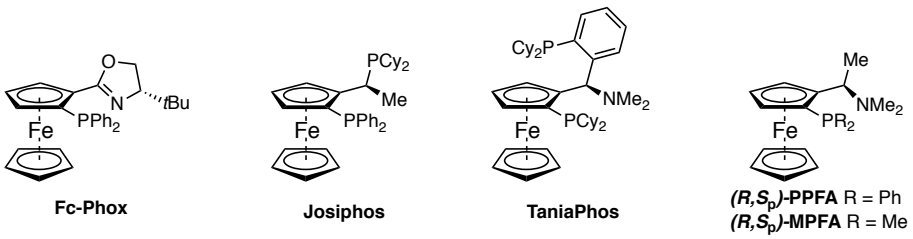


Figure 1.2. Examples of ferrocenes-based ligands.

Because of the general applicability of the *ortho*-metalation strategy, the degree of denticity and the nature of the binding fragments of chiral ferrocene-based ligands is easily tuned. Additionally, the scaffold offers the possibility to functionalize only one or both cyclopentadienyl rings. However, because of the methodology applied, the majority the ligands are based on a 1,2-disubstituted ferrocene scaffold, where only one cyclopentadienyl ring is functionalized with the two substituents on contiguous positions. In the case of Ugi´s amine-derived ligands, the amine serving as metalation directing group is easily modified or can be used as binding point. Hence, this design allows combining different coordination properties of binding centers.

Ferrocene-based ligands are mostly represented by bidentate ligands divided in three main categories, *P,N*-, *P,P*- and *P,S*-ligands, involving the excellent coordination properties of phosphorus with that of other donor atoms. As many catalytically active transition metal complexes adopt a square planar geometry, the strong *trans*-effect of the phosphorus produces an additional asymmetry.

Following the introduction of Ugi's amine, *P,N*-ligands were the first developed with the introduction of α-(2-dimethylphosphinoferrocenyl) ethyldimethylamine (MPFA) and α-(2-diphenylphosphinoferrocenyl) ethyldimethylamine (PPFA) (Figure 1.2) by Hayashi in 1974[121] for the

121 Hayashi T.; Yamamoto K.; Kumada M. *Tetrahedron Lett.* **1974**, *15*, 4405–4408.

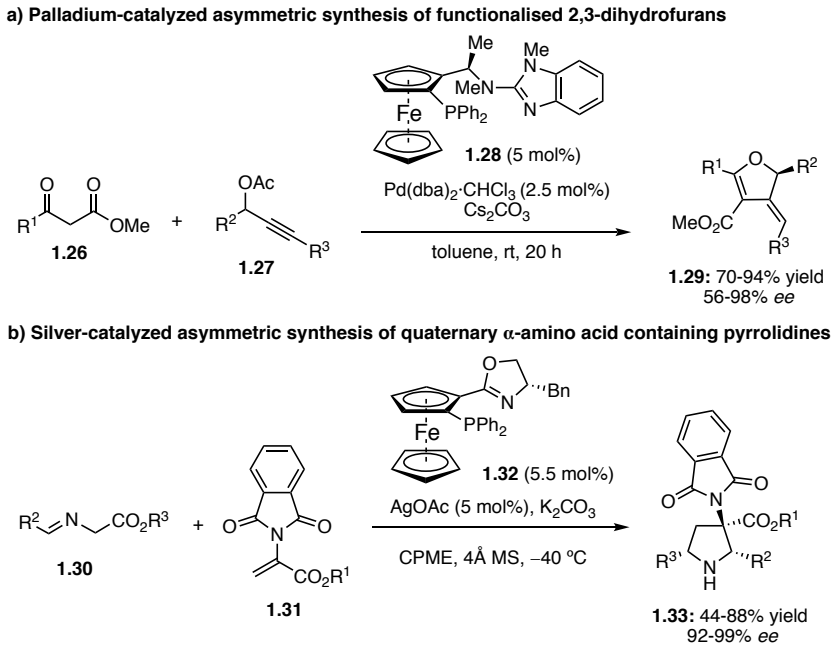
enantioselective rhodium-catalyzed hydrosilylation of ketones. This design has been intensively investigated and further developed with the introduction of ferrocenyl oxazoline.[117,122] The syntheses of these ligands are easily achieved by *ortho*-lithiation of chiral ferrocenyl amines or ferrocenyl oxazoline followed by reaction with a chlorophosphine. Additionally, the amine moiety can be substituted giving access to wide variety of modifications. Since its introduction, this design has been expended and several synthetic routes have been developed to access more complex structures.[123] Therefore, electronic and steric properties of both the phosphine and the amine can be tuned. This class of ligands has been successfully applied in combination with different metals for a wide variety of reactions[97] such as the enantioselective palladium-catalyzed formal (3+2) cycloaddition of propargylic acetate **1.27** with β-ketoesters **1.26** reported by Hu[124] (Scheme 1.6a) or the enantioselective silver-catalyzed 1,3-dipolar cycloaddition of azomethine ylides **1.30** to α-aminoacrylates **1.31** disclosed by Deng[125] (Scheme 1.6b).

122 Selected examples: (a) McCartney, D.; Nottingham, C.; Müller-Bunz, H.; Guiry, P. J. *J. Org. Chem.* **2015**, *80*, 10151–10162. (b) Dai, L.; Xu, D.; Dong, X.; Zhou, Z. *Tetrahedron Asymmetry* **2015**, *26*, 350–360. (c) Onodera, G.; Nishibayashi, Y.; Uemura, S. *Angew. Chem. Int. Ed.* **2006**, *45*, 3819–3822.

123 Noël, T.; Van Der Eycken, J. *Green Process. Synth.* **2013**, *2*, 297–309.

124 Zhou, Y.; Zhu, F. L.; Liu, Z. T.; Zhou, X. M.; Hu, X. P. *Org. Lett.* **2016**, *18*, 2734–2737.

125 Wang, Z.; Luo, S.; Zhang, S.; Yang, W. L.; Liu, Y. Z.; Li, H.; Luo, X.; Deng, W. P. *Chem. Eur. J.* **2013**, *19*, 6739–6745.

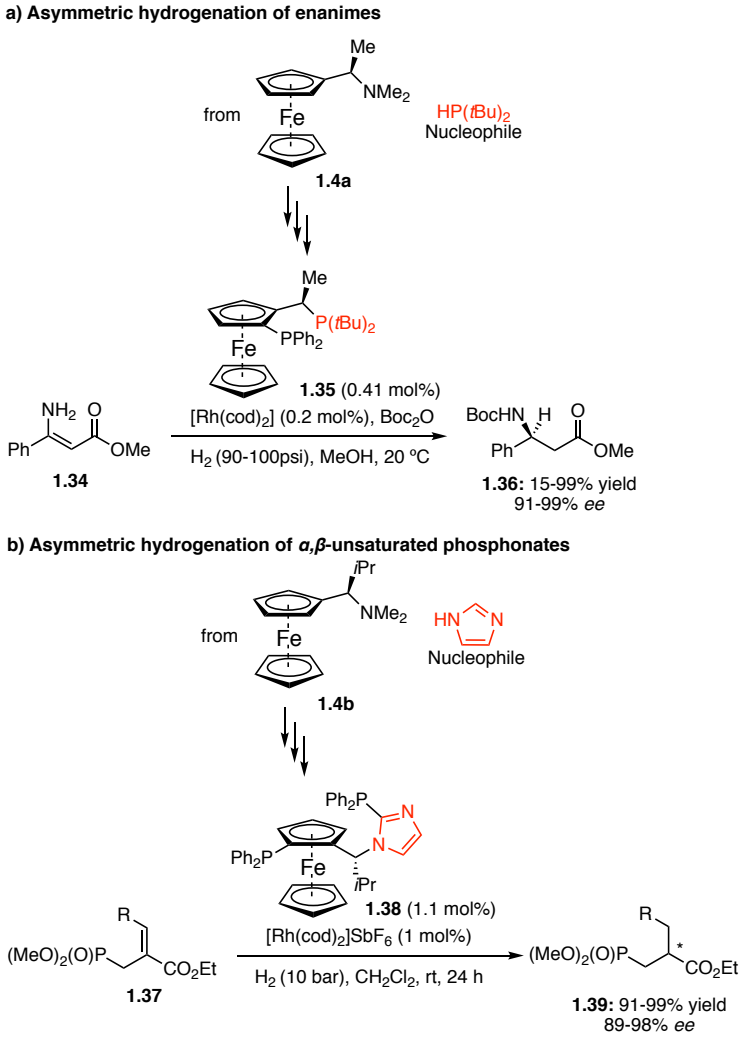


Scheme 1.6. Ferrocene-based *P,N*-ligands and applications in asymmetric catalysis.

Among planar chiral ferrocene-based bidentate ligands, *P,P*-ligands such as Taniaphos and Josiphos ligands are likely the most ubiquitous and have been proven efficient for enantioselective hydrogenations and other reactions (Scheme 1.7). The privileged synthetic route for this scaffold is by *ortho*-metalation of a chiral ferrocene and reaction with a chlorophosphine. The second phosphine can be introduced by direct displacement of the *ortho*-metalation directing group with a free phosphine (Scheme 1.7a). An example is the Josiphos-type ligand **1.35** employed by Hansen and Rosner[126] for the rhodium-catalyzed asymmetric hydrogenation of enamines **1.34** (Scheme 1.7a). The second phosphine can also be supported by the nucleophilic moiety that displaced the *ortho*-metalation directing

126 Hansen, K. B.; Rosner, T.; Kubryk, M.; Dormer, P. G.; Armstrong, J. D. *Org. Lett.* **2005**, *7*, 4935–4938.

group such as the ligand **1.38** reported Zheng[127] for the enantioselective hydrogenation of β-substituted α,β-unsaturated phosphonate **1.37** (Scheme 1.7b).



Scheme 1.7. Ferrocene-based *P,P*-ligands and application to asymmetric hydrogenation.

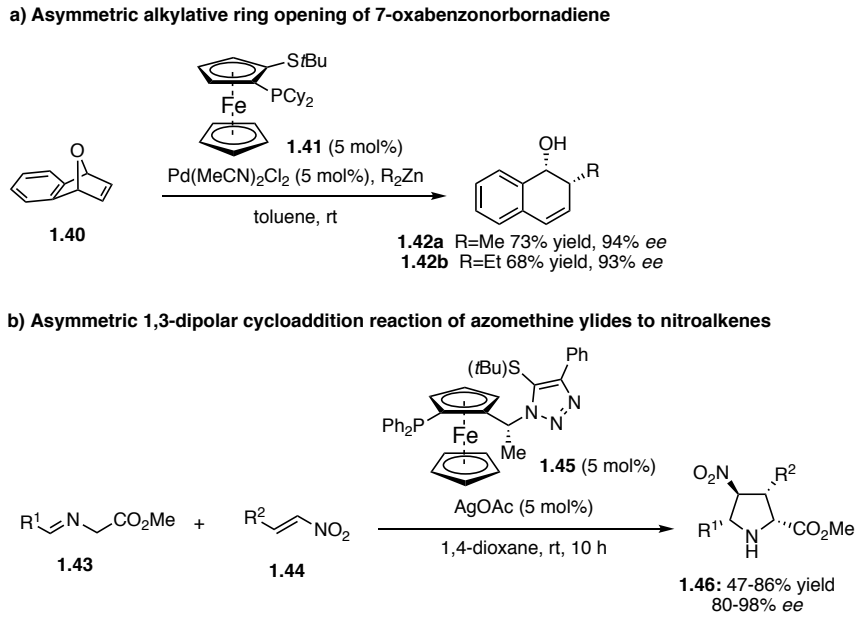
127 Wang, D. Y.; Hu, X. P.; Hou, C. J.; Deng, J.; Yu, S. B.; Duan, Z. C.; Huang, J. Di; Zheng, Z. *Org. Lett.* **2009**, *11*, 3226–3229.

More recent reports demonstrate the potential of planar chiral ferrocene *P,S*-ligands in asymmetric catalysis.[128] This type of ligand displays a high tunability and is readily accessible from a wide variety of chiral ferrocenes. In 2002 the group of Carretero reported the synthesis of the ligand **1.41**[129] and its application to palladium-catalyzed asymmetric ring opening of oxabenzonorbornadiene **1.40** with dialkyl-zinc reagents (Scheme 1.8a). Fukuzawa disclosed in 2016 the ligand **1.45** employed in the asymmetric silver(I)-catalyzed 1,3-dipolar cycloaddition of azomethine ylides **1.43** and nitroalkenes **1.44** (Scheme 1.8b).[130]

128 (a) Albinati, A.; Pregosin, P. S.; Wick, K. *Organometallics* **1996**, *15*, 1994–1996. (b) Spencer, J.; Gramlich, V.; Häusel, R.; Togni, A. *Tetrahedron Asymmetry* **1996**, *7* ,41–44. (c) Evans, D. A.; Campos, K. R.; Tedrow, J. S.; Michael, F. E.; Gagné, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 7905–7920. (d) Enders, D.; Peters, R.; Lochtman, R.; Raabe, G.; Runsink, J.; Bats, J. W. *Eur. J. Org. Chem.* **2000**, *20*, 3399–3426.

129 Priego, J.; García Mancheño, O.; Cabrera, S.; Gómez Arrayás, R.; Llamas, T.; Carretero, J. C. *Chem. Commun.* **2002**, *21*, 2512–2513.

130 Kimura, M.; Matsuda, Y.; Koizumi, A.; Tokumitsu, C.; Tokoro, Y.; Fukuzawa, S. I. *Tetrahedron* **2016**, *72*, 2666–2670.



Scheme 1.8. Ferrocene-based *P,S*-ligands and application to asymmetric catalysis.

In addition to these common bidentate ferrocene-derived ligands, other designs have been reported such as *P,C*-ligands,[131] *P,O*-ligands,[132] *N,O*-ligands,[133] *P*-chirogenic ligands[134] or 1,1'-ferrocene-based ligands.[135]

131 (a) Csizmadiová, J.; Mečiarová, M.; Almássy, A.; Horváth, B.; Šebesta, R. *Organomet. Chem.* **2013**, *737*, 47–52. (b) Csizmadiová, J.; Mečiarová, M.; Rakovský, E.; Horváth, B.; Šebesta, R. *Eur. J. Org. Chem.* **2011**, *30*, 6110–6116

132 (a) Bayda, S.; Cassen, A.; Daran, J. C.; Audin, C.; Poli, R.; Manoury, E.; Deydier, E. *J. Organomet. Chem.* **2014**, *772*, 258–264. (b) Mateus, N.; Routaboul, L.; Daran, J. C.; Manoury, E. *J. Organomet. Chem.* **2006**, *691*, 2297–2310.

133 (a) Nottingham, C.; Benson, R.; Müller-Bunz, H.; Guiry, P. J. *J. Org. Chem.* **2015**, *80*, 10163–10176. (b) Zhao, W. X.; Liu, G. J.; Wang, J.; Li, F.; Liu, L. *Tetrahedron Asymmetry* **2016**, *27*, 1139–1144.

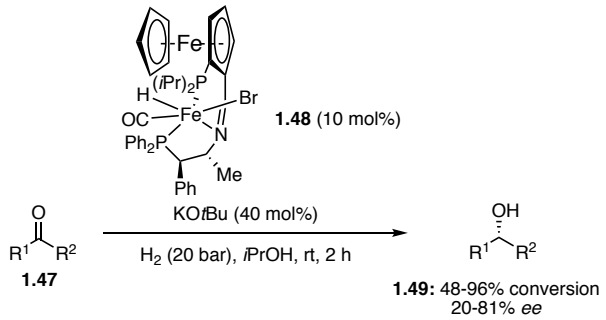
134 Chen W.; Mbafor W.; Roberts S. M.; Whittall J. *J. Am. Chem. Soc.* **2006**, *128*, 3922–3923.

135 Selected examples: (a) Zhang W.; Yoneda Y. I.; Kida T.; Nakatsuji Y.; Ikeda I.; *Tetrahedron Asymmetry*, **1998**, *9*, 3371–3380. (b) Schwink, L.; Knochel, P. *Chem. Eur. J.* **1998**, *4*, 950–968. (c) Kang, J.; Lee, J. H.; Im, K. S. *J. Mol. Catal. A Chem.*

Additional Ferrocene-Based Chiral Ligands

Along the well-established bidentate ferrocene-based ligands, other denticity are encountered but in a limited number.

Morris[136] reported a planar chiral tridentate ferrocene-based ligand providing moderate level of enantioselectivity in the iron-catalyzed asymmetric hydrogenation of ketones **1.47** using complex **1.48** (Scheme 1.9).



Scheme 1.9. Ferrocene-based *P,P,N*-ligand and its application to asymmetric iron-catalyzed hydrogenation of ketones.

Only few monodentate ferrocene-based ligands have been reported. Non-planar chiral ferrocene phosphinite ligands have been used as ligand in Ir- and Ru-catalyzed transfer hydrogenation.[137] The number of reports describing the synthesis

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2003, *196*, 55–63. (d) Tsarev, V. N.; Konkin, S. I.; Shyryaev, A. A.; Davankov, V. A.; Gavrilov, K. N. *Tetrahedron Asymmetry* **2005**, *16*, 1737–1741.

136 Zirakzadeh, A.; Kirchner, K.; Roller, A.; Stöger, B.; Widhalm, M.; Morris, R. H. *Organometallics* **2016**, *35*, 3781–3787.

137 (a) Ak, B.; Aydemir, M.; Ocak, Y. S.; Durap, F.; Kayan, C.; Baysal, A.; Temel, H. *Inorganica Chim. Acta* **2014**, *409* (PART B), 244–253. (b) Ak, B.; Aydemir, M.; Durap, F.; Meriç, N.; Baysal, A. *Inorganica Chim. Acta* **2015**, *438*, 42–51. (c) Ak, B.; Aydemir, M.; Durap, F.; Meriç, N.; Elma, D.; Baysal, A. *Tetrahedron Asymmetry* **2015**, *26*, 1307–1313. (d) Ak, B.; Durap, F.; Aydemir, M.; Baysal, A. *Appl. Organomet. Chem.* **2015**, *29*, 764–770. (e) Durap, F.; Karakaş, D. E.; Ak, B.; Baysal, A.; Aydemir, M. *J. Organomet. Chem.* **2016**, *818*, 92–97. (f) Meriç, N.; Aydemir, M. *Organomet. Chem.* **2016**, *819*, 120–128. (g) Abdlhmed Al-bayati, Y.

of planar chiral NHC type ligands and their application in asymmetric catalysis[138] has recently increased. However, reports on chiral monodentate phosphine ferrocene ligands remain scarce.[139]

Synthesis and Applications of 1,3-Disubstituted Ferrocenes

The synthesis of 1,2-disubstituted ferrocenes from monosubstituted ferrocenes has been intensively studied resulting in well-established synthetic methods to access these scaffolds. In sharp contrast, reports concerning the synthesis of 1,3-disubstituted, or 1,2,3-trisubstituted ferrocenes are less common even if these compounds appear promising for different applications.[140]

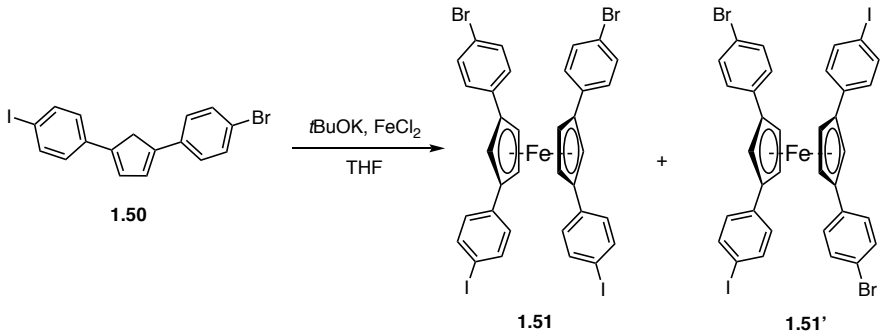
W.; Karakaş, D. E.; Meriç, N.; Aydemir, M.; Durap, F.; Baysal, A. *Appl. Organomet. Chem.* **2018**, *32*, 1–10.

138 (a) Fitzpatrick, K. P.; Schwamb, C. B.; Check, C. T.; Jang, K. P.; Barsoum, D. N.; Scheidt, K. A. *Organometallics* **2020**, *39*, 2705-2712. (b) John, J.; Wilson-Konderka, C.; Metallinos, C. *Adv. Synth. Catal.* **2015**, *357*, 2071–2081. (c) Check, C. T.; Jang, K. P.; Schwamb, C. B.; Wong, A. S.; Wang, M. H.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2015**, *54*, 4264–4268. (d) Yasue, R.; Yoshida, K. *Organometallics* **2019**, *38*, 2211–2217.

139 (a) Hayashi, T.; Hayashizaki, K.; Kiyoi, T.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 8153–8156. (b) Murakami, M.; Minamida, R.; Itami, K.; Sawamura, M.; Ito, Y. *Chem. Commun.* **2000**, *23*, 2293–2294. (c) Pedersen, H. L.; Johannsen, M. *J. Org. Chem.* **2002**, *67*, 7982–7994. (d) Thimmaiah, M.; Luck, R. L.; Fang, S. *J. Organomet. Chem.* **2007**, *692*, 1956–1962. (e) Ogasawara, M.; Arae, S.; Watanabe, S.; Nakajima, K.; Takahashi, T. *ACS Catal.* **2016**, *6*, 1308–1315.

140 (a) Farrington, E. J.; Viviente, M.; Williams, B. S.; Koten, V.; Brown, M. *Chem. Commun.* **2002**, 308–309. (b) Deschenaux, R.; Marendaz, J. L. *J. Chem. Soc. Chem. Commun.* **1991**, 14, 909–910. (c) Muraoka, T.; Kinbara, K.; Wakamiya, A.; Yamaguchi, S.; Aida, T. *Chem. Eur. J.* **2007**, *13*, 1724–1730. (d) Lim, J. Y. C.; Beer, P. D. *Eur. J. Inorg. Chem.* **2017**, 220–224. (d) Kai, H.; Nara, S.; Kinbara, K.; Aida, T. *J. Am. Chem. Soc.* **2008**, *130*, 6725–6727. (e) Muraoka, T.; Kinbara, K.; Aida, T. *Nature* **2006**, *440*, 512–515. (f) Fukino, T.; Fujita, N.; Aida, T. *Org. Lett.* **2010**, *12*, 3074–3077. (g) Westwood, J.; Coles, S. J.; Collinson, S. R.; Gasser, G.; Green, S. J.; Hursthouse, M. B.; Light, M. E.; Tucker, J. H. R. *Organometallics* **2004**, *23*, 946–951. (h) Kuklin, S. A.; Sheloumov, A. M.; Dolgushin, F. M.; Ezernitskaya, M. G.; Peregudov, A. S.; Petrovskii, P. V.; Koridze, A. A. *Organometallics* **2006**, *25*, 5466–5476. (i) Koridze, A. A.; Kuklin, S. A.; Sheloumov, A. M.; Dolgushin, F. M.; Lagunova, V. Y.; Petukhova, I. I.;

Most of the reported 1,3-disubstituted ferrocenes are achiral or synthesized as racemates and reports on the preparations of these scaffolds in an enantioselective manner are scarce.[141] The synthesis of 1,1',3,3'-substituted ferrocenes can be achieved from 1,3-disubstituted cyclopentadienes (Scheme 1.10).



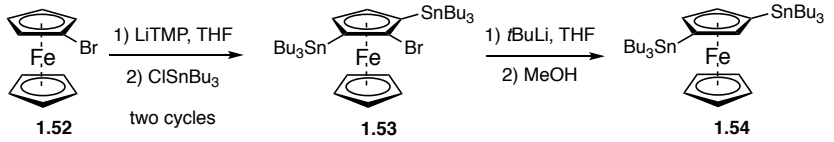
Scheme 1.10. 1,3-Disubstitued ferrocene synthesis from 1,3-disubstitued cyclopentadienes.

Few examples of 1,3-disubstituted ferrocenes have been mainly prepared by *ortho*-metalation of a monosubstituted ferrocene. Two different synthetic approaches have been used. In one case the starting material is a monosubstituted ferrocene bearing a labile metalation directing group. The directing group is able to direct the metalation on both *ortho*-positions. 1,3-Disubstitued ferrocenes are

Ezernitskaya, M. G.; Peregudov, A. S.; Petrovskii, P. V.; Vorontsov, E. V.; Baya, M.; Poli, R. *Organometallics* **2004**, *23*, 4585–4593. (j) Mamane, V.; Peluso, P.; Aubert, E.; Weiss, R.; Wenger, E.; Cossu, S.; Pale, P. *Organometallics* **2020**, *39*, 3936–3950. (k) Camarasa-Gómez, M.; Hernangómez-Pérez, D.; Inkpen, M. S.; Lovat, G.; Fung, E. D.; Roy, X.; Venkataraman, L.; Evers, F. *Nano Lett.* **2020**, *20*, 6381–6386. (l) Zirakzadeh, A.; Herlein, A.; Groß, M. A.; Mereiter, K.; Wang, Y.; Weissensteiner, W. *Organometallics* **2015**, *34*, 3820–3832.

141 (a) Ferber, B.; Top, S.; Welter, R.; Jaouen, G. *Chem. Eur. J.* **2006**, *12*, 2081–2086. (b) D'Antona, N.; Lambusta, D.; Morrone, R.; Nicolosi, G.; Secundo, F. *Tetrahedron Asymmetry* **2004**, *15*, 3835–3840. (c) Steurer, M.; Tiedl, K.; Wang, Y.; Weissensteiner, W. *Chem. Commun.* **2005**, 39, 4929–4931. (d) Steurer, M.; Wang, Y.; Mereiter, K.; Weissensteiner, W. *Organometallics* **2007**, *26*, 3850–3859.

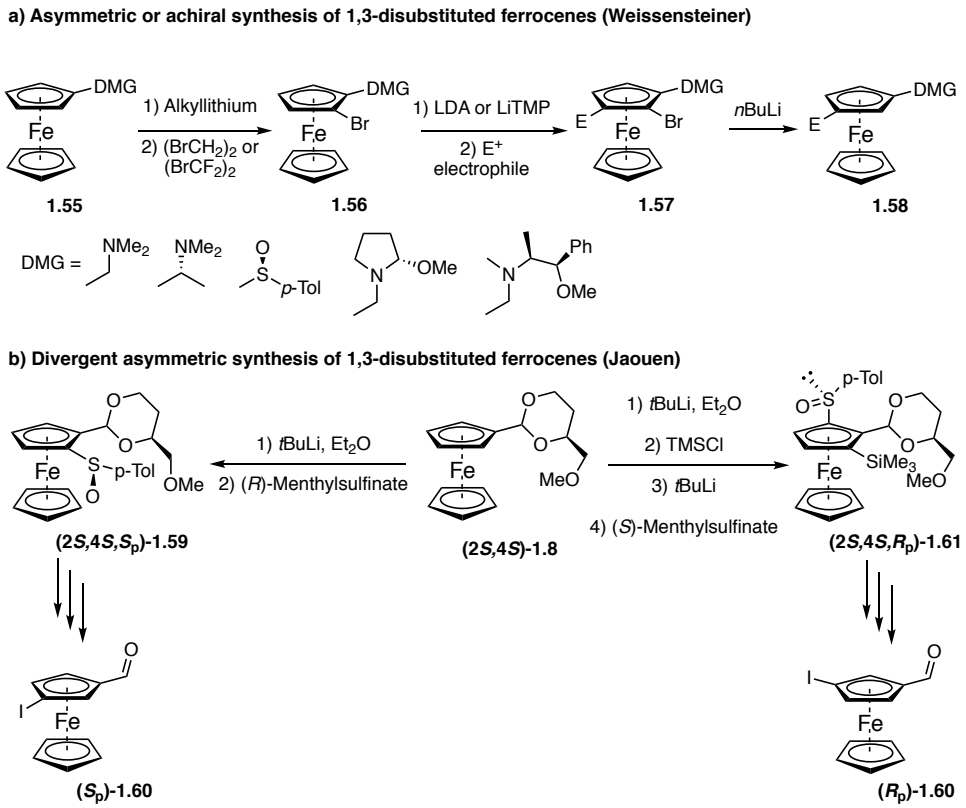
synthesized by repeating two times the *ortho*-lithiation/electrophile addition sequence yielding 1,2,3-trisubstitued ferrocenes. Removal of the directing group delivers a 1,3-disubstitued ferrocene as exemplified with the synthesis of the 1,3-di(tributylstannyl)ferrocene **1.54** from bromoferrocene **1.52** (Scheme 1.11).



1.52 **1.53** **1.54**

Scheme 1.11. Synthesis of achiral 1,3-disubstitued ferrocenes.

In the second case, the metalation directing group remains as one of the substituents of the final 1,3-disubstitued ferrocene (Scheme 1.12). These products are synthesized by a first *ortho*-metalation and reaction with an electrophile introducing a second, labile, metalation directing group. A second *ortho*-metalation selective to the last introduced group is carried out, followed by reaction with an electrophile and removal of the labile metalation directing group, yielding a 1,3-disubstitued ferrocene. This methodology can be applied in the synthesis of achiral 1,3-disubstituted ferrocenes with identical substituents, or chiral 1,3-disubstituted ferrocenes with distinct substituents. For the asymmetric synthesis of 1,3-disubstituted ferrocenes, the lithiation reaction is carried out in an enantio- or diastereoselective manner. Thus, Weissensteiner[141c,d] and Jaouen[141a] reported the enantioselective synthesis of 1,3-disubstituted, and 1,2,3-tribustituted ferrocenes by application of this methodology.



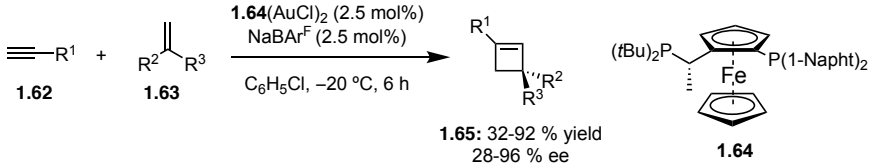
Scheme 1.12. Synthesis of chiral 1,3-disubstitued ferrocenes.

Chiral ferrocene-based ligands have been extensively used in a wide variety of metal-catalyzed transformations. However, they remain relatively absent in the field of gold(I) catalysis. Ferrocene-based gold(I) complexes are known and studied for their biological activity[142] but have been seldom used in the field of catalysis and recent reports mainly focus on their use as redox switchable catalytic systems for achiral transformations.[143]

142 Bjelosevic, H.; Guzei, I. A.; Spencer, L. C.; Persson, T.; Kriel, F. H.; Hewer, R.; Nell, M. J.; Gut, J.; Van Rensburg, C. E. J.; Rosenthal, P. J.; Coates, J.; Darkwa, J.; Elmroth, S. K. C. *J. Organomet. Chem.* **2012**, *720*, 52–59.

143 (a) Ibáñez, S.; Poyatos, M.; Dawe, L. N.; Gusev, D.; Peris, E. *Organometallics* **2016**, *35*, 2747–2758. (b) Klenk, S.; Rupf, S.; Suntrup, L.; Van Der Meer, M.;

Only few reports describe the use of chiral ferrocene-based ligand for asymmetric gold(I) catalysis[8,47,144] in which chiral ferrocene-based gold(I) complexes often provided low to moderate enantioinduction. However, our group reported the use of digold(I)-Josiphos complexes for the gold(I)-catalyzed [2+2] cycloaddition of terminal alkynes **1.62** with alkenes **1.63** achieving good yields and high enantioselectivities in most cases (Scheme 1.13).[144d]



Scheme 1.13. Gold(I)-catalyzed synthesis of chiral cyclobutenes.

Ferrocene continues to play a prominent role in asymmetric catalysis as a chiral ligand scaffold and also, more recently, in the design of new organocatalysts. Yet, despite the existence of a wide variety of ferrocene-based ligands, to our knowledge there is no report of a bulky dialkylarylphosphine-ferrocene ligand analogue to JohnPhos-type ligand and only few achiral 1,3-disubstitued ferrocene ligands are described.[145]

Sarkar, B. *Organometallics* **2017**, *36*, 2026–2035. (c) Veit, P.; Volkert, C.; Förster, C.; Ksenofontov, V.; Schlicher, S.; Bauer, M.; Heinze, K. *Chem. Commun.* **2019**, *55*, 4615–4618. (d) Straube, A.; Coburger, P.; Dütsch, L.; Hey-Hawkins, E. *Chem. Sci.* **2020**, *11*, 10657–10668. (e) Schulz, J.; Cisarova, I.; Gyepes, R.; Stepnicka, P. *Angew. Chem. Int. Ed.* **2020**. https://doi.org/10.1002/anie.202014359.

144 (a) Hashmi, A. S. K.; Hamzié, M.; Rominger, F.; Bats, J. W. *Chem. Eur. J.* **2009**, *15*, 13318–13322. (b) Barreiro, E. M.; Broggini, D. F. D.; Adrio, L. A.; White, A. J. P.; Schwenk, R.; Togni, A.; Hii, K. K. *Organometallics* **2012**, *31*, 3745–3754. (c) Wu, Z.; Retailleau, P.; Gandon, V.; Voituriez, A.; Marinetti, A. *Eur. J. Org. Chem.* **2016**, *2016*, 70–75. (d) 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.

145 Lerayer, E.; Radal, L.; Nguyen, T. A.; Dwadnia, N.; Cattey, H.; Amardeil, R.; Pirio, N.; Roger, J.; Hierso, J. C. *Eur. J. Inorg. Chem.* **2020**, *2020*, 419–445.

Objective

Considering the importance of biaryl phosphine ligands in homogenous gold(I) catalysis and their ability to induce high level of enantioselectivity, we aimed at the synthesis of 1-(2'-phosphinylaryl)-3-aryl ferrocene ligands, a new class of ferrocene-based ligands (Figure 1.3). This design uses ferrocene as an isostere of the JohnPhos' bottom aryl ring. We sought to use the planar chirality offered by a 1,3-disubstitued ferrocene scaffold to provide a chiral environment proximal to the catalytic site considering the linear dicoordination and the outer-sphere mechanism characteristic of gold(I) catalysis.

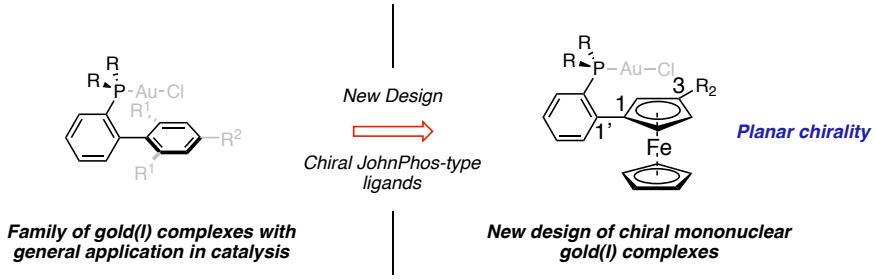


Figure 1.3. 1,3-Disubstitued ferrocene ligand design.

No chiral 1,3-diaryl substituted ferrocene ligand has yet been reported. Our goal was to develop a suitable synthetic route to access gold(I) complexes, catalysts for the enantioselective formal [4+2] cycloaddition of 1,6-enynes.

Results and Discussion

Design

We postulated that the specificities of ferrocene could be advantageously exploited to obtain a chiral analogue of JohnPhos-type gold(I) complex in which the chiral information would be proximal to the catalytic site (Figure 1.4). The rigidity of ferrocene and the bulky alkyl substituents of the phosphine, essential to ensure the collinearity between the aryl-ferrocene bond and P–Au bond, would provide a well-defined geometry to the complex. The planar chirality of the ferrocene scaffold would generate the desired asymmetry of the ligand.

Our group previously reported a chiral JohnPhos-type ligand relying on a remote C_2-symmetric pyrrolidine (Figure 1.4). This element is required to provides the same chiral environment to all the possible rotamers and therefore making them equivalent. We envisioned that a ferrocene bearing a substituent in position 3 relative to the aryl-phosphine moiety will display a similar chiral environment. This design suppresses the requirement of a C_2-symmetric chiral element. The steric hindrance offered by the bottom cyclopentadiene ring of the ferrocene would ensure that the phosphine and bulky aryl groups are pointing above the plane of the top cyclopentadiene ring. The ferrocene scaffold would act as a spacer, isostere to the bottom aryl ring of JohnPhos-type ligands, between the coordinating phosphine moiety and the substituent providing the chiral environment as well as being the source of chirality. As noted in the introduction, for ferrocene-based ligands bearing an element of chirality additional to the planar chirality, each element of chirality has a certain influence on the control of the enantioinduction. Therefore, we decided to synthesize an exclusively planar chiral ferrocene-based ligand, thus eliminating the possibility of match-mismatch issues and facilitating investigations on the mode of action of the gold(I) complex. This design is based on a mononuclear gold(I) complex.

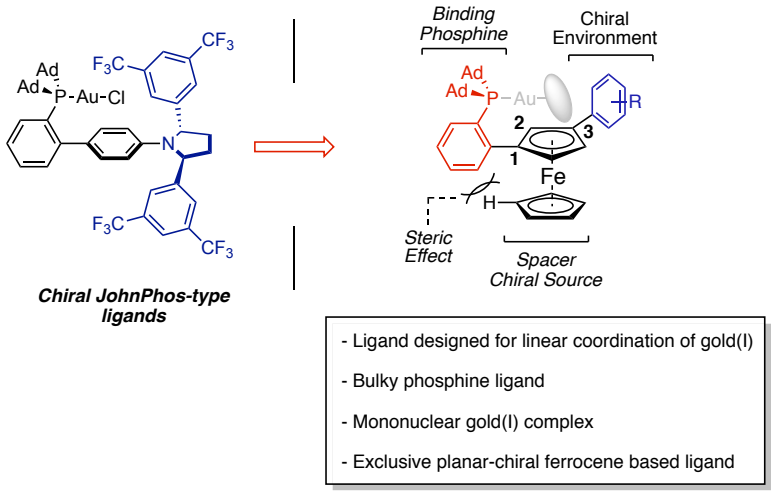
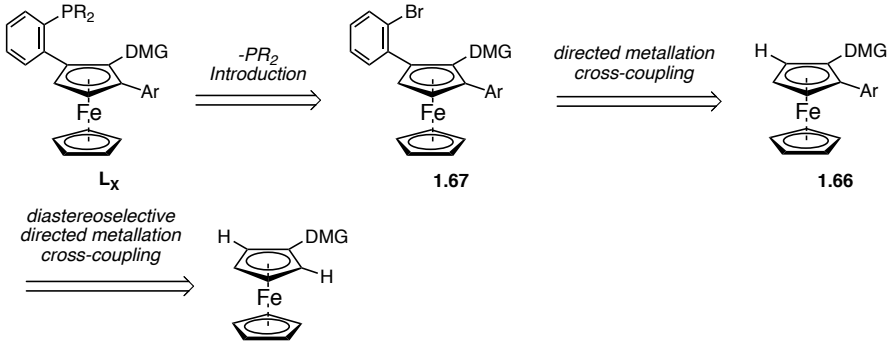


Figure 1.4. Properties of 1,3-diaryl ferrocene ligand.

Synthetic Development

We envisioned that the strategy of iterative *ortho*-directed metalation around a directing metalation group (DMG), followed by transmetalation and palladium-catalyzed cross-coupling reactions would provide a synthetic route to access the desired 1,2,5-substituted chiral ligands (Scheme 1.14).



Scheme 1.14. Retrosynthetic analysis of chiral ferrocene ligands **L**X.

This synthetic route relies on a directed lithiation and introduction of an aryl substituent yielding the planar chiral ferrocene **1.66**. The chirality can be

introduced by diastereoselective lithiation when using a chiral metalation directing group or by enantioselective lithiation using a chiral base.

Diastereoselective metalation appeared more appealing for several factors. In the case of a diastereoselective *ortho*-lithiation occurring with incomplete selectivity, the products obtained from an enantiopure starting material would be a mixture of two diastereomers and therefore potentially separable to obtain the enantiopure product. Unlike the case of diastereoselective metalation, the use of chiral base yielding a mixture of enantiomers would require more tedious purification to obtain the enantiopure product. Additionally, ferrocenes bearing a chiral group able to direct lithiation in a diastereoselective manner are well established as described in the introduction.[100,101,102] On the other hand, the use of a chiral base, mainly BuLi·(–)-sparteine, was confronted with the recent shortage of (–)-sparteine supply.[146] In addition, only few reports are available on the required cross-coupling sequence.[147] Therefore, several chiral ferrocenes were considered as starting material for the synthesis of the ligands.

First, we examined known chiral ferrocenes able to achieve diastereoselective *ortho*-lithiation/directed metalation on both *ortho*-positions of the directing group. The chiral ferrocenyl-acetal **1.8** introduced by Kagan requires a tedious synthesis as well as using a poorly available, but recyclable, chiral auxiliary (Scheme 1.1b). In the case of the well know Ugi´s amine **1.4,** low yields are reported in cross-coupling reactions with aryl halides and its preparation is tedious (Scheme 1.1a), disadvantage recently overcame by the work of Wang who

146 (a) Coady D. J.; Engler A. C.; Horn H. W.; Bajjuri K. M.; Fukushima K.; Jones G. O.; Nelson A.; Rice J. E.; Hedrick J. L. *ACS Macro Lett.* **2012**, *1*, 19–22. (b) Todd R.; Rubio G.; Hall D. J.; Tempelaar S.; Dove A. P.; *Chem. Sci.* **2013**, *4*, 1092–1097.

147 (a) Laufer, R. S.; Veith, U.; Taylor, N. J.; Snieckus, V. *Org. Lett.* **2000**, *2*, 629–631. (b) Laufer, R.; Veith, U.; Taylor, N. J.; Snieckus, V. *Can. J. Chem.* **2006**, *84*, 356–369. (c) Erb, W.; Roisnel, T.; Dorcet, V. *Synth.* **2019**, *51*, 3205–3213.

reported a straightforward enantioselective synthesis of a solid Ugi´s amine analogue.[148] Chiral ferrocenyl-oxazolines **1.12** are readily accessible from commercially available sources and commonly used in sequential enantioselective deprotonation however failed to achieve the desired cross-coupling reaction.

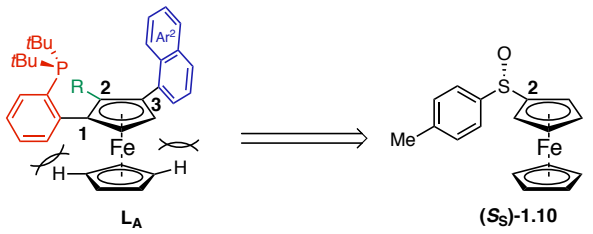
Finally, Kagan's chiral ferrocenyl *p*-tolylsulfoxide **1.10**, readily available enantiopure in decadegram scale in a 1 or 2 steps procedure from commercially available sources, stable and crystalline, appeared to be the best choice. However, the direct *ortho*-lithiation on both *ortho*-positions of the sulfoxide has not been reported. Pleasingly, the sulfoxide directing group is removable by treatment with *t*BuLi.[149]

We first targeted the lead ligand $\mathbf{L_A}$ (Scheme 1.15) bearing a 1-naphtyl substituent to investigate the optimal synthetic route for this unprecedented design. This choice was motivated by geometrical parameters. Because of the rigidity of the scaffold, the angle imposed by the C_3-C_{Nap} bond and the bulkiness of the ring Ar^2, the naphtyl group is expected to be forced above the plane of the top cyclopentadiene ring to limit the steric repulsion with the bottom cyclopentadiene ring.[139c] Hence, Ar^2 is proximal to the reactive site of the related gold(I) complex. Finally, 1-bromonaphthalene is readily available. Although ferrocenes are challenging substrates in cross-coupling reactions, the palladium-catalyzed Negishi cross-coupling between ferrocenyl-zinc chloride and aryl halides has been reported.[149,150]

148 Dong, W. W.; Li, Y. N.; Chang, X.; Shen, C.; Wang, C. J. *ACS Catal.* **2020**, 12954–12959.

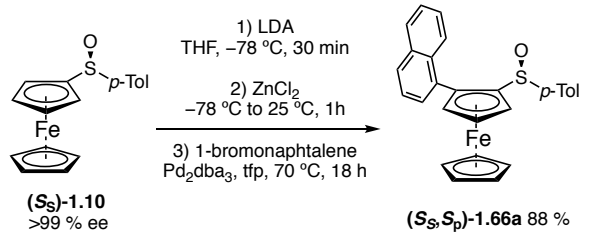
149 Riant, O.; Argouarch, G.; Guillaneux, D.; Samuel, O.; Kagan, H. B. A *J. Org. Chem.* **1998**, *63*, 3511–3514.

150 Cotton, H. K.; Huerta, F. F.; Bäckvall, J. E. *Eur. J. Org. Chem.* **2003**, *15*, 2756–2763.



Scheme 1.15. Lead development of ligand $\mathbf{L_A}$.

The sulfoxide-ferrocene **1.10** was synthesized according to a modification of the procedure reported by Kagan's (Scheme 1.1c). With the enantiopure sulfoxide in hand, the synthesis commenced by the introduction of the naphtyl moiety using the conditions reported by Johannsen[139c] delivering the expected product **1.66** in 88% yield (Scheme 1.16). Sulfoxide **1.10** was diastereoselectively lithiated with LDA at –78 ºC and the lithiated intermediate was transmetalated with $ZnCl_2$ to form an organo-zinc species, which underwent a Pd-catalyzed Negishi cross-coupling with 1-bromonaphtalene delivering product **(S_S,S_p)-1.66.**

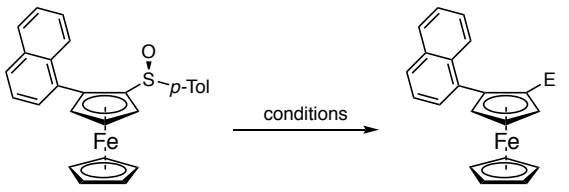


Scheme 1.16 Negishi cross-coupling of sulfoxide **1.10.**

Using similar metalation conditions did not yield the second *ortho*-lithiation of the ferrocene and led us to consider the installation of another *ortho*-lithiation directing group. Known as a directing group for *ortho*-lithiation, we first synthesized the sulfone **1.68a** by oxidation of the sulfoxide **1.66a** with *m*-CPBA (Table 1.1, entry 1).[109] When treated with LDA at –78 ºC in THF, no metalation of

the sulfone **1.68a** was observed and the starting material decomposed when the temperature raised to *ca.* 0 ºC. Sulfone **1.68a** decomposed upon treatment by *n*BuLi at –78 ºC in THF. We then turned our attention to a strategy of Li-sulfoxide exchange yielding the corresponding ferrocenyl-lithium and subsequently reacting this intermediate with an appropriate electrophile. As amides and di-ethers are known as lithiation directing group,[102,107a] we reacted the ferrocene sulfoxide **1.66a** with *t*BuLi and attempted to react the lithiated intermediate with carbamoyl chlorides and MOMCl. Full conversion of the sulfoxide **1.66a** to the corresponding lithiated species was observed in all cases. Although TLC analysis suggested the formation of traces of the desired products, results were not reproducible and isolations failed (Table 1.1, entries 1, 5, 6). Only the morpholine carboxamide **1.68c** was isolated in low yield (Table 1.1, entry 3). Similarly, in presence of *i*PrMgCl·LiCl, the sulfoxide **1.66a** was converted into the corresponding ferrocenyl-magnesium-chloride, although this intermediate also failed to achieve the desired reaction (Table 1.1, entry 4). Similarly to **1.68a**, treatment of **1.68c** with base lead only to no reaction or decomposition of the starting material.

Table 1.1. Sulfoxide-DMG exchange.



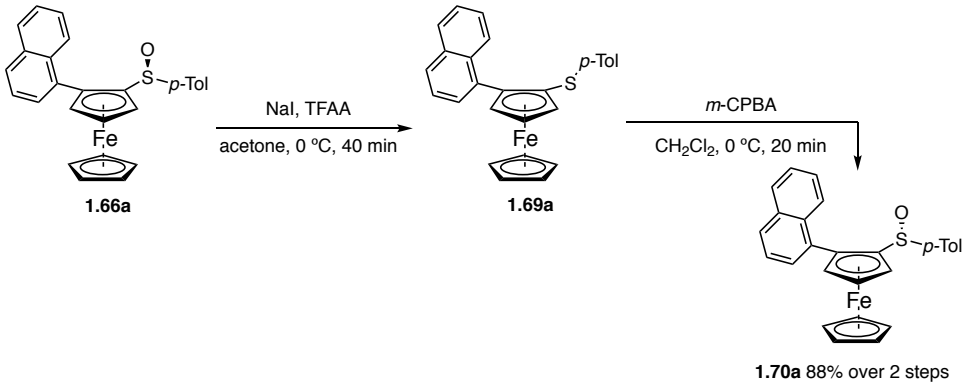
1.66a

1.68a E = SO_2*p*-tol
1.68b E = MOM
1.68c E = CON-morph
1.68d E = CON*i*Pr_2
1.68e E = $CONEt_2$

entry	conditions	product (yield %)
1	*m*-CPBA, CH_2Cl_2, 0 ºC, 1 h	**1.68a** (76%)
2	*t*BuLi, THF, –78 ºC, 10 min then MOMCl –78 to 24 ºC	**1.68b** (traces)
3	*t*BuLi, THF, –78 ºC, 10 min then 4-morpholine carbamoyl chloride	**1.68c** (32%)
4	*i*PrMgCl·LiCl, THF, 0 to 24 ºC, 1 h then 4-morpholine carbamoyl chloride	**1.68c** (traces)
5	*t*BuLi, THF, –78 ºC, 10 min *N,N*-diisopropylamine carbamoyl chloride	**1.68d** (<5%)
6	*t*BuLi, THF, –78 ºC, 10 min *N,N*-diethylamine carbamoyl chloride	**1.68e** (traces)

Finally, based on the work of Sasamori[151] we synthesize sulfoxide **1.70a**, diastereomer of **1.66a**, reported to act as *ortho*-lithiation directing group. The inversion of configuration of the sulfoxide was achieved by treatment of sulfoxide **1.66a** with TFAA in presence of NaI in acetone at 0 ºC yielding the corresponding sulfide **1.69a** followed by a diastereoselective oxidation with *m*-CPBA in CH_2Cl_2 at 0 ºC (Scheme 1.17).

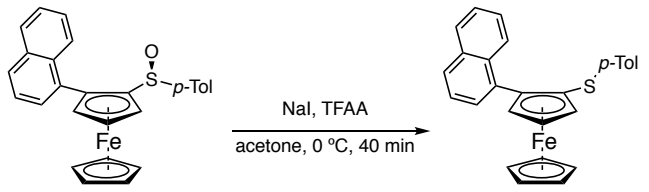
151 Sasamori, T.; Sakagami, M.; Niwa, M.; Sakai, H.; Furukawa, Y.; Tokitoh, N. *Chem. Commun.* **2012**, *48*, 8562–8564.



Scheme 1.17. Sulfoxide's inversion of configuration.

Under the conditions reported by Sasamori (Table 1.2, entries 1-2) the reduction occurred but only with modest conversion. Addition of a large excess of TFAA and NaI provided only slightly increased conversion (Table 1.2, entries 3-4). We hypothesized that the low conversion was due to side reactions consuming TFAA and NaI before their reaction with the sterically hindered sulfoxide. Full conversion of sulfoxide **1.70a** was achieved by a second addition of TFAA and NaI after 20 min of reaction time giving rise to sulfide **1.69a** in good yields (Table 1.2, entries 3-5). Decreasing the reaction time reduced apparent degradation. Additionally, quenching the crude mixture with ice cold aq. NaOH and Na_2SO_3 provided a cleaner crude product and facilitated the work-up while limiting degradation.

Table 1.2. Sulfoxide reduction´s conditions optimization.



1.66a **1.69a**

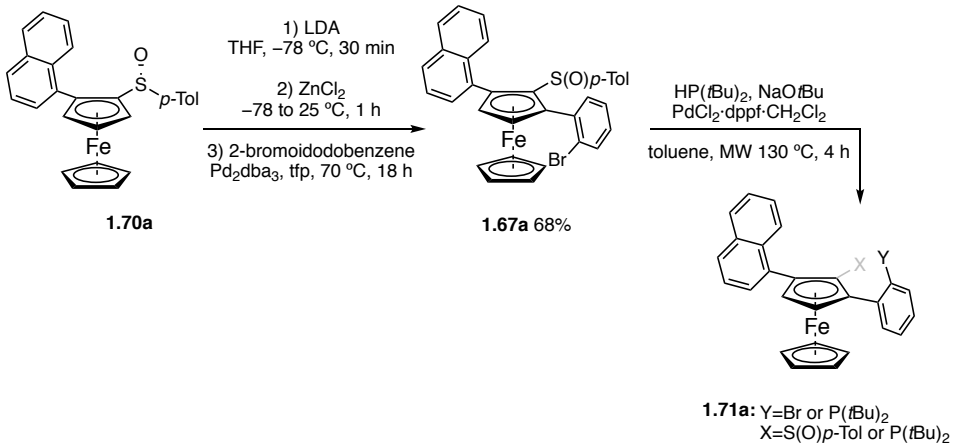
entry	TFAA: NaI (eq)	time (min)	conversion (%)
1	2	15	70
2	2	30	75
3	3	15	75
4	5	30	80
5	2 + 2	20 + 20	>90

The oxidation of the sulfide **1.69a** with *m*-CPBA delivered the desired sulfoxide **1.70a** in good yield (>95%). The complete inversion of configuration was confirmed by ^{1}H NMR. The optimized conditions proved to be a suitable synthetic route toward the target, easily scalable and delivering the sulfoxide in good yield over two steps (Scheme 1.17). The efficiency of this sequence proved to be strongly dependent of the quality of TFAA and *m*-CPBA.

The *ortho*-metalation of **1.70a** occurred smoothly upon treatment with LDA in THF at −78 ºC. The subsequent transmetalation with $ZnCl_2$ and palladium-catalyzed Negishi cross-coupling with 2-bromoiodobenzene afforded the aryl bromide **1.67a** in 68% yield (Scheme 1.18).

Our attempts to introduce the di-*tert*-butylphosphine (P(*t*Bu)$_2$) moiety on substrate **1.67a** by palladium-catalyzed cross-coupling yielded a complex mixture of products, which failed to be isolated as they appeared to be unstable and quickly degraded. Encouragingly, ^{31}P NMR analysis of the reaction crude displayed a peak at δ = 20.0 ppm (162 MHz, $CDCl_3$) that was attributed to the desired aryl di-*tert*-

butylphosphine. Another peak, δ = 58.2 ppm (162 MHz, $CDCl_3$), was attributed to X = P(O)*t*Bu_2 by comparison of the reported value for FcP(O)*t*Bu_2 (δ = 58.6 MHz, $CDCl_3$).[152] It was hypothesized that the sulfoxide moiety acted as a *pseudo*-halide and the phosphine cross-coupling could therefore occur at this position yielding the mixture of products **1.71a** (Scheme 1.18).



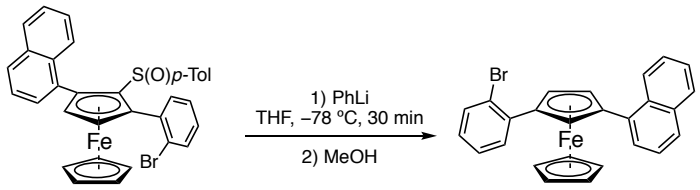
Scheme 1.18. Negishi cross-coupling and introduction of bulky phosphine.

Hence, we targeted the synthesis of 2-bromophenyl ferrocene **1.72a** displaying a single reactive site for palladium-catalyzed phosphine cross-coupling. Based on the work of Knochel,[153] treatment of the sulfoxide **1.67a** with PhLi at –78 ºC allowed the removal of the sulfoxide group by Li-sulfoxide exchange and the following protonolysis yielded the desired product **1.72a**. The reaction proceeds with 62% conversion and furnished the desired product in 60% yield (Table 1.3, entry 1). Addition of more PhLi or longer reaction time provided **1.72a** in 67-71% yield (Table 1.3, entry 2-4).

152 Baillie, C.; Zhang, L.; Xiao, J. *J. Org. Chem.* **2004**, *69*, 7779–7782.

153 Kloetzing, R. J.; Knochel, P. *Tetrahedron Asymmetry* **2006**, *17*, 116–123.

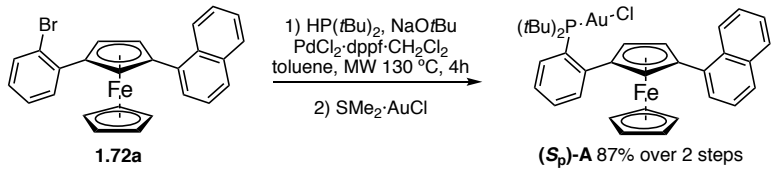
Table 1.3. Desufloxidation of the 2-bromphenyl ferrocene **1.67a**.



1.67a **1.72a**

entry	1.67a:PhLi	time	conversion (%)	yield (%)
1	1:2	30 min	62	60
2	1:3	30 min	70	69
3	1:3	1 h	69	67
4	1:5	30 min	74	71

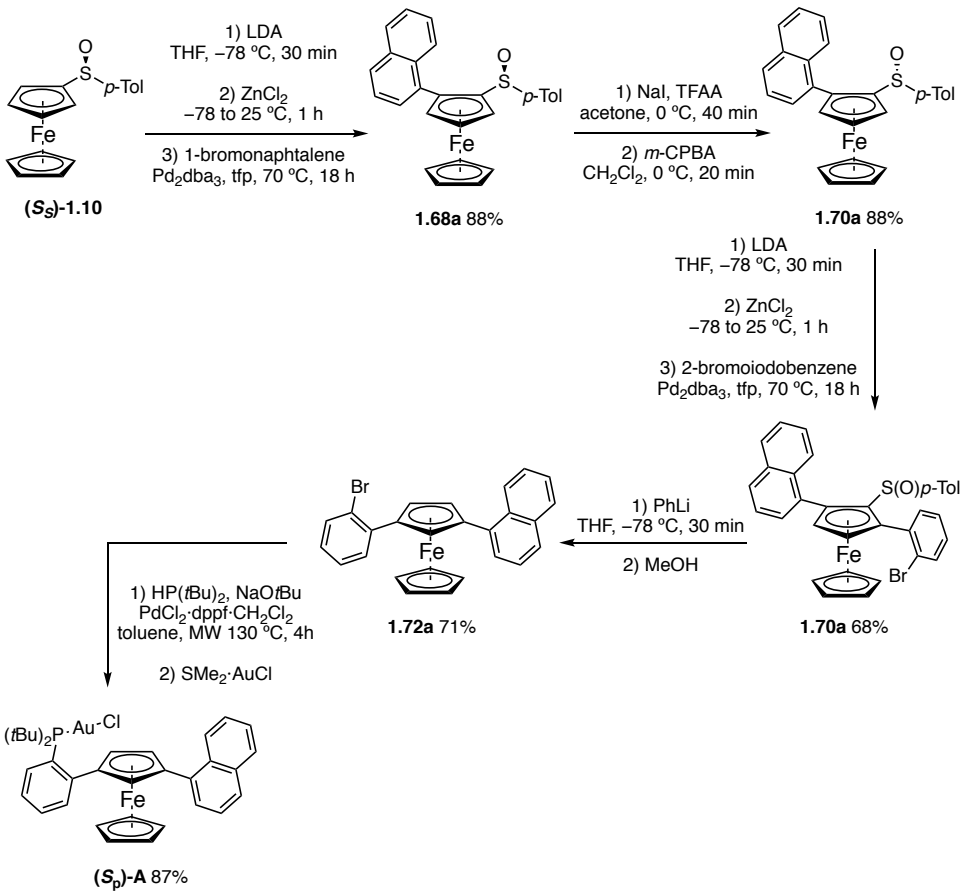
The cross-coupling between the aryl-bromide **1.72a** and di-*tert*-butylphosphine was carried out followed by complexation with $Me_2S{\cdot}AuCl$ to prevent the possible oxidation of the phosphine. The sequence proceeds smoothly and provided complex **(S_p)-A** in 87% yield (Scheme 1.19).



1.72a **(S_p)-A** 87% over 2 steps

Scheme 1.19. Introduction of bulky dialkyphosphine.

This step concludes the synthetic route developed to access the desired chiral gold(I) complex **(S_p)-A** (Scheme 1.20).



Scheme 1.20. Synthesis of the gold(I) complex **(S_p)-A.**

Complex **(S_p)-A** was used as precatalyst in the formal [4+2] cycloaddition of 1,6-enyne **30a** in presence of $AgBF_4$ in 1,2-dichloroethane at 24 ºC, providing the desired product **31a** with low enantiomeric ratio (Scheme 1.21). Despite providing low enantioinduction, this ligand validates the potential of the concept and drove us to its improvement.

Scheme 1.21. Gold(I)-catalyzed [4+2] cycloisomerization of the 1,6-enyne **30a**.

Design Development

While developing the synthetic route, we hypothesized that an *ortho*-substituted phenyl in position 3 could be beneficial for the enantioinduction as it would provide a better shielding of the catalytic site (Figure 1.4). Because of the rigidity of the scaffold and the geometry of the biaryl moiety, the Ar^2 group is forced on the top of the ferrocene core. In addition, a biaryl moiety would be closer to the catalytic site than the naphtyl group. To minimize the steric repulsion, substituents at the biaryl would be pointing *trans* with respect of the iron atom. This design also provides tunability to the ligand as biaryls are readily accessible from commercial sources and both steric and electronic properties can be modulated.

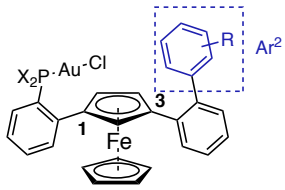
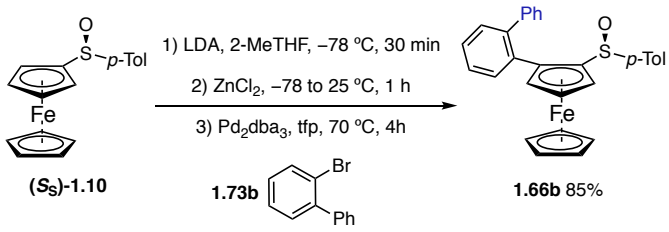


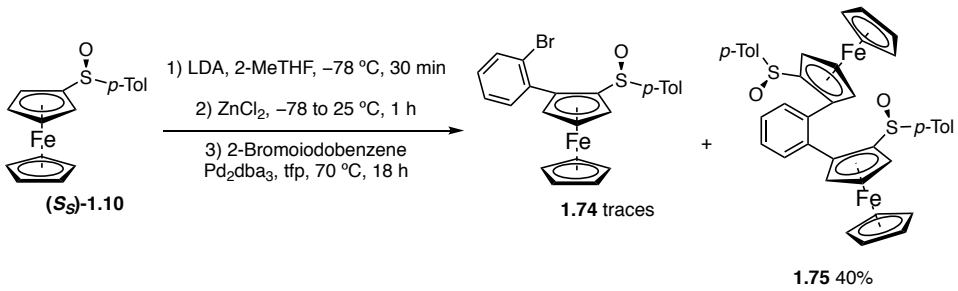
Figure 1.4. Biaryl-type ferrocene ligand.

The synthesis of these ligands started using the synthetic pathway developed to access **(S_p)-A**. The Negishi cross-coupling between the chiral sulfoxide and the 2-bromobiaryl **1.73b** yielded the desired product **1.66b** in good yield (Scheme 1.22). The product **1.66b** also proved to be easier to purify than the naphtyl counterpart **1.66a**. Substituting THF by 2-MeTHF provided higher yields and reproducibility as well as a simplified work-up and an easier purification of the product.



Scheme 1.22. Negishi cross-coupling with 2-bromobiphenyl.

Following this preliminary result, we aimed at the synthesis of various biaryl-ferrocenes **1.66** with diverse electronic and steric properties to study their impact on the enantioselectivity of the reaction and activity of the gold(I) complex. We first targeted the aryl bromide **1.74** that could be modified by cross-coupling reactions thus offering a modular approach (Scheme 1.23). However, only product **1.75** was isolated in 40% yield while the desired aryl bromide was a minor product. Similar results were previously reported by Johannsen.[154]



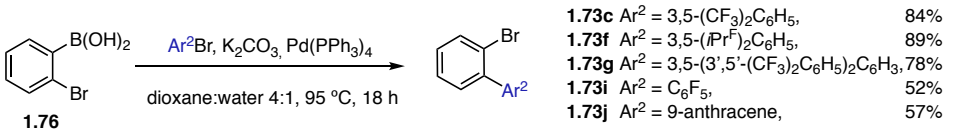
Scheme 1.23 Modular synthesis of 2-bromoaryl ferrocene. **1.74**.

Therefore, we investigated a synthetic route starting from the coupling between 2-halo-1,1'-biaryl with chiral ferrocene **1.10**.

The *o*-bromobiaryls **1.73b,f,g,i,j** bearing electron-withdrawing groups were easily obtained in moderate to good yields by palladium-catalyzed Suzuki-

154 Jensen, J. F.; Søtofte, I.; Sørensen, H. O.; Johannsen, M. *J. Org. Chem.* **2003**, *68*, 1258–1265.

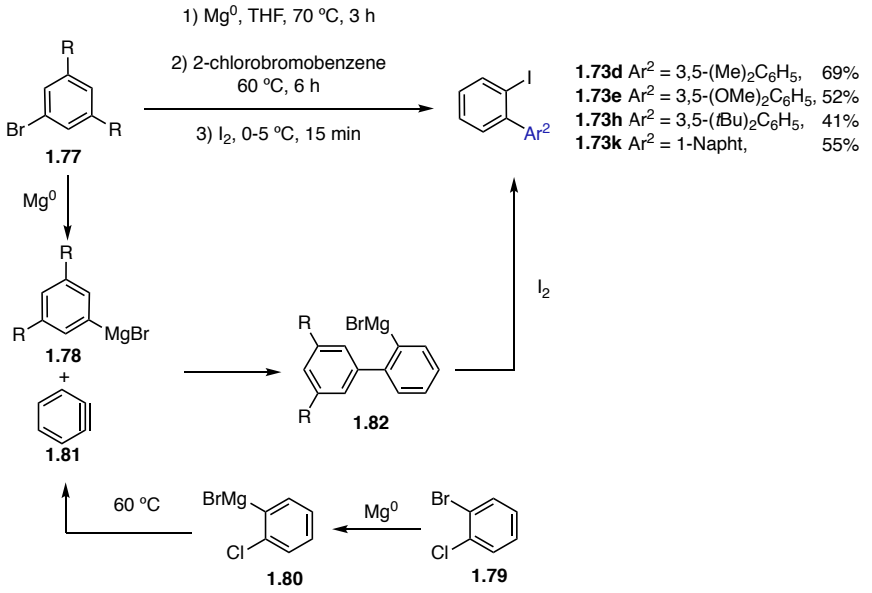
Miyaura cross-coupling between *o*-bromobenzene boronic acid and the corresponding aryl-bromides under microwave irradiation or simple thermal conditions (Scheme 1.24).



Scheme 1.24. Synthesis of 2-bromobiaryls by Suzuki-Miyaura cross-coupling.

However, electron-rich aryl-bromides provided the desired products along with side products making the purification challenging and poorly suitable for scale-up. An alternative synthetic route relying on aryne chemistry was therefore employed based on a procedure reported by Buchwald (Scheme 1.25).[155] Grignard reagents **1.78**, synthesized from the corresponding aryl bromides **1.77** and Mg^0, were reacted with benzyne (**1.81**). The resulting biaryl Grignard intermediate **1.82** was then was treated with elemental iodine providing the desired *o*-iodobiaryls compounds **1.73**. Benzyne (**1.81**) was generated in situ from 2-chlorobromobenzene **1.79** by heating 2-chlorophenyl magnesium bromide **1.80**. The desired product was obtained in similar moderate yields than using Suzuki-Miyaura cross-coupling but with cleaner reaction profiles thus simplifying the purification issue. The procedure was easily scaled-up to multigram batches to meet our needs.

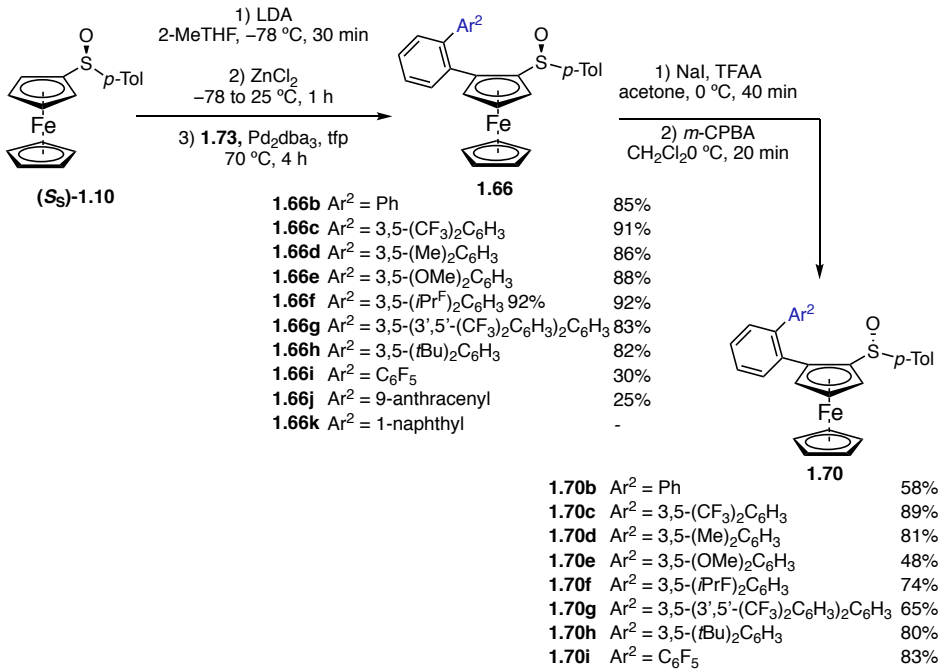
155 Tomori, H.; Fox, J. M.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 5334–5341.



Scheme 1.25. Synthesis of 2-iodobiaryls.

With the desired family of *o*-halobiaryls in hand we started the synthesis of the associate family of ligands.

The reaction sequence involving sulfoxide-directed diastereoselective *ortho*-lithiation, transmetalation with $ZnCl_2$ followed by palladium-catalyzed Negishi cross-coupling was carried under the optimized reactions conditions delivering sulfoxides **1.66a-h** usually in good yield (Scheme 1.26). However, product **1.66i** and **1.66j** were obtained in 30% and 25% yields respectively. We attributed these low yields to the high steric hindrance due to the presence of substituents in both *ortho*-positions of the Ar^2 ring. Independently, we later developed suitable conditions for palladium/copper-catalyzed Stille cross-coupling of aryl halides with tributylstannyl-ferrocene (discussed in Chapter 3). This pathway allows the synthesis of **1.66i** in a slightly improved 45% yield. The inversion of configuration of the sulfoxides was carried out on delivering products **1.70b-i** in moderate to good yields (Scheme 1.26).



Scheme 1.26. Negishi cross-coupling with 2-bromobiaryls.

Coupling product **1.66k** (Ar^2 = 1-Naphtyl) was obtained as an inseparable mixture of two atropoisomers (2:1) due to the high rotational barrier of the biphenyl bond (Figure 5). Thus, we focus our attention on symmetric biaryl scaffolds.

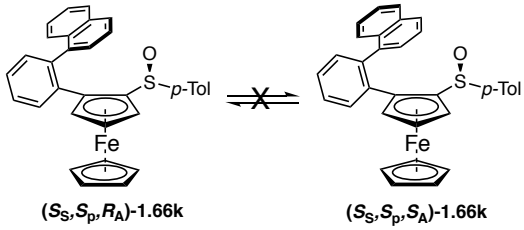
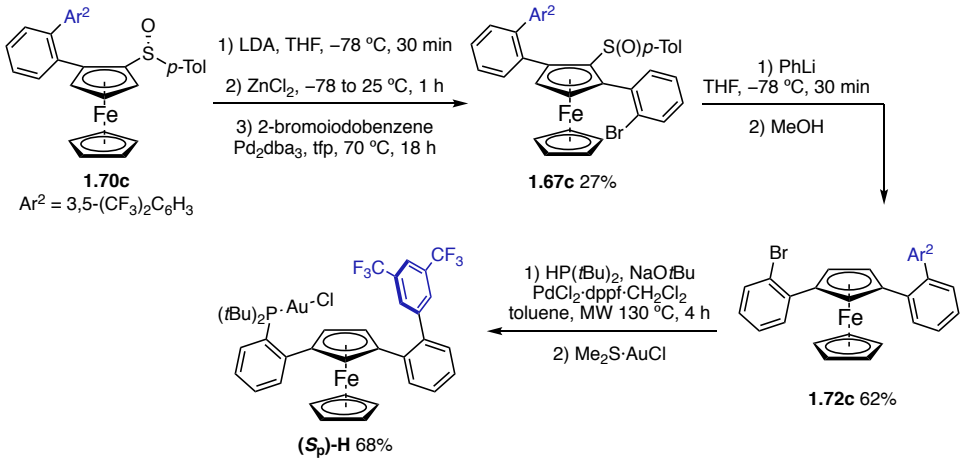


Figure 5. Atropoisomers of biaryl ferrocene **1.66k**.

The reaction sequence involving *ortho*-lithiation, transmetalation with $ZnCl_2$ and palladium-catalyzed Negishi cross-coupling provided poor results. While the reaction delivered **1.67a** in 68% yield during our discovery route, the same conditions applied to **1.70c** delivered the product in 27% yield and 65%

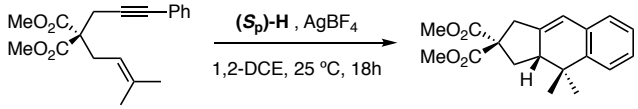
starting material was recovered (Scheme 1.27). Additionally, under those conditions, the sulfoxides **1.70h** and **1.70i** functionalized with 3,5-(tBu)$_2$C$_6$H$_3$ and C$_6$F$_5$ biaryls, respectively, fully decomposed upon treatment with LDA.

Nonetheless the synthesis of complex **(S_p)-H** was completed to examine to reactivity of this new modified scaffold.



Scheme 1.27. Synthesis of complex **(S_p)-H.**

The complex **(S_p)-H** was used as precatalyst in the formal [4+2] cycloaddition of 1,6-enyne **30a** in presence of $AgBF_4$ in 1,2-DCE at 24 ºC, providing **31a** in 70% yield and an improved 82:18 *er* (Scheme 1.28).

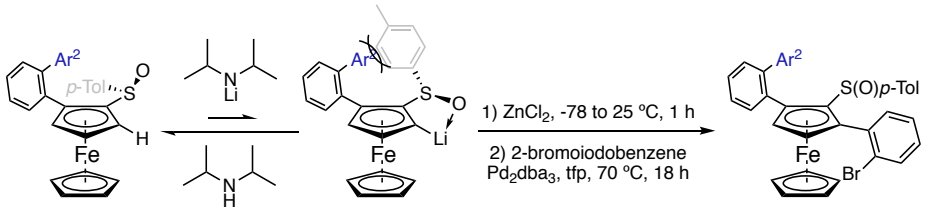


Scheme 1.28. Gold(I)-catalyzed formal [4+2] cycloaddition of 1,6-enyne **30**.

To easily access a family of ligands we first focused our efforts to optimize the synthetic route addressing the low conversion encountered in the reaction of **1.70** to **1.67** and the desulfoxidation of **1.67** to **1.72** (Scheme 1.27).

We hypothesized that the low conversion of the reaction sequence from **1.70c** to **1.67c** was caused by the bulkiness of the biaryl substituent. Indeed, the steric interactions between the biaryl and tolyl moieties could disfavor the conformation required for the sulfoxide to direct the deprotonation leading low conversions in the metalation.

Table 1.4. Directed lithiation of sulfoxide **1.70c.**

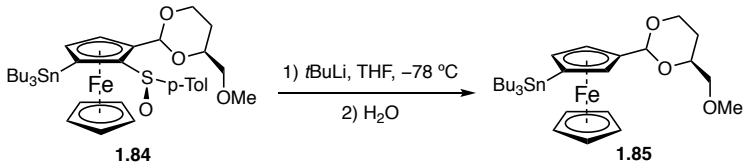


1.70c Ar² = 3,5-$(CF_3)_2C_6H_3$ **1.83c** **1.67c**

entry	**1.70c** : LDA	conversion (%)	yield (%)
1	1:1.5	30	21
2	1:3	35	28
3	1:5	38	30

Upon addition of an excess of base, conversion and yield only improved slightly (Table 1.4), consequently another strategy was designed. As the equilibrium disfavored the formation of the lithiated species **1.83**, we hypothesized that carrying out the lithiation in the presence of an electrophile could displace the equilibrium by trapping the ferrocenyl-lithium generated *in situ*, thus driving the reaction to full conversion. The employed electrophile has to be stable toward the base and the product has to be able to provide similar reactivity as intermediate **1.67**.

Based on the work of Jaouen describing a selective ferrocene-sulfoxide cleavage with *t*BuLi in presence of a tributylstananyl group (Scheme 1.29)[141a] we investigated the use of tributyl chlorostannane as electrophile.

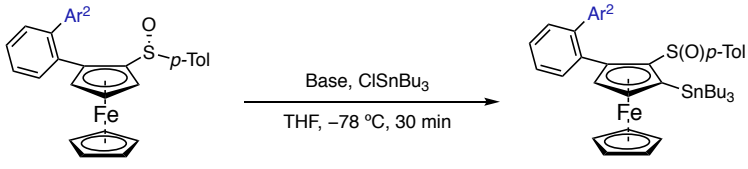


1.84 **1.85**

Scheme 1.29. Selective sulfoxide/Li exchange.

The use of tributyl chlorostannane brings several advantages: it reacts slowly with hindered amides bases and Li-Sn exchanges have been reported as well as the iodine cleavage of C–Sn bond yielding the reactive C–I bond.[101a] Brief optimization of the reaction conditions provided a procedure yielding quantitatively desired product **1.86c** very cleanly. LDA was inferior to the more basic and less nucleophilic LiTMP allowing the use of only a little excess of electrophile.

Table 1.5. Optimization of the directed metalation-stannylation of the ferrocene **1.70**.



1.70c
$Ar^2 = 3,5\text{-}(CF_3)_2C_6H_3$

1.86c

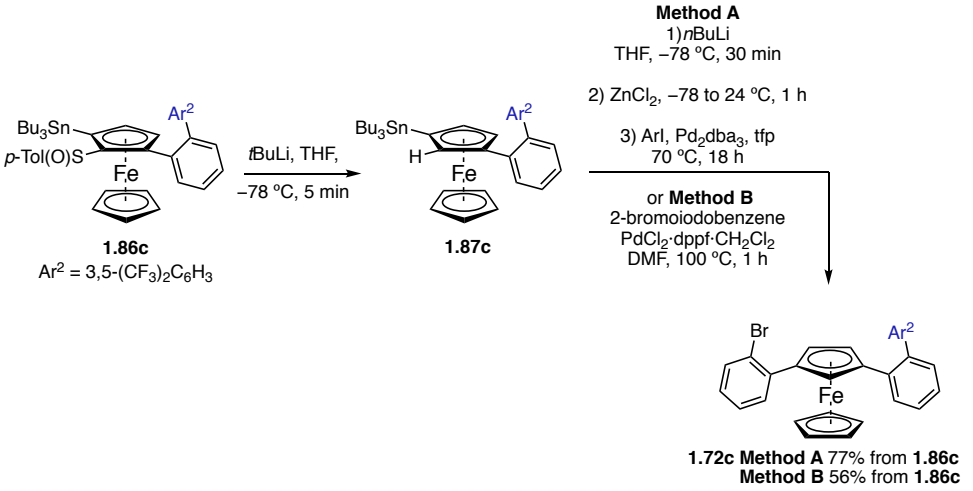
entry	ratio **1.70c** : Base : $ClSnBu_3$	base	conversion (%)	yield (%)
1	1 : 1.5 : 1.1	LDA	50	-
2	1 : 2.5 : 1.1	LDA	72	-
3	1 : 2.5:1.4	LDA	>99	96
4	1 : 1.1 : 1.5	LiTMP	>99	>95

Pleasingly, the sulfoxide removal in **1.86c** upon treatment with *t*BuLi proceeded with full conversion (Scheme 1.30), a net improvement with respect to

the average 60% conversion obtained previously using PhLi during our initial investigation (Table 1.3).

This synthetic pathway has, however, some drawbacks: the inherent toxicity of organostannanes and the instability of the intermediate **1.86** that quickly degraded upon storage at 5 ºC. The products **1.86** and **1.87** are very sticky thick oils, which makes their handling difficult. However, these drawbacks are negligible as those steps proceed cleanly and no formal isolation is required.

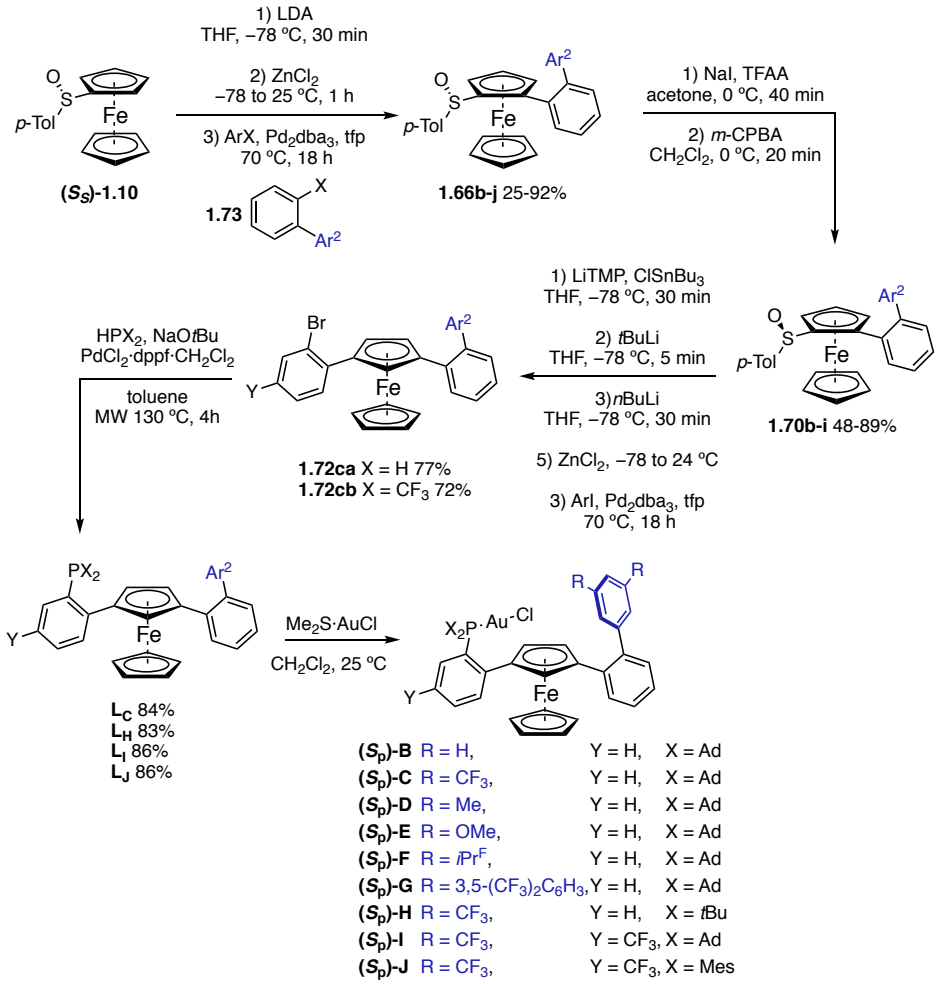
To continue the synthesis of the desired complexes, intermediate **1.87c** was treated with *n*BuLi cleanly delivering the corresponding ferrocenyl-lithium. Subsequent transmetalation of this intermediate with $ZnCl_2$ and Negishi cross-coupling with 2-bromoiodobenzene provided the aryl bromide **1.72c** (Scheme 1.30, Method A). To further simplify the synthetic route, Stille cross-coupling between intermediate **1.87c** and 2-bromoiodobenzene was tested but product **1.86c** was obtained with lower yields (Scheme 1.30, Method B) and a more difficult purification. Thus, we used the original three steps procedure.



Scheme 1.30. Sulfoxide removal and Negishi cross-coupling.

The palladium-catalyzed phosphine cross-coupling with substrate **1.72c** provided the ligand in good yields (Scheme 1.27). Gratifyingly, the ligand $\mathbf{L_C}$ obtained using the optimized route did not exhibit noticeable degradation over storage for 2 months at 5 ºC. The instability initially observed was possibly due to the presence of impurities as the purification of the free ligand proved to be challenging.

With the optimized synthetic pathway in hand, we accomplished the synthesis of complexes **(*S*$_p$)-B-J**. Noteworthy, no purifications were required from the sulfoxide **1.70** to obtain the pure gold(I) complexes allowing the quick synthesis of a family of complexes.



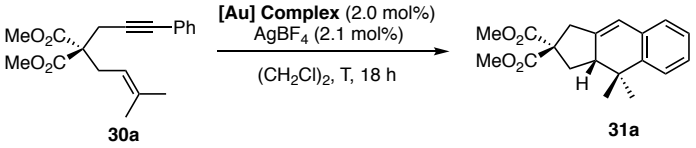
Scheme 1.31. Optimized synthesis of complexes **(*S*p)-B-J.**

The developed synthetic route allowed the synthesis of a family of ligands functionalized with biaryls groups displaying different steric and electronic properties. Similarly, the phosphine moiety has been modified.

We studied the efficiency of our new catalysts in the [4+2] cycloaddition of 1,6-enyne **30a** (Table 1.6). Complexes **(*S*p)-C, (*S*p)-H** and **(*S*p)-I** bearing a 1,3-bistrifluoromethylbenzene outperformed the other complexes with the exception of the simple biphenyl **(*S*p)-B**. Steric hindrance appeared to have a detrimental

influence in the enantioinduction as well as the presence of electron-rich aromatic systems. Decreasing the temperature from 0 to –20 ºC led to a slight increase in the enantioselectivity at the expense of longer reaction times (Table 1.6, entry 5). Further decreasing the temperature from –20 to –30 ºC did not improve the enantiomeric ratio and requires longer reaction times to proceed to full conversion (Table 1.6, entry 6). Additionally, the presence of *m*-CF_3 substituent relative to the phosphorus induces a slightly lower activity of the complex but with a slight increase of enantioselectivity (Table 1.6, entry 7). With the exception of complex **(*S*$_P$)-G** (Table 1.6, entry 11), all complexes displayed good activity and led to full conversion within 18 h at 0 ºC. Complex **(*S*$_p$)-J** gave product **31a** as a racemic mixture (Table 1.6, entry 12).

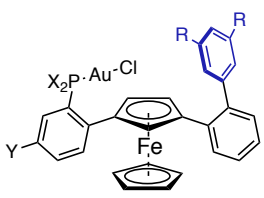
Table 1.6. Screening of gold(I) complexes **(S_p)-B-J** in the [4+2] cycloaddition of enyne **30a**.



30a **31a**

entry	[Au] complex	time (h)	temperature (ºC)	enantiomeric ratio (isolated yield %)
1	**(S_p)-B**	18	0	76:24
2	**(S_p)-H**	18	0	82:18
3	**(S_p)-C**	18	0	83:17
4	**(S_p)-C**	1	24	80:20
5	**(S_p)-C**	36	–20	88:12 (70)
6	**(S_p)-C**	96	–30	89:11
7	**(S_p)-I**	48	–20	89:11 (65)
8	**(S_p)-F**	18	0	63:37
9	**(S_p)-D**	18	0	54:46
10	**(S_p)-E**	18	0	64:36
11	**(S_p)-G**	7 d	0	57:43
12	**(S_p)-J**	6	0	<51:49

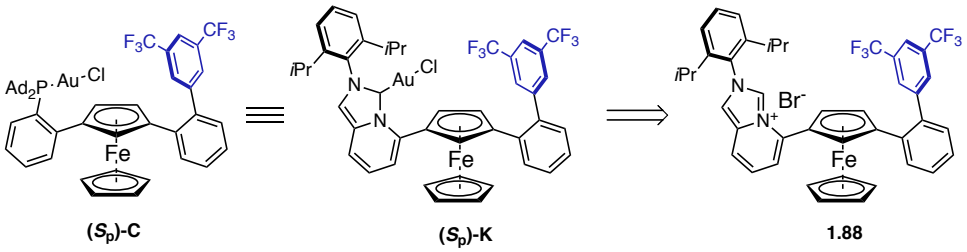
[a]Reactions carried out on 0.03 mmol scale until full conversion monitored by GC-MS. [b]Determined by HPLC on chiral stationary phase.



(S_p)-B R = H, Y = H, X = Ad
(S_p)-C R = CF_3, Y = H, X = Ad
(S_p)-D R = Me, Y = H, X = Ad
(S_p)-E R = OMe, Y = H, X = Ad
(S_p)-F R = iPr^F, Y = H, X = Ad
(S_p)-G R = 3,5-$(CF_3)_2C_6H_3$, Y = H, X = Ad
(S_p)-H R = CF_3, Y = H, X = *t*Bu
(S_p)-I R = CF_3, Y = CF_3, X = Ad
(S_p)-J R = CF_3, Y = CF_3, X = Mes

Complexes **(S_p)-B-J** provided low to moderate enantioinduction in the cycloisomerization of the 1,6-enyne **30a**. Before proceeding to further investigations of these new gold(I) complexes, we decided to investigate further modifications of the ligand design. We envisioned that, with the optimized synthetic route in hand, we could modify the core off the ligand using another rigid coordination moiety.

In addition of the phosphine complex **(S_p)-C**, we targeted its NHC analogue **(S_p)-K** (Scheme 1.22) based on the imidazo[1,5-*a*]pyridine (ImPy) framework initially reported by Lassaletta[156] and Glorius[157] and recently used in biaryl chiral ligands for gold(I) catalysis by Zhang.[84] Similarly, ImPy ligand **1.88** was envisioned to have the aryl and ferrocene moieties orthogonally arranged with the NHC moiety being forced above the plane of the ferrocene core to reduce steric interactions. The rigidity of the scaffold would suppress the issues encountered with the possible C–P bond rotation, which required bulky substituents to ensure that the catalytic site remain above the ferrocene scaffold. This NHC type ligand would provide different electronic properties as well as chiral environment, with the 6,5-fused rings geometry tilting away the C–Au–substrate axis from the cyclopentadienyl ring compared to the phosphine analogue leading to different reactivity.

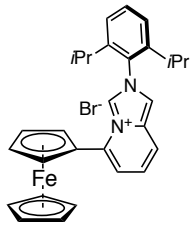


Scheme 1.32. NHC-type complex **(S_p)-K.**

We focused our attention on the synthesis of achiral NHC precursor **1.89** (Figure 1.5) in order to develop a suitable synthetic route applicable to the synthesis of the chiral complex **(S_p)-K**.

156 Alcarazo, M.; Roseblade, S. J.; Cowley, A. R.; Fernández, R.; Brown, J. M.; Lassaletta, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 3290–3291.

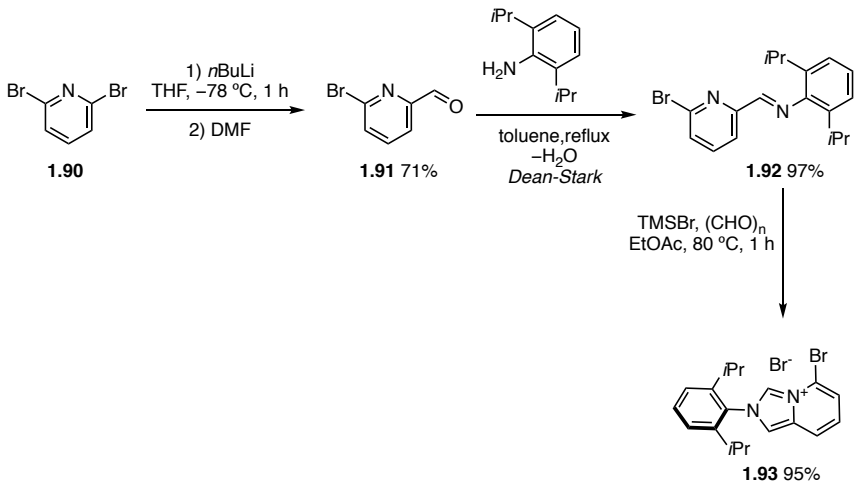
157 Burstein, C.; Lehmann, C. W.; Glorius, F. *Tetrahedron* **2005**, *61*, 6207–6217.



1.89

Figure 1.5. Achiral NHC-ferrocene ligand precursor **1.89**

Our synthesis of the model ligand precursor **1.89** commenced with the condensation between 6-bromopicolinaldehyde **1.91**, readily synthesized from 1,6-dibromopyridine **1.90**, and 2,6-diisopropylaniline. The resulting imine **1.92** was reacted with paraformaldehyde in the presence of TMSBr in EtOAc at 80 ºC following the procedure described by César and Bastin[158] yielding the desired 5-bromo-2-(2,6-diisopropylphenyl)imidazo[1,5-*a*]pyridin-2-ium bromide salt **1.93** (Scheme 1.23).

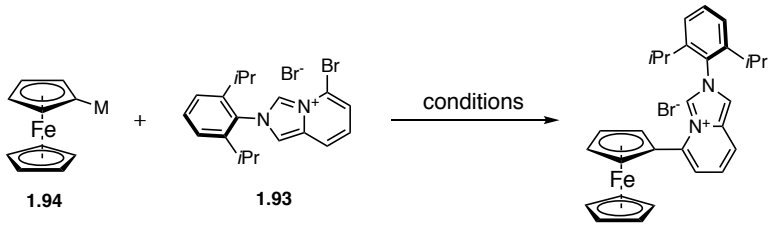


Scheme 1.33. Synthesis of NHC-precursor **1.93**.

158 Azouzi, K.; Duhayon, C.; Benaissa, I.; Lugan, N.; Canac, Y.; Bastin, S.; César, V. *Organometallics* **2018**, *37*, 4726–4735.

To achieve the cross-coupling between the NHC-precursor **1.93** and the ferrocene moiety we first investigated the palladium-catalyzed Suzuki-Miyaura cross-coupling between the aryl bromide **1.93** and ferrocenyl boronic acid **1.95** under the reported conditions.[84,157] However no product was detected. Similarly, under the conditions developed for the palladium/copper-catalyzed Stille cross-coupling of aryl halides with tributylstannyl ferrocene no traces of the desired product were observed (Table 1.7).

Table 1.7. Attempt of coupling between NHC and ferrocene moieties.

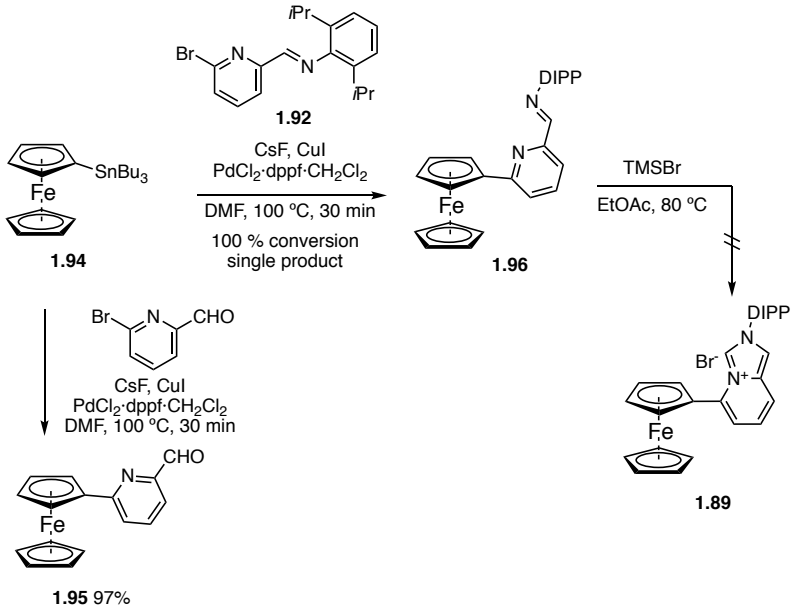


1.94 **1.93** **1.89**

entry	M	conditions	**1.89**
1	$B(OH)_2$	Na_2CO_3, $Pd(PPh_3)_4$ DME/H_2O 80 ºC	-
2	$B(OH)_2$	K_2CO_3, $Pd(PPh_3)_4$ dioxane/H_2O 95 ºC	-
3	$SnBu_3$	CsF, CuI, $PdCl_2$·dppf·CH_2Cl_2 DMF, 100 ºC, 1 h	-

However, the same procedure delivered aldehyde **1.95** in excellent yield (Scheme 1.34). Encouraged by this result, the Stille cross-coupling was carried out between tributylstannyl-ferrocene **1.94** and the imine **1.93** to increase the convergence of the synthetic route. The reaction occurred smoothly and reached full conversion; TLC and GC-Mass analysis displayed a clean reaction profile and the product was detected but the resulting imine-ferrocene **1.96** was prone to hydrolysis and could not be isolated. Therefore, we used the crude imine in the

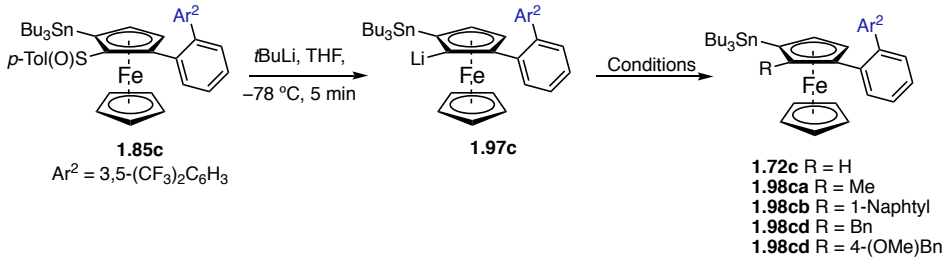
attempted NHC cyclization. However, the desired compound **1.89** could not be isolated and ^{1}H NMR of the crude product revealed the presence of a paramagnetic species.



Scheme 1.34. Attempted cyclization of NHC precursor.

We also investigated the introduction of a third substituent on the top cyclopentadiene ring from lithiated intermediate **1.97c**, resulting from the Li-sulfoxide exchange. Our attempts did not provide satisfactory results; reacting lithiated intermediate **1.97c** with MeI provided an inseparable mixture of the methylated and protonated products and no product was detected upon transmetalation with $ZnCl_2$ followed by a Negishi cross-coupling with benzyl bromides or 1-bromonaphtalene (Table 1.8).

Table 1.8. Functionalization at C_2 from **1.85c**.



1.85c
$Ar^2 = 3,5\text{-}(CF_3)_2C_6H_3$

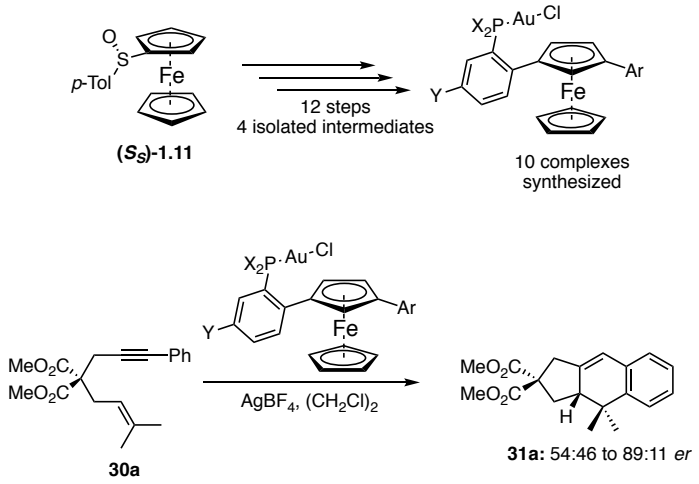
1.97c

1.72c R = H
1.98ca R = Me
1.98cb R = 1-Naphtyl
1.98cd R = Bn
1.98cd R = 4-(OMe)Bn

entry	conditions	product (ratio **1.98c : 1.72c**)
1	MeI	**1.98ca** (82:18-94:6)
2	$ZnCl_2$, –78 to 24 ºC, 30 min then 1-bromonaphtalene, Pd_2dba_3, tfp	**1.98cb** (0:100)
3	$ZnCl_2$, –78 to 24 ºC, 30 min then BnBr, Pd_2dba_3, tfp	**1.98cd** (0:100)
4	$ZnCl_2$, –78 to 24 ºC, 30 min then 4-(OMe)BnBr, Pd_2dba_3, tfp	**1.98ce** (0:100)

Conclusion

We developed a synthetic route for the synthesis of a new family of chiral 1-(2'-dialkylarylphosphine)-3-aryl ferrocene ligands, which are analogues of JohnPhos-type ligands, and have prepared their corresponding gold(I) complexes. The 1,3-substitution was designed to position the substituent proximal to the active site of the gold(I) catalyst considering the linear coordination of the metal and outer-sphere mechanism in gold(I)-catalyzed reactions. Additional efforts were made to obtain related ligands based on this scaffold. The potential of the developed gold(I) complexes as chiral catalysts was tested in the formal [4+2] cycloaddition of the enyne **30a**.



Scheme 1.35. Synthesis and application of chiral JohnPhos-type ferrocene ligands.

Experimental Section

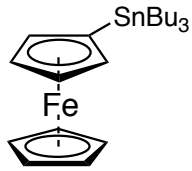
General Information

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 performed in dry solvents (passed through an activated alumina column on a PureSolv™ solvent purification system). 2-MeTHF was dried by distillation over Na/benzophenone and TMP was dried by distillation over CaH_2. TFAA was distilled over P_4O_{10} and stored under argon prior to use. Reactions were followed using a GC-MS apparatus, by TLC (thin layer chromatography). 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 $KMnO_4$ 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 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). Coupling constants (*J*) are reported in Hertz (Hz). Mass spectra were recorded on a Waters LCT Premier Spectrometer (ESI and APCI) or on an Autoflex Broker Daltonics (MALDI and LDI). 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 1.9 mL (100 mm pathlength) cells. Chiral HPLC analyses were performed on an Agilent Technologies 1200 series. SFC analyses were performed on an Agilent Technologies 1260 Infinity II and a Waters ACQUITY UPC^2 System with diode array detector. X-ray diffraction data were collected at 100 K on a Rigaku MicroMax-007HF, Mo Kαrotating anode, equipped with a Pilatus 200 K detector oron a Bruker APEX DUO, Mo KαMicrofocus source E025 IuS anode, equipped with an APEX DUO detector using omega scans

Synthetic Procedures and Characterizations of Compounds

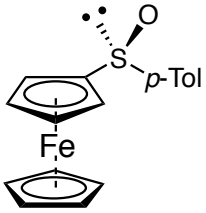
Tri-*n*-butylstannylferrocene 1.94



Ferrocene (11.9 g, 64 mmol) was charged in a flask, THF (30 ml) and hexane (30 ml) were added and the suspension was stirred for 30 min then cooled to 0 ºC in an ice bath. *t*BuLi (1.7 M, 75 ml, 128 mmol, 2 equiv) was added over 30 min keeping the temperature of the reaction mixture below 5 ºC. The reaction mixture was stirred another 30 min and nBu$_3$SnCl (25.8 mL, 96 mmol, 1.5 equiv) was added over 10 min keeping the temperature of the reaction mixture below 5 ºC. The reaction mixture was stirred another 30 min and hydrolysis was performed by addition of NaOH 1M (100 ml). After stirring for 30 min the product was extracted with Et_2O (3x100 ml). The organic layer was washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude oil was diluted with hexane and filtered through a pad of neutral alumina. The filtrate was concentrated under reduced pressure and remaining ferrocene sublimated by heating the crude material at 90 ºC for 12 h. The pure product (24.1 g, 50.7 mmol, 79% yield) was obtained by distillation under reduced pressure.

The obtained characterization data were in agreement with those reported in literature.[101a]

(*S*S)-(*p*-Tolyl-sulfoxide)ferrocene (*S*S)-1.10

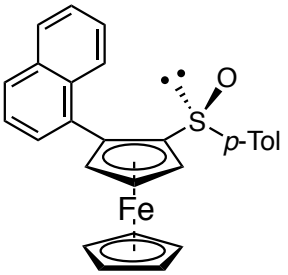


(Tri-*n*-butylstannyl)ferrocene **1.94** (20.7 g, 41.0 mmol) was charged in a flask evacuated and backfilled with Ar (3x) then THF (145 mL) was added, the mixture was stirred until being homogenous and cooled to –78 ºC in a dry ice/acetone bath. *n*BuLi (2.5 M, 16.4 mL, 43.0 mmol, 1.05 equiv) was added over 30 min keeping the temperature below –70 ºC, the mixture was stirred another 15 min. This mixture was transferred via cannula to a suspension of (*S*)-Menthyl-*p*-tolylsulfinate in THF (100 mL) at –78 ºC over 30 min keeping temperature below –75 ºC. The reaction mixture was stirred another 15 min before water (25 ml) was added. The reaction mixture was warmed up to room temperature and diluted with Et_2O (400 mL) and filtered over cotton. Water (600 mL) was added and phases were separated, the aqueous layer was extracted with Et_2O (3x100 mL), reunited organic layer was washed with NaOH 0.5 M (100 mL), water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by flash chromatography over silica gel (eluent cyclohexane: Et_2O 50:50 then Et_2O:CH_2Cl_2 80:20) giving 11.97 g of the pure product. The solid was recrystallized from boiling MTBE under argon, the solution was let slowly cool down to 24 ºC overnight then cooled to –20 ºC for 20 h. The orange needles were filtered and washed with cold Et_2O giving 10.6 g (84% yield) of the enantiopure product. The mother liquor was concentrated to dryness under reduced pressure and the remaining solid recrystallized in the same manner with seeding from the first fraction, giving 0.51 g (4% yield) of the enantiopure product.

The obtained characterization data were in agreement with those reported in literature. [101a]

Synthesis of the Lead

(S_S,S_p)-2-(1-Naphtyl)-1-(*p*-tolyl-sulfoxide)ferrocene 1.66a



Sulfoxide **(S_S)-1.10** (3.2 g, 9.87 mmol) was charged in a 3-neck flask under argon, dissolved in dry 2-MeTHF (106 mL) and the solution cooled to –78 ºC under vigorous stirring.

LDA was prepared by addition of *n*BuLi (2.5 M, 5.53 mL, 1.4 equiv, 13.82 mmol) to a solution of diisopropylamine (1.95 mL, 1.4 equiv, 13.82 mmol) in 2-MeTHF (15 mL) at –78 ºC then the solution was allowed to warm up to room temperature and was stirred 10 min.

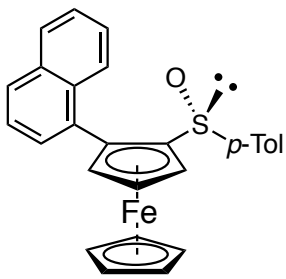
The LDA solution was added to the sulfoxide suspension at –78 ºC keeping the temperature below –75 ºC, the suspension turned to a clear red homogeneous solution during the addition of LDA and the mixture was stirred for 30 min at the same temperature then was slowly transferred via cannula to a suspension of $ZnCl_2$ (2.15 g, 1.6 equiv, 15.8 mmol) in 2-MeTHF (15 mL) at –78 ºC. After the end of the addition the reaction mixture was stirred 15 min at –78 ºC, allowed to warm up to room temperature and stirred for 1 h.

Tris-*o*-furylphosphine (183 mg, 8 mol %, 0.79 mmol) and Pd_2dba_3 (181 mg, 2 mol %, 0.197 mmol) were stirred 30 min in 2-MeTHF (3mL) giving a bright yellow solution that was added to the previously prepared zinc reagent followed by 1-bromonaphtalene (1.66 mL, 2.45g, 1.2 equiv, 11.84 mmol) and the reaction mixture was stirred 12 h at 60 ºC.

The reaction was quenched by addition of 5% aq. citric acid (100 mL), the mixture was stirred for 30 min then filtered over pad of Celite®. Phases were separated and the organic layer was washed with 5% aq. citric acid, water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purifier by flash chromatography over silica gel (eluent toluene:EtOAc:Et_2O 6:1:0.1) to yield to the pure product (3.89 g, 9.85 mmol, 88%) as an orange foam. The obtained characterization data were in agreement with those reported in literature.[139c]

M.p = 201-202 ºC (CH_2Cl_2), **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 8.25 (d, *J* = 7.7 Hz, 1H), 7.86 (d, *J* = 8.2 Hz, 1H), 7.83 (d, *J* = 8.1 Hz, 1H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.52 (d, *J* = 8.5 Hz, 1H), 7.44 – 7.36 (m, 3H), 7.26 (t, *J* = 7.6 Hz, 1H), 7.08 (d, *J* = 8.1 Hz, 2H), 4.68 – 4.65 (m, 1H), 4.59 (t, *J* = 2.6 Hz, 1H), 4.35 (s, 6H), 2.28 (s, 3H). **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 141.2, 140.9, 133.8, 133.7, 131.9, 131.5, 129.4, 128.5, 128.4, 126.1, 126.0, 125.9, 125.3, 125.0, 96.6, 90.1, 74.4, 71.4, 69.2, 68.6, 21.4. α_D^{589} = +134.9 deg.cm^2.g^{-1} ($CHCl_3$, c 0.05, 298 K).

(R_S,S_p)-2-(1-Naphtyl)-1-(*p*-tolyl-sulfoxide)ferrocene 1.70a



A flask was charged with sodium iodide (1.0 g, 2 equiv, 6.66 mmol) and sulfoxide **1.66a** (1.50 g, 3.33 mmol) in acetone (10 mL). The solution was cooled down in an ice bath and TFAA (2.1 g, 0.93 mL, 2 equiv, 6.66 mmol) in acetone (20 mL) was slowly added and the mixture was stirred 10 min. The reaction was monitored by TLC analysis and reagents were added sequentially again until reaction reached full conversion. After completion of the reaction, the crude was poured in NaOH aq. (0.5 M, 50 mL) at 0 ºC and $Na_2S_2O_3$ sat. (5 mL) was added, the mixture was allowed to warm up to room temperature while stirred for 30 min.

The crude was diluted with Et_2O (10 mL) and water (150 mL) and phases were separate. The organic layer was washed with water, $NaHCO_3$ sat. and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was eluted through a silica plug with cyclohexane:Et_2O 90:10 and concentrated under reduced pressure yielding the desired product (1.29 g, 2.97 mmol, 89%) as an orange gum used directly in the next step.

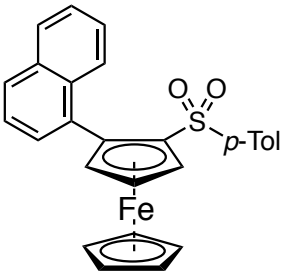
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.90 (d, *J* = 8.5 Hz, 1H), 7.79 (t, *J* = 8.7 Hz, 2H), 7.53 (dd, *J* = 8.2, 7.2 Hz, 1H), 7.38 (ddd, *J* = 8.1, 6.7, 1.3 Hz, 1H), 7.32 – 7.27 (m, 1H), 6.73 (s, 4H), 4.70 (dd, *J* = 2.6, 1.5 Hz, 1H), 4.63 (dd, *J* = 2.5, 1.5 Hz, 1H), 4.55 (t, *J* = 2.6 Hz, 1H), 4.34 (s, 5H), 2.11 (s, 3H).

The residue (1.22 g, 2.81 mmol) was dissolved in CH_2Cl_2 (6.2 mL) and cooled in an ice bath. *m*-CPBA (606 mg, 77% Wt, 0.96 equiv, 2.70 mol) in CH_2Cl_2 (12.5 mL) was added dropwise and the mixture was stirred 20 min. The reaction was monitored by TLC analysis, the crude was poured in NaOH aq. (0.5 M, 50 mL) at 0 ºC and mixture was allowed to warm up to room temperature while stirred for 30 min.

The crude was diluted with Et_2O (30 mL) and water (50 mL) and phases were separated. The organic layer was washed with NaOH (0.5 M), water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purifier by flash chromatography over silica gel (eluent cyclohexane:Et_2O:$CHCl_3$ gradient from 100:0:0 to 70:20:10) to yield the pure product (1.24 g, 2.75 mmol, 88%) as an orange foam.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.30 (dd, *J* = 7.1, 1.2 Hz, 1H), 7.91 – 7.82 (m, 2H), 7.61 (dd, *J* = 8.3, 7.1 Hz, 1H), 7.44 – 7.37 (m, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.22 – 7.15 (m, 1H), 6.82 – 6.75 (m, 4H), 4.82 – 4.78 (m, 1H), 4.61 – 4.58 (m, 2H), 4.56 (s, 5H), 2.15 (s, 3H). **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 143.9, 141.1, 133.1, 133.8, 132.2, 130.7, 129.5, 128.6, 128.5, 126.2, 126.0, 125.8, 125.5, 124.0, 97.1, 89.1, 73.5, 71.6, 68.7, 64.0, 21.3.

(S_p)-2-(1-Naphtyl)-1-(*p*-tolylsulfone)ferrocene 1.68a

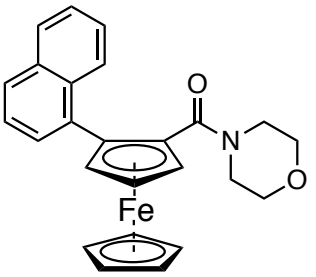


Sulfoxide **1.66a** (0.20 mg, 0.44 mmol) was dissolved in CH_2Cl_2 (2 mL) and cooled in an ice bath, *m*-CPBA (0.10 g, 77% Wt, 1.3 equiv, 0.58 mmol) was added and the reaction mixture was stirred 20 min at 0 ºC then 30 min at room temperature. The reaction was monitored by TLC analysis.The reaction mixture was poured in NaOH aq. (0.5 M, 5 mL) at 0 ºC and mixture was allowed to warm up to room temperature while stirred for 30 min.

The crude was diluted with Et_2O (5 mL) and water (10 mL) and phases were separated. The organic layer was washed with NaOH (0.5 M), water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purifier by flash chromatography over silica gel (eluent cyclohexane:Et_2O:$CHCl_3$ gradient from 100:0:0 to 80:10:10) to yield the pure product (1.24 g, 2.75 mmol, 76%) as an orange foam.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (dd, *J* = 7.1, 1.2 Hz, 1H), 7.86 (d, *J* = 8.2 Hz, 1H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.61 (dd, *J* = 8.3, 7.1 Hz, 1H), 7.28 – 7.23 (m, 1H), 6.86 – 6.81 (m, 1H), 6.81 – 6.76 (m, 2H), 6.59 (d, *J* = 8.5 Hz, 1H), 6.51 (d, *J* = 8.0 Hz, 2H), 5.08 (dd, *J* = 2.7, 1.5 Hz, 1H), 4.70 (s, 5H), 4.59 (t, *J* = 2.6 Hz, 1H), 4.48 – 4.45 (m, 1H), 2.05 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 142.7, 138.4, 133.9, 132.8, 131.6, 130.2, 128.6, 128.4, 127.9, 126.8, 125.4, 125.2, 125.1, 125.0, 92.0, 89.7, 75.0, 71.7, 70.1, 68.6, 21.3. **HRMS** (ESI+) calculated for $[C_{27}H_{22}FeNaO_2S]^+$ 489.0582 m/z; found $[M + Na]^+$: 489.0584.

(S_p)-2-(1-Naphtyl)-1-(4-morpholinecarboxamide)ferrocene 1.68c

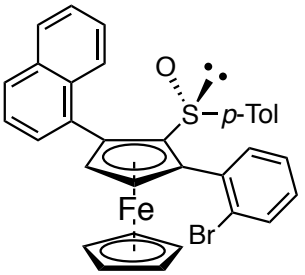


Sulfoxide **1.70a** (150 mg, 0.33 mmol) was dissolved in THF (2 mL) and cooled to –78 ºC. *t*BuLi (1.7 M, 0.15 mL, 1.1 equiv, 0.37 mmol) was added and the reaction mixture was stirred 20 min at –78 ºC then morpholine-4-carbonyl chloride (60 mg, 1.2 equiv, 0.40 mmol) was added. The mixture was stirred at the same temperature for 10 min then allowed to warm up to 24 ºC and stirred for 30 min.

The crude was diluted with Et_2O (5 mL) and water (10 mL) and phases were separated. The organic layer was washed with NaOH (0.5 M), water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purifier by flash chromatography over silica gel (eluent cyclohexane:EtOAc gradient from 100:0 to 60:40) to yield to the pure product (45 mg, 0.11 mmol, 32%) as an orange foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 – 8.11 (m, 1H), 7.90 – 7.85 (m, 1H), 7.81 (dt, *J* = 8.3, 1.1 Hz, 1H), 7.51 (dd, *J* = 8.2, 7.2 Hz, 1H), 7.48 – 7.37 (m, 2H), 4.69 (d, *J* = 2.5 Hz, 2H), 4.49 (t, *J* = 2.4 Hz, 1H), 4.36 (s, 5H), 3.81 – 2.52 (m, 8H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 168.4, 134.0, 133.8, 132.4, 129.9, 128.8, 127.9, 126.2, 125.8, 125.3, 125.2, 86.8, 85.9, 71.6, 70.7, 69.8, 67.5, 66.1. 47.3 (brs). 42.7 (brs). **HRMS** (ESI+) calculated for $[C_{25}H_{23}FeNaO_2]^+$ 448.0970 m/z; found $[M + Na]^+$: 448.0971.

(R_S,S_p)-2-(1-Naphtyl)-5-(2-bromophenyl)-1-(*p*-tolyl-sulfoxide)ferrocene 1.67a



In a flame dried flask under argon sulfoxide **1.70a** (400 mg, 0.888 mmol) was dissolved in dry THF (9.5 mL) and cooled to –78 ºC.

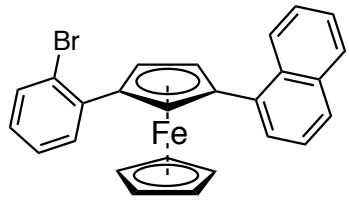
LDA was prepared by addition of *n*BuLi (2.5 M, 0.50 mL, 1.4 equiv, 1.24 mmol) to a solution of diisopropylamine (175 µL, 1.4 equiv, 1.24 mmol) in dry THF (1.33 mL) at –78 ºC then the solution was allowed to warm up to 24 ºC and was stirred 10 min. The LDA solution was added to the sulfoxide solution at –78 ºC and the mixture was stirred for 30 min at the same temperature then $ZnCl_2$ (194 mg, 1.6 equiv, 1.42 mmol) in dry 2-MeTHF (1 mL) was quickly added. The reaction mixture was stirred 5 min at –78 ºC, allowed to warm up to 24 ºC and stirred for 1 h.

Tris-*o*-furylphosphine (16 mg, 8 mol %, 71 µmol) and Pd_2dba_3 (16 mg, 2 mol %, 18 µmol) were stirred 30 min in 2-MeTHF (0.2 mL) giving a bright yellow solution that was added to the previously prepared zinc reagent followed by 1-bromo-2-iodobenzene (223 µL, 503 mg, 2 equiv, 1.78 mmol) and the reaction mixture was stirred for 18 h at 60 ºC.

The reaction was quenched by addition of 5% aq. citric acid (50 mL), the mixture was stirred for 30 min then filtered over pad of Celite®. Phases were separated and the organic layer was washed with 5% aq. citric acid, water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purifier by flash chromatography over silica gel (eluent gradient of cyclohexane:(EtOAc:Et_2O 6:1:0.1) 100:0 to 0:100) yielding the pure product (365 mg, 0.604 mmol, 68%) as an orange foam. The product quickly degraded and was used in the next step without extensive analysis.

M.p = >215 ºC (decomposition, CH_2Cl_2), **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.42 (dd, *J* = 7.1, 1.2 Hz, 1H), 8.39 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.93 – 7.89 (m, 2H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.65 (dd, *J* = 8.3, 7.1 Hz, 1H), 7.48 (dddd, *J* = 23.3, 8.3, 6.8, 1.4 Hz, 2H), 7.34 (td, *J* = 7.5, 1.3 Hz, 1H), 7.22 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.05 (ddd, *J* = 8.0, 7.3, 1.7 Hz, 1H), 6.69 – 6.63 (m, 2H), 6.50 – 6.44 (m, 2H), 4.81 (dd, *J* = 22.4, 2.6 Hz, 2H), 4.67 (s, 5H), 2.14 (s, 3H). **HRMS** (ESI+) calculated for $[C_{33}H_{26}BrOS^{56}Fe]^+$ 605.0234 m/z; found $[M + Na]^+$: 605.0222.

(S_p)-1-(2-Bromophenyl)-3-(1-naphtyl)ferrocene 1.72a



PhLi was prepared as follows: in a flame dried flask charged with iodobenzene (150 µL, 275 mg, 2 equiv, 1.32 mmol) in Et_2O (4.3 mL) at 0 ºC, *n*BuLi (2.5 M, 1.3 mL, 4 equiv, 2.64 mmol) was added dropwise then the reaction mixture was stirred at the same temperature for 30 min.

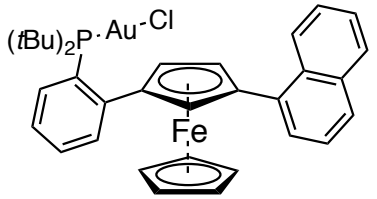
In a flame dried flask charged with sulfoxide **1.67a** (0.40 g, 0.66 mmol) in THF (5 mL) at –78 ºC the PhLi solution was dropwise and the solution was stirred at the same temperature for 30 min. The reaction was quenched by addition of *i*PrOH (1 mL) and allowed to warm up to room temperature.

The crude mixture was diluted with Et_2O (10 mL) and 5% citric acid aq. (25 mL) was added and phases were separated. The organic layer was washed with 5% citric acid aq., water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was filtered over a plug of silica gel (eluent gradient of pentane:$CHCl_3$ 90:10) yielding the product (192 mg, 411 µmmol, 63%) as an orange gum used directly in the next step.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 – 8.63 (m, 1H), 7.92 (dd, *J* = 7.2, 1.3 Hz, 1H), 7.90 – 7.86 (m, 1H), 7.83 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.79 (dt, *J* = 8.3, 1.2 Hz, 1H),

7.61 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.54 – 7.46 (m, 3H), 7.32 (ddd, *J* = 7.8, 7.3, 1.4 Hz, 1H), 7.11 (ddd, *J* = 8.0, 7.3, 1.7 Hz, 1H), 5.30 (t, *J* = 1.5 Hz, 1H), 5.00 (dd, *J* = 2.5, 1.5 Hz, 1H), 4.85 (dd, *J* = 2.6, 1.5 Hz, 1H), 4.16 (s, 5H).

(S_p)-1-(2-Di-*tert*-butylphosphanebenzene)-3-(1-naphtyl)ferrocene gold(I) chloride, Complex (S_p)-A



Aryl bromide **1.72a** (90 mg, 193 µmol), dppf·$PdCl_2$·CH_2Cl_2 (7.9 mg, 5 mol %) were charged in a microwave vial then the vial was evacuated and backfilled with argon (2x). In a glovebox under argon then *t*BuONa (24 mg, 1.3 equiv, 250 µmol), toluene (1.2 mL) and HP(*t*Bu)$_2$ (43 µL, 34 mg, 1.2 equiv, 231 µmol) were sequentially added. The reaction mixture was heated under microwave irradiation at 140 ºC for 4 h.

The reaction mixture was diluted with toluene (3 mL) filtered and concentrated under reduced pressure. The crude was purified by flash chromatography over silica gel (eluent gradient of pentane:Et_2O 95:5) yielding the product (104 mg) as an orange gum. The phosphine quickly oxidized was used was used in the next step without extensive analysis.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (ddd, *J* = 7.8, 3.9, 1.4 Hz, 1H), 7.97 (dd, *J* = 7.2, 1.3 Hz, 1H), 7.89 – 7.84 (m, 1H), 7.80 – 7.75 (m, 2H), 7.52 – 7.44 (m, 3H), 7.38 (tdd, *J* = 7.2, 1.4, 0.7 Hz, 1H), 7.22 (td, *J* = 7.5, 1.5 Hz, 1H), 5.29 (dt, *J* = 2.0, 1.4 Hz, 1H), 4.73 – 4.70 (m, 2H), 4.14 (s, 5H), 1.23 (d, *J* = 11.7 Hz, 9H), 1.11 (d, *J* = 11.6 Hz, 9H). **^{13}C NMR** (101 MHz, CD_2Cl_2) δ 146.0 (d, *J* = 10.8 Hz), 137.5 (d, *J* = 7.4 Hz), 135.7, 134.4, 134.4 (d, *J* = 2.7 Hz), 131.8, 130.6 (d, *J* = 2.3 Hz), 128.9, 128.8, 127.4, 127.3, 127.2, 126.8, 126.2 (d, *J* = 7.0 Hz), 125.8, 125.6 (d, *J* = 5.8

Hz), 92.6 (d, *J* = 7.8 Hz), 86.6, 76.9, 71.9, 71.4 (d, *J* = 2.6 Hz), 70.8, 38.6 (dd, *J* = 30.9, 25.6 Hz), 31.2 (dd, *J* = 81.2, 6.8 Hz). **^{31}P NMR** (202 MHz, $CDCl_3$) δ 20.58.

The crude product (55 mg, 103 µmol) was dissolved in CH_2Cl_2 (0.65 mL), $Me_2S{\cdot}AuCl$ (33 mg, 1.1 equiv 114 µmol) was added to the solution and the mixture was stirred 30 min.

The crude mixture was concentrated under reduced pressure and purified by flash chromatography over silica gel (eluent gradient of cyclohexane:EtOAc 80:20) yielding the pure **(S_p)-A** (68 mg, 88.9 µmol, 87%) as light orange powder.

M.p = 156-160 ºC (CH_2Cl_2), **^{1}H NMR** (400 MHz, CD_2Cl_2) δ 9.15 – 9.10 (m, 1H), 8.59 (ddd, *J* = 7.9, 4.5, 1.5 Hz, 1H), 8.07 (dd, *J* = 7.2, 1.3 Hz, 1H), 7.88 (d, *J* = 8.1 Hz, 1H), 7.84 – 7.75 (m, 2H), 7.58 (dddd, *J* = 13.4, 8.5, 7.0, 1.5 Hz, 2H), 7.52 – 7.45 (m, 2H), 7.45 – 7.39 (m, 1H), 5.08 (dd, *J* = 2.4, 1.5 Hz, 1H), 4.98 (t, *J* = 1.5 Hz, 1H), 4.92 – 4.89 (m, 1H), 4.16 (s, 4H), 1.55 (d, *J* = 15.5 Hz, 9H), 1.23 (d, *J* = 15.6 Hz, 9H). **^{13}C NMR** (101 MHz, CD_2Cl_2) δ 146.0 (d, *J* = 10.9 Hz), 137.5 (d, *J* = 7.3 Hz), 135.7, 134.5, 134.4 (d, *J* = 2.7 Hz), 131.9, 130.6 (d, *J* = 2.4 Hz), 128.8 (d, *J* = 9.7 Hz), 127.4 (d, *J* = 14.7 Hz), 127.3, 126.8, 126.2 (d, *J* = 7.1 Hz), 125.8, 125.7, 125.6, 92.6 (d, *J* = 7.7 Hz), 86.6, 76.9, 71.9, 71.4, 71.4, 70.8, 38.6 (dd, *J* = 30.7, 25.6 Hz), 31.2 (dd, *J* = 81.3, 6.8 Hz). **^{31}P NMR** (162 MHz, CD_2Cl_2) δ 63.9. **HRMS** (ESI+) calculated for $[C_{34}H_{37}AuClNaP^{56}Fe]^+$ 787.1229 m/z; found [M + Na]$^+$: 787.1229. $\boldsymbol{\alpha_D^{589}}$ = –87.8 deg.cm^2.g^{-1} ($CHCl_3$, c 0.05, 298 K).

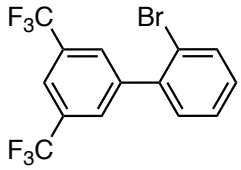
Synthesis of *ortho*-Halobiaryls

General procedure A: Synthesis of 2-bromo-1,1'-biphenyl

A flask was charged with (2-bromophenyl)boronic acid (1 equiv), K_2CO_3 (2 equiv) water:1,4-dioxane 1:4 (0.24 M) and the corresponding aryl halide (1.05 equiv). Argon was bubbled in the suspension for 15 min. $Pd(PPh_3)_4$ (1.5 mol %) was added and the mixture was stirred at 95 ºC for 18 h. The reaction mixture was concentrated under reduced pressure, water (1 vol) and EtOAc (0.25 vol) were added to the residue and phases were separated. The aqueous layer was extracted with EtOAc

(x2), the reunited organic layer was washed with water (x2) and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by short path distillation under reduced pressure unless stated otherwise.

2-Bromo-3',5'-bis(trifluoromethyl)-1,1'-biphenyl 1.73b

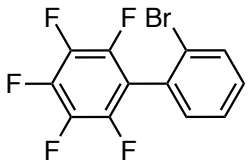


The compound was synthesized according to the general procedure **A** using (2-bromophenyl)boronic acid (2.0 g, 10 mmol), K_2CO_3 (2.76 g, 20 mmol), water (5.0 mL), 1,4-dioxane (20 mL), 1-bromo-3,5-bis(trifluoromethyl)benzene (1.8 mL, 3.1 g, 10.5 mmol) and $Pd(PPh_3)_4$ (173 mg).

The pure product was obtained as a colorless oil (3.1 g, 8.4 mmol, 84%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.89 (s, 2H), 7.72 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.45 – 7.41 (m, 1H), 7.37 – 7.33 (m, 1H), 7.30 (td, *J* = 7.7, 1.8 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 143.0, 139.7, 133.7, 131.6 (q, *J* = 33.4 Hz), 131.2, 130.3, 130.0 – 129.8 (m), 128.0, 123.5 (q, *J* = 272.8 Hz), 122.4, 121.7 (q, *J* = 3.8 Hz). **^{19}F NMR** (471 MHz, $CDCl_3$) δ -62.93. **HRMS** (APCI+) calculated for $[C_{14}H_7BrF_6]^+$ 367.9630 m/z; found $[M]^+$: 367.9636.

2'-Bromo-2,3,4,5,6-pentafluoro-1,1'-biphenyl 1.73i

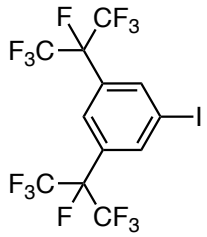


The compound was synthesized according to the general procedure **A** using (2-bromophenyl)boronic acid (4.0 g, 20 mmol), K_2CO_3 (5.53 g, 40 mmol), water (20.0 mL), 1,4-dioxane (80 mL), 1-bromo-2,3,4,5,6-pentafluorobenzene (2.74 mL, 5.4 g, 22.0 mmol)) and $Pd(PPh_3)_4$ (346 mg).

The product was obtained as a colorless oil (3.33 g, 10.3 mmol, 52%). The obtained characterization data were in agreement with those reported in literature.[159]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.47 – 7.41 (m, 1H), 7.39 – 7.33 (m, 1H), 7.29 (dd, *J* = 7.5, 1.8 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.20 (d, *J* = 248.5 Hz), 141.39 (d, *J* = 254.7 Hz), 137.68 (d, *J* = 252.8 Hz), 133.32, 132.14, 131.27, 128.17 (q, *J* = 1.8 Hz), 127.72, 124.46, 115.37 (td, *J* = 19.1, 4.0 Hz).**^{19}F NMR** (376 MHz, $CDCl_3$) δ -139.64 – -139.90 (m), -154.15 (t, *J* = 20.9 Hz), -162.11 (td, *J* = 22.3, 8.0 Hz).

1-Iodo-3,5-bis(perfluoropropan-2-yl)benzene



Cu* (36.6 g, 6.4 equiv, 0.58 mol, freshly prepared by reduction of $Cu(SO_4)$ with Zn dust in water[160]) was suspended in dry DMF (164 mL) and 1,3-dibromobenzene (10.9 mL, 90 mmol) was added. The reaction flask was evacuated and backfilled with argon (2x) then 1,1,1,2,3,3,3-heptafluoro-2-iodopropane (33.3 ml, 2.6 equiv, 234 mmol) was added and the mixture was stirred at 90 ºC for 40 h. The reaction mixture was filtered over Celite® and the pad of Celite® was washed with Et_2O (5x). The filtrate was diluted with water (1 L) and phases were separated, the aqueous layer was extracted with Et_2O (3x), the reunited organic layer was washed with 5% Na_2SO_3 aq. water and brine, dried of $MgSO_4$ and concentrated under reduced pressure. The crude was purifier by short path distillation under reduced pressure allowing the pure product (29.75 g, 72 mmol, 80%).

159 Li, Z.; Twieg, R. J. *Chem. Eur. J.* **2015**, *21*, 15534–15539.

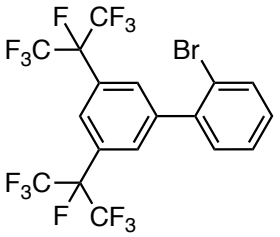
160 Arlt, A.; Toyama, H.; Takada, K.; Hashimoto, T.; Maruoka, K. *Chem. Commun.* **2017**, *53*, 4779–4782.

(Two reactions run in parallel) The crude (3.1 g, 7.49 mmol) was added dropwise over 2 h into a solution of I_2 (1.05 g, 0.55 equiv, 4.12 mmol) in oleum (20% Wt SO_3 in H_2SO_4, 15 mL, 1 equiv, 7.49 mmol, obtain by distillation from H_2SO_4 over P_4O_{10} at 160 ºC). After the addition the reaction was stirred for 26 h at 65 ºC. The reaction was monitored by GC-MS. The reaction was carefully poured over crushed ice (100 mL). 5% Na_2SO_3 aq. was added and the mixture was stirred for 30 min. The phases were separated and the aqueous layer was extracted with Et_2O (3x) the reunited organic layer was washed with water (2x), $NaHCO_3$ aq. and brine, dried of $MgSO_4$ and concentrated under reduced pressure. The crude was purifier by short path distillation under reduced pressure allowing the pure product (6.1 g, 11.3 mmol, 75%).

The obtained characterization data were in agreement with those reported in literature.[161]

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 1.7 Hz, 2H), 7.81 (s, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 139.0 – 136.6 (m), 130.0 (dd, *J* = 21.1, 2.3 Hz), 123.7 – 122.1 (m), 124.7 – 116.3 (m), 94.7 (t, *J* = 2.6 Hz), 90.7 (heptd, *J* = 204.9, 33.6 Hz). **^{19}F NMR** (471 MHz, $CDCl_3$) δ -75.6 (d, *J* = 7.6 Hz), -182.3 (hept, *J* = 7.4 Hz).

2-Bromo-3',5'-bis(perfluoropropan-2-yl)-1,1'-biphenyl 1.73f



The compound was synthesized according to the general procedure **A** using (2-bromophenyl)boronic acid (1.20 g, 6.0 mmol), K_2CO_3 (1.66 g, 40 mmol), water

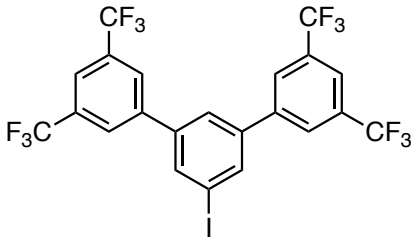
161 Fujiki, K.; Ichikawa, J.; Kobayashi, H.; Sonoda, A.; Sonoda, T. *J. Fluor. Chem.* **2000**, *102*, 293–300.

(5.0 mL), 1,4-dioxane (20 mL), 1-iodo-3,5-bis(perfluoropropan-2-yl)benzene (3. 4 g, 6.3 mmol)) and $Pd(PPh_3)_4$ (104 mg).

The pure product was obtained as a colorless oil (3.03g, 5.32 mmol, 89%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 2.8 Hz, 3H), 7.73 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.44 (td, *J* = 7.5, 1.2 Hz, 1H), 7.36 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.34 – 7.28 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 143.1 (t, *J* = 2.5 Hz), 139.9, 133.9, 131.2, 130.3, 129.9 (d, *J* = 9.8 Hz), 128.2 (dd, *J* = 20.8, 2.3 Hz), 128.1, 122.5 (d, *J* = 12.4 Hz), 120.6 (dd, *J* = 287.4, 27.8 Hz), 91.4 (dp, *J* = 204.0, 33.3 Hz). **^{19}F NMR** (471 MHz, $CDCl_3$) δ -75.54 (d, *J* = 7.3 Hz), -182.08 (hept, *J* = 7.3 Hz). **HRMS** (APCI+) calculated for $[C_{18}H_7BrF_{14}]^+$ 567.9502 m/z; found $[M]^+$: 567.9501.

5'-Iodo-3,3'',5,5''-tetrakis(trifluoromethyl)-1,1':3',1''-terphenyl



A flame dried flask under argon was charged with 1,3,5-tribromobenzene (6.30 g, 20.0 mmol) and Et_2O (90.0 ml) and the suspension was cooled to –78 ºC in a dry ice/acetone bath. *n*BuLi (2.5 M, 8.4 mL, 1.05 equiv, 21.0 mmol) was added dropwise over 5 min and the solution was stirred for an additional 30 min. TMSCl (2.8 mL, 2.4 g, 1.1 equiv, 22.0 mmol) was added at –78 ºC, the reaction was stirred for 10 min at the same temperature then allowed to warm up to room temperature and stirred for 30 min.

The reaction was quenched by addition of $NaHCO_3$ sat. (50 mL) and phases were separated. The aqueous layer was extracted with Et_2O, the reunited organic layer was washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was submitted to short path distillation under reduced pressure yielding the product used as such in the next step.

A flask was charged with (3,5-dibromophenyl)trimethylsilane (2.31 g, 7.5 mmol), (3,5-bis(trifluoromethyl)phenyl)boronic acid (5.80 g, 3 equiv, 22.5 mmol), Na_2CO_3 (1.35 g, 1.7 equiv, 12.7 mmol), toluene (22.5 mL) and water (4.5 mL) and argon was bubbled in the suspension for 15 min while stirred at 24 ºC room temperature then $Pd(PPh_3)_4$ (217 mg, 2.5 mol %) was added. The reaction mixture was stirred at reflux for 18 h. The reaction was monitored by GC-MS analysis.

The mixture was cooled to room temperature and filtered. Water (20 mL) was added, and phases were separated. The aqueous layer was extracted with EtOAc (2x), the reunited organic layer was washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product (3.51 g) was used without purification in the next step.

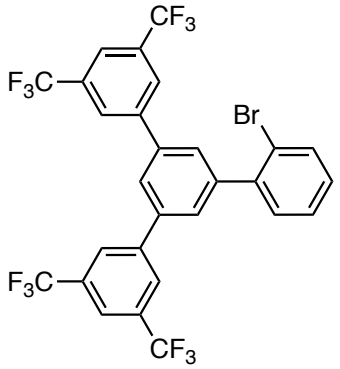
The crude product (3.0 g, 5.2 mmol) was dissolved in CH_2Cl_2 (34 mL) and cooled to 0 ºC in an ice bath and a solution ICl (1.7 g, 2 equiv, 10 mmol) in CH_2Cl_2 (34 mL) was added dropwise keeping the temperature below 10 ºC. The reaction was kept for an additional 30 min in the cold bath and warmed up to room temperature and stirred for 5 h. The reaction was monitored by GC-MS analysis.

The reaction was quenched by addition of $Na_2S_2O_3$ sat. then water (150 mL) was added, and phases were separated. The aqueous layer was extracted with Et_2O, the reunited organic layer was washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was eluted through a plug of silica gel with cyclohexane then recrystallized from boiling *n*-hexane yielding the pure product (2.33 g, 3.71 mmol) as colorless needles. The obtained characterization data were in agreement with those reported in literature.[162]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 6H), 7.94 (s, 2H), 7.70 (t, J = 1.7 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.5, 141.3, 136.7, 132.7 (q, J = 33.6 Hz), 127.6 (d, J = 3.9 Hz), 125.9, 123.3 (q, J = 272.8 Hz), 122.4 – 122.0 (m), 95.9.**^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.88.

162 Sevov, C. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 10625–10631.

5'-(2-Bromophenyl)-3,3'',5,5''-tetrakis(trifluoromethyl)-1,1':3',1''-terphenyl 1.73g



The compound was synthesized according to the general procedure **A** using (2-bromophenyl)boronic acid (502 mg, 2.50 mmol), K_2CO_3 (691 mg, 5.00 mmol), water (2.0 mL), 1,4-dioxane (8.0 mL), 5'-iodo-3,3'',5,5''-tetrakis(trifluoromethyl)-1,1':3',1''-terphenyl (1.65 g, 2.63 mmol)) and $Pd(PPh_3)_4$ (43 mg).

Purification by flash chromatography (eluent, pentane:toluene, 99.7:0.3) afforded to title compound (1.29 g, 1.96 mmol, 78%) as a white solid.

M.p. = 174.3 – 175.5 ºC ($CHCl_3$). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.10 (s, 4H), 7.94 (s, 2H), 7.79 (t, *J* = 1.8 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.72 (d, *J* = 1.7 Hz, 2H), 7.48 – 7.43 (m, 2H), 7.33 – 7.28 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 143.5, 142.7, 141.2, 139.6, 133.6, 132.6 (q, *J* = 33.4 Hz), 131.3, 129.8, 129.1, 127.9, 127.9 – 127.4 (m), 125.5, 123.4 (q, *J* = 272.8 Hz), 122.7, 121.8 (p, *J* = 3.8 Hz). **^{19}F NMR** (471 MHz, $CDCl_3$) δ -62.87. **HRMS** (APCI+) calculated for $[C_{28}H_{13}BrF_{12}]^+$ 656.0004 m/z; found $[M]^+$: 656.0009.

General procedure B: Synthesis of 2-iodo-1,1'-biphenyl

In an oven dried flask was charged with magnesium turning (0.61 g, 2.5 equiv, 25.0 mmol) covered with THF (4 mL) iodine (cat.) and 1 drop of 1,2-dibromoethane were added. The iodine solution was stirred 15 min at reflux yielding a colorless solution then the corresponding aryl bromide (1.2 equiv, 12.0 mmol) in THF (16 mL) was added dropwise at reflux over 15 min. The reaction mixture was stirred 3

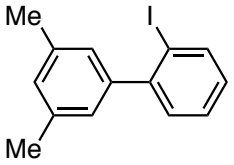
h at reflux then cooled down to room temperature. 1-bromo-2-chlorobenzene (1.17 mL, 1 equiv, 10.0 mmol) was added and the reaction mixture was heated to 60 ºC for 6 h. The reaction was followed by GC-MS analysis.

The reaction mixture was cooled to 0 ºC with an ice bath and iodine (3.05 g, 1.2 equiv, 12 mmol) in THF (20 mL) was added dropwise keeping the temperature below 5 ºC. The reaction mixture was stirred additionally 10 min at 0 ºC then 30 min at room temperature.

NH_4Cl sat. (5 mL) and $Na_2S_2O_3$ sat. (2 mL) were added to the reaction mixture that was stirred for 1 h. The crude mixture was filtered, diluted with EtOAc (50 mL) and water (200 mL) and phases were separated. The aqueous layer was extracted with EtOAc (2x50 mL), the reunited organic layer was washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure.

The crude was purified by flash column chromatography over silica gel.

2-Iodo-3',5'-dimethyl-1,1'-biphenyl 1.73d



The compound was synthesized according to the general procedure **B** using 1-bromo-3,5-dimethylbenzene (1.63 mL, 2.2 g).

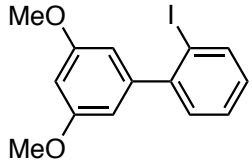
Purification by flash column chromatography over silica gel (eluent, pentane:toluene, 95:5) afforded to title compound (2.13 g, 69.1 mmol, 69%) mixed with small amount of inseparable impurities as a colorless thick oil. The obtained characterization data were in agreement with those reported in literature.[163]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.37 (td, *J* = 7.4, 1.2 Hz, 1H), 7.31 – 7.28 (m, 1H), 7.04 – 6.98 (m, 2H), 6.96 (dt, *J* = 1.7, 0.7 Hz, 2H),

163 Leverenz, M.; Merten, C.; Dreuw, A.; Bach, T. *J. Am. Chem. Soc.* **2019**, *141*, 20053–20057.

2.38 (q, *J* = 0.7 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 147.0, 144.3, 139.6, 137.5, 130.16, 129.32, 128.7, 128.1, 127.2, 98.8, 21.5.

2-Iodo-3',5'-dimethoxy-1,1'-biphenyl 1.73e

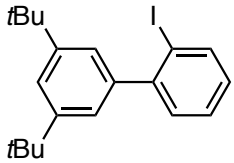


The compound was synthesized according to the general procedure **B** using 1-bromo-3,5-dimethoxybenzene (2.2 g).

Purification by flash column chromatography over silica gel (eluent, pentane:Et_2O, 95:5) afforded to title compound (1.77 g, 53.0 mmol, 52%) as a colorless thick oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.38 (td, *J* = 7.5, 1.3 Hz, 1H), 7.33 – 7.29 (m, 1H), 7.03 (ddd, *J* = 7.9, 7.3, 1.8 Hz, 1H), 6.50 – 6.47 (m, 3H), 3.83 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.4, 146.7, 146.2, 139.7, 130.0, 129.0, 128.2, 107.7, 100.0, 98.4, 55.6. **HRMS** (ESI+) calculated for $[C_{14}H_{14}IO_2]^+$ 341.0033 m/z; found $[M + H]^+$: 341.0028.

3',5'-Di-*tert*-butyl-2-iodo-1,1'-biphenyl 1.73h



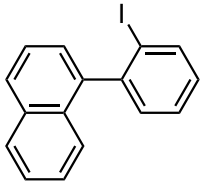
3',5'-di-*tert*-butyl-2-iodo-1,1'-biphenyl was synthesized according to the general procedure **B** using 1-bromo-3,5-di-*tert*-butylbenzene (3.23 g).

Purification by flash column chromatography over silica gel (eluent, pentane:toluene, 95:5) afforded to title compound (1.61 g, 41.0 mmol, 41%) mixed with small amount of inseparable impurities as a colorless thick oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (ddd, *J* = 7.9, 1.2, 0.5 Hz, 1H), 7.43 (t, *J* = 1.8 Hz, 1H), 7.42 – 7.34 (m, 2H), 7.20 (d, *J* = 1.9 Hz, 2H), 7.02 (ddd, *J* = 8.0, 6.8, 2.2

Hz, 1H), 1.37 (s, 18H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.25, 147.67, 143.16, 139.80, 130.37, 128.59, 128.21, 123.97, 121.33, 99.11, 35.11, 31.64. **HRMS** (APCI+) calculated for $[C_{20}H_{25}I]^+$ 392.0996 m/z; found $[M]^+$: 392.0996.

1-(2-Iodophenyl)naphthalene 1.73k



The compound was synthesized according to the general procedure **B** using 1-bromo-naphtalene (1.68 mL, 2.5 g).

Purification by recrystallization from boiling *n*-hexane (10 mL/g) afforded to title compound (1.82 g, 59.0 mmol, 55%) as colorless prisms. The obtained characterization data were in agreement with those reported in literature.[164]

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.95 – 7.90 (m, 2H), 7.57 – 7.52 (m, 1H), 7.52 – 7.48 (m, 1H), 7.47 (td, *J* = 7.5, 1.3 Hz, 1H), 7.44 – 7.39 (m, 2H), 7.36 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.33 (dd, *J* = 6.9, 1.2 Hz, 1H), 7.14 (ddd, *J* = 8.0, 7.4, 1.7 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 145. 8, 142.6, 139.5, 133.9, 131.8, 131.3, 129.4, 128.6, 128.5, 128.3, 127.3, 126.5, 126.4, 126.3, 125.6, 101.0.

Synthesis of Ferrocene Gold(I) Complexes

General procedure C: Negishi cross-coupling of (*p*-tolylsulfoxide)ferrocene with 2-halo-1,1'-biaryl.

Sulfoxide **(*S*$_S$)-1.10** (1 equiv) was charged in a 3-neck flask, the atmosphere was evacuated and backfilled with argon (2x) and dry 2-MeTHF (0.08 M, 1 volume) was added. After complete dissolution of the solid the reaction mixture was cooled to –78 ºC under vigorous stirring.

164 Zhu, C.; Zhao, Y.; Wang, D.; Sun, W. Y.; Shi, Z. *Sci. Rep.* **2016**, *6*, 1–9.

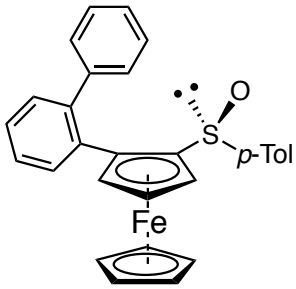
LDA was prepared by addition of *n*BuLi (1.5 equiv) to a solution of diisopropylamine (1.5 equiv) in 2-MeTHF (0.15 volume) at –78 ºC, after completion of the addition the solution was allowed to warm up to room temperature and was stirred for 10 min.

The LDA solution was added to the sulfoxide suspension at –78 ºC keeping the temperature below –75 ºC, the suspension turned to a clear red homogeneous solution, and the mixture was stirred for an additional 30 min at the same temperature. The solution was slowly transferred via cannula to a suspension of $ZnCl_2$ (1.6 equiv) in 2-MeTHF (0.10 volume) at –78 ºC. After completion of the addition the reaction mixture was stirred 15 min at –78 ºC, allowed to warm up to 24 ºC and stirred for an additional 1 h.

Tris-*o*-furylphosphine (8 mol %) and Pd_2dba_3 (2 mol %) were stirred 30 min in 2-MeTHF (200 $mg.mL^{-1}$) giving a bright yellow solution that was added to the previously prepared aryl-zinc reagent followed by the corresponding arylhalide (1.05 equiv) and the reaction mixture was stirred 5 h at 70 ºC.

The reaction was quenched by addition of 5% aq. citric acid (5 volumes), the mixture was stirred for 30 min then filtered over pad of Celite®. Phases were separated and the organic layer was washed with 5% aq. citric acid, water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by flash chromatography over silica gel.

(S_S,S_p)-2-(2,1'-Biphenyl)-1-(*p*-tolyl-sulfoxide)ferrocene 1.66b

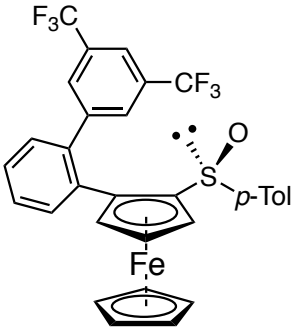


The compound was synthetized according to the general procedure **C** using sulfoxide **(S_S)-1.10** (486 mg, 1.50 mmol) in 2-MeTHF (15 mL), LDA (prepared from diisopropylamine (0.32 mL), *n*BuLi (2.5M, 0.90 mL) in 2-MeTHF (2.3 mL)), $ZnCl_2$ (327 mg) in 2Me-THF (1.5 mL), tris-*o*-furylphosphine (28 mg), Pd_2dba_3 (27 mg) and 2-bromo-1,1'-biphenyl (367 mg).

The crude was purified by flash chromatography over silica gel (eluent, cylcohexane:Et_2O:$CHCl_3$ 100:0:0 to 70:20:10) yielding the title compound (608 mg, mmol, 85%) as an orange foam.

M.p. = 93 – 95 ºC (CH_2Cl_2), **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 8.31 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.69 – 7.65 (m, 2H), 7.49 (td, *J* = 7.5, 1.4 Hz, 1H), 7.41 (td, *J* = 7.5, 1.4 Hz, 1H), 7.36 – 7.32 (m, 2H), 7.28 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.19 – 7.14 (m, 3H), 6.94 – 6.88 (m, 2H), 4.18 (s, 5H), 4.11 (t, *J* = 2.6 Hz, 1H), 4.01 (dd, *J* = 2.6, 1.4 Hz, 1H), 3.82 (dd, *J* = 2.6, 1.5 Hz, 1H), 2.42 (s, 3H). **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 143.5, 142.0, 141.8, 140.9, 134.7, 133.2, 130.1, 129.9, 129.7, 128.0, 127.0, 126.8, 125.5, 95.5, 90.6, 74.4, 71.4, 68.8, 67.7, 21.6. **HRMS** (ESI+) calculated for $[C_{29}H_{24}NaOS^{56}Fe]^+$ 499.0776 m/z; found $[M + Na]^+$: 499.0784. $\boldsymbol{\alpha_D^{589}}$ = –19.8 deg.cm^2.g^{-1} ($CHCl_3$, c 0.05, 298 K).

(S_S,S_p)-2-(3',5'-Bis(trifluoromethyl)-2,1'-biphenyl)-1-(*p*-tolyl-sulfoxide)ferrocene 1.66c

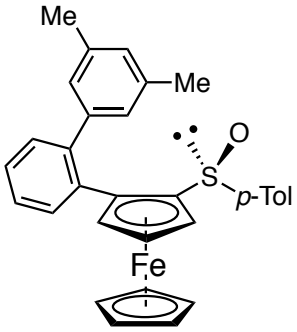


The compound was synthetized according to the general procedure **C** using sulfoxide **(S_S)-1.10** (2.42 g, 10.00 mmol) in 2-MeTHF (101 mL), LDA (prepared from diisopropylamine (2.12 mL), *n*BuLi (2.5M, 6.0 mL) in 2-MeTHF (15.0 mL)), $ZnCl_2$ (2.18 g) in 2-MeTHF (10 mL), tris-*o*-furylphosphine (186 mg), Pd_2dba_3 (183 mg) and 2-bromo-3',5'-bis(trifluoromethyl)-1,1'-biphenyl **1.73c** (3.88 g).

The crude was purified by flash chromatography over silica gel (eluent, cylcohexane:Et_2O:$CHCl_3$ 100:0:0 to 70:20:10) yielding the title compound (5.56 g, 9.08 mmol, 91%) as an orange foam.

M.p. = 86 – 87 ºC (CH_2Cl_2), **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 8.47 – 8.43 (m, 1H), 7.68 (s, 1H), 7.59 (td, *J* = 7.6, 1.4 Hz, 1H), 7.52 – 7.46 (m, 3H), 7.35 – 7.31 (m, 2H), 7.30 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.26 – 7.22 (m, 2H), 4.32 (s, 5H), 4.17 (dd, *J* = 2.7, 1.4 Hz, 1H), 4.14 (t, *J* = 2.6 Hz, 1H), 3.67 (dd, *J* = 2.6, 1.5 Hz, 1H), 2.34 (s, 3H). **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 143.9, 141.6, 140.8, 140.3, 135.3, 133.7, 131.0 (q, *J* = 32.9 Hz), 130.3 (d, *J* = 4.0 Hz), 129.7, 129.5, 128.5, 128.4, 125.0, 123.8 (q, *J* = 272.8 Hz), 120.5 (p, *J* = 3.9 Hz), 95.8, 89.5, 74.2, 71.4, 69.1, 69.0, 21.5. **^{19}F NMR** (471 MHz, CD_2Cl_2) δ -63.09. **HRMS** (ESI+) calculated for $[C_{31}H_{22}F_6NaOS^{56}Fe]^+$ 635.0537 m/z; found $[M + Na]^+$: 635.0514. α_D^{589} = +134.9 deg.cm^2.g^{-1} ($CHCl_3$, c 0.05, 298 K).

(S_S,S_p)-2-(3',5'-Dimethyl-2,1'-biphenyl)-1-(*p*-tolyl-sulfoxide)ferrocene 1.66d

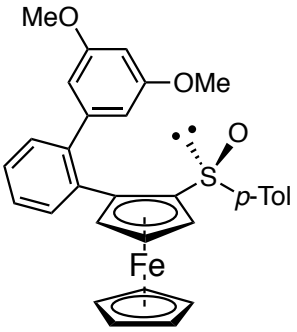


The compound was synthetized according to the general procedure **C** using sulfoxide **(S_S)-1.10** (486 mg, 1.50 mmol) in 2-MeTHF (12.5 mL), LDA (prepared from diisopropylamine (0.27 mL), *n*BuLi (2.5M, 0.75 mL) in 2-MeTHF (1.9 mL)), $ZnCl_2$ (273mg) in 2-MeTHF (1.3 mL), tris-*o*-furylphosphine (23 mg), Pd_2dba_3 (23 mg) and 2-bromo-3',5'-dimethyl-1,1'-biphenyl **1.73d** (405 mg)

The crude was purified by flash chromatography over silica gel (eluent, cylcohexane:Et_2O:$CHCl_3$ 100:0:0 to 70:20:10) yielding the title compound (544 g, 1.08 mmol, 86%) as an orange foam.

M.p. = 192 – 194 ºC (CH_2Cl_2). **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 8.34 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.58 – 7.52 (m, 2H), 7.45 (td, *J* = 7.6, 1.5 Hz, 1H), 7.37 (td, *J* = 7.5, 1.4 Hz, 1H), 7.29 – 7.24 (m, 2H), 7.22 (dd, *J* = 7.7, 1.4 Hz, 1H), 6.78 (bs, 1H), 6.39 (bs, 2H), 4.22 (s, 5H), 4.14 (dd, *J* = 2.7, 1.5 Hz, 1H), 4.11 (t, *J* = 2.6 Hz, 1H), 3.81 (dd, *J* = 2.6, 1.5 Hz, 1H), 2.37 (s, 3H), 2.14 (s, 6H). **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 143.5, 141.6, 141.4, 137.2, 134.8, 133.2, 129.8, 129.6, 128.2, 127.8, 127.7, 126.6, 125.1, 95.2, 90.2, 74.4, 71.2, 68.4, 68.2, 21.4, 21.2. **HRMS** (ESI+) calculated for $[C_{31}H_{29}OS^{56}Fe]^+$ 505.1283 m/z; found $[M + H]^+$: 505.1277. $\boldsymbol{\alpha_D^{589}}$ = +202.4 deg.cm^2.g^{-1} ($CHCl_3$, c 0.050, 298 K).

(S_S,S_p)-2-(3',5'-Dimethoxy-2,1'-biphenyl)-1-(*p*-tolyl-sulfoxide)ferrocene 1.66e

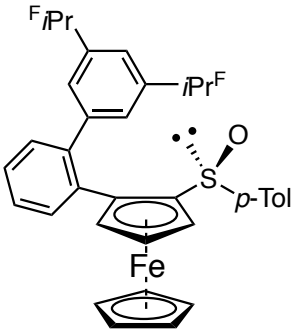


The compound was synthetized according to the general procedure **C** using sulfoxide **(S_S)-1.10** (405 mg, 1.25 mmol) in 2-MeTHF (12.5 mL), LDA (prepared from diisopropylamine (0.27 mL), *n*BuLi (2.5M, 0.75 mL) in 2-MeTHF (1.9 mL)), $ZnCl_2$ (273mg) in 2-MeTHF (1.3 mL), tris-*o*-furylphosphine (23 mg), Pd_2dba_3 (23 mg) and 2-bromo-3',5'-dimethoxy-1,1'-biphenyl **1.73e** (446 mg).

The crude was purified by flash chromatography over silica gel (eluent, CH_2Cl_2:Et_2O: 100:0 to 95:5) yielding the title compound (589 mg, 1.10 mmol, 88%) as an orange foam.

M.p. = 98 – 101 ºC (CH_2Cl_2), **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 8.26 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.71 – 7.67 (m, 2H), 7.50 (td, *J* = 7.5, 1.5 Hz, 1H), 7.43 (td, *J* = 7.5, 1.4 Hz, 1H), 7.38 – 7.35 (m, 2H), 7.34 (dd, *J* = 7.6, 1.4 Hz, 1H), 6.28 – 6.23 (m, 3H), 4.18 (s, 5H), 4.17 (t, *J* = 2.6 Hz, 1H), 3.96 (dd, *J* = 2.5, 1.4 Hz, 1H), 3.88 (dd, *J* = 2.6, 1.4 Hz, 1H), 3.64 (s, 6H), 2.45 (s, 3H). **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 160.6, 143.9, 143.8, 142.0, 140.7, 134.5, 133.1, 129.8, 129.7, 128.2, 127.2, 125.6, 107.9, 99.8, 95.5, 91. 6, 74.2, 71.2, 69.1, 67.0, 55.9, 21.6. **HRMS** (ESI+) calculated for $[C_{31}H_{28}NaO_3S^{56}Fe]^+$ 559.1001 m/z; found $[M + Na]^+$: 559.0994. $\boldsymbol{\alpha_D^{589}}$ = –122.6 deg.cm^2.g^{-1} ($CHCl_3$, c 0.05, 298 K).

(S_S,S_p)-2-(3',5'-Bis(perfluoroisopropyl)-2,1'-biphenyl)-1-(*p*-tolyl-sulfoxide)ferrocene 1.66f

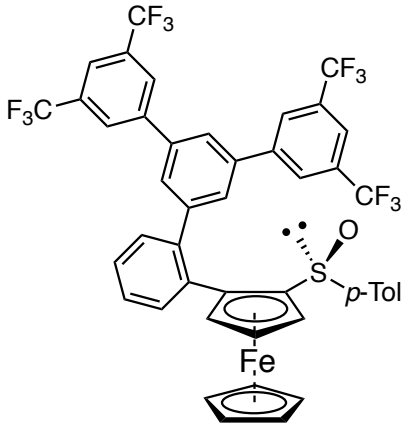


The compound was synthetized according to the general procedure **C** using sulfoxide **(S_S)-1.10** (486 mg, 1.50 mmol) in 2-MeTHF (15 mL), LDA (prepared from diisopropylamine (0.32 mL), *n*BuLi (2.5M, 0.90 mL) in 2-MeTHF (2.3 mL)), $ZnCl_2$ (327 mg) in 2-MeTHF (1.5 mL), tris-*o*-furylphosphine (28 mg), Pd_2dba_3 (27 mg) and 2-bromo-3',5'-bis(perfluoroisopropyl)-1,1'-biphenyl **1.73f** (570 mg).

The crude was purified by flash chromatography over silica gel (eluent, cylcohexane:Et_2O:$CHCl_3$ 100:0:0 to 70:20:10) yielding the title compound (654 mg, 1.38 mmol, 92%) as an orange foam.

M.p. = 89 – 90 ºC (CH_2Cl_2). **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 8.47 – 8.41 (m, 1H), 7.66 (s, 1H), 7.64 – 7.53 (m, 3H), 7.48 (td, *J* = 7.6, 1.4 Hz, 1H), 7.43 (d, *J* = 2.1 Hz, 2H), 7.31 – 7.25 (m, 3H), 4.27 (d, *J* = 1.8 Hz, 5H), 4.08 (t, *J* = 2.6 Hz, 1H), 4.01 (dt, *J* = 2.7, 1.6 Hz, 1H), 3.59 (dd, *J* = 2.5, 1.4 Hz, 1H), 2.38 (s, 3H). **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 144.56 – 144.16 (m), 141.73, 140.59, 140.52, 134.95, 133.83, 130.16 (d, *J* = 10.2 Hz), 129.83, 129.71, 128.49, 127.75 (dd, *J* = 20.8, 2.6 Hz), 125.29, 121.35 (t, *J* = 12.0 Hz), 124.58 – 117.07 (m), 95.70, 91.51 (dp, *J* = 204.1, 33.3 Hz), 89.48, 73.73, 71.41, 69.00, 68.84, 21.48. **^{19}F NMR** (376 MHz, CD_2Cl_2) δ -75.55 (d, *J* = 7.3 Hz), -181.99 (p, *J* = 7.2 Hz). **HRMS** (ESI+) calculated for $[C_{35}H_{23}OS^{56}Fe]^+$ 813.0591 m/z; found $[M + H]^+$: 813.0576. **α_D^{589}** = +106.1 deg.cm^2.g^{-1} ($CHCl_3$, c 0.050, 298 K).

(S_S,S_p)-2-(3',5'-Bis(3',5'-bis(3'',3''',5'',5'''-bis(trifluoromethyl)benzene)-2,1'-terphenyl)-1-(*p*-tolyl-sulfoxide)ferrocene 1.66g



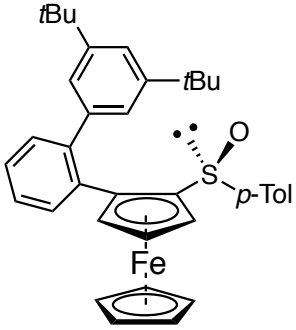
The compound was synthetized according to the general procedure **C** using sulfoxide **(S_S)-1.10** (486 mg, 1.50 mmol) in 2-MeTHF (15 mL), LDA (prepared from diisopropylamine (0.32 mL), *n*BuLi (2.5M, 0.90 mL) in 2-MeTHF (2.3 mL)), $ZnCl_2$ (327 mg) in 2-MeTHF (1.5 mL), tris-*o*-furylphosphine (28 mg), Pd_2dba_3 (27 mg) and 5'-(2-bromophenyl)-3,3",5,5"-tetrakis(trifluoromethyl)-1,1':3',1"-terphenyl **1.73g** (1.1 g).

The crude was purified by flash chromatography over silica gel (eluent, cylcohexane:Et_2O:$CHCl_3$ 100:0:0 to 80:10:10) yielding the title compound (1.13 g, 1.25 mmol, 83%) as an orange foam.

M.p. = 125 – 128 ºC (CH_2Cl_2). **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 8.43 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.96 (s, 4H), 7.94 (s, 2H), 7.63 – 7.58 (m, 2H), 7.56 – 7.47 (m, 4H), 7.24 (d, *J* = 1.7 Hz, 2H), 7.14 – 7.10 (m, 2H), 4.32 (s, 5H), 4.27 (t, *J* = 2.6 Hz, 1H), 4.23 (dd, *J* = 2.6, 1.4 Hz, 1H), 3.97 (dd, *J* = 2.5, 1.4 Hz, 1H), 2.30 (s, 3H). **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 143.47, 143.17, 141.79, 141.66, 140.65, 139.17, 135.27, 133.21, 132.21 (q, *J* = 33.2 Hz), 129.84, 129.50, 129.36, 128.59, 128.09 (q, *J* = 3.7 Hz), 127.79, 125.08, 124.67, 123.88 (q, *J* = 272.8 Hz), 121.65 (p, *J* = 3.9 Hz), 96.37, 90.76, 74.38, 71.40, 68.97, 67.82, 21.35. **^{19}F NMR** (471 MHz, CD_2Cl_2) δ -63.00. **HRMS** (ESI+) calculated for $[C_{45}H_{28}F_{12}NaOS^{56}Fe]^+$ 923.0911

m/z; found $[M + Na]^+$: 923.0911. α_D^{589} = +100.6 deg.cm^2.g^{-1} ($CHCl_3$, c 0.05, 298 K).

(S_S,S_p)-2-(3',5'-Di-*tert*-butyl-2,1'-biphenyl)-1-(*p*-tolyl-sulfoxide)ferrocene 1.66h

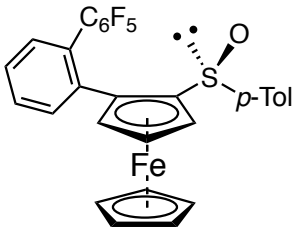


The compound was synthetized according to the general procedure **C** using sulfoxide **(S_S)-1.10** (486 mg, 1.50 mmol) in 2-MeTHF (15 mL), LDA (prepared from diisopropylamine (0.32 mL), *n*BuLi (2.5M, 0.90 mL) in 2-MeTHF (2.3 mL)), $ZnCl_2$ (327 mg) in 2-MeTHF (1.5 mL), tris-*o*-furylphosphine (28 mg), Pd_2dba_3 (27 mg) and 2-bromo-3',5'-di-*tert*-butyl-1,1'-biphenyl **1.73h** (620 mg).

The crude was purified by flash chromatography over silica gel (eluent, cylcohexane:Et_2O:$CHCl_3$ 100:0:0 to 70:20:10) yielding the title compound (727 mg, 1.24 mmol, 82%) as an orange foam.

M.p. = 109 – 111 ºC (CH_2Cl_2), **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 8.32 (ddd, *J* = 7.7, 1.5, 0.5 Hz, 1H), 7.71 – 7.65 (m, 2H), 7.48 (td, *J* = 7.5, 1.5 Hz, 1H), 7.42 (td, *J* = 7.5, 1.5 Hz, 1H), 7.39 – 7.31 (m, 3H), 7.22 (t, *J* = 1.9 Hz, 1H), 6.88 (d, *J* = 1.9 Hz, 2H), 4.18 (s, 5H), 4.06 (t, *J* = 2.6 Hz, 1H), 3.92 (dd, *J* = 2.7, 1.4 Hz, 1H), 3.75 (dd, *J* = 2.6, 1.5 Hz, 1H), 2.42 (s, 3H), 1.22 (s, 18H). **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 150.45, 144.57, 141.74, 141.05, 140.70, 134.47, 133.41, 130.00, 129.72, 128.04, 126.72, 125.64, 124.76, 120.41, 95.13, 91.20, 74.33, 71.21, 68.78, 67.79, 35.08, 31.64, 21.60. **HRMS** (ESI+) calculated for $[C_{37}H_{40}NaOS^{56}Fe]^+$ 611.2041 m/z; found $[M + Na]^+$: 611.2038. α_D^{589} = +81.3 deg.cm^2.g^{-1} ($CHCl_3$, c 0.05, 298 K).

(S_S,S_p)-2-(2',3',4',5',6'-Pentafluoro-2,1'-biphenyl)-1-(*p*-tolyl-sulfoxide)ferrocene 1.66i

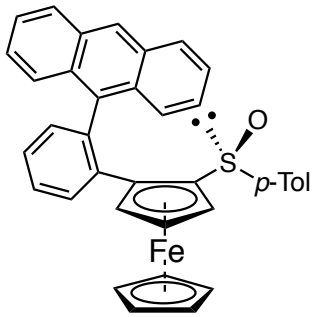


The compound was synthetized according to the general procedure **C** using sulfoxide **(S_S)-1.10** (486 mg, 1.50 mmol) in 2-MeTHF (15 mL), LDA (prepared from diisopropylamine (0.32 mL), *n*BuLi (2.5M, 0.90 mL) in 2-MeTHF (2.3 mL)), $ZnCl_2$ (327 mg) in 2-MeTHF (1.5 mL), tris-*o*-furylphosphine (28 mg), Pd_2dba_3 (27 mg) and 2'-bromo-2,3,4,5,6-pentafluoro-1,1'-biphenyl **1.73i** (509 mg).

The crude was purified by flash chromatography over silica gel (eluent, cylcohexane:Et_2O:$CHCl_3$ 100:0:0 to 80:10:10) yielding the title compound (250 mg, 0.44 mmol, 30%) as an orange foam.

M.p. = 87 – 89 ºC (CH_2Cl_2). **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 8.40 (ddd, *J* = 7.9, 1.4, 0.5 Hz, 1H), 7.72 – 7.68 (m, 2H), 7.63 (td, *J* = 7.7, 1.4 Hz, 1H), 7.46 (td, *J* = 7.6, 1.3 Hz, 1H), 7.37 – 7.32 (m, 2H), 7.25 (dtd, *J* = 7.7, 1.4, 0.5 Hz, 1H), 4.25 (t, *J* = 2.6 Hz, 1H), 4.15 (dd, *J* = 2.7, 1.5 Hz, 1H), 4.13 (s, 4H), 3.97 (ddd, *J* = 2.4, 1.4, 0.7 Hz, 1H), 2.43 (s, 3H). **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 141.9, 141.1, 136.2, 134.6, 131.5 – 131.2 (m), 129.9, 129.7, 129.7, 129.6, 128.0, 127.9, 127.1 – 126.9 (m), 125.7, 95.7, 88.2 (d, *J* = 2.1 Hz), 71.8, 71.4, 71.4, 69.6, 69.0, 21.6. **^{19}F NMR** (471 MHz, CD_2Cl_2) δ -139.80 (ddd, *J* = 2605.6, 23.5, 8.1 Hz), -156.46 (t, *J* = 20.9 Hz), -163.47 (dtd, *J* = 202.3, 22.1, 8.2 Hz). **HRMS** (ESI+) calculated for $[C_{29}H_{19}F_5NaOS^{56}Fe]^+$ 589.0318 m/z; found $[M + Na]^+$: 589.0314. $\boldsymbol{\alpha_D^{589}}$ = +19.3 deg.cm^2.g^{-1} ($CHCl_3$, c 0.05, 298 K).

(S_S,S_p)-2-(9'-Anthracenyl -2,1'-biphenyl)-1-(*p*-tolyl-sulfoxide)ferrocene 1.66j



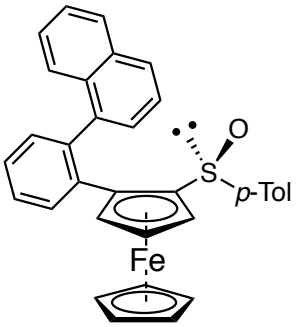
The compound was synthetized according to the general procedure **C** using sulfoxide **(S_S)-1.10** (567 mg, 1.75 mmol) in 2-MeTHF (18 mL), LDA from diisopropylamine (0.38 mL), *n*BuLi (2.5M, mL, 1.0 mL) in 2-MeTHF (2.7 mL), $ZnCl_2$ (382 mg) in 2-MeTHF (1.8 mL), tris-*o*-furylphosphine (33 mg), Pd_2dba_3 (33 mg) and 9-(2-bromophenyl)anthracene (733 mg).

The crude was purified by flash chromatography over silica gel (eluent, cylcohexane:Et_2O:$CHCl_3$ 100:0:0 to 60:30:10) yielding the title compound (251 mg, 0.44 mmol, 25%) as an orange foam.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (dd, *J* = 7.9, 1.3 Hz, 1H), 8.40 (s, 1H), 8.05 (d, *J* = 9.2 Hz, 0H), 7.86 (d, *J* = 8.5 Hz, 1H), 7.74 (d, *J* = 8.7 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.66 (td, *J* = 7.7, 1.4 Hz, 1H), 7.52 – 7.41 (m, 3H), 7.34 – 7.27 (m, 3H), 7.20 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.15 – 7.10 (m, 2H), 4.04 (s, 5H), 3.87 (dd, *J* = 2.6, 1.5 Hz, 1H), 3.59 (t, *J* = 2.7 Hz, 1H), 3.28 (dd, *J* = 2.7, 1.4 Hz, 1H), 2.44 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.0, 140.9, 138.3, 136.5, 135.9, 133.6, 132.4, 131.3, 131.3, 131.2, 129.7, 129.4, 128.8, 127.7, 127.6, 127.4, 127.2, 126.8, 126.5, 126.0, 125.6, 125.5, 124.9, 94.8, 87.7, 71.3, 71.2, 69.0 (d, *J* = 3.3 Hz), 68.6, 21.6 (d, *J* = 2.3 Hz).

(S_S,S_p)-2-(1'-Naphtyl -2,1'-biphenyl)-1-(*p*-tolyl-sulfoxide)ferrocene 1.66k



The compound was synthetized according to the general procedure **C** using sulfoxide **(S_S)-1.10** (567 mg, 1.75 mmol) in 2-MeTHF (18 mL), LDA from diisopropylamine (0.38 mL), *n*BuLi (2.5M, mL, 1.0 mL) in 2-MeTHF (2.7 mL), $ZnCl_2$ (382 mg) in 2-MeTHF (1.8 mL), tris-*o*-furylphosphine (33 mg), Pd_2dba_3 (33 mg) and 1-(2-iodophenyl)naphthalene **1.73k** (607 mg).

The crude was purified by flash chromatography over silica gel (eluent, cylcohexane:Et_2O:$CHCl_3$ 100:0:0 to 60:30:10) yielding an inseparable mixture of 2 atropoisomeres as an orange foam.

General procedure D: inversion of sulfoxide configuration

Reduction step: In a flask the corresponding sulfoxide (1 equiv) was dissolved in acetone (0.2 M, 1 volume), sodium iodide (2 equiv) was added and after complete dissolution of the salt the solution was cooled in an ice bath. A solution of TFAA (2 equiv) in acetone (1 volume) was added to the sulfoxide solution and the mixture was stirred an additional 10 min. The reaction was monitored by TLC analysis and reagents were added sequentially again until reaction reached full conversion. After completion of the reaction, the crude mixture was poured in NaOH aq. (0.5 M, 10 volumes) at 0 ºC and $Na_2S_2O_3$ sat. was added, the mixture was allowed to warm up to room temperature while stirred for 30 min.

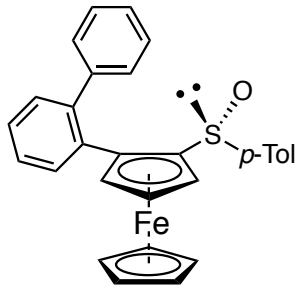
The crude was diluted with Et_2O and water and phases were separated. The organic layer was washed with water, $NaHCO_3$ sat. and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was eluted through a silica

plug with cyclohexane:Et_2O 90:10 and concentrated under reduced pressure yielding the desired product as an orange gum used directly in the next step.

Oxidation step: The residue (1 equiv) was dissolved in CH_2Cl_2 and cooled in an ice bath, *m*-CPBA (77% Wt, 1 equiv) in CH_2Cl_2 was added dropwise and the mixture was stirred 20 min. The reaction was monitored by TLC analysis. After completion the reaction mixture was poured in NaOH aq. (0.5 M) at 0 ºC and mixture was allowed to warm up to room temperature while stirred for 30 min.

The crude was diluted with Et_2O and water and phases were separated. The organic layer was washed with NaOH aq. (2x), water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by flash chromatography over silica gel.

(R_S,S_p)-2-(2,1'-Biphenyl)-1-(*p*-tolyl-sulfoxide)ferrocene 1.70b



The compound was synthesized according to the general procedure **D**.

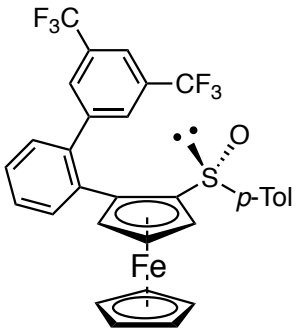
Reduction step: Using sulfoxide **1.66b** (495 mg, 1.04 mmol) and NaI (311 mg) in acetone (4.6 mL), TFAA (0.29 mL) in acetone (4.6 mL). NaI and TFAA were added 1 time again. The work up yield the sulfide (362 mg) as orange oil used without further purification.

Oxidation step: Using the sulfide (322 mg) in CH_2Cl_2 (2.3 mL) and *m*-CPBA (157 mg, 77% Wt) in CH_2Cl_2 (4.6 mL).

The crude was purified by flash chromatography over silica gel cylcohexane:Et_2O:$CHCl_3$ 100:0:0 to 80:10:10) yielding the title compound (256 mg, 537 μmol, 58% over 2 steps) as an orange foam.

M.p. = 154 – 155 ºC (CH_2Cl_2). **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 8.28 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.49 (td, *J* = 7.6, 1.5 Hz, 1H), 7.39 (td, *J* = 7.5, 1.4 Hz, 1H), 7.22 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.13 – 7.06 (m, 5H), 7.00 (t, *J* = 7.5 Hz, 2H), 4.72 (dd, *J* = 2.6, 1.5 Hz, 1H), 4.37 (s, 5H), 4.12 (t, *J* = 2.5 Hz, 1H), 3.70 (dd, *J* = 2.5, 1.5 Hz, 1H), 2.26 (s, 3H). **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 144.2, 143.0, 141.8, 141.7, 133.5, 130.6, 129.9, 129.6, 128.0, 127.8, 127.3, 126.8, 124.3, 96.2, 88.1, 73.6, 71.5, 67.9, 63.4, 21.4. **HRMS** (ESI+) calculated for $[C_{29}H_{25}{}^{56}Fe\ OS]^+$ 477.0970 m/z; found $[M + H]^+$: 477.0973. α_D^{589} = –308.2 deg.cm^2.g^{-1} ($CHCl_3$, c 0.05, 298 K).

(R_S,S_p)-2-(3',5'-Bis(trifluoromethyl)-2,1'-biphenyl)-1-(*p*-tolyl-sulfoxide)ferrocene 1.70c



The compound was synthesized according to the general procedure **D**.

Reduction step: Using sulfoxide **1.70c** (4.00 g, 6.53 mmol) and NaI (1.96 g) in acetone (24 mL), TFAA (1.8 mL) in acetone (24 mL). NaI and TFAA were added 1 time again. The work up yields the sulfide (3.6 g) as orange oil used without further purification.

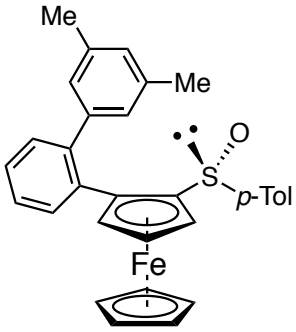
Oxidation step: Using the sulfide (3.6 g) in CH_2Cl_2 (31 mL) and *m*-CPBA (1.35 g, 77% Wt) in CH_2Cl_2 (16 mL).

The crude was purified by flash chromatography over silica gel cylcohexane:Et_2O:$CHCl_3$ 100:0:0 to 80:10:10) yielding the title compound (3.55 g, 5.80 mmol, 89% over 2 steps) as an orange foam.

M.p. = 76 – 79 ºC (CH_2Cl_2). **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 8.33 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.65 – 7.59 (m, 2H), 7.49 (td, *J* = 7.6, 1.3 Hz, 1H), 7.29 (dd, *J* = 7.7, 1.3

Hz, 1H), 7.04 (s, 4H), 6.80 (s, 2H), 4.84 (dd, *J* = 2.6, 1.5 Hz, 1H), 4.40 (s, 5H), 4.17 (t, *J* = 2.5 Hz, 1H), 3.56 – 3.52 (m, 1H), 2.20 (s, 3H). **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 144.0, 143.5, 142.1, 139.8, 134.0, 133.8, 131.0 (q, *J* = 33.2 Hz), 130.2, 130.1, 130.0 (q, *J* = 3.7 Hz), 128.9, 128.6, 123.8, 123.6 (q, *J* = 272.8 Hz), 120.7 – 120.4 (m), 96.4, 86.7, 73.1, 71.6, 68.4, 63.6, 21.3. **^{19}F NMR** (471 MHz, CD_2Cl_2) δ -63.29. **HRMS** (ESI+) calculated for $[C_{31}H_{22}F_6{}^{56}FeNaOS]^+$ 635.0538 m/z; found $[M + Na]^+$: 635.0530. $\boldsymbol{\alpha_D^{589}}$ = –122.6 deg.cm^2.g^{-1} ($CHCl_3$, c 0.05, 298 K).

(*R*$_S$,*S*$_p$)-2-(3',5'-Dimethyl-2,1'-biphenyl)-1-(*p*-tolyl-sulfoxide)ferrocene 1.70d



The compound was synthesized according to the general procedure **D**.

Reduction step: Using sulfoxide **1.66d** (514 mg, 1.02 mmol) and NaI (305 mg) in acetone (4.5 mL), TFAA (0.29 mL) in acetone (4.5 mL). NaI and TFAA were added 1 time again. The work up yields the sulfide (480 mg) as orange oil used without further purification.

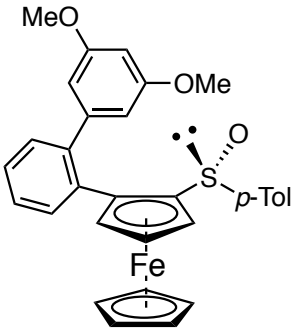
Oxidation step: Using the sulfide (480 mg) in CH_2Cl_2 (2.5 mL) and *m*-CPBA (220 mg, 77% Wt) in CH_2Cl_2 (5.0 mL).

The crude was purified by flash chromatography over silica gel (eluent, cylcohexane:Et_2O:$CHCl_3$ 100:0:0 to 70:20:10) yielding the title compound (417 mg, 827 µmol, 81% over 2 steps) as an orange foam.

M.p. = 210 – 211 ºC (CH_2Cl_2). **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 8.25 (ddd, *J* = 7.8, 1.4, 0.5 Hz, 1H), 7.47 (td, *J* = 7.6, 1.4 Hz, 1H), 7.37 (td, *J* = 7.5, 1.4 Hz, 1H), 7.20 (ddd, *J* = 7.7, 1.4, 0.5 Hz, 1H), 7.13 – 7.03 (m, 4H), 6.74 – 6.69 (m, 1H), 5.93 (s, 2H), 4.76 (dd, *J* = 2.6, 1.5 Hz, 1H), 4.37 (s, 4H), 4.12 (t, *J* = 2.6 Hz, 1H), 3.71 (dd,

J = 2.5, 1.5 Hz, 1H), 2.24 (d, *J* = 0.7 Hz, 3H), 1.99 (q, *J* = 0.7 Hz, 6H). **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 144.4, 143.2, 141.6, 141.2, 137.1, 133.3, 130.3, 129.9, 128.1, 127.8, 127.4, 127.0, 124.1, 96.0, 88.1, 73.5, 71.4, 67.7, 62.7, 21.3, 21.0. **HRMS** (ESI+) calculated for $[C_{31}H_{29}OS^{56}Fe]^+$ 505.1283 m/z; found $[M+H]^+$: 505.1273. $\boldsymbol{\alpha_D^{589}}$ = –212.2 deg.cm^2.g^{-1} ($CHCl_3$, c 0.050, 298 K).

(R_S,S_p)-2-(3',5'-Dimethoxy-2,1'-biphenyl)-1-(*p*-tolyl-sulfoxide)ferrocene 1.70e



The compound was synthesized according to the general procedure **D**.

Reduction step: Using sulfoxide **1.66e** (622 mg, 1.16 mmol) and NaI (348 mg) in acetone (5.1 mL), TFAA (0.32 mL) in acetone (5.1 mL). NaI and TFAA were added 2 time again. The work up yield to the sulfide (520 mg) as orange oil used without further purification.

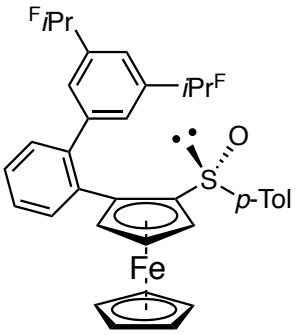
Oxidation step: Using the sulfide (520 mg) in CH_2Cl_2 (2.6 mL) and *m*-CPBA (224 mg, 77% Wt) in CH_2Cl_2 (5.2 mL).

The crude was purifier by flash chromatography over silica gel (eluent, cyclohexane:Et_2O:$CHCl_3$ 100:0:0 to 70:20:10) yielding the title compound (301 mg, 561 µmol, 48% over 2 steps) as an orange foam.

M.p. = >170 ºC (decomposition, CH_2Cl_2), **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 8.30 (ddd, *J* = 7.8, 1.4, 0.5 Hz, 1H), 7.51 (td, *J* = 7.6, 1.5 Hz, 1H), 7.40 (td, *J* = 7.5, 1.4 Hz, 1H), 7.30 (ddd, *J* = 7.7, 1.5, 0.5 Hz, 1H), 7.11 – 7.03 (m, 4H), 6.19 (t, *J* = 2.3 Hz, 1H), 5.67 (d, *J* = 2.3 Hz, 2H), 4.76 (dd, *J* = 2.6, 1.5 Hz, 1H), 4.38 (s, 5H), 4.17 (t, *J* = 2.6 Hz, 1H), 3.80 (dd, *J* = 2.5, 1.5 Hz, 1H), 3.32 (s, 6H), 2.25 (s, 3H). **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 160.6, 143.9, 143.8, 142.0, 140.7, 134.5, 133.1, 129.8,

129.8, 128.2, 127.2, 125.6, 107.9, 99.8, 95.5, 91.6, 74.2, 71.2, 69.1, 67.0, 55.9, 21.6. **HRMS** (ESI+) calculated for $[C_{31}H_{28}NaO_3S^{56}Fe]^+$ 559.1001 m/z; found [M + Na]$^+$: 505.0997. α_D^{589} = –221.3 deg.cm^2.g^{-1} ($CHCl_3$, c 0.050, 298 K).

(R_S,S_p)-2-(3',5'-Bis(perfluoroisopropyl)-2,1'-biphenyl)-1-(*p*-tolyl-sulfoxide)ferrocene 1.70f



The compound was synthesized according to the general procedure **D**.

Reduction step: Using sulfoxide **1.66f** (235 mg, 235 µmol) and NaI (87 mg) in acetone (1.3 mL), TFAA (0.12 mL) in acetone (1.3 mL). NaI and TFAA were added 2 times again. The work up yields the sulfide (204 mg) as orange oil used without further purification.

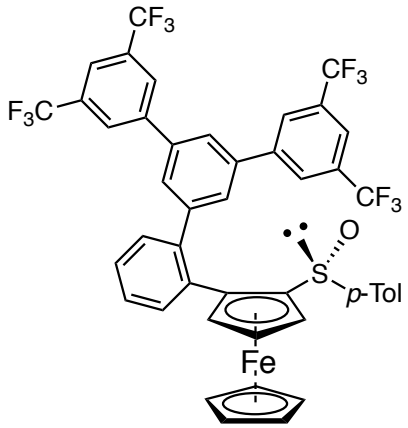
Oxidation step: Using the sulfide (130 mg) in CH_2Cl_2 (0.42 mL) and *m*-CPBA (36 mg, 77% Wt) in CH_2Cl_2 (0.84 mL).

The crude was purified by flash chromatography over silica gel (eluent, cyclohexane:Et_2O:$CHCl_3$ 100:0:0 to 70:20:10) yielding the title compound (110 mg, 135 µmol, 74% over 2 steps) as an orange foam.

M.p. = 148 – 150 ºC (CH_2Cl_2). **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 8.39 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.66 – 7.59 (m, 2H), 7.49 (td, *J* = 7.6, 1.3 Hz, 1H), 7.31 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.11 – 7.03 (m, 4H), 7.00 (s, 2H), 4.76 (dd, *J* = 2.7, 1.5 Hz, 1H), 4.39 (s, 5H), 4.14 (t, *J* = 2.6 Hz, 1H), 3.46 (dd, *J* = 2.6, 1.5 Hz, 1H), 2.23 (s, 3H). **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 144.01 (d, *J* = 4.9 Hz), 143.99 (d, *J* = 4.8 Hz), 141.9, 139.9, 134.3, 133.9, 130.5, 130.1, 130.0 (d, *J* = 10.9 Hz), 129.0, 128.5, 127.8 (dd, *J* = 20.8, 2.3 Hz), 123.6, 121.4 (t, *J* = 11.1 Hz), 120.7 (qd, *J* = 287.2, 27.5 Hz),

96.4, 91.3 (dp, J = 204.3, 33.2 Hz), 86.6, 72.7, 71.8, 68.6, 64.2, 21.2. **^{19}F NMR** (471 MHz, CD_2Cl_2) δ -76.14 (dp, J = 22.9, 7.8 Hz), -182.62 (hept, J = 7.3 Hz). **HRMS** (ESI+) calculated for $[C_{35}H_{22}F_{14}NaOS^{56}Fe]^+$ 835.0409 m/z; found $[M+Na]^+$: 835.0392. $\boldsymbol{\alpha_D^{589}}$ = –89.0 deg.cm^2.g^{-1} ($CHCl_3$, c 0.05, 298 K).

(R_S,S_p)-2-(3',5'-Bis(3',5'-bis(3'',3''',5'',5'''-bis(trifluoromethyl)benzene)-2,1'-terphenyl)-1-(*p*-tolyl-sulfoxide)ferrocene 1.70g



The compound was synthesized according to the general procedure **D**.

Reduction step: Using sulfoxide **1.66g** (1.057 mg, 1.174 mmol) and NaI (352 mg) in acetone (4.3 mL), TFAA (0.33 mL) in acetone (4.3 mL). NaI and TFAA were added 2 time again. The work up yields the sulfide (1.023 g) as orange oil used without further purification.

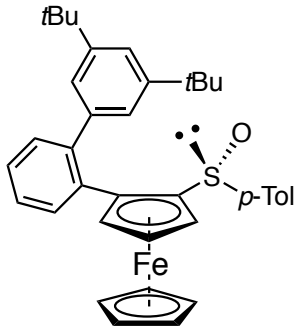
Oxidation step: Using the sulfide (1.023 g) in CH_2Cl_2 (3.0 mL) and *m*-CPBA (259 mg, 77% Wt) in CH_2Cl_2 (6.0 mL).

The crude was purifier by flash chromatography over silica gel (eluent, cyclohexane:Et_2O:$CHCl_3$ 100:0:0 to 85:7.5:7.5) yielding the title compound (689 mg, 765 µmol, 65% over 2 steps) as an orange foam.

M.p. = 146 – 147 ºC (CH_2Cl_2). **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 8.38 (dd, J = 7.7, 1.4 Hz, 1H), 7.93 (s, 2H), 7.77 (s, 4H), 7.62 (td, J = 7.5, 1.5 Hz, 1H), 7.54 (td, J = 7.5, 1.4 Hz, 1H), 7.49 – 7.44 (m, 2H), 6.93 – 6.86 (m, 2H), 6.54 (s, 2H), 6.51 (d, J = 8.1 Hz, 2H), 5.07 (dd, J = 2.6, 1.5 Hz, 1H), 4.48 (s, 5H), 4.37 (t, J = 2.5 Hz, 1H),

3.89 (dd, J = 2.4, 1.5 Hz, 1H), 1.76 (s, 3H). **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 144.5, 143.3, 142.8, 141.5, 141.2, 139.3, 134.1, 133.5, 132.3 (q, J = 33.3 Hz), 130.6, 129.7, 129.2, 128.8, 128.4, 128.2 (q, J = 3.8 Hz), 125.0, 123.54 (d, J = 272.7 Hz), 123.5, 121.8 (p, J = 4.0 Hz), 97.3, 88.1, 73.6, 71.7, 68.2, 63.2, 20.9. **^{19}F NMR** (471 MHz, CD_2Cl_2) δ -63.04. **HRMS** (ESI+) calculated for $[C_{45}H_{28}F_{12}NaOS^{56}Fe]^+$ 923.0912 m/z; found $[M + Na]^+$: 923.0916. $\boldsymbol{\alpha_D^{589}}$ = –119.7 deg.cm^2.g^{-1} ($CHCl_3$, c 0.050, 298 K).

(R_S,S_p)-2-(3',5'-Di-*tert*-butyl-2,1'-biphenyl)-1-(*p*-tolyl-sulfoxide)ferrocene 1.70h



The compound was synthesized according to the general procedure **D**.

Reduction step: Using sulfoxide **1.66h** (687 mg, 1.17 mmol) and NaI (350 mg) in acetone (4.3 mL), TFAA (0.33 mL) in acetone (4.3 mL). NaI and TFAA were added 2 time again. The work up yields the sulfide (622 mg) as orange oil used without further purification.

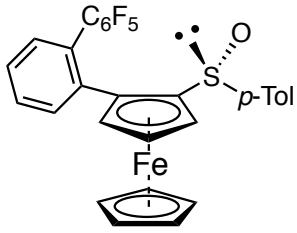
Oxidation step: Using the sulfide (622 mg) in CH_2Cl_2 (2.8 mL) and *m*-CPBA (243 mg, 77% Wt) in CH_2Cl_2 (5.6 mL).

The crude was purified by flash chromatography over silica gel (eluent, cyclohexane:Et_2O:$CHCl_3$ 100:0:0 to 80:10:10) yielding the title compound (550 mg, 934 μmol, 80% over 2 steps) as an orange foam.

M.p. = 101 – 103 ºC (CH_2Cl_2). **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 8.31 (dd, J = 7.7, 1.4 Hz, 1H), 7.50 (td, J = 7.5, 1.5 Hz, 1H), 7.42 (td, J = 7.5, 1.4 Hz, 1H), 7.34 (dd, J = 7.7, 1.5 Hz, 1H), 7.17 (t, J = 1.8 Hz, 1H), 7.06 (s, 4H), 6.44 (s, 2H), 4.69 – 4.65

(m, 1H), 4.36 (s, 4H), 4.08 (t, *J* = 2.6 Hz, 1H), 3.62 (dd, *J* = 2.6, 1.5 Hz, 1H), 2.24 (s, 3H), 1.04 (s, 18H). **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 150.4, 144.5, 143.9, 141.4, 140.4, 133.7, 133.5, 130.6, 130.1, 128.0, 127.1, 124.5, 123.7, 120.5, 95.9, 88.3, 73.4, 71.5, 68.1, 63.4, 34.8, 31.4, 21.4. **HRMS** (ESI+) calculated for $[C_{37}H_{41}OS^{56}Fe]^+$ 589.2223 m/z; found $[M + H]^+$: 589.2218. α_D^{589} = –217.5 deg.cm^2.g^{-1} ($CHCl_3$, c 0.05, 298 K).

(*R*$_S$,*S*$_p$)-2-(2',3',4',5',6'-Pentafluoro-2,1'-biphenyl)-1-(*p*-tolyl-sulfoxide)ferrocene 1.70i



The sulfoxide was synthesized according to the general procedure **D**.

Reduction step: Using sulfoxide **1.66i** (222 mg, 1.06 mmol) and NaI (115 mg) in acetone (1.7 mL), TFAA (0.11 mL) in acetone (1.7 mL). NaI and TFAA were added 1 time again. The work up yields the sulfide (192 mg) as orange oil used without further purification.

Oxidation step: Using the sulfide (192 mg) in CH_2Cl_2 (0.90 mL) and *m*-CPBA (78 mg, 77% Wt) in CH_2Cl_2 (1.8 mL).

The crude was purified by flash chromatography over silica gel (eluent, cyclohexane:Et_2O:$CHCl_3$ 100:0:0 to 70:20:10) yielding the title compound (181 mg, 320 µmol, 83% over 2 steps) as an orange foam.

M.p. = >200 ºC (decomposition, CH_2Cl_2), **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 8.43 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.64 (td, *J* = 7.7, 1.4 Hz, 1H), 7.45 (td, *J* = 7.6, 1.3 Hz, 1H), 7.26 – 7.20 (m, 3H), 7.19 – 7.12 (m, 2H), 4.51 (dd, *J* = 2.6, 1.5 Hz, 1H), 4.41 (s, 5H), 4.22 (t, *J* = 2.6 Hz, 1H), 3.89 – 3.85 (m, 1H), 2.32 (s, 3H). **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 146.1-143.9 (m), 145.2-142.8 (m), 143.3, 142.2-139.9 (m),141.5, 136.6, 134.0, 131.5, 129.8, 129.8, 127.9, 126.7, 124.5 (d, *J* = 2.4 Hz), 116.2, 97.5,

87.4 (d, J = 1.7 Hz), 71.9, 70.3, 68.9, 66.4, 21.5. **^{19}F NMR** (471 MHz, CD_2Cl_2) δ -140.58 (ddd, J = 1631.5, 23.3, 8.0 Hz), -156.29 (t, J = 20.7 Hz), -162.92 – -163.80 (m). **HRMS** (ESI+) calculated for $[C_{29}H_{19}F_5NaOS^{56}Fe]^+$ 589.0319 m/z; found [M + Na]$^+$: 589.0316. $\boldsymbol{\alpha_D^{589}}$ = –354.9 deg.cm^2.g^{-1} (CHCl3, c 0.51, 298 K).

General procedure E: stannylation, sulfoxide removal and Negishi coupling sequence

Stannylation: The corresponding sulfoxide (1 equiv) was charged in a flask, the atmosphere was evacuated and back-filed with argon (2x) and THF (0.33 M, 1 volume) followed by $ClSnBu_3$ (1.05 equiv) were added. After complete dissolution of the solid the reaction mixture was cooled to –78 ºC.

LiTMP was prepared by addition of *n*BuLi (1.55 equiv) to a solution of 2,2,6,6-tetramethylpiperidine (1.6 equiv) in THF (0.5 volume) at –78 ºC, after completion of the addition the solution was allowed to warm up to room temperature and was stirred 10 min.

The LiTMP solution was added dropwise to the sulfoxide suspension at –78 ºC and the mixture was stirred for 15 min at the same temperature. The reaction was monitored by TLC analysis. After completion, the reaction was quenched by addition of *i*PrOH and allowed to warm up to room temperature.

The reaction mixture was diluted with Et_2O, 5% aq. citric acid (10 volumes) was added and phases were separated. The organic layer was washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was eluted through a silica plug with cyclohexane:Et_2O 90:10 and concentrated under reduced pressure yielding the desired product as an orange gum used in the next step without further purification.

Sulfoxide removal: Under an atmosphere of argon the residue was dissolved in THF (0.15 M) and the solution was cooled to –78 ºC then *t*BuLi (1.7 M, 1.4 equiv) was added and the reaction mixture was stirred at the same temperature for 5 min. The reaction was monitored by TLC analysis. After completion, the reaction was quenched by addition of *i*PrOH and allowed to warm up to room temperature.

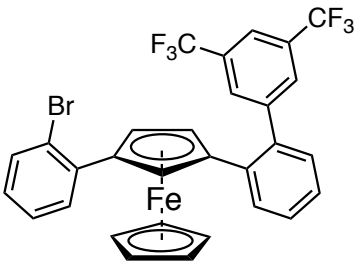
The reaction mixture was diluted with Et_2O, 5% aq. citric acid (10 volumes) was added and phases were separated. The organic layer was washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was eluted through a silica plug with cyclohexane:Et_2O 95:5 and concentrated under reduced pressure yielding the desired product as an orange thick oil used in the next step without further purification.

Negishi cross-coupling: Under an atmosphere of argon the residue was dissolved in THF (0.23 M) and the solution was cooled to –78 ºC then *n*BuLi (2.5 M, 1.1 equiv) was added and the reaction mixture was stirred at the same temperature for 30 min. The lithium-tin exchange was monitored by TLC analysis. After complete lithiation, a THF solution of $ZnCl_2$ (100 $mg.mL^{-1}$, 1.2 equiv) was added to the ferrocenyl-lithium at –78 ºC and the solution was stirred for 10 min the same temperature then allowed to warm up to room temperature and stirred for an additional 30 min.

Tris-*o*-furylphosphine (10 mol %) and Pd_2dba_3 (2.5 mol %) were stirred 30 min in THF (200 $mg.mL^{-1}$) giving a bright yellow solution that was added to the previously prepared zinc reagent followed by the corresponding arylhalide (1.1 equiv) and the reaction mixture was stirred 18 h at 70 ºC. The reaction was monitored by TLC analysis (eluent pentane:Et_2O 99.9:0.1)

The reaction was quenched by addition of 5% aq. citric acid (10 volumes), the mixture was stirred for 30 min, Et_2O (5 volumes) was added and the mixture was filtered over pad of Celite®. Phases were separated and the organic layer was washed with 5% aq. citric acid, water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purifier by flash chromatography over silica gel.

(S_p)-3-(3',5'-Bis(trifluoromethyl)-2,1'-biphenyl)-1-(2-bromophenyl)ferrocene 1.72ca



The compound was synthesized accord to the general procedure **E**.

The stannylation step was performed using the sulfoxide **1.70c** (1.50 g, 2.45 mmol), $ClSnBu_3$ (0.70 mL) in THF (7.5 mL) and LiTMP prepared from TMP (0.75 mL), *n*BuLi (1.7 mL) in THF (3.7 mL). The work up yielded to the stannyl-ferrocene (2.17 g) as red oil used without further purification.

The sulfoxide removal step was performed using the stannyl-ferrocene (2.17 g) in THF (14.5 mL) and *t*BuLi (2.0 mL). The work up yielded the tributylstannyl-ferrocene (1.72 g) as red oil used without further purification.

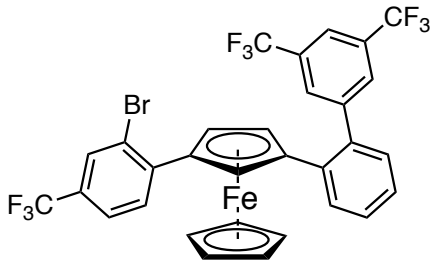
The Negishi coupling step was performed using the stannyl-ferrocene (1.72 g) in THF (9.1 mL), *n*BuLi (1.0 mL), $ZnCl_2$ THF solution (2.3 mL). Then Tris-*o*-furylphosphine (49 mg), Pd_2dba_3 (48 mg) in THF (0.5 mL) and 1-bromo-2-iodobenzene (300 µL, 0.660 mg).

Purification by flash chromatography over silica gel (eluent, pentane:$CHCl_3$, 95:5 to 85:15) afforded to title compound (1.02 g, 1.62 mmol, 77%) as red gum with low amount of inseparable impurities.

M.p. = 105 – 106 ºC (CH_2Cl_2). **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 7.99 (dt, *J* = 7.8, 0.9 Hz, 1H), 7.80 – 7.76 (m, 1H), 7.71 – 7.67 (m, 2H), 7.63 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.52 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.48 (td, *J* = 7.6, 1.4 Hz, 1H), 7.37 (td, *J* = 7.5, 1.3 Hz, 1H), 7.30 – 7.22 (m, 2H), 7.06 (ddd, *J* = 8.0, 7.3, 1.7 Hz, 1H), 4.71 (d, *J* = 0.9 Hz, 1H), 4.71 (s, 1H), 4.14 (dd, *J* = 2.4, 1.7 Hz, 1H), 4.05 (s, 5H). **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 144.5, 138.8, 138.5, 137.3, 134.0, 132.4, 132.2, 131.5 (q, *J* = 33.1 Hz), 130.5 (d, *J* = 3.8 Hz), 130.3, 128.7, 128.0, 127.3, 127.2, 123.9 (q, *J* =

272.8 Hz), 122.5, 120.8 (dt, *J* = 7.9, 3.9 Hz), 86.8, 86.8, 72.9, 72.0, 70.9, 70.7. **^{19}F NMR** (471 MHz, CD_2Cl_2) δ -63.23. **HRMS** (ESI+) calculated for $[C_{30}H_{19}BrF_6{}^{56}Fe]^+$ 627.9918 m/z; found $[M + H]^+$: 627.9918. **α_D^{589}** = –62.0 deg.cm^2.g^{-1} ($CHCl_3$, c 0.05, 298 K).

(S_p)-3-(3',5'-Bis(trifluoromethyl)-2,1'-biphenyl)-1-(2-bromo-4-trifluoromethyphenyl)ferrocene 1.72cb



The compound was synthesized accord to the general procedure **E**.

The stannylation step was performed using the sulfoxide **1.70c** (1.80 g, 2.94 mmol), $ClSnBu_3$ (0.83 mL, 1.0 g) in THF (8.9 mL) and LiTMP prepared from TMP (0.80 mL), *n*BuLi (1.8 mL) in THF (4.4 mL). The work up yielded the stannyl-ferrocene (2.65 g) as red oil used without further purification.

The sulfoxide removal step was performed using the stannyl-ferrocene (2.65 g) in THF (18 mL) and *t*BuLi (2.4 mL). The work up yielded the tributylstannyl-ferrocene (2.12 g) as red oil used without further purification.

The Negishi coupling step was performed using the stannyl-ferrocene (1.15 g) in THF (5.0 mL), *n*BuLi (0.66 mL), $ZnCl_2$ THF solution (1.2 mL). Then Tris-*o*-furylphosphine (42 mg), Pd_2dba_3 (41 mg) in THF (0.1 mL) and 1-bromo-2-iodo-4-(trifluormethyl)benzene (582 mg).

Purification by flash chromatography over silica gel (eluent, pentane:$CHCl_3$, 98:2 to 90:10) afforded to title compound (757 mg, 1.09 mmol, 72%) as an orange foam. **M.p. =** 109 – 110 ºC (CH_2Cl_2). **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 7.98 (ddd, *J* = 7.8, 1.4, 0.5 Hz, 1H), 7.79 (dq, *J* = 1.7, 0.9 Hz, 2H), 7.72 (dt, *J* = 8.2, 1.0 Hz, 1H), 7.70 – 7.67 (m, 2H), 7.52 – 7.47 (m, 2H), 7.39 (td, *J* = 7.5, 1.4 Hz, 1H), 7.30 (ddd, *J* =

7.7, 1.4, 0.5 Hz, 1H), 4.79 (dd, *J* = 2.6, 1.5 Hz, 1H), 4.74 (t, *J* = 1.5 Hz, 1H), 4.23 (dd, *J* = 2.6, 1.5 Hz, 1H), 4.07 (s, 5H).**^{13}C NMR** (126 MHz, CD_2Cl_2) δ 144.4, 143.4, 138.5, 136.8, 132.4, 132.1, 131.5 (q, *J* = 33.1 Hz), 130.9 (q, *J* = 3.9 Hz), 130.4 (q, *J* = 3.8 Hz), 130.3, 129.3 (q, *J* = 33.0 Hz), 128.7, 127.3, 123.9 (d, *J* = 3.7 Hz), 123.8 (q, *J* = 272.2 Hz), 123.8 (q, *J* = 272.7 Hz), 122.2, 120.8, 87.6, 84.8, 72.8, 72.1, 71.3, 70.9. **^{19}F NMR** (471 MHz, CD_2Cl_2) δ -63.10, -63.26. **HRMS** (ESI+) calculated for $[C_{31}H_{18}BrF_9{}^{56}Fe]^+$ 695.9794 m/z; found $[M + H]^+$: 695.9787. $\boldsymbol{\alpha_D^{589}}$ = –91.7 deg.cm^2.g^{-1} ($CHCl_3$, c 0.05, 298 K).

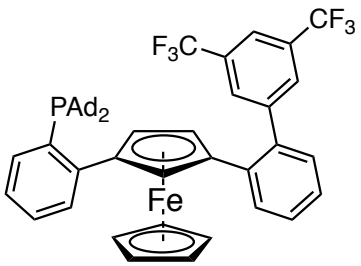
General procedure F: Phosphine cross coupling

A microwave vial was charged with the corresponding (2-bromophenyl)ferrocene **1.72** (1 equiv) and dppf·$PdCl_2$·CH_2Cl_2 adduct (5 mol %) then in a glovebox under argon atmosphere NaO*t*Bu (1.1 equiv), the phosphine (1.2 equiv) and toluene were sequentially added. The reaction mixture was heated under microwave irradiation at 140 ºC for 4 h.

The crude mixture was diluted with Et_2O, filtered and concentrated under reduced pressure.

The crude product was purified by flash column chromatography over silica gel or filtered over silica gel plug and used as such.

(S_p)-L$_C$

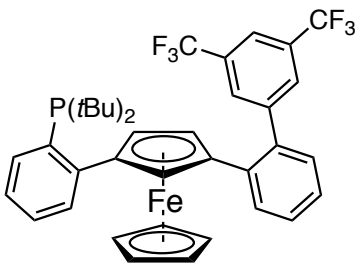


The ligand was synthesized according to the general procedure **F** using (2-bromophenyl)ferrocene **1.72ca** (600 mg, 954 µmol), dppf·$PdCl_2$·CH_2Cl_2 adduct (39 mg), NaO*t*Bu (101 mg), $HPAd_2$ (356 mg) and toluene (0.31 M, 3 mL).

Purification by flash column chromatography over silica gel (eluent pentane:$CHCl_3$ 95:5 then pentane: Et_2O 98:2) afforded the title compound (685 mg, 805 µmol, 84%) as an orange gum.

M.p. = 138 – 142 ºC (CH_2Cl_2). **^{1}H NMR** (400 MHz, CD_2Cl_2) δ 8.03 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.95 (ddd, *J* = 8.0, 3.9, 1.5 Hz, 1H), 7.84 (s, 1H), 7.80 – 7.77 (m, 3H), 7.76 (d, *J* = 1.5 Hz, 1H), 7.46 (td, *J* = 7.6, 1.5 Hz, 1H), 7.33 (tt, *J* = 7.4, 1.7 Hz, 2H), 7.24 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.17 (td, *J* = 7.5, 1.4 Hz, 1H), 5.11 (t, *J* = 1.6 Hz, 1H), 4.76 (dt, *J* = 2.4, 1.1 Hz, 1H), 3.92 (s, 5H), 3.64 (dd, *J* = 2.6, 1.5 Hz, 1H), 1.99 – 1.80 (m, 20H), 1.68 (d, *J* = 2.7 Hz, 10H). **^{13}C NMR** (101 MHz, CD_2Cl_2) δ 147.2 (d, *J* = 29.0 Hz), 144.8, 137.9 (d, *J* = 64.0 Hz), 137.4 (d, *J* = 2.0 Hz), 134.0 (d, *J* = 32.1 Hz), 132.3 (d, *J* = 6.6 Hz), 131.8, 131.4 (q, *J* = 33.1 Hz), 130.7, 130.6, 128.7, 128.2, 126.5, 124.2, 123.9 (q, *J* = 272.8 Hz), 121.1 – 120.7 (m), 89.2 (d, *J* = 7.8 Hz), 84.0, 76.4 (d, *J* = 11.7 Hz), 73.8 (d, *J* = 15.2 Hz), 71.9, 68.7, 42.3 (dd, *J* = 13.5, 11.4 Hz), 37.7 (dd, *J* = 26.9, 9.7 Hz), 37.4, 29.5 (d, *J* = 8.6 Hz). **^{31}P NMR** (202 MHz, CD_2Cl_2) δ 23.6. **^{19}F NMR** (471 MHz, CD_2Cl_2) δ -63.0. **HRMS** (ESI+) calculated for $[C_{50}H_{50}F_6{}^{56}FeP]^+$ 851.2899 m/z; found $[M + H]^+$: 851.2863. **α_D^{589}** = +66.9 deg.cm^2.g^{-1} ($CHCl_3$, c 0.050, 298 K).

(S_p)-L_H

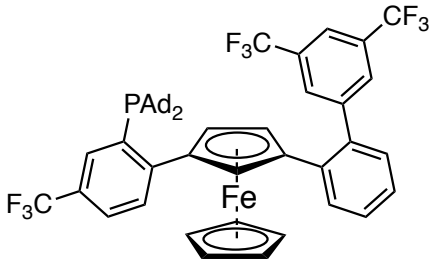


The ligand was synthesized according to the general procedure **F** using (2-bromophenyl)ferrocene **1.72ca** (76 mg, 0.12 mmol), dppf·$PdCl_2$·CH_2Cl_2 adduct (5 mg), NaO*t*Bu (11 mg), HP(*t*Bu)$_2$ (24 µL, 19 mg) and toluene (0. 23 M, 0.50 mL).

Purification by flash column chromatography over silica gel (eluent pentane:$CHCl_3$ 95:5 then pentane: Et_2O 98:2) afforded the title compound (71 mg, 0.10 mol, 83%) as an orange foam.

M.p. = 149 – 152 ºC (CH_2Cl_2). **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 8.03 (ddd, *J* = 7.9, 1.3, 0.5 Hz, 1H), 7.93 (ddd, *J* = 7.9, 3.9, 1.4 Hz, 1H), 7.83 (s, 1H), 7.77 – 7.73 (m, 3H), 7.46 (ddd, *J* = 7.8, 7.3, 1.4 Hz, 1H), 7.35 – 7.30 (m, 2H), 7.22 (ddd, *J* = 7.7, 1.4, 0.5 Hz, 1H), 7.18 (td, *J* = 7.5, 1.4 Hz, 1H), 5.07 (td, *J* = 1.5, 0.9 Hz, 1H), 4.68 (dt, *J* = 2.6, 1.3 Hz, 1H), 3.95 (s, 5H), 3.70 (dd, *J* = 2.6, 1.5 Hz, 1H), 1.11 (d, *J* = 11.6 Hz, 18H). **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 146.8, 146.5, 144.9, 138.1, 137.7, 136.8, 136.5, 135.9 (d, *J* = 2.7 Hz), 132.3 (d, *J* = 6.5 Hz), 131.9, 131.5 (q, *J* = 33.1 Hz), 130.5 (d, *J* = 4.1 Hz), 128.6, 128.4, 126.5, 123.9 (q, *J* = 272.7 Hz), 121.0, 89.4 (d, *J* = 7.9 Hz), 84.3, 76.5 (d, *J* = 12.5 Hz), 73.7 (d, *J* = 14.1 Hz), 71.9, 68.8, 32.9 (dd, *J* = 26.3, 15.6 Hz), 30.8 (dd, *J* = 15.9, 9.1 Hz). **^{31}P NMR** (202 MHz, CD_2Cl_2) δ 17.4. **^{19}F NMR** (471 MHz, CD_2Cl_2) δ -62.9. **HRMS** (ESI+) calculated for $[C_{38}H_{38}F_6FeP]^+$ 695.1960 m/z; found $[M + H]^+$: 695.1928. $\boldsymbol{\alpha_D^{589}}$ = +92.1 deg.cm^2.g^{-1} ($CHCl_3$, c 0.050, 298 K).

(S_p)-L$_I$

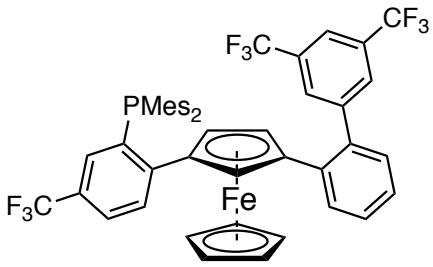


The ligand was synthesized according to the general procedure **F** using (2-bromophenyl)ferrocene **1.72cb** (500 mg, 717 µmol), dppf·$PdCl_2$·CH_2Cl_2 adduct (29 mg), NaO*t*Bu (76 mg), $HPAd_2$ (239 mg) and toluene (0.6 M, 1.2 mL).

Purification by flash column chromatography over silica gel (eluent pentane:$CHCl_3$ 95:5 then pentane: Et_2O 97:3) afforded the title compound (567 mg, 617 µmol, 86%) as an orange foam.

M.p. = 142 – 144 ºC (CH_2Cl_2). **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 8.06 – 8.00 (m, 3H), 7.84 (s, 1H), 7.76 (s, 2H), 7.57 – 7.53 (m, 1H), 7.48 (ddd, *J* = 7.9, 7.3, 1.4 Hz, 1H), 7.34 (td, *J* = 7.5, 1.3 Hz, 1H), 7.28 – 7.24 (m, 1H), 5.17 (t, *J* = 1.5 Hz, 1H), 4.87 (ddd, *J* = 2.3, 1.5, 0.6 Hz, 1H), 3.93 (s, 4H), 3.73 (dd, *J* = 2.6, 1.5 Hz, 1H), 1.99 – 1.87 (m, 13H), 1.87 – 1.80 (m, 6H), 1.78 – 1.63 (m, 13H). **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 151.8 (d, *J* = 27.9 Hz), 144.7, 137.7 (d, *J* = 4.1 Hz), 135.0, 134.7, 134.0 (d, *J* = 4.1 Hz), 132.4 (d, *J* = 6.1 Hz), 131.9, 131.5 (q, *J* = 33.1 Hz), 130.7, 130.6 (d, *J* = 3.4 Hz), 128.8, 126.8, 126.2, 125.5 (d, *J* = 31.8 Hz), 124.6 (d, *J* = 4.0 Hz), 123.9 (q, *J* = 272.8 Hz), 121.1 – 120.8 (m), 86.9 (d, *J* = 6.9 Hz), 85.1, 76.4 (d, *J* = 12.0 Hz), 73.9 (d, *J* = 16.6 Hz), 72.1, 69.6, 42.3 (dd, *J* = 19.7, 13.5 Hz), 38.0 (dd, *J* = 27.3, 12.6 Hz), 37.3, 29.5 (d, *J* = 8.7 Hz). **^{31}P NMR** (202 MHz, CD_2Cl_2) δ 23.42. **^{19}F NMR** (471 MHz, CD_2Cl_2) δ -62.87, -63.08. **HRMS** (ESI+) calculated for $[C_{51}H_{49}F_9{}^{56}FeP]^+$ 919.2773 m/z; found $[M + H]^+$: 919.2740. **α_D^{589}** = +23.4 deg.cm^2 .g^{-1} (CHCl3, c 0.51, 302 K).

(S_p)-L_J



The ligand was synthesized according to the general procedure **F** using (2-bromophenyl)ferrocene **1.72cb** (70 mg, 0.10 mmol), dppf·$PdCl_2$·CH_2Cl_2 adduct (4 mg), NaO*t*Bu (mg), $HPMes_2$ (30 mg) and toluene (0.2 M, 0.50 mL).

Purification by flash column chromatography over silica gel (eluent pentane:$CHCl_3$ 95:5 then pentane: Et_2O 97:3) afforded the title compound (77 mg, 87 µmol, 86%) as an orange foam.

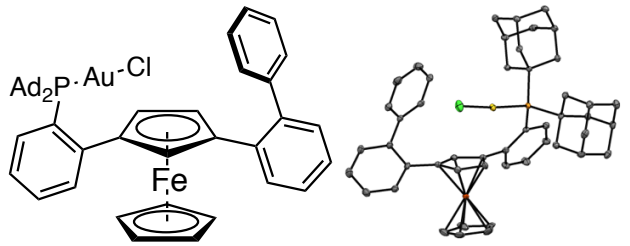
M.p. = 168 – 170 ºC (CH_2Cl_2). **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 7.97 (dd, *J* = 8.3, 4.7 Hz, 1H), 7.82 (s, 1H), 7.79 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.72 – 7.68 (m, 2H), 7.53

– 7.47 (m, 1H), 7.44 (t, *J* = 2.8 Hz, 1H), 7.40 (td, *J* = 7.6, 1.5 Hz, 1H), 7.32 (td, *J* = 7.5, 1.4 Hz, 1H), 7.23 (dd, *J* = 7.7, 1.4 Hz, 1H), 6.86 (dd, *J* = 16.9, 3.1 Hz, 4H), 4.85 (q, *J* = 1.4 Hz, 1H), 4.48 (dt, *J* = 2.6, 1.7 Hz, 1H), 3.94 (s, 5H), 3.74 (dd, *J* = 2.7, 1.5 Hz, 1H), 2.29 (s, 3H), 2.26 (s, 3H), 2.05 (d, *J* = 1.7 Hz, 12H). **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 149.3 (d, *J* = 30.5 Hz), 144.5, 143.5 (d, *J* = 16.6 Hz), 142.8 (d, *J* = 16.2 Hz), 139.0 (d, *J* = 57.4 Hz), 137.9, 137.1 (d, *J* = 25.5 Hz), 137.1, 131.9 (d, *J* = 20.7 Hz), 131.6 (q, *J* = 33.3 Hz), 131.6, 131.4, 131.3 (d, *J* = 5.5 Hz), 131.1 (q, *J* = 4.1 Hz), 130.6 , 130.6, 130.5 (d, *J* = 3.8 Hz), 127.2 (q, *J* = 32.1 Hz), 126.9, 126.7, 124.6 (q, *J* = 3.7 Hz), 122.8 (d, *J* = 272.1 Hz), 121.0 (p, *J* = 3.8 Hz), 86.4, 85.4 (d, *J* = 6.7 Hz), 74.5 (d, *J* = 6.8 Hz), 72.2, 71.2 (d, *J* = 13.9 Hz), 70.7, 23.0 (dd, *J* = 23.3, 16.4 Hz), 21.1 (d, *J* = 7.1 Hz).**^{31}P NMR** (202 MHz, CD_2Cl_2) δ -24.48. **^{19}F NMR** (471 MHz, CD_2Cl_2) δ -63.01, -63.17. **HRMS** (ESI+) calculated for $[C_{49}H_{40}AuClF_9Na^{56}FeP]^+$ 1141.1320 m/z; found $[M + Na]^+$: 1141.1312. **α_D^{589}** = – 103.0 deg.cm^2.g^{-1} ($CHCl_3$, c 0.050, 298 K).

General procedure G: Complexation

$Me_2S{\cdot}AuCl$ (1.05 equiv) and ligand (1.0 equiv) were dissolved in CH_2Cl_2 (0.2 M). The reaction mixture was stirred at 24 ºC for 15 min. The mixture was filtered through a syringe filter and concentrated under reduced pressure. The residue was purified by flash column chromatography over silica gel using the indicated eluent or additional crystallization.

(S_p)-B



The complex was synthesized accord to the general procedures **E, F, G**.

The stannylation step was performed using the sulfoxide **1.70b** (170 mg, 357 µmol), $ClSnBu_3$ (0.10 mL) in THF (0.90 mL) and LiTMP prepared from TMP (0.09 mL), *n*BuLi (0.21 mL) in THF (0.31 mL). The work up yielded the stannyl-ferrocene (2.17 g) as red oil used without further purification.

The sulfoxide removal step was performed using the tributylstannyl-ferrocene (0.27 g) in THF (2.2 mL) and *t*BuLi (0.38 mL). The work up yielded the tributylstannyl-ferrocene (0.21 g) as red oil used without further purification.

The Negishi coupling step was performed using the tributylstannyl-ferrocene (0.10 g) in THF (0.53 mL), *n*BuLi (0.07 mL), $ZnCl_2$ (THF solution, 0.13 mL). Then Tris-*o*-furylphosphine (4 mg), Pd_2dba_3 (4 mg) in THF (0.15 mL) and 1-bromo-2-iodobenzene (23 µL, 50 mg).

The crude product was eluted through a silica plug with pentane:$CHCl_3$ solvent mixture allowing the desired product (56 mg) as an orange foam used with further purification

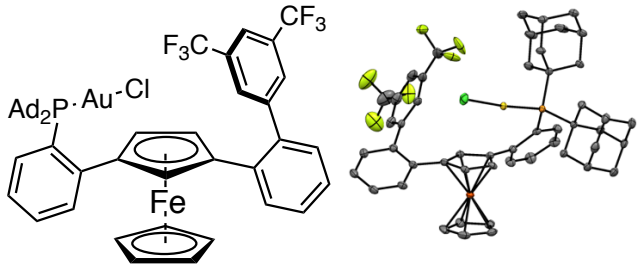
The ligand was synthesized according to the general procedure using the crude product (50 mg, 0.10 mmol), dppf·$PdCl_2$·CH_2Cl_2 adduct (4 mg), NaO*t*Bu (11 mg), $HPAd_2$ (34 mg) and toluene (0.2 M, 0.50 mL). The reaction mixture was diluted with tolune and filtered over silica then concentrated under reduced pressure. The crude product was dissolved in CH_2Cl_2 (0.50 mL) and Me_2S·AuCl (33 mg) was added.

Purification by flash column chromatography (pentane/EtOAc 80:20) followed by a crystallization by layering a concentrated solution of the complex in CH_2Cl_2 with

*n*hexane and pentane afforded the title compound (44 mg, 46 µmol, 27% over 5 steps) as a red solid.

M.p. = 195 – 198 ºC (CH_2Cl_2), **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 8.16 (ddd, *J* = 8.0, 4.5, 1.5 Hz, 1H), 7.89 – 7.84 (m, 1H), 7.69 (td, *J* = 8.3, 7.8, 1.4 Hz, 1H), 7.58 – 7.53 (m, 2H), 7.43 – 7.34 (m, 2H), 7.31 – 7.18 (m, 5H), 7.07 (tt, *J* = 7.4, 1.3 Hz, 1H), 4.92 (dd, *J* = 2.4, 1.5 Hz, 1H), 4.73 (dt, *J* = 2.5, 1.3 Hz, 1H), 3.97 (s, 5H), 3.92 (t, *J* = 1.5 Hz, 1H), 2.44 – 2.36 (m, 3H), 2.33 – 2.25 (m, 2H), 2.16 – 2.07 (m, 3H), 2.02 – 1.92 (m, 6H), 1.89 – 1.73 (m, 7H), 1.72 – 1.62 (m, 7H). **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 147.0 (d, *J* = 10.8 Hz), 142.8, 141.3, 137.1 (d, *J* = 7.3 Hz), 137.1, 135.3 (d, *J* = 1.9 Hz), 131.4, 130.9, 130.0 (d, *J* = 2.3 Hz), 128.4, 127.2, 126.3, 125.2 (d, *J* = 6.6 Hz), 124.3, 124.0, 90.8 (d, *J* = 7.9 Hz), 86.6, 75.4, 73.2, 72.2, 70.8 (d, *J* = 2.9 Hz), 43.9 (dd, *J* = 107.5, 22.3 Hz), 42.6 (dd, *J* = 101.0, 2.8 Hz), 36.7 (d, *J* = 8.5 Hz), 29.3 (dd, *J* = 10.0, 2.0 Hz).**^{31}P NMR** (202 MHz, CD_2Cl_2) δ 66.87. **HRMS** (ESI+) calculated for $[C_{48}H_{51}AuClNa^{56}FeP]^+$ 969.2324 m/z; found $[M + Na]^+$: 969.2338. **α_D^{589}** = +28.0 deg.cm^2.g^{-1} ($CHCl_3$, c 0.050, 298 K).

(S_p)-C



The complex was synthesized according to the general procedure **G** using ligand **L$_C$** (200 mg, 0.235 mmol) and $Me_2S{\cdot}AuCl$ (73 mg) in CH_2Cl_2 (1.2 mL).

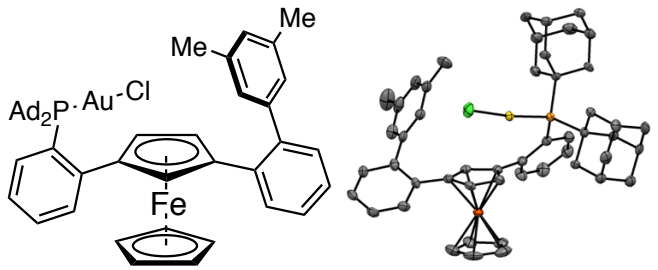
Purification by flash column chromatography (pentane/EtOAc 85:15) afforded the title compound as an orange foam (255 mg, 0.235 mmol, 98%). Optional; a recrystallization was carried out by dissolving the product into CH_2Cl_2 (200 mg.mL^{-1}, 1 volume) at room temperature, to this solution was added boiling *n*-hexane (10 volumes) under vigorous stirring immediately stopped after complete

mixing. The product crystallized as orange needles (suitable for X-ray diffraction) while the solution cooled to 24 ºC, the solution was cooled to 5 ºC for an additional 5 h and the filtered. The product was washed with cold *t*BuOMe and dried for 24 h under vacuum at 50 ºC allowing the pure complex (234 mg, 0.216 mmol, 92%) as orange needles. Under storage at 5 ºC no degradation of the complex was observable over 6 months.

Single crystals suitable for X-ray diffraction were obtained by layering a concentrated solution of the complex in CH_2Cl_2 with pentane.

M.p. = 232 – 234 ºC (CH_2Cl_2). **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 8.21 (ddd, *J* = 7.9, 4.4, 1.5 Hz, 1H), 8.16 (bs, 2H), 7.89 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.87 (s, 1H), 7.75 (td, *J* = 7.8, 1.4 Hz, 1H), 7.44 (tdd, *J* = 8.6, 6.6, 1.5 Hz, 2H), 7.38 – 7.32 (m, 1H), 7.29 (td, *J* = 7.5, 1.3 Hz, 1H), 7.12 (dd, *J* = 7.7, 1.5 Hz, 1H), 4.67 (t, *J* = 1.6 Hz, 1H), 4.54 (dd, *J* = 2.6, 1.5 Hz, 1H), 4.18 (dd, *J* = 2.6, 1.5 Hz, 1H), 3.94 (s, 5H), 2.20 – 2.04 (m, 12H), 1.99 (s, 6H), 1.69 (d, *J* = 3.1 Hz, 12H). **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 146.3 (d, *J* = 10.6 Hz), 145.7, 137.5, 137.4, 137.3 (d, *J* = 7.0 Hz), 135.4 (d, *J* = 2.4 Hz), 131.4, 131.2 (q, *J* = 33.1 Hz), 130.1 (d, *J* = 2.2 Hz), 129.8, 128.6, 126.0, 125.5 (d, *J* = 6.8 Hz), 124.6, 124.3, 124.0 (q, *J* = 272.7 Hz), 121.1 (p, *J* = 4.1 Hz), 92.3 (d, *J* = 7.2 Hz), 83.4, 73.7, 73.5, 72.1, 70.2, 43.6 (dd, *J* = 81.7, 23.4 Hz), 42.5 (dd, *J* = 34.0, 2.6 Hz), 36.7, 29.3 (dd, *J* = 21.2, 10.0 Hz). **^{31}P NMR** (202 MHz, CD_2Cl_2) δ 65.58. **^{19}F NMR** (471 MHz, CD_2Cl_2) δ -62.62. **HRMS** (ESI+) calculated for $[C_{50}H_{49}AuF_6{}^{56}FeP]^+$ 1047.2487 m/z; found $[M]^+$: 1047.2500. $\boldsymbol{\alpha_D^{589}}$ = +4.8 deg.cm^2.g^{-1} ($CHCl_3$, c 0.050, 298 K).

(S_p)-D



The complex was synthesized accord to the general procedures **E, F, G.**

The stannylation step was performed using the sulfoxide **1.70d** (124 mg, 246 µmol), $ClSnBu_3$ (0.07 mL) in THF (0.88 mL) and LiTMP prepared from TMP (0.07 mL), *n*BuLi (0.15 mL) in THF (0.44 mL). The work up yielded the tributylstannyl-ferrocene (0.20 mg) as red oil used without further purification.

The sulfoxide removal step was performed using the tributylstannyl-ferrocene (0.20 g) in THF (1.5 mL) and *t*BuLi (.20 mL). The work up yielded the stannyl-ferrocene (0.17 g) as red oil used without further purification.

The Negishi coupling step was performed using the tributylstannyl-ferrocene (0.17 g) in THF (1.1 mL), *n*BuLi (0.12 mL), $ZnCl_2$ (THF solution, 0.42 mL). Then Tris-*o*-furylphosphine (6 mg), Pd_2dba_3 (6 mg) in THF (0.2 mL) and 1-bromo-2-iodobenzene (36 µL, 79 mg).

The crude product was eluted through a silica plug with pentane:$CHCl_3$ 85:15 solvent mixture allowing the desired product (82 mg) as an orange foam used with further purification

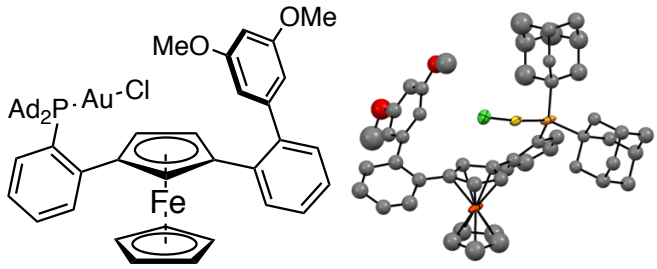
The ligand was synthesized according to the general procedure using the crude product (75 mg, 0.14 mmol), dppf·$PdCl_2$·CH_2Cl_2 adduct (6 mg), NaO*t*Bu (16 mg), $HPAd_2$ (51 mg) and toluene (0.2 M, 0.75 mL). The reaction mixture was diluted with toluene and filtered over silica then concentrated under reduced pressure. The crude product was dissolved in CH_2Cl_2 (0.75 mL) and Me_2S·AuCl (47 mg) was added.

Purification by flash column chromatography (pentane/EtOAc 80:20) followed by a crystallization by layering a concentrated solution of the complex in CH_2Cl_2 with

*n*hexane and pentane afforded the title compound (51 mg, 52 µmol, 24% over 5 steps) as a red solid.

M.p. = >200 ºC (decomposition, CH_2Cl_2), **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 8.22 (ddd, *J* = 8.0, 4.4, 1.5 Hz, 1H), 7.82 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.72 (td, *J* = 7.8, 1.4 Hz, 1H), 7.48 – 7.35 (m, 1H), 7.36 – 7.27 (m, 2H), 7.22 (td, *J* = 7.4, 1.3 Hz, 1H), 7.16 – 7.10 (m, 3H), 6.86 (tt, *J* = 1.7, 0.8 Hz, 1H), 4.76 – 4.74 (m, 1H), 4.73 – 4.70 (m, 1H), 4.36 (t, *J* = 1.5 Hz, 1H), 3.90 (s, 5H), 2.39 – 2.29 (m, 9H), 2.29 – 2.20 (m, 3H), 2.12 – 2.05 (m, 3H), 2.05 – 1.98 (m, 3H), 1.97 – 1.87 (m, 6H), 1.81 – 1.71 (m, 6H), 1.71 – 1.61 (m, 6H). **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 147.3 (d, *J* = 10.6 Hz), 143.0, 141.4, 137.6, 137.3 (d, *J* = 7.4 Hz), 136.8, 135.3 (d, *J* = 2.3 Hz), 131.4, 130.2, 129.8 (d, *J* = 2.3 Hz), 128.4, 128.1, 127.0, 125.8, 125.1 (d, *J* = 6.8 Hz), 124.0 (d, *J* = 41.0 Hz), 90.8 (d, *J* = 7.7 Hz), 85.6, 74.5, 72.2, 71.8 (d, *J* = 2.4 Hz), 71.6, 43.6 (dd, *J* = 88.5, 23.5 Hz), 42.5 (dd, *J* = 81.5, 2.5 Hz), 37.6 – 35.6 (m), 29.3 (dd, *J* = 9.8, 3.1 Hz), 21.7. **^{31}P NMR** (162 MHz, CD_2Cl_2) δ 65.9. **HRMS** (ESI+) calculated for $[C_{50}H_{55}AuClNa^{56}FeP]^+$ 997.2639 m/z; found $[M + Na]^+$: 997.2653. **α_D^{589}** = +20.4 deg.cm^2.g^{-1} ($CHCl_3$, c 0.050, 298 K).

(S_p)-E



The complex was synthesized accord to the general procedures **E, F, G.**

The stannylation step was performed using the sulfoxide **1.70e** (260 mg, 485 µmol), $ClSnBu_3$ (0.14 mL) in THF (1.7 mL) and LiTMP prepared from TMP (0.13 mL), *n*BuLi (0.30 mL) in THF (0.87 mL). The work up yielded the tributylstannyl-ferrocene (0.38 mg) as red oil used without further purification.

The sulfoxide removal step was performed using the stannyl-ferrocene (0.38 g) in THF (2.7 mL) and *t*BuLi (0.36 mL). The work up yielded the tributylstannyl-ferrocene (0.29 g) as red oil used without further purification.

The Negishi coupling step was performed using the tributylstannyl-ferrocene (0.29 g) in THF (1.8 mL), *n*BuLi (0.19 mL), $ZnCl_2$ THF solution (0.35mL). Then Tris-*o*-furylphosphine (10 mg), Pd_2dba_3 (10 mg) in THF (0.2 mL) and 1-bromo-2-iodobenzene (60 µL, 131 mg).

The crude product was eluted through a silica plug with pentane:$CHCl_3$ 85:15 solvent mixture allowing the desire product (82 mg) as an orange foam used with further purification

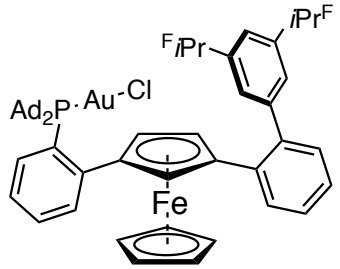
The ligand was synthesized according to the general procedure the crude product (70 mg, 0.13 mmol), dppf·$PdCl_2$·CH_2Cl_2 adduct (5 mg), NaO*t*Bu (161 mg), $HPAd_2$ (38 mg) and toluene (0.24 M, 0.55 mL). The reaction mixture was diluted with toluene and filtered over silica then concentrated under reduced pressure. The crude product was dissolved in CH_2Cl_2 (0.55 mL) and Me_2S·AuCl (41 mg) was added.

Purification by flash column chromatography (pentane/EtOAc 70:30) followed by a crystallization by layering a concentrated solution of the complex in CH_2Cl_2 with *n*hexane and pentane afforded the title compound (28 mg, 28 µmol, 12% over 5 steps) as a red solid.

M.p. = >200 ºC (decomposition, CH_2Cl_2), **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 8.25 (ddd, *J* = 8.0, 4.4, 1.5 Hz, 1H), 7.82 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.72 (t, *J* = 7.9 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 1H), 7.40 – 7.27 (m, 2H), 7.22 (td, *J* = 7.4, 1.3 Hz, 1H), 7.12 (dd, *J* = 7.6, 1.5 Hz, 1H), 6.64 (bs, 2H), 6.30 (t, *J* = 2.4 Hz, 1H), 4.76 – 4.73 (m, 1H), 4.64 (s, 1H), 4.40 (s, 1H), 3.93 (s, 5H), 3.80 (s, 6H), 2.34 – 2.24 (m, 3H), 2.24 – 2.16 (m, 3H), 2.09 – 2.03 (m, 3H), 2.03 – 1.97 (m, 3H), 1.97 – 1.92 (m, 3H), 1.92 – 1.85 (m, 3H), 1.78 – 1.71 (m, 6H), 1.71 – 1.62 (m, 6H). **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 160.8, 146.9 (d, *J* = 10.6 Hz), 145.8, 140.9, 137.5 (d, *J* = 7.4 Hz), 137.0, 135.2 (d, *J* = 2.3 Hz), 131.1, 130.0 (d, *J* = 2.3 Hz), 129.8, 127.4, 125.5, 125.3 (d, *J* = 6.8 Hz), 124.4, 124.1, 100.2, 91.8 (d, *J* = 7.7 Hz), 84.7, 74.0, 72.2, 71.7, 43.6 (dd, *J* = 75.6, 23.4 Hz), 42.9 (d, *J* = 2.6 Hz), 42.2 (d, *J* = 2.7 Hz), 36.7 (d, *J* =

12.8 Hz), 29.3 (t, J = 9.5 Hz). **^{31}P NMR** (162 MHz, CD_2Cl_2) δ 65.93. **HRMS** (ESI+) calculated for $[C_{50}H_{55}AuClNaO_2{}^{56}FeP]^+$ 1029.2537 m/z; found $[M + Na]^+$: 1029.2520. $\boldsymbol{\alpha_D^{589}}$ = +45.6 deg.cm^2.g^{-1} ($CHCl_3$, c 0.050, 298 K).

(S_p)-F



The complex was synthesized accord to the general procedures **E, F, G.**

The stannylation step was performed using the sulfoxide **1.70f** (303 mg, 373 µmol), $ClSnBu_3$ (0.11 mL) in THF (1.3 mL) and LiTMP prepared from TMP (0.10 mL), *n*BuLi (0.22 mL) in THF (0.67 mL). The work up yielded the tributylstannyl-ferrocene (0.41 mg) as red oil used without further purification.

The sulfoxide removal step was performed using the tributylstannyl-ferrocene (0.41 g) in THF (2.3 mL) and *t*BuLi (0.30 mL). The work up yielded the tributylstannyl-ferrocene (0.33 g) as red oil used without further purification.

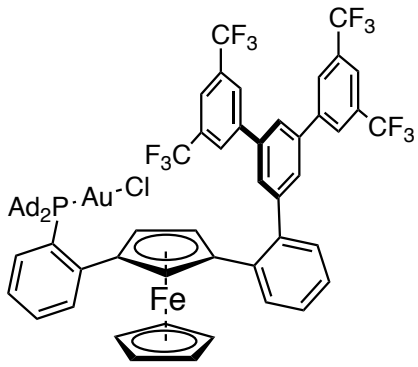
The Negishi coupling step was performed using the tributylstannyl-ferrocene (0.33 g) in THF (1.5 mL), *n*BuLi (0.19 mL), $ZnCl_2$ THF solution (0.28 mL). Then Tris-*o*-furylphosphine (10 mg), Pd_2dba_3 (10 mg) in THF (0.2 mL) and 1-bromo-2-iodobenzene (48 µL). The crude product was eluted through a silica plug with pentane:$CHCl_3$ 85:15 solvent mixture allowing the desire product (224 mg) as an orange foam used with further purification.

The ligand was synthesized according to the general procedure using the crude product (170 µg, 205 mmol), dppf·$PdCl_2$·CH_2Cl_2 adduct (8 mg), NaO*t*Bu (22 mg), $HPAd_2$ (68 mg) and toluene (0.24 M, 0.85 mL). The reaction mixture was diluted with toluene and filtered over silica then concentrated under reduced pressure. The crude product was dissolved in CH_2Cl_2 (0.85 mL) and Me_2S·AuCl (73 mg) was

added. Purification by flash column chromatography (pentane/EtOAc 80:20) compound (132 mg, 103 μmol, 37% over 5 steps) as a red solid. Crystallization by layering a concentrated solution of the complex in CH_2Cl_2 with cyclohexane allowed the product as orange needles unsuitable for X-ray diffraction.

M.p. = 195 – 205 ºC (CH_2Cl_2). **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 8.19 – 8.11 (m, 1H), 8.62 – 7.70 (m, 2H), 7.91 – 7.86 (m, 2H), 7.77 (td, *J* = 7.7, 1.4 Hz, 1H), 7.49 – 7.41 (m, 2H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.30 (td, *J* = 7.4, 1.1 Hz, 1H), 7.14 (dd, *J* = 7.7, 1.4 Hz, 1H), 5.01 (s, 1H), 4.42 (s, 1H), 3.91 (s, 5H), 3.79 (s, 1H), 2.25 (dd, *J* = 5.8, 2.9 Hz, 6H), 2.14 – 1.98 (m, 9H), 1.98 – 1.92 (m, 3H), 1.81 – 1.70 (m, 6H), 1.70 – 1.58 (m, 6H). **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 146.1, 146.1, 137.8, 137.4 (d, *J* = 7.4 Hz), 137.2, 135.4 (d, *J* = 2.0 Hz), 131.4, 130.1 (d, *J* = 2.3 Hz), 129.4, 128.6, 127.9 (d, *J* = 21.0 Hz), 125.8, 125.5 (d, *J* = 6.6 Hz), 124.4 (d, *J* = 39.0 Hz), 121.8 (d, *J* = 12.3 Hz), 120.8 (qdd, *J* = 287.0, 28.1, 3.5 Hz), 92.2 (d, *J* = 6.7 Hz), 93.2 – 90.3 (m), 83.2, 74.4, 73.3, 72.0 (d, *J* = 2.7 Hz), 68.7, 43.8 (dd, *J* = 87.0, 22.1 Hz), 42.5 (dd, *J* = 107.2, 2.8 Hz), 36.6 (d, *J* = 13.5 Hz), 29.2 (dd, *J* = 35.6, 9.7 Hz). **^{31}P NMR** (202 MHz, CD_2Cl_2) δ 66.39. **^{19}F NMR** (376 MHz, CD_2Cl_2) δ -75.68, -182.14. **HRMS** (ESI+) calculated for $[C_{54}H_{49}AuClF_{14}Na^{56}FeP]^+$ 1305.1944 m/z; found $[M + Na]^+$: 1305.1970. **α_D^{589}** = +34.9 deg.cm^2.g^{-1} ($CHCl_3$, c 0.050, 298 K).

(S_p)-G



The complex was synthesized accord to the general procedures **E, F, G.**

The stannylation step was performed using the sulfoxide **1.70g** (640 mg, 711 µmol), $ClSnBu_3$ (0.201 mL) in THF (2.5 mL) and LiTMP prepared from TMP (0.19 mL), *n*BuLi (0.44 mL) in THF (1.3 mL). The work up yielded the tributylstannyl-ferrocene (0.80 mg) as red oil used without further purification.

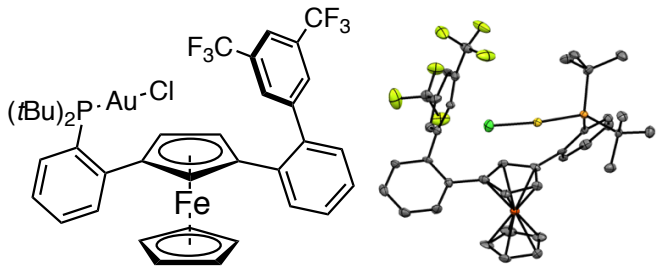
The sulfoxide removal step was performed using the tributylstannyl-ferrocene (0.80 g) in THF (4.1 mL) and *t*BuLi (.55 mL). The work up yielded the tributylstannyl-ferrocene (0.61 g) as red oil used without further purification.

The Negishi coupling step was performed using the tributylstannyl-ferrocene (0.61 g) in THF (2.5 mL), *n*BuLi (0.27 mL), $ZnCl_2$ THF solution (0.95 mL). Then Tris-*o*-furylphosphine (13 mg), Pd_2dba_3 (13 mg) in THF (0.4 mL) and 1-bromo-2-iodobenzene (82 µL). The crude product was eluted through a silica plug with pentane:$CHCl_3$ 90:10 solvent mixture allowing the desired product (290 mg) as an orange foam used with further purification.

The ligand was synthesized according to the general procedure using the crude product (70 mg, 205 µmol), dppf·$PdCl_2$·CH_2Cl_2 adduct (4 mg), NaO*t*Bu (8 mg), $HPAd_2$ (29 mg) and toluene (0.15 M, 0.50 mL). The reaction mixture was diluted with toluene and filtered over silica then concentrated under reduced pressure. The crude product was dissolved in CH_2Cl_2 (0.50 mL) and Me_2S·AuCl (43 mg) was added. The resulting mixture was stirred for 30 min at 24 ºC. Purification by flash column chromatography (pentane/EtOAc 90:10) compound (65 mg, 43 µmol, 43% over 5 steps) as a red solid. No crystal suitable for X-ray diffraction were obtained. **M.p. =** >180 ºC (decomposition, CH_2Cl_2), **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 8.36 (s, 2H), 8.26 (ddd, *J* = 8.0, 4.4, 1.5 Hz, 1H), 8.24 – 8.15 (m, 3H), 7.94 – 7.88 (m, 3H), 7.84 (s, 1H), 7.80 (t, *J* = 1.8 Hz, 1H), 7.71 (td, *J* = 7.8, 1.4 Hz, 1H), 7.47 – 7.41 (m, 2H), 7.36 – 7.31 (m, 1H), 7.29 (td, *J* = 7.5, 1.2 Hz, 1H), 7.19 (dd, *J* = 7.6, 1.5 Hz, 1H), 4.83 – 4.79 (m, 1H), 4.51 – 4.47 (m, 1H), 4.46 – 4.42 (m, 1H), 3.96 (s, 5H), 2.21 – 2.11 (m, 3H), 2.11 – 2.02 (m, 3H), 2.02 – 1.94 (m, 6H), 1.94 – 1.86 (m, 3H), 1.85 – 1.76 (m, 3H), 1.71 – 1.61 (m, 6H), 1.58 – 1.48 (m, 6H), 1.44 – 1.36 (m, 3H). **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 147.3 (d, *J* = 10.6 Hz), 146.9, 144.1, 140.3, 140.0, 138.4 (d, *J* = 7.3 Hz), 138.3, 136.2 (d, *J* = 2.2 Hz), 133.4 (d, *J* = 37.2 Hz), 132.6,

131.7, 131.1 (d, J = 2.3 Hz), 130.6, 130.2 (d, J = 13.9 Hz), 129.2, 126.6 (d, J = 6.8 Hz), 126.6, 125.7, 125.4, 124.9 (q, J = 272.8 Hz), 122.8 (p, J = 3.9 Hz), 94.0, 85.2, 74.7, 74.3, 73.1, 72.0, 44.4 (dd, J = 31.4, 23.5 Hz), 43.4 (dd, J = 30.0, 2.7 Hz), 37.5 (dd, J = 30.9, 1.6 Hz), 30.2 (d, J = 9.9 Hz). **^{31}P NMR** (202 MHz, CD_2Cl_2) δ 65.61. **^{19}F NMR** (471 MHz, CD_2Cl_2) δ -63.04. **HRMS** (ESI+) calculated for $[C_{64}H_{55}AuF_{12}{}^{56}FeP]^+$ 1335.2861 m/z; found $[M\text{-}Cl^-]^+$: 1335.2804. **α_D^{589}** = +78.8 deg.cm^2.g^{-1} ($CHCl_3$, c 0.050, 302 K).

(S_p)-H



The complex was synthesized according to the general procedure **G** using ligand **L_H** (55 mg, 79 µmol) and $Me_2S{\cdot}AuCl$ (25 mg) in CH_2Cl_2 (0.40 mL).

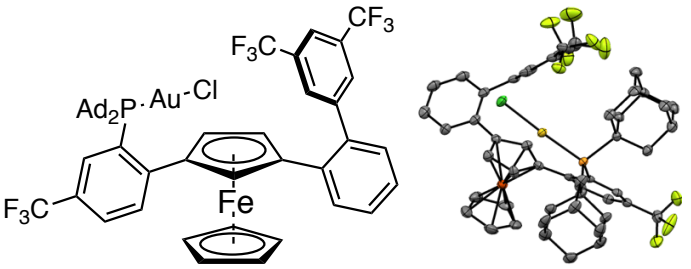
Purification by flash column chromatography (pentane/EtOAc 85:15 afforded the title compound (69 mg, 74 µmol, 94%) as an orange foam.

Single crystals suitable for X-ray diffraction were obtained by layering a concentrated solution of the complex in CH_2Cl_2 with pentane.

M.p. = 160 – 161 ºC (CH_2Cl_2). **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 8.21 (ddd, J = 7.9, 4.5, 1.5 Hz, 1H), 8.11 (s, 2H), 7.91 (ddd, J = 8.0, 1.3, 0.5 Hz, 1H), 7.82 (s, 1H), 7.72 (td, J = 8.1, 1.3 Hz, 1H), 7.50 – 7.41 (m, 2H), 7.34 (ddt, J = 8.0, 7.2, 1.4 Hz, 1H), 7.28 (td, J = 7.5, 1.3 Hz, 1H), 7.08 (ddd, J = 7.6, 1.5, 0.5 Hz, 1H), 4.54 (ddd, J = 2.6, 1.5, 0.5 Hz, 1H), 4.48 (t, J = 1.5 Hz, 1H), 4.40 (dd, J = 2.6, 1.5 Hz, 1H), 4.00 (s, 5H), 1.37 (d, J = 15.5 Hz, 9H), 1.25 (d, J = 15.5 Hz, 9H). **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 145.9, 145.6 (d, J = 10.9 Hz), 137.5, 137.4, 137.2 (d, J = 7.4 Hz), 134.3 (d, J = 2.7 Hz), 131.5, 131.3 (q, J = 33.0 Hz), 130.9, 130.5 (d, J = 2.3 Hz), 130.1, 128.6, 127.0 (d, J = 43.1 Hz), 126.2 (d, J = 7.0 Hz), 126.0, 124.0 (q, J =

272.8 Hz), 121.2 (p, J = 3.9 Hz), 92.4 (d, J = 7.5 Hz), 83.9, 73.5, 73.3, 72.1, 71.1, 38.5 (dd, J = 41.1, 25.5 Hz), 31.1 (dd, J = 16.4, 6.7 Hz). **^{31}P NMR** (202 MHz, CD_2Cl_2) δ 63.86. **^{19}F NMR** (471 MHz, CD_2Cl_2) δ -62.61. **HRMS** (ESI+) calculated for $[C_{38}H_{37}AuClF_6Na^{56}FeP]^+$ 949.1133 m/z; found $[M + Na]^+$: 949.1118. **α_D^{589}** = +69.5 deg.cm^2.g^{-1} ($CHCl_3$, c 0.050, 298 K).

(S_p)-I



The complex was synthesized according to the general procedure **G** using ligand **L$_I$** (300 mg, 327 µmol) and $Me_2S{\cdot}AuCl$ (106 mg) in CH_2Cl_2 (1.5 mL).

Purification by flash column chromatography (pentane/EtOAc 80:20) afforded the title compound (371 mg, 322 µmol, 98%) as an orange foam.

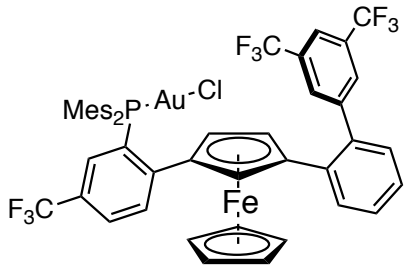
Optional: a recrystallization was carried out by dissolving the product into CH_2Cl_2 (200 mg.mL^{-1}, 1 volume) at room temperature, to this solution was added boiling *n*-hexane (10 volumes). The product crystallized as long orange needles (suitable for X-ray diffraction) while the solution cooled to 24 ºC, the solution was cooled to 5 ºC for an additional 5 h and the filtered. The product was washed with cold Et_2O and dried for 24 h under vacuum at 50 ºC allowing the pure complex (314 mg, 0.273 mmol, 84%) as orange needles. Under storage at 5 ºC no degradation of the complex observable over 6 months.

Single crystals suitable for X-ray diffraction were obtained by evaporation of a supersaturated solution of the complex in cyclohexane:$CHCl_3$.

M.p. = 232 – 234 ºC (CH_2Cl_2), **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 8.32 (dd, J = 8.3, 3.9 Hz, 1H), 8.14 (s, 2H), 8.01 (d, J = 7.3 Hz, 1H), 7.89 (dd, J = 8.1, 1.2 Hz, 1H), 7.86 (s, 1H), 7.68 (d, J = 8.3 Hz, 1H), 7.45 (td, J = 7.6, 1.5 Hz, 1H), 7.31 (td, J =

7.5, 1.3 Hz, 1H), 7.14 (dd, *J* = 7.7, 1.5 Hz, 1H), 4.66 (s, 1H), 4.64 (s, 1H), 4.34 – 4.30 (m, 1H), 3.96 (s, 5H), 2.27 – 2.13 (m, 4H), 2.13 – 2.05 (m, 8H), 2.05 – 1.96 (m, 5H), 1.70 (dd, *J* = 7.3, 3.2 Hz, 12H). **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 151.1 (d, *J* = 10.1 Hz), 145.5, 137.7 (d, *J* = 7.0 Hz), 137.4, 137.0, 132.1 (p, *J* = 3.6 Hz), 131.5, 131.3 (q, *J* = 33.1 Hz), 131.0, 129.9, 128.6, 127.2 (qd, *J* = 32.9, 6.8 Hz), 126.5 – 126.3 (m), 126.3, 125.7, 124.4, 124.4 (q, *J* = 270.4 Hz), 124.0 (q, *J* = 273.0 Hz), 121.1 (p, *J* = 3.9 Hz), 90.1 (d, *J* = 6.9 Hz), 84.3, 73.6, 73.4, 72.4, 71.1, 43.9 (dd, *J* = 95.2, 22.2 Hz), 42.5 (dd, *J* = 37.3, 2.6 Hz), 36.5 (d, *J* = 3.5 Hz), 29.2 (dd, *J* = 22.9, 9.9 Hz). **^{31}P NMR** (202 MHz, CD_2Cl_2) δ 63.25. **^{19}F NMR** (471 MHz, CD_2Cl_2) δ -63.08, -62.59. **HRMS** (ESI+) calculated for $[C_{51}H_{48}AuClF_9Na^{56}FeP]^+$ 1173.1946 m/z; found $[M + Na]^+$: 1173.1942. $\boldsymbol{\alpha_D^{589}}$ = +27.9 deg.cm^2.g^{-1} ($CHCl_3$, c 0.050, 298 K).

(S_p)-J



The complex was synthesized according to the general procedure **G** using ligand **L$_J$** (30 mg, 34 µmol) and $Me_2S{\cdot}AuCl$ (10 mg) in CH_2Cl_2 (0.17 mL).

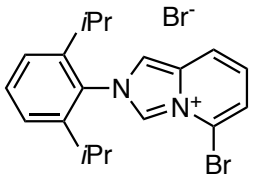
Purification by flash column chromatography (pentane/EtOAc 80:20 afforded the title compound (32 mg, 29 µmol, 85%) as a red solid.

No crystal suitable for X-ray diffraction were obtained.

M.p. = 171 – 174 ºC (CH_2Cl_2). **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 8.08 (s, 2H), 8.07 – 8.02 (m, 1H), 7.89 (s, 1H), 7.63 (d, *J* = 8.3 Hz, 1H), 7.44 – 7.36 (m, 2H), 7.29 (dtd, *J* = 16.1, 7.3, 1.6 Hz, 2H), 7.14 – 7.11 (m, 1H), 7.04 (d, *J* = 4.1 Hz, 2H), 7.00 (d, *J* = 3.9 Hz, 2H), 4.59 (dt, *J* = 2.9, 1.6 Hz, 1H), 4.56 (s, 1H), 4.17 (s, 1H), 3.89 (s, 5H), 2.43 – 2.40 (m, 3H), 2.36 (d, *J* = 0.9 Hz, 3H), 2.33 – 2.23 (m, 12H). **^{13}C**

NMR (126 MHz, CD_2Cl_2) δ 150.6 (d, *J* = 14.5 Hz), 145.2, 143.2 (d, *J* = 10.6 Hz), 142.7 (d, *J* = 10.7 Hz), 142.5 (dd, *J* = 16.3, 2.5 Hz), 137.5, 136.1, 133.9 (d, *J* = 8.7 Hz), 132.5 (dd, *J* = 22.6, 9.2 Hz), 131.7, 131.5 (q, *J* = 32.9 Hz), 131.3 – 131.1 (m), 131.0, 130.7 (d, *J* = 51.4 Hz), 129.5, 128.7, 128.4 (qd, *J* = 32.9, 9.5 Hz), 127.4 – 127.2 (m), 126.5, 125.5 (dd, *J* = 57.6, 5.3 Hz), 124.1 (q, *J* = 272.3 Hz), 123.9 (q, *J* = 273.1 Hz), 121.5 – 121.2 (m), 85.3 (d, *J* = 7.9 Hz), 85.2, 73.4, 72.5 (d, *J* = 3.2 Hz), 72.3, 71.7, 25.0 (dd, *J* = 10.9, 2.5 Hz), 21.2 (d, *J* = 4.0 Hz). **^{31}P NMR** (202 MHz, CD_2Cl_2) δ 5.53. **^{19}F NMR** (471 MHz, CD_2Cl_2) δ -62.61, -63.39. **HRMS** (ESI+) calculated for $[C_{49}H_{40}AuClF_9{}^{56}FePNa]^+$ 1141.1320 m/z; found $[M + Na]^+$: 1141.1312. $\boldsymbol{\alpha_D^{589}}$ = –30.0 deg.cm^2.g^{-1} ($CHCl_3$, c 0.050, 298 K).

5-Bromo-2-(2,6-diisopropylphenyl)-2*H*-imidazo[1,5-*a*]pyridin-4-ium bromide 1.93

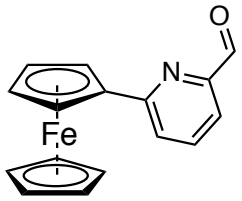


A flask was charged with 6-bromopicolinaldehyde (1.0 g, 5.38 mmol), 2,6-diisopropylaniline (1.06 mL, 1.0 g, 1.05 equiv) and toluene (10 mL). A Dean-Stark apparatus was adapted to the flask and the reaction was refluxed for 18 h. The solvent was removed under reduced pressure and the resulting solid was used as such.

The crude product (1.05 g, 3.04 mmol) and paraformaldehyde (100 mg, 1.1 equiv) were suspended in EtOAc (18.5 mL) and the mixture was heated to reflux. TMSBr (0.43 mL, 1.1 equiv) was added dropwise and the mixture was stirred for 30 min at reflux then allowed to cool to room temperature. The solid was filtered off and washed with Et_2O (2x) affording the product (1.26 g, 2.88 mmol, 94%) used without further purification. The obtained characterization data were in agreement with those reported in literature.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (s, 1H), 9.02 (d, *J* = 1.7 Hz, 1H), 8.72 (d, *J* = 9.2 Hz, 1H), 7.61 (t, *J* = 7.9 Hz, 1H), 7.56 (d, *J* = 7.2 Hz, 1H), 7.37 (d, *J* = 7.9 Hz, 3H), 2.15 (hept, *J* = 6.8 Hz, 2H), 1.21 (dd, *J* = 6.8, 2.0 Hz, 12H).

6-Ferrocenylpicolinaldehyde 1.93



A flask was charged with tributylstannyl-ferrocene **1.94** (200 mg, 1.05 equiv), CsF (121 mg, 2 equiv), $PdCl_2 \cdot dppf \cdot CH_2Cl_2$ (0.3 mg, 0.1 mol%), 6-bromopicolinaldehyde (74 mg, 0.40 mmol) and DMF (1.2 mL, 1 volume). The mixture was stirred for 5 min at 24 ºC. CuI (0.8 mg, 1 mol%) was added and the atmosphere was evacuated and backfilled with argon (2x). The mixture was stirred for 30 min in an oil bath preheated to 100 ºC. The reaction was monitored by TLC analysis.

After completion of the reaction the crude mixture was cooled down to room temperature, diluted with water (10 volumes), stirred for 30 min and filtered over a pad of Celite® and Celite® was washed with Et_2O. Phases were separated and the aqueous layer was extracted with Et_2O (2x). The reunited organic layer was washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography over silica gel (eluent pentane: Et_2O 97:3) yielding the pure product (112 mg, 385 μmol, 97%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.08 (d, *J* = 0.5 Hz, 1H), 7.76 – 7.72 (m, 2H), 7.63 – 7.58 (m, 1H), 5.00 (t, *J* = 1.9 Hz, 2H), 4.46 (t, *J* = 2.0 Hz, 2H), 4.05 (s, 4H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 194.4, 160.6, 152.7, 136.9, 124.2, 118.3, 82.7, 70.5, 69.8, 67.7. **HRMS** (ESI+) calculated for $[C_{16}H_{13}NNaO^{54}Fe]^+$ 312.0285 m/z; found $[M + Na]^+$: 312.0295.

Chapter II

Application of Planar Chiral Mononuclear Gold(I) Complexes in Catalysis and Study of their Mode of Action

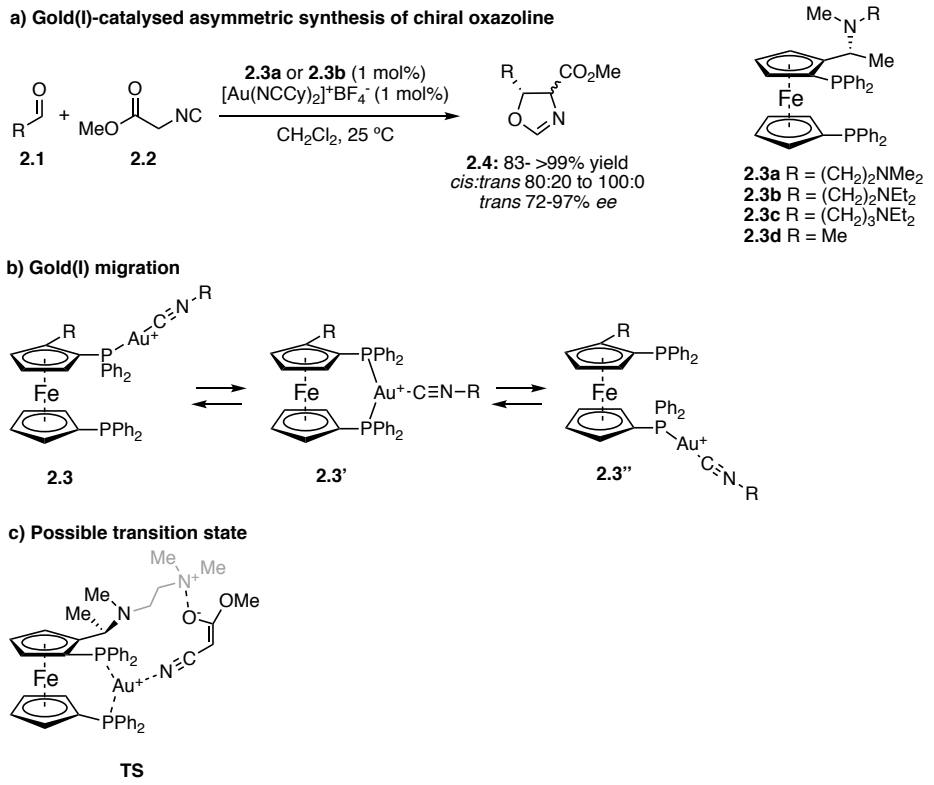
Introduction

Successful asymmetric gold(I)-catalyzed transformations are usually resulting from extensive screenings of ligands, solvents, and additives. Although high throughput experiments become more available and provide a powerful tool to achieve the desired results in a short period of time, they require important resources and are strongly dependent on available catalysts and ligands. The challenge of developing new chiral gold(I) catalysts is related to the incomplete understanding of the enantiocontrol in gold(I)-catalyzed transformations. In this regard, the analysis of the working mode of new catalysts could provide important knowledge that would allow narrowing the number of screening experiments required for the development of new asymmetric reactions.

The seminal report by Ito and Hayashi described the first enantioselective gold(I)-catalyzed transformation.[8] This work described the asymmetric synthesis of oxazolines **2.4** from isocyanoacetates **2.2** and aldehydes **2.1** catalyzed by a gold(I) complex of the trifunctional diphosphine ferrocenyl amine ligand **2.3** displaying central and planar chirality (Scheme 2.1). The amine function is essential to the reaction, as it is suggested necessary to form the enolate intermediate and to form the ion pair with the protonated ammonium group. The use of a longer tether with the ligand results in drastic decrease of enantioselectivity and the ligand **2.3d** provides nearly racemic product. Mechanistic studies carried out by Togni[165] on the mode of action of this catalyst suggest an equilibrium between the linear coordinated species **2.3** and **2.3''** by migration of Au coordinated to the isocyanate fragment from one phosphorus atom to another. The species **2.3'** suggested in the original report is proposed as an intermediate or transition state of the interconversion between **2.3** and **2.3''**. This report by Togni

165 (a) Pastor, S. D.; Togni, *J. Am. Chem. Soc.* **1989**, *1*, 2333–2334. (b) Togni, A.; Pastor, S. D. *J. Org. Chem.* **1990**, *55*, 1649–1664.

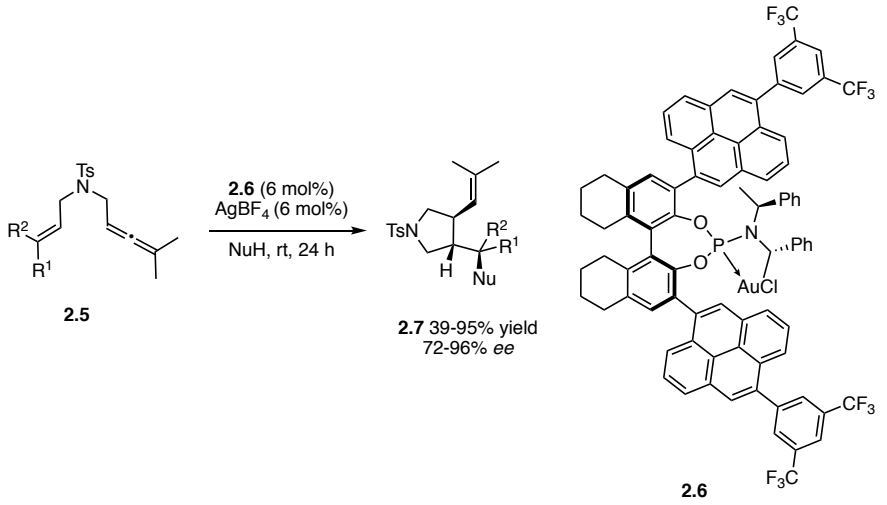
also demonstrated that both planar and central chirality are involved in the high diastereo- and enantiocontrol.



Scheme 2.1. Asymmetric synthesis of oxazolines catalyzed by a bifunctional gold(I) complex.

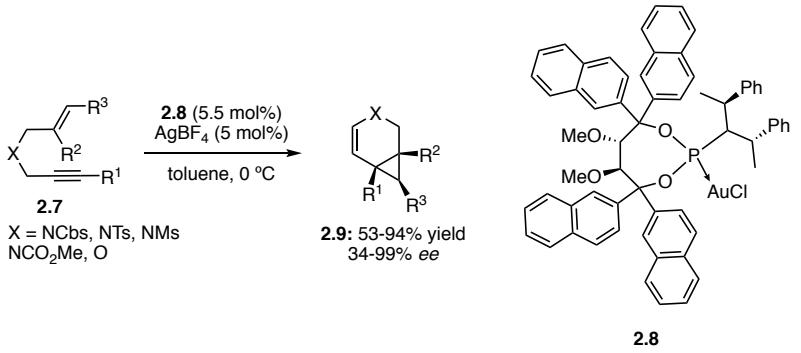
In 2011 Toste reported the application of chiral gold(I) complex **2.6**, using the octahydro-BINOL-derived phosphoramidite ligand, for the asymmetric alkoxycyclization of the *N*-tethered allene-alkene **2.5** (Scheme 2.2).[44] The chirality of the catalyst is provided by the BINOL backbone, the presence of bis(1-phenylethyl)amine group provides steric bulk and increase the helical pitch of the scaffold. The presence of bulky pyrenyl groups creates a wall around the reactive site in which the substrate can adopt two conformations displaying different

substrate-catalyst interactions, which are responsible of the enantiocontrol of the reaction.



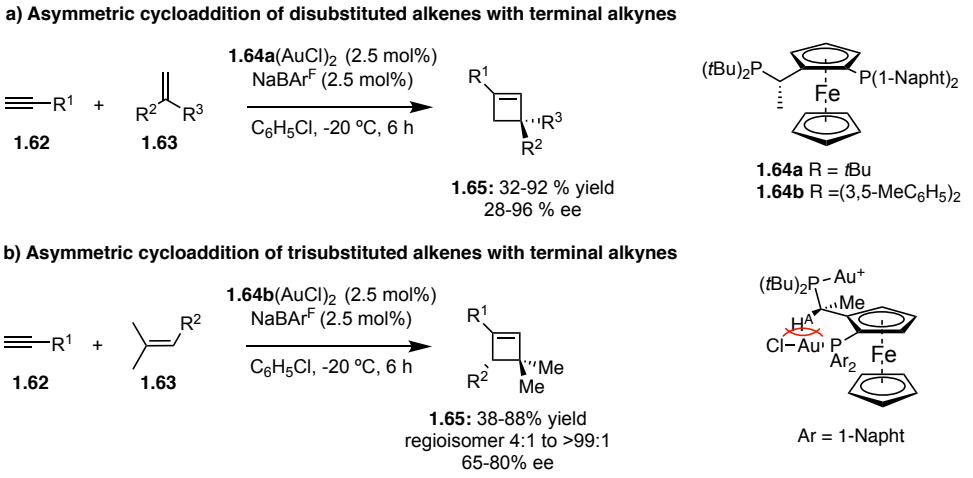
Scheme 2.2. Gold(I)-catalyzed asymmetric alkoxycyclization of *N*-tethered allene-alkene **2.5**.

In the case of TADDOL-phosphoramidite-based complex **2.8** introduced by Fürstner in 2012 for the cycloisomerization of *N*- and *O*-tethered enynes[45] an electrostatic effect was observed in addition of the chiral pocket created by the ligand (Scheme 2.3). In this system, the partial positive charge at the benzylic carbon resulting of the activation of the alkyne is stabilized by interaction with the adjacent naphthyl substituent.



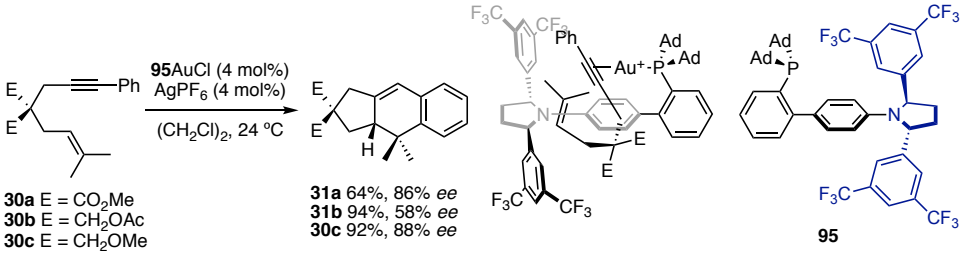
Scheme 2.3. Gold(I)-catalyzed asymmetric cycloisomerization of *N*- and *O*-tethered enynes **2.7**.

In 2017 our group reported the synthesis of chiral cyclobutenes **1.65** catalyzed by digold(I) complexes of Josiphos-type ligands **1.64** (Scheme 2.4).[144d] The gold(I)-catalyzed cycloaddition of terminal alkynes with 1,1'-disubstituted alkenes was carried out using ligands **1.64a**, while ligand **1.64b** provided higher enantioselectivity for the cycloaddition of terminal alkynes with trisubstituted alkenes. The active species was proposed to be a monocationic complex obtained by treatment of the digold(I) complex with one equivalent of $NaBAr^F_4$ as chloride abstractor. While the reaction occurs at the $(t\text{Bu})_2$P-Au(I) metallic center, only traces of racemic product were observed in absence of the second metallic center $(\text{naphthyl})_2$P-AuCl, highlighting the non-innocent role of this center. Theoretical investigations support that π-π-interaction between the aromatic systems of the alkene and alkyne is important for the enantiocontrol.



Scheme 2.4. Enantioselective synthesis of cyclobutenes catalyzed by Josiphos digold(I) complexes.

Recently our group introduced a new ligand design achieving high level of enantioselectivity in the gold(I)-catalyzed [4+2] cycloaddition of the 1,6-enynes **30** (Scheme 2.5).[95] Theoretical studies revealed the existence of attractive non-covalent interactions between the aromatic substituents of the pyrrolidine and both the aromatic and –OMe substituents of the substrate.



Scheme 2.5. Gold(I)-catalyzed [4+2] cycloaddition of 1,6-enynes with **95**·Au complex.

Objective

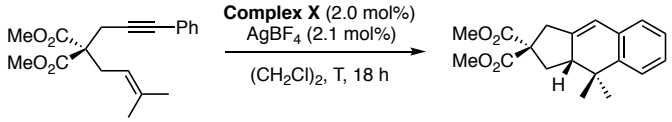
With a new family of chiral ferrocene gold(I) complexes in hand we aimed to investigate the optimal conditions for the gold(I)-catalyzed formal [4+2] cycloaddition of 1,6-enynes. Additionally, we wanted to explore the potential of these complexes as catalysts in other asymmetric reactions.

Results and Discussion

Application of Gold(I) Complexes B-J in Homogenous Catalysis

The performance of each ligand was investigated in the [4+2] cycloaddition of 1,6-enyne **30a** (Table 2.1).

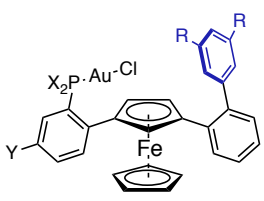
Table 2.1. Screening of gold(I) complexes for the cycloisomerization of the 1,6-enyne **30a**.



30a **31a**

entry	X	times (h)	temperature (ºC)	enantiomeric ratio (yield %)
1	**(S_p)-B**	18	0	77:23
2	**(S_p)-H**	18	0	82:18
3	**(S_p)-C**	18	0	83:17
4	**(S_p)-C**	1	24	80:20
5	**(S_p)-C**	36	–20	88:12 (70)
6	**(S_p)-C**	96	–30	89:11
7	**(S_p)-I**	48	–20	89:11 (65)
8	**(S_p)-F**	18	0	63:37
9	**(S_p)-D**	18	0	54:46
10	**(S_p)-E**	18	0	64:36
11	**(S_p)-G**	168	0	57:43
12	**(S_p)-J**	6	24	<49:51

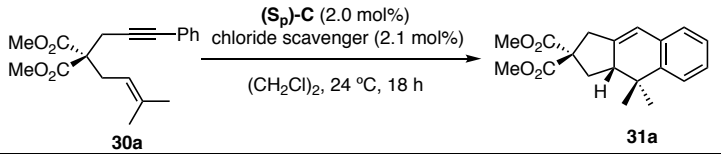
[a] Reactions carried out on 0.03 mmol scale until full conversion of **30,** monitored by GC-MS. [b] Determined by HPLC on chiral stationary phase.



(S_p)-B R = H, Y = H, X = Ad
(S_p)-C R = CF_3, Y = H, X = Ad
(S_p)-D R = Me, Y = H, X = Ad
(S_p)-E R = OMe, Y = H, X = Ad
(S_p)-F R = iPr^F, Y = H, X = Ad
(S_p)-G R = 3,5-$(CF_3)_2C_6H_3$, Y = H, X = Ad
(S_p)-H R = CF_3, Y = H, X = *t*Bu
(S_p)-I R = CF_3, Y = CF_3, X = Ad
(S_p)-J R = CF_3, Y = CF_3, X = Mes

A brief screening of chloride abstractors revealed that $AgBF_4$ provides the highest enantioselectivity (Table 2.2). Although $AgNTf_2$ induces similar levels of enantioselectivity, enyne **30a** was not fully converted after 18 h reaction time. Conversion of enyne **30a** was only observed when a silver salts were employed as chloride abstractor.

Table 2.2. Screening of chloride abstractors for the asymmetric cycloisomerization of 1,6-enyne **30a.**



30a **31a**

entry	chloride abstractor	conversion (%)	enantiomeric ratio[b]
1	$AgBF_4$	>99	83:17
2	$AgPF_6$	>99	80:21
3	$AgSbF_6$	>99	76:24
4	$AgNTf_2$	90	82:18
5	$NaBAr^F{}_4$	*n.d* [c]	-
6	KPF_6	*n.d* [c]	-
7	$NaSbF_6$	*n.d* [c]	-

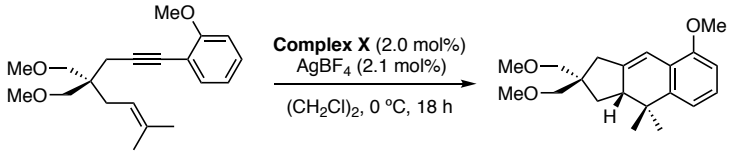
[a]Reactions carried out on 0.03 mmol scale**.** [b]Determined by HPLC on chiral stationary phase. [c]no detection

Ligand **(S_p)-C** provided 89:11 *er* in the formal [4+2] cycloaddition of 1,6-enyne **30a**. We turned our attention to the $-(CH_2OMe)_2$ tethered 1,6-enynes since these type of substrates have been previously found by our group to undergo cycloisomerization in high yield and enantioselectivity.[95]

We first proceeded to a ligand screening using the 1,6-enyne **30p** as substrate (Table 2.3). The strong disparity in enantioinduction between the different complexes previously observed in the cyclization on enyne **30a** was much less marked with enyne **30p**. However, the same trend was observed: the complexes functionalized with electron-rich and bulky biaryls systems gave the

lowest enantioinduction. In certain cases, an unknown minor by-product was observed by ^{1}H-NMR and GC-MS, which was not characterized. Decreasing the temperature increases the enantioinduction but also favors the formation of this side product (Table 2.3, entries 3-5). Gratifyingly, decreasing the temperature to –25 ºC allowed us to access product **31p** in 94:6 *er* at the expense of a slightly longer reaction time and decreased yield (Table 2.3, entry 5).

Table 2.3. Screening of gold(I) complexes in the cycloisomerization of 1,6-enyne **30p**.[a]



30p **31p**

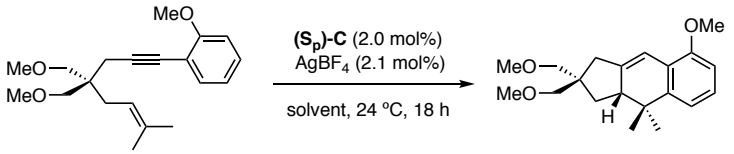
entry	X	yield (%)[b]	*er*[c]	side product (integration %[b])
1	(*S*$_p$)-**B**	88	87:13	15
2	(*S*$_p$)-**H**	93	85:15	8
3	(*S*$_p$)-**C**	95	88:12	10
4	(*S*$_p$)-**C**[d]	92	83:17	*n.d*[e]
5	(*S*$_p$)-**C**[f]	81 (91 brsm)	94:6	16
6	(*S*$_p$)-**I**	92	89:11	14
7	(*S*$_p$)-**F**	95	73:27	8
8	(*S*$_p$)-**D**	95	82:18	10
9	(*S*$_p$)-**E**	96	74:26	8
10	(*S*$_p$)-**F**	89	56:44	8
11	(*S*$_p$)-**J**[g]	89	<49:51	7

[a]0.06mmol scale. [b]Yield determined by ^{1}H NMR using 1,1,2-trichloroethane as internal standard. [c]*er* determined by chiral-SFC. [d]performed at 24 ºC. [e]no detection. [f]performed at –25 ºC. [g]Reaction performed over 96 h.

We then proceeded to screen different solvents (Table 2.4). The reaction performed in 1,2-dichloroethane delivered the desired product with the high yield and good enantioselectivity (Table 2.4, entries 1 and 2). The reaction also proceeded smoothly in CH_2Cl_2 but in slightly lower yield (Table 2.4, entries 3 and 4). The use of aromatic solvents led to lower yields, increased the formation of the side product and longer reaction times were required to achieve full conversion

(Table 2.4, entries 5-7). In methylcyclohexane the reaction only proceeded with 45% conversion over 7 days with noticeable formation side products (Table 2.4, entry 8). Therefore, we decided to perform the gold(I)-catalyzed reactions using complex **(S_p)-C** at –25 ºC in 1,2-dichloroethane.

Table 2.4. Screening of solvent for the cycloisomerization of 1,6-enyne **30p**.



30p **31p**

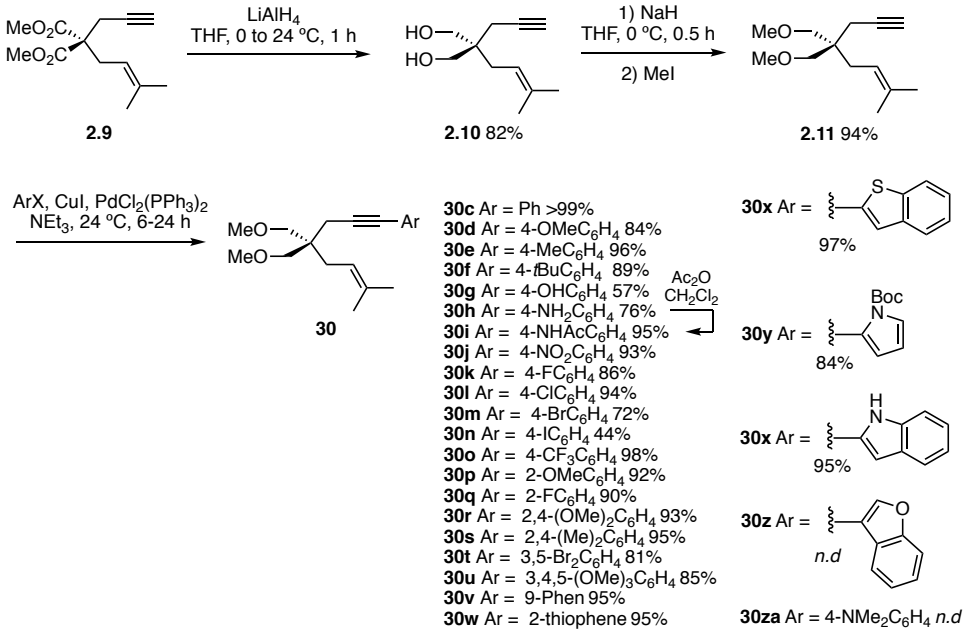
entry	solvent	time	yield (%)[b]	*er*[c]	side product (integration %)
1	$(CH_2Cl)_2$	18 h	92	83:17	*n.d*[d]
2	$(CH_2Cl)_2$[e]	18 h	81 (91 brsm)	94:6	16
3	CH_2Cl_2	18 h	90	85:15	*n.d*[d]
4	CH_2Cl_2[e]	24 h	82	95:5	16
5	toluene	5 d	75	88:12	12
6	toluene[e]	5 d	*n.d*[d]	-	-
7	$PhCF_3$	48 h	77	86:14	*n.d*[d]
8	Methyl-cyclohexane	7 d	26 (57 brsm)	84:16	12

[a]0.06 mmol scale. [b]Yield determined by ^{1}H-NMR using 1,1,2-trichloroethane as internal standard. [c]*er* determined by chiral-SFC. [d]no detection. [e]Reaction performed at –25 ºC.

Scope of the [4+2] Cycloaddition with Complex C

With the optimized conditions in hand, we synthesized a library of 1,6-arylenynes to investigate the scope the [4+2] cycloaddition with our new gold(I)-complex **C**. The synthesis of –$(CH_2OMe)_2$ tethered 1,6-arylenynes was achieved starting from 1,6-enyne **2.9** as depicted in Scheme 2.6. The dimethyl malonate moiety was reduced by treatment of 1,6-enyne **2.9** with $LiAlH_4$ giving diol **2.10**, which was subsequently methylated. The resulting methoxymethyl tethered terminal alkyne **2.11** was used as substrate for palladium-catalyzed Sonogashira cross-coupling with aryl halides with various electronic and steric properties

delivering the desired aryl-substituted 1,6-enynes **30c-x**. The purification of the cross-coupling reaction was facilitated by addition of cysteine as palladium scavenger during the work-up.

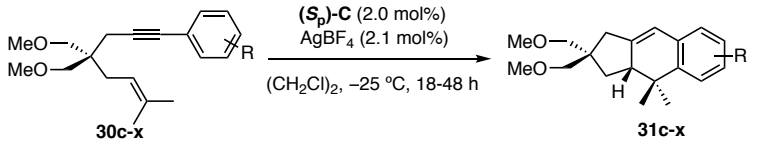


Scheme 2.6. Synthesis of the 1,6-arylenynes **30c-x.**

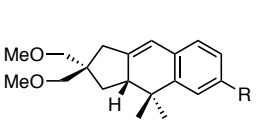
With substrates **30c-x** in hand, we proceeded to explore the scope of the [4+2] cycloaddition using the previously optimized conditions (Table 2.5). Bulky substituents, electron-donating and electron-withdrawing groups in *para* and *ortho* positions were well tolerated and the cyclization reactions proceed in high to excellent yields and enantiomeric ratios in all cases (**30c-q**). The cyclization of free phenol **30g** was carried out at −10 ºC as the substrate is insoluble in 1,2-dichloroethane at −25 ºC and yielded the product **31g** with good enantioselectivity. The free aniline **30h** remained unreacted after 7 d at 24 ºC in presence of both complex **1e** and **(S_p)-C.** After acetylation with acetic anhydride, the protected derivative **30i** delivered the desired product but at a slower rate and a mixture of **30h**:**31h** 2.7:1 was obtained after extended reaction time (72 h). 2,4-Disubstituted

substrates **30r** and **30s** reacted smoothly delivering respectively products **31r** and **31s** in good yields and high enantiomeric ratios. Trimethoxy-substituted arylenyne **30u** furnished the desired product **31u** in excellent yield and good enantiomeric ratio. Phenanthrene-substituted enyne **30v** delivered product **31v** in excellent yield and enantioselectivity. Sulfur-containing heterocycles **30w** and **30x**, respectively bearing thiophene and benzothiophene as heteroaromatic moieties reacted smoothly affording the corresponding products **31w** and **31x** in high yields and good enantiomeric ratio. Electron-rich nitrogen-containing heterocycles were unreactive; both protected *N*-Boc-pyrrole arylenyne **30y** and free indole arylenyne **30z** remained unreacted after 7 d at 24 ºC in the presence of both complexes **1e** and **(S_p)-C**. The 3,5-dibromophenyl-substituted 1,6-arylenyne **30t** undergoes formal [4+2] cycloaddition reaction delivering product **31t** quantitatively but only in 77:23 *er*.

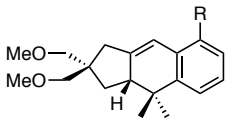
Table 2.5. Scope of the formal [4+2] cycloaddition of enynes **30**.



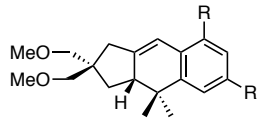
30c-x **31c-x**



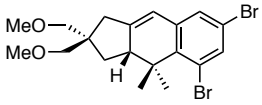
31c R = H >99%, 96:4 *er*
31d R = OMe 95%, 93:7 *er*
31e R = Me 92%, 95:5 *er*
31f R = *t*Bu >99%, 96:4 *er* (–10 °C)
31h R = NH_2 *n.d* -
31i R = NHAc 66%, 90:10 *er*
31j R = NO_2 95%, 95:5 *er*
31k R = F 76%, 94:6 *er*
31l R = Cl 92%, 95:5 *er*
31m R = Br 87%, 95:5 *er*
31n R = I 89%, 96:4 *er*
31o R = CF_3 91%, 96:4 *er*



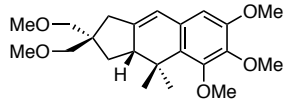
31p R = OMe 85%, 95:5 *er*
31q R = F 72%, 91:9 *er*



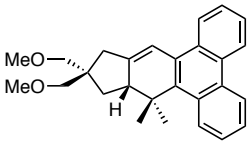
31r R = OMe **L_B·AuCl** >99%, 97:3 *er*
L_G·AuCl >99%, 98:2 *er*
31s R = Me 92%, 95:5 *er*



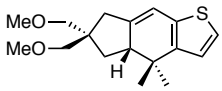
31t >99%, 77:23 *er*



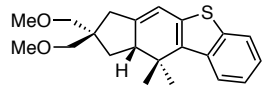
31u 98%, 92:8 *er*



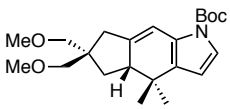
31v >99%, 97:3 *er*



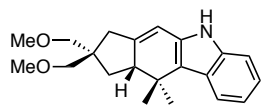
31w >99%, 96:4 *er*



31x >99%, 95:5 *er*



31y *n.d*



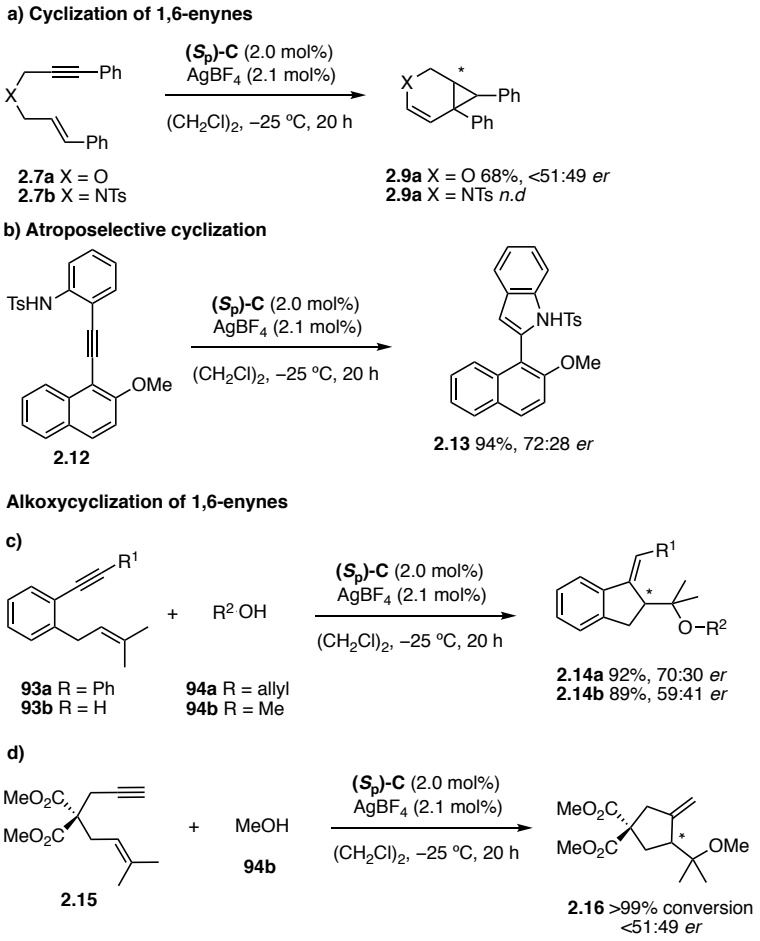
31z *n.d*

In the presence of the complex **(S_p)-I**, substrate **30r** yielded quantitatively **31r** in 98:2 *er*. Unlike malonate tethered 1,6-enyne **30a,** no long reaction time was required to achieve full conversion of enyne **30r** with complex **(S_p)-I** compared to complex **(S_p)-C**. The absolute configuration of product **31** was assigned by correlation with previously reported results.[95]

Unsuccessful Enantioselective Transformations

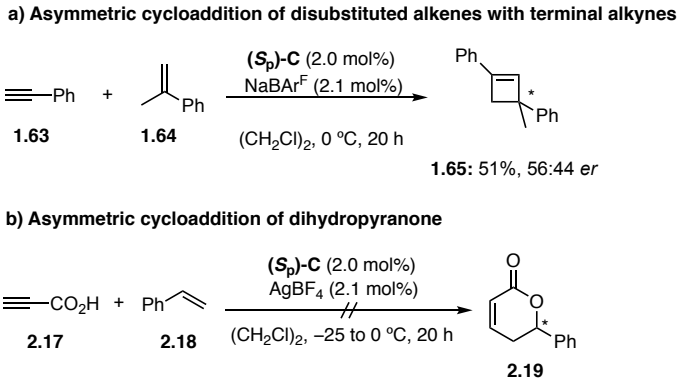
Along with the enantioselective formal [4+2] cycloaddition of 1,6-enynes **30c-x** catalyzed with complex **(S_p)-C** we investigated various transformations using the optimized conditions previously developed.

Under optimized conditions, the *O*-tethered 1,6-enyne **2.7a** undergo cycloisomerization delivering product **2.9a** as a racemate (Scheme 2.7a). The *N*-tethered 1,6-enyne **2.7b** remained unchanged after extended reaction time. The gold(I)-catalyzed atroposelective cyclization of substrate **2.12** occurred smoothly delivering the expected biaryl product **2.13** in good yield but with low enantioinduction (Scheme 2.7b). On the other hand, the alkoxycyclization of the enyne **93a** in the presence of allyl alcohol **94a** delivered product **2.14**, by a 5-*exo*-dig cyclization, in good yield but low enantioselectivity (Scheme 2.7c). Decreasing the temperature did not increased the enantiomeric ratio of the product. Similarly, under optimized conditions, enyne **2.15** delivered the expected product as racemic mixture.



Scheme 2.7. Unsuccessful gold(I)-catalyzed enantioselective cyclizations.

Complex **(*S*p)-C**, in combination with $NaBAr^F_4$, catalyzed the [2+2] cycloaddition of phenylacetylene (**1.63**) with α-methylstyrene (**1.64**) delivering product **1.65** in moderate yield and poor enantioselectivity (Scheme 2.8). The reaction did not proceed at –10 ºC. Finally, the developed catalytic system did not show any catalytic activity in the formal [4+2] annulation of propiolic acid (**2.17**) and styrene (**2.18**) to form dihydropyranone **2.19.**



Scheme 2.8. Unsuccessful gold(I)-catalyzed cycloaddition reactions.

Computational Studies[166]

The new chiral ferrocene-based gold(I) catalyst was analyzed using SambVca 2.1 web tool (Figure 1).[167] As shown by the steric profile, the aromatic biphenyl substituents on the ferrocenyl scaffold provides steric hindrance to the complex **(S_p)-H**. This sterically demanding ligand shows a buried volume of 57.6 % as well as a distinct occupation of western quadrants bearing the gold atom in the center.

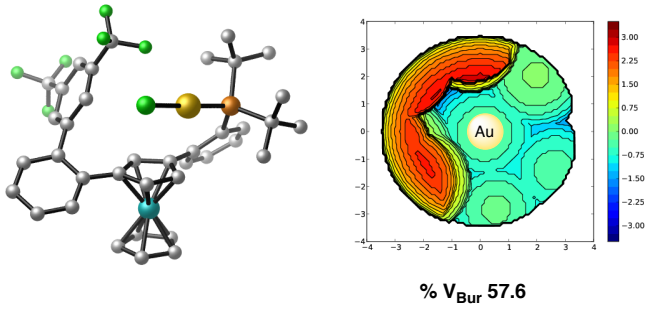


Figure 1. Steric maps and CYLview representation of complex **(S_p)-H**.

166 Studies performed by Dr. Imma Escofet.

167 Favilene, L.; Cao, Z.; Petta, A.; Serra, L.; Poater, A.; Oliva, R.; Scarano, V.; Cavallo, L. *Nat. Chem.* **2019**, *11*, 872–879.

We turned our attention to study the origin of the enantioinduction observed in the formal [4+2] cycloaddition of enynes **30**. The spatial arrangement of enynes **30** and their ability to interact with the active site of the complex is responsible of the absolute configurations of the products as well as the efficiency of the chiral transfer. The enantioselectivity arises from the combination of the orientation of the substrate binding with gold(I) (Figure 2.2, ***A*** and ***B***) and the orientation of the enantiotopic faces of the alkene (*Re* and *Si*).

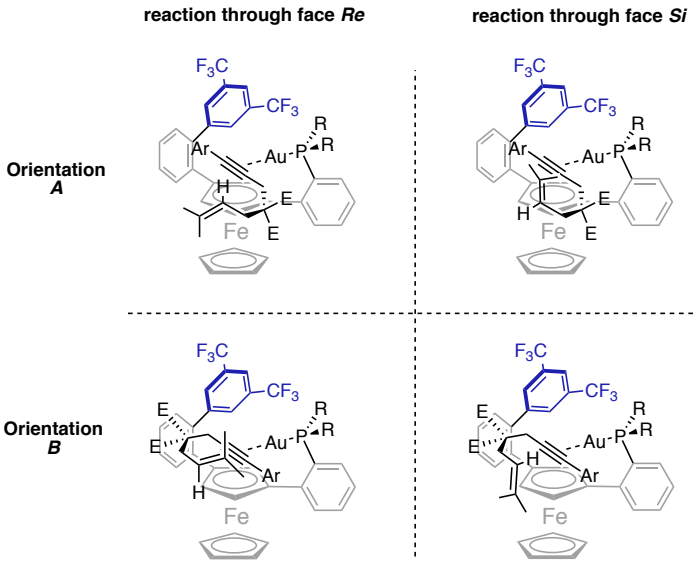


Figure 2.2. Possible orientations substrate-catalyst with the ferrocene gold(I) complex.

In order to rationalize the working mode of our new arylphosphine-ferrocene gold(I) complex, we studied the cyclization of enyne **30c** by DFT calculations.[166] To simplify DFT calculations, the reaction coordinates for the cyclization of enyne **30c** were calculated using the gold(I) complex **(S_p)-H** which gave similar results compared to our best catalyst **(S_p)-C**. Previous works in our group highlighted the importance of non-covalent interactions in the folding of the substrate in the chiral environment of the catalyst. Analysis of the orientation of the substrate coordinated with gold(I) through the alkyne revealed that only

orientation ***A*** is possible due to the steric hindrance of the -$(CH_2OMe)_2$ tether that prevents the substrate to fit in the chiral environment in orientation ***B*** (Figure 2.2).

Hence, calculations focused on the nucleophilic attack of the alkene from the two enantiotopic faces (Figure 2.3, *Re* or *Si*) at the $[LAu(\eta^2\text{-alkyne})]^+$ complex **Int1a** to **Int2a-b**, as the enantio-determining step of the reactions. Possible minima resulting from different pathways were calculated. The calculated energy difference between the lowest transition states that lead to **Int2a** (yielding **(*R*)-31c**) and **Int2b** (yielding **(*S*)-31c**) is $\Delta G^{\ddagger}_{R\text{-}S}$ = 1.2 kcal/mol in favor of $\mathbf{TS_{Int1\text{-}2a}}$. Therefore, cyclopropyl gold carbene **Int2a** with the *R* absolute configuration is preferentially formed.

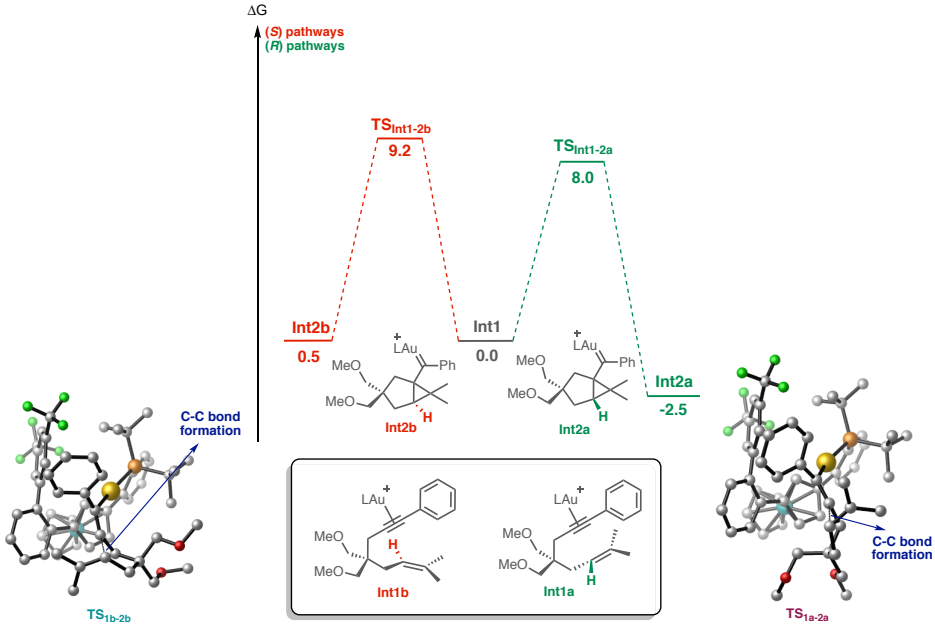


Figure 2.3. Free energy profiles for the 5-*exo*-dig enantioselective cyclization reaction of 1,6-enyne **30c** with catalyst **(S_p)-H**. (*S*) pathways are depicted in red and (*R*) pathways in green. The energy values are given in kcal/mol and represent the relative free energies. CYLview representation of the two possible transition states. Hydrogen atoms have been omitted for clarity.

These results are in good agreement with the experimental results in which **(*R*)-31c** formed in 96:4 *er*. The lowest transition state $\mathbf{TS_{Int1\text{-}2a}}$ was found to be stabilized by non-covalent interactions between the substrate and the chiral environment of the catalyst. The energy difference between $\mathbf{TS_{Int1\text{-}2a}}$ and $\mathbf{TS_{Int1\text{-}2b}}$ explain the enantioselectivity of the reaction. Noteworthy, the π-π-interaction between the aromatic ring of the substrate and the biphenyl group occurs through Ar^3 and Ar^2 via T-shaped π-stacking (Figure 2.4). Calculations revealed that in the substrate-catalyst adduct, the catalyst adopts an unexpected the spatial organization where the cyclopentadiene ring and the adjacent phenyl ring of the biaryl moiety are coplanar and the phosphino group $P(t\text{Bu})_2$ is turned toward the biphenyl substituent. The preferred upward orientation of the allyl moiety of the substrate (reaction through face *Si*) presumably minimizes steric interactions with the Cp ring and Ar^1.

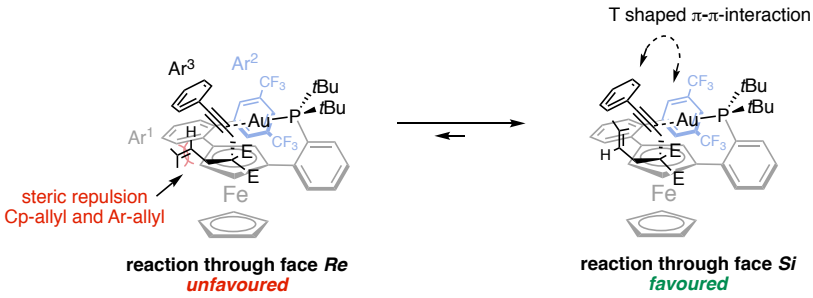


Figure 2.4. Substrate-catalyst interactions.

We further examined the attractive interactions between the aromatic moieties of the substrates and the aromatic substituents of the catalyst. As revealed by NCI plots,[168] non-covalent interactions play a fundamental role in the chiral folding of the substrate in the chiral environment of this new ferrocene-based

168 (a) Johnson, E. R.; Keinan, S.; Mori-Sanchez, P.; Contreras-Garcia, J.; Cohen, A. J.; Yang, W. *J. Am. Chem. Soc.* **2010**, *132*, 6498–6506. (b) Contreras-Garcia, J.; Johnson, E. R.; Keinan, S.; Chaudret, R.; Piquemal, J. P.; Beratan, D. N.; Yang, W. *J. Chem. Theory Comput.* **2011**, *7*, 625–632.

gold(I) catalysts and also in the stabilization of the corresponding transition states (Figure 2.5). Hence, larger green surfaces were found in the NCI plots in the lowest-energy transition state $\mathbf{TS_{Int1\text{-}2a}}$ in comparison to $\mathbf{TS_{Int1\text{-}2b}}$ corresponding to higher attractive non-covalent substrate-ligand interactions.

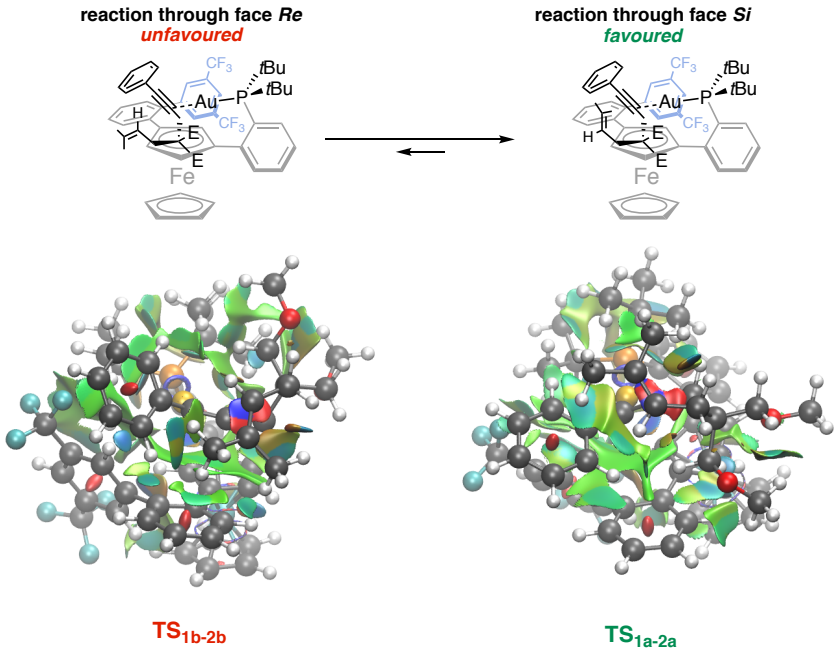


Figure 2.5. The lowest energy transition states (NCI plot). Strong attractive interactions are blue (C−C bond formation), weak attractive interactions are green (non-covalent interactions), and strong repulsive interactions are red. Color code: P, orange; Au, yellow; F, cyan; O, red; C, gray; Fe, blue, and H, white.

In addition, we conducted theoretical studies with enynes **30l**, **30n**, **30s** and **30t**, bearing a substituted aryl ring as substrates. **(S_p)-H** was used as gold complex.

Aryl enynes **30l** and **30n** bearing respectively *para*-chloro and *para*-iodo substituents, were examined computationally (Figure 2.6). The activation energy to reach **Int2a-*p*Cl** was lower than the other possible pathway to reach **Int2b-*p*Cl** by at least 1.1 kcal/mol. Therefore, in agreement with our experimental results (95:5 *er*), cyclopropyl gold(I) carbene **Int2a-*p*Cl** with the *R* absolute configuration is preferentially formed. Similarly, **Int2a-*p*I** is preferentially formed *via* **TSInt1-2a-*p*I** that requires 1.5 kcal/mol less than competing *S* pathway through **TSInt1-2b-*p*I**. In addition, a similar study was carried out for the 2,4-dimethylphenyl-substituted enyne **30s**. Having a methyl group in *ortho* and *para* position of the aryl ring of the substrate was crucial to achieve higher $\Delta\Delta G^{\ddagger}_{R\text{-}S}$ = 1.4 kcal/mol. Interestingly, in this case the energy barriers were found to be lower than in the other cases (**TSInt1-2a-2Me =** 4.1 kcal/mol and **TSInt1-2b-2Me** = 5.5 kcal/mol).

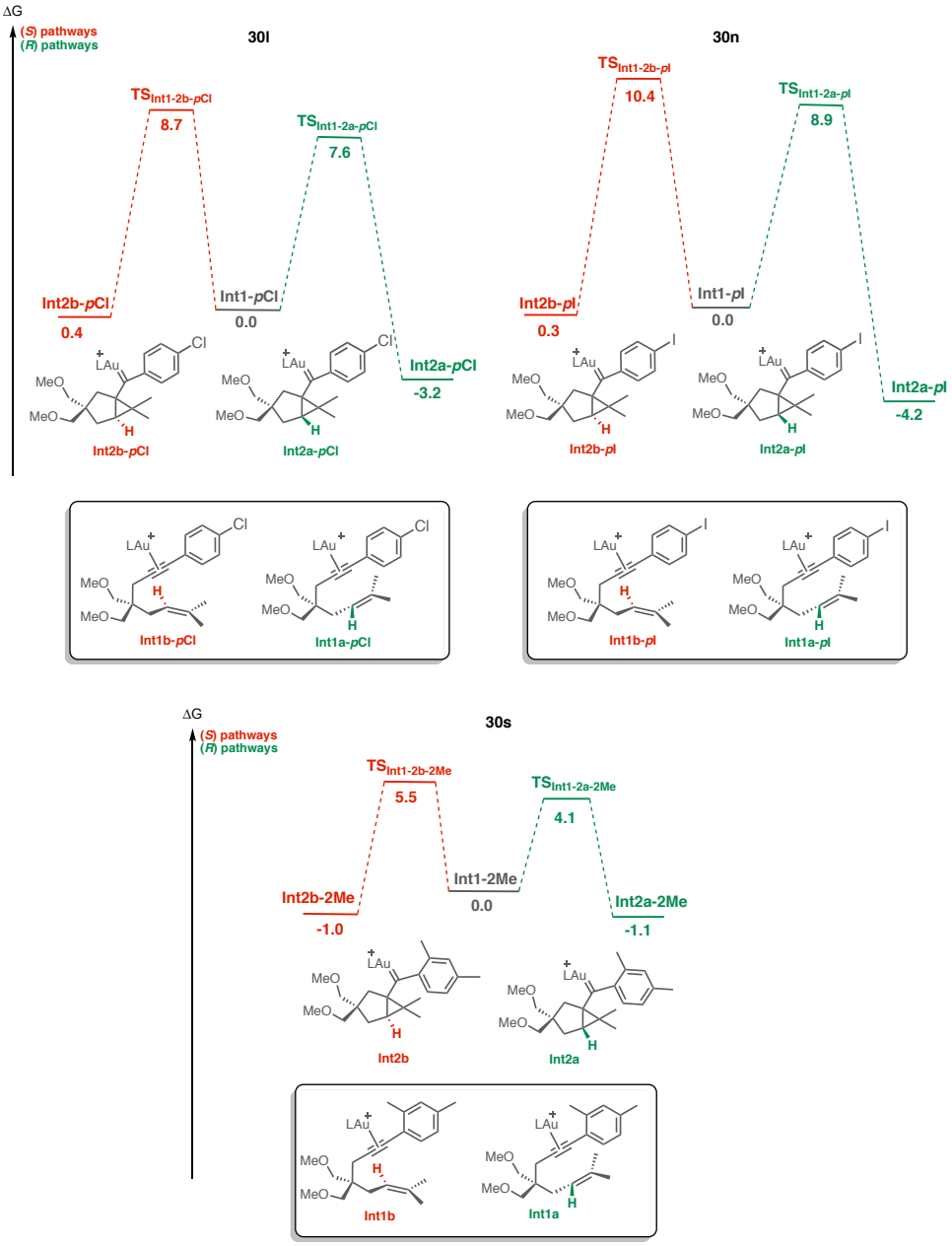


Figure 2.6. Free energy profiles for the 5-*exo*-dig enantioselective cyclization reactions of **30l**, **30n**, **30s** with catalyst **(*Sp*)-H**. (*S*) pathways are depicted in red and (*R*) pathways in green. The energy values are given in kcal/mol and represent the relative free energies.

In the case of 3,5-dibromo-arylenyne **30t**, activation energies similar to those of **30l** and **30n** were found for the two possible pathways, **TSInt1-2a-2Br** and **TSInt1-2b-2Br** (Figure 2.7). However, formation of **Int2a-2Br** was favored only by 0.3 kcal/mol, in good agreement with the low experimental enantiomeric ratio obtained (77:23 *er*). It was hypothesized that this lower enantioselectivity was due to the bulkiness of bromine atoms. Because of their size and position on the aryl group, one of the bromines is located close to the $–CF_3$ group of the ligand preventing strong substrate-catalyst interaction. This hypothesis can also explain the slight erosion of enantioinduction observed in the cyclization of the 3,4,5-trimethoxy substituted arylenyne **30u** relative to the other methoxy substituted arylenynes **30r** and **30d.**

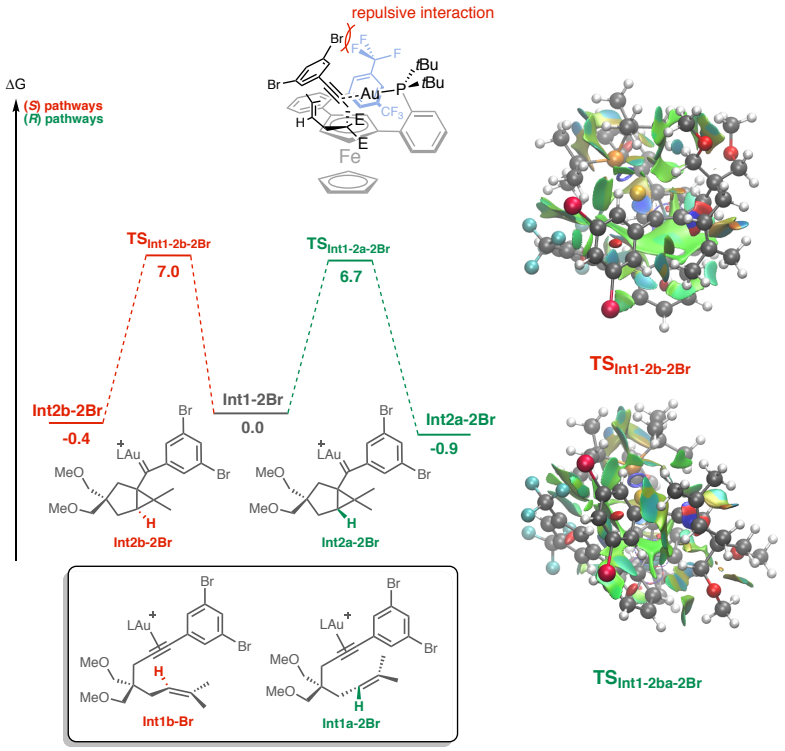
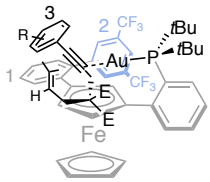


Figure 2.7. Free energy profiles for the 5-*exo*-dig enantioselective cyclization reaction of **30t** (2Br) with catalyst **(*S*p)-H**. (*S*) pathways are depicted in red and (*R*) pathways in green. The energy values are given in kcal/mol and represent the relative free energies. The lowest energy transition states (NCI plot). 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; Fe, blue, and H, white. Energy values are given in kcal/mol relative and represent the relative free energies.

In the cyclization of arylenynes **30c-x**, the non-covalent π-π-interactions between the aryl ring of the substrates and the aryl ring of the catalyst play a crucial role in the folding of each substrate in the chiral environment of the complex and in the stabilization of the transition states **TSInt1-2a**. On the other hand, the nature of the tether plays a role by directing the orientation of the substrate in the chiral environment. In agreement with our experiment, the alkene reacts preferentially through face *Si* yielding **(*R*)-31** enantiomers as major product.

Table 2.6 Free energies in kcal/mol and referred to each **Int1**. Calculated *er* according to Curtin-Hammett principle.



	$\Delta\Delta G^{\ddagger}_{R\text{-}S}$	*er* (theoric)	*er* (experimental)
$TS_{1a\text{-}2a}$ / $TS_{1b\text{-}2b}$	1.2	90:10	96:4
$TS_{1a\text{-}2a\text{-}2Br}$ / $TS_{1b\text{-}2b\text{-}2Br}$	0.3	63:37	77:23
$TS_{1a\text{-}2a\text{-}2Me}$ / $TS_{1b\text{-}2b\text{-}2Me}$	1.4	93:7	95:5
$TS_{1a\text{-}2a\text{-}pI}$ / $TS_{1b\text{-}2b\text{-}pI}$	1.5	94:6	96:4
$TS_{1a\text{-}2a\text{-}pCl}$ / $TS_{1b\text{-}2b\text{-}pCl}$	1.1	90:10	95:5

We observed that enyne **30a** bearing a malonate tether cyclized with lower enantioinduction (88:12). It was hypothesized that the malonate tether renders orientation **B** less unfavorable and that in this orientation the alkene would preferentially react through *Re* face to minimize the steric repulsion between the alkene substituents and the cyclopentadiene ring (Figure 2.8). The outcome of this reaction is the favored formation of **(*S*)-31a**.

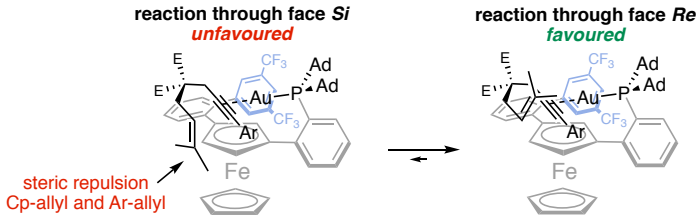
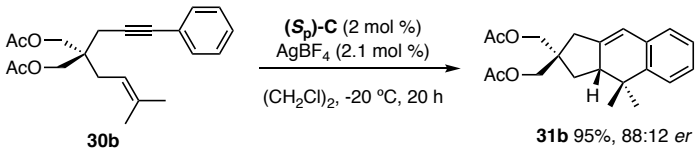


Figure 2.8. Possible orientations substrate-catalyst with malonate tethered 1,6-enynes.

Therefore, the tether plays an important role in the enantiodiscrimination by the chiral catalyst. Unlike previously reported by our group,[95] the tether of the enyne is not providing attractive non-covalent interactions with the catalyst but steric repulsion orienting the substrate in the chiral environment.

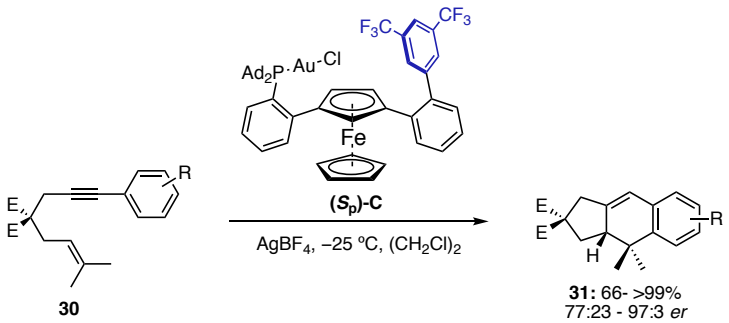
To support our hypothesis, an additional experiment was carried out to confirm the influence of steric properties of the tether (Scheme 2.7). Substituting the $-(CH_2OMe)_2$ tether by $-(CH_2OAc)_2$ provided a lower enantioinduction (88:12 *er*) in the cyclization of the 1,6-arylenyne **30b** catalyzed by **(S_p)-C**, and confirms the important role of the steric properties of the tether of the enyne.



Scheme 2.7. Formal [4+2] cycloaddition of enyne **30b**.

Conclusion

We developed a catalytic system suitable for the enantioselective synthesis of 1,2-dihydronaphthalenes in good yields and enantioselectivities by [4+2] cycloaddition of 1,6-arylenynes (scheme 2.8). In addition, we studied computationally the mode of action of our chiral arylphosphine-ferrocene gold(I) complex in the asymmetric cyclization of 1,6-arylenynes. Geometrical parameters of the tether of the 1,6-enynes induce a specific binding orientation and a non-covalent attractive π-π-interaction between the aromatic ring of the substrate and the biphenyl group of the catalyst play a crucial role in the chiral folding of substrates and providing the key stabilizations to the transition states.



Scheme 2.8. Application of complex **C** to enantioselective cyclization of enynes **30**.

Experimental section

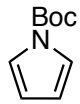
General Information

General information is provided in the Experimental Section of **Chapter 1**.

Synthetic Procedures and Characterizations of Compounds

Synthesis of Substrates

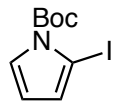
tert-Butyl 1*H*-pyrrole-1-carboxylate



A flask was charged with acetonitrile (30.0 mL), pyrrole (2.0 g, 2.1 mL, 30 mmol) and DMAP (0.55 g, 0.15 equiv, 4.5 mmol) then Boc_2O (7.8 g, 1.2 equiv, 36 mol) was added and the reaction mixture was stirred 4 h at room temperature. The reaction mixture was concentrated under reduced pressure (max 50mbars, 40 ºC). The residue was purified by filtration over basic alumina plug eluted with cyclohexane allowing the pure product (4.1 g, 25 mmol, 82%) as a colorless oil. The obtained characterization data were in agreement with those reported in literature.[169]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (t, *J* = 2.3 Hz, 2H), 6.21 (d, *J* = 2.3 Hz, 2H), 1.60 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.1, 120.1, 112.0, 83.7, 28.1.

tert-Butyl 2-iodo-1*H*-pyrrole-1-carboxylate



A flask charged with diisopropylamine (3.0 g, 4.2 mL, 1.2 equiv, 29 mmol) in THF (32 mL) was cooled to –78 ºC in a dry ice/acetone bath then *n*BuLi (2.5 M, 11 mL,

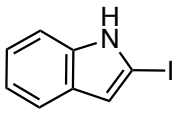
169 Salman, H.; Abraham, Y.; Tal, S.; Meltzman, S.; Kapon, M.; Tessler, N.; Speiser, S.; Eichen, Y. *Eur. J. Org. Chem.* **2005**, *11*, 2207–2212.

1.1 equiv, 27 mmol) was added dropwise keeping the temperature below –60 ºC. The solution was stirred an additional 5 min in the cold bath then 20 min at room temperature. The LDA solution was cooled again to –78 ºC and tert-butyl 1H-pyrrole-1-carboxylate (4.1 g, 25 mmol) in THF (8.0 mL) was added dropwise keeping the temperature of the solution below -75 ºC. The solution was stirred 1 h at –78 ºC changing from a pink suspension to a clear pale-yellow solution. $ZnCl_2$ (4.0 g, 1.2 equiv, 29 mmol) was added under Argon counter flow and the mixture was stirred 10 min at –78 ºC then 1 h at 0 ºC in an ice bath. iodine (7.5 g, 1.2 equiv, 29 mmol) in THF (20 mL) was added dropwise keeping the temperature around 5 ºC. The mixture was stirred 15 min at the same temperature then allowed to warm up to room temperature and stirred 1h. The reaction was quenched by addition of $Na_2S_2O_3$ sat. and stirred for 30 min. The crude mixture was diluted with EtOAc (100 mL) and filtered over a pad of Celite®. 5% citric acid aq. (250 mL) was added and phases were separated. The aqueous phase was extracted with EtOAc (2x50 mL), reunited organic layer was washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure (>50mbars, 40 ºC). The crude was purified by flash chromatography over silica gel (eluent cyclohexane:CH_2Cl_2 93:7) yielding the title compound (4.2 g, 14 mmol, 58%) as a pale-yellow oil. The obtained characterization data were in agreement with those reported in literature.[170]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (dd, *J* = 3.5, 1.8 Hz, 1H), 6.53 (dd, *J* = 3.4, 1.8 Hz, 1H), 6.17 (t, *J* = 3.4 Hz, 1H), 1.62 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.4, 125.7, 125.1, 113.7, 85.1, 63.3, 28.2.

170 L'Helgoual'ch, J. M.; Seggio, A.; Chevallier, F.; Yonehara, M.; Jeanneau, E.; Uchiyama, M.; Mongin, F. *J. Org. Chem.* **2008**, *73*, 177–183.

2-Iodo-1*H*-indole



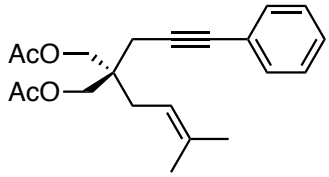
An oven dried flask under argon charged with indole (1.17 g, 10.0 mmol) and THF (20 mL) and the solution was cooled to –78 ºC in a dry ice/acetone bath. *n*BuLi (2.5 M, 4.2 mL, 1.05 equiv, 10.5 mmol) was added dropwise to suspension and the mixture was stirred for 30 min at –78 ºC after the end of the addition. CO_2 was bubbled through the solution at –78 ºC for 10 min. The solvent was evaporated under vacuum at 0 ºC, the residue was redissolved in THF (20 mL) and the solution was cooled to –78 ºC. *t*BuLi (1.7 M, 6.2 mL, 1.05 equiv, 10.5 mmol) was added dropwise and the solution was stirred for 1 h at the same temperature. 1,2-diiodoethane was added to the solution at –78 ºC under argon counter flow and the suspension was stirred for 1 h at the same temperature. Water was added to the solution and the mixture was allowed to warm up to room temperature.

The crude mixture was diluted with NH_4Cl sat. (200 mL) and Et_2O (30 mL) and phases were separated. The aqueous phase was extracted with Et_2O (2x), reunited organic layer was washed with 5 % Na_2SO_3 aq., water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by flash chromatography over silica gel (eluent cyclohexane:Et_2O 80:20) yielding the title compound (2.0 g, 8.2 mmol, 82%) as a pale yellow solid.

The obtained characterization data were in agreement with those reported in literature.[171]

171 Bergman, J.; Venemalm, L. *J. Org. Chem.* **1992**, *73*, 2495–2497.

2-(3-Methylbut-2-en-1-yl)-2-(3-phenylprop-2-yn-1-yl)propane-1,3-diyl diacetate 30b



A flask was charged with 2-(3-methylbut-2-en-1-yl)-2-(3-phenylprop-2-yn-1-yl)propane-1,3-diol[172] (100 mg, 1 equiv, 387 μmol) and Ac_2O (0.15 μL, 16 mg, 4 equiv, 1.55 mmol) in CH_2Cl_2 (2.0 mL) and the reaction was stirred at 24 ºC for 20 h. The reaction was monitored by GC-MS analysis. $NaHCO_3$ sat. (1 mL) was added and the mixture was stirred for 0.5. The crude mixture was diluted with water (15 mL) and extracted with Et_2O (3x5 mL). The reunited organic layer was washed with $NaHCO_3$ sat. water and brine, dried over $MgSO_4$ and concentrated under reduced pressure.

Purification by flash chromatography (eluent, cyclohexane:EtOAc, 90:10) afforded to title compound (128 mg, 0.377 mmol, 97%) as a colorless oil. The obtained characterization data were in agreement with those reported in literature.[95]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.35 (m, 2H), 7.31 – 7.26 (m, 3H), 5.14 (tp, *J* = 7.9, 1.4 Hz, 1H), 4.13 – 4.00 (m, 4H), 2.47 (s, 2H), 2.26 – 2.21 (m, 2H), 2.07 (s, 6H), 1.73 (d, *J* = 1.4 Hz, 3H), 1.65 (d, *J* = 1.4 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.0, 136.1, 131.7, 128.4, 128.0, 123.6, 117.7, 85.4, 83.4, 65.9, 41.3, 30.3, 26.3, 23.2, 21.0, 18.0.

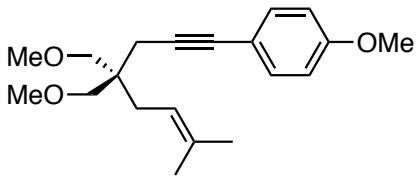
General procedure H: Sonogashira cross-coupling

A MW was charged with $PdCl_2(PPh_3)_2$ (1.0 mol %) and copper(I) iodide (2.0 mol %) and the corresponding aryl halide (1.1 equiv) if solid then evacuated/backfilled with Argon. NEt_3 (0.36 M, 20 equiv) and aryl halide (1.1 equiv) if liquid were added and the solution was stirred 10 min at room temperature. The alkyne (1

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

equiv) was added and the mixture was stirred at 25 ºC for 18 h unless stated otherwise. *i*PrOH:H_2O 4:1 (1 vol) and cysteine was added (*ca.* equal mass of $PdCl_2(PPh_3)_2$) were added to the reaction mixture and stirred for 30 min then filtered over Celite®. The pad of Celite® was washed with Et_2O, 5% aq. citric acid (15 vol) was added to the filtrate and phases were separated. The aqueous layer was extracted with Et_2O (2x). The reunited organic layer was washed with NH_4Cl sat. water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The desired product was purified by flash chromatography over silica gel.

1-(4,4-Bis(methoxymethyl)-7-methyloct-6-en-1-yn-1-yl)-4-methoxybenzene 30d

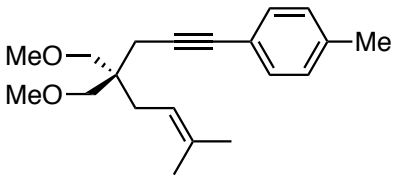


The compound was synthesized according to the general procedure **H** using $PdCl_2(PPh_3)_2$ (5 mg), copper(I) iodide (2.7 mg), 1-iodo-4-methoxybenzene (184 mg) and 4,4-bis(methoxymethyl)-7-methyloct-6-en-1-yne (175 µL, 150 mg, 0.428 mmol) in NEt_3 (2.0 mL).

Purification by flash chromatography (eluent, pentane:Et_2O, 90:10) afforded to title compound (105 mg, 0.359 mmol, 84%) as a colorless oil. The obtained characterization data were in agreement with those reported in literature.[95]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.29 (m, 2H), 6.85 – 6.78 (m, 2H), 5.22 – 5.13 (m, 1H), 3.80 (s, 3H), 3.34 (s, 6H), 3.33 – 3.24 (m, 4H), 2.37 (s, 2H), 2.15 (d, *J* = 7.9 Hz, 2H), 1.73 (d, *J* = 1.3 Hz, 3H), 1.68 – 1.63 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.2, 134.6, 133.0, 119.4, 116.5, 114.0, 85.9, 82.1, 74.7, 59.5, 55.4, 43.2, 30.3, 26.3, 23.1, 17.9.

1-(4,4-Bis(methoxymethyl)-7-methyloct-6-en-1-yn-1-yl)-4-methylbenzene 30e

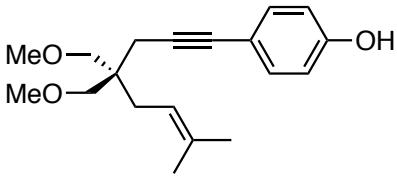


The compound was synthesized according to the general procedure **H** using $PdCl_2(PPh_3)_2$ (5 mg), copper(I) iodide (2.7 mg), 1-iodo-4-methylbenzene (171 mg) and 4,4-bis(methoxymethyl)-7-methyloct-6-en-1-yne (175 µL, 150 mg, 0.713 mmol) in NEt_3 (2.0 mL).

Purification by flash chromatography (eluent, pentane:Et_2O, 98:2) afforded to title compound (207 mg, 0.689 mmol, 96%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 7.12 – 7.05 (m, 2H), 5.22 – 5.14 (m, 1H), 3.34 (s, 6H), 3.32 – 3.24 (m, 4H), 2.38 (s, 2H), 2.33 (s, 3H), 2.15 (d, *J* = 7.9 Hz, 2H), 1.73 (s, 3H), 1.66 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.6, 134.6, 131.6, 129.1, 121.2, 119.4, 86.8, 82.4, 74.7, 43.2, 30.3, 26.3, 23.1, 21.5, 17.9. **HRMS** (ESI+) calculated for $[C_{20}H_{28}NaO_2]^+$ 323.1982 m/z; found $[M + Na]^+$: 323.1980.

4-(4,4-Bis(methoxymethyl)-7-methyloct-6-en-1-yn-1-yl)phenol 30g

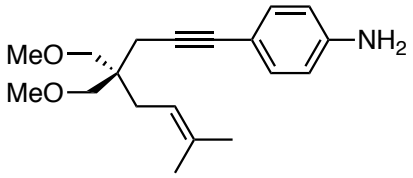


The compound was synthesized according to the general procedure **H** using $PdCl_2(PPh_3)_2$ (5 mg), copper(I) iodide (2.7 mg), 4-iodophenol (173 mg) and 4,4-bis(methoxymethyl)-7-methyloct-6-en-1-yne (175 µL, 150 mg, 0.428 mmol) in NEt_3 (2.0 mL).

Purification by flash chromatography (eluent, pentane:Et_2O, 85:15) afforded to title compound (122 mg, 0.403 mmol, 57%) as a colorless thick oil which crystallized upon standing.

M.p. = 84.5 – 85.6 ºC ($CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31 – 7.25 (m, 2H), 6.78 – 6.71 (m, 2H), 5.17 (tp, *J* = 7.8, 1.4 Hz, 1H), 5.10 (s, 1H), 3.34 (s, 6H), 3.33 – 3.25 (m, 4H), 2.36 (s, 2H), 2.14 (d, *J* = 7.9 Hz, 2H), 1.73 (s, 3H), 1.66 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.3, 134.7, 133.2, 119.4, 116.6, 115.4, 85.8, 82.1, 74.7, 59.5, 43.2, 30.3, 26.3, 23.0, 17.9. **HRMS** (ESI+) calculated for $[C_{19}H_{26}NaO_3]^+$ 325.1774 m/z; found $[M + Na]^+$: 325.1759.

4-(4,4-Bis(methoxymethyl)-7-methyloct-6-en-1-yn-1-yl)aniline 30h

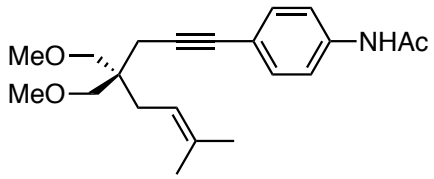


The compound was synthesized according to the general procedure **H** using $PdCl_2(PPh_3)_2$ (5 mg), copper(I) iodide (2.7 mg), 4-iodoaniline (172 mg) and 4,4-bis(methoxymethyl)-7-methyloct-6-en-1-yne (175 µL, 150 mg, 0.428 mmol) in NEt_3 (2.0 mL).

Purification by flash chromatography (eluent, pentane:Et_2O, 82:18) afforded to title compound (164 mg, 0.544 mmol, 76%) as a colorless oil.

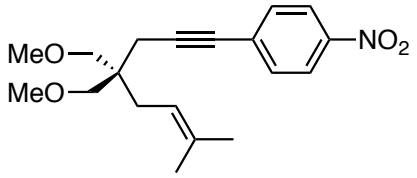
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.20 (m, 2H), 6.68 – 6.60 (m, 2H), 5.25 – 5.15 (m, 1H), 3.36 (s, 6H), 3.34 – 3.25 (m, 4H), 2.38 (s, 2H), 2.16 (d, *J* = 7.9 Hz, 2H), 1.75 (d, *J* = 1.3 Hz, 3H), 1.70 – 1.65 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.6, 134.5, 132.9, 119.5, 115.0, 114.2, 85.0, 82.6, 74.7, 59.5, 43.2, 30.3, 26.3, 23.1, 17.9. **HRMS** (ESI+) calculated for $[C_{19}H_{28}NO_2]^+$ 302.2115 m/z; found $[M + H]^+$: 302.2114.

_N_-(4-(4,4-Bis(methoxymethyl)-7-methyloct-6-en-1-yn-1-yl)phenyl)acetamide 30i



Aniline **30h** (75 mg, 1 equiv, 0.25 mmol) was dissolved in CH_2Cl_2 (0.5 mL) and Ac_2O (47 µL, 2 equiv, 0.50 mmol) was added. The mixture was stirred at 24 ºC for 18 h. The reaction was monitored by TLC analysis. $NaHCO_3$ sat. (1 mL) was added and the mixture was stirred for 1 h. The crude mixture was diluted with water (5 mL) and extracted with CH_2Cl_2 (3x2 mL). The reunited organic layer was washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography over silica gel (eluent, cyclohexane:EtOAc, 30:70) afforded to title compound (81 mg, 0.24 mmol, 95%) as a colorless solid. **M.p.** = <40 ºC (CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 – 7.40 (m, 2H), 7.34 (d, *J* = 8.6 Hz, 3H), 5.16 (tp, *J* = 7.9, 1.4 Hz, 1H), 3.34 (s, 6H), 3.31 – 3.23 (m, 4H), 2.37 (s, 2H), 2.16 (s, 3H), 2.14 (d, *J* = 8.0 Hz, 2H), 1.73 (d, *J* = 1.4 Hz, 3H), 1.65 (d, *J* = 1.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.4, 137.4, 134.6, 132.4, 120.1, 119.5, 119.3, 87.2, 82.0, 74.7, 59.5, 43.2, 30.4, 26.3, 24.8, 23.1, 17.9.

1-(4,4-Bis(methoxymethyl)-7-methyloct-6-en-1-yn-1-yl)-4-nitrobenzene 30j

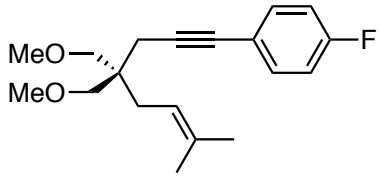


The compound was synthesized according to the general procedure **H** using $PdCl_2(PPh_3)_2$ (5 mg), copper(I) iodide (2.7 mg), 1-bromo-4-nitrobenzene (158 mg) and 4,4-bis(methoxymethyl)-7-methyloct-6-en-1-yne (175 µL, 150 mg, 0.713 mmol) in NEt_3 (2.0 mL).

Purification by flash chromatography (eluent, pentane:Et_2O, 97:3) afforded to title compound (220 mg, 0.664 mmol, 93%) as a colorless oil. The obtained characterization data were in agreement with those reported in literature.[95]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 – 8.12 (m, 2H), 7.58 – 7.50 (m, 2H), 5.18 (tp, *J* = 7.9, 1.4 Hz, 1H), 3.37 (s, 6H), 3.30 (d, *J* = 1.6 Hz, 4H), 2.47 (s, 2H), 2.18 (d, *J* = 7.9 Hz, 2H), 1.76 (s, 3H), 1.67 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.8, 135.0, 132.4, 131.3, 123.7, 119.1, 81.1, 74.6, 59.5, 43.2, 30.5, 26.3, 23.4, 17.9.

1-(4,4-Bis(methoxymethyl)-7-methyloct-6-en-1-yn-1-yl)-4-fluorobenzene 30k

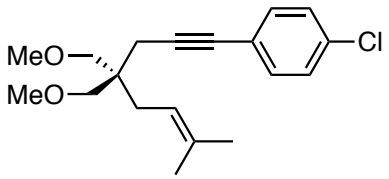


The compound was synthesized according to the general procedure **H** using $PdCl_2(PPh_3)_2$ (5 mg), copper(I) iodide (2.7 mg), 1-bromo-4-fluorobenzene (82 µL, 131 mg) and 4,4-bis(methoxymethyl)-7-methyloct-6-en-1-yne (175 µL, 150 mg, 0.713 mmol) in NEt_3 (2.0 mL).

Purification by flash chromatography (eluent, pentane:Et_2O, 98:2) afforded to title compound (188 mg, 0.618 mmol, 86%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.32 (m, 2H), 7.02 – 6.93 (m, 2H), 5.16 (tq, *J* = 7.8, 1.4 Hz, 1H), 3.34 (s, 6H), 3.31 – 3.24 (m, 4H), 2.37 (s, 2H), 2.14 (d, *J* = 8.1 Hz, 2H), 1.73 (d, *J* = 1.3 Hz, 3H), 1.68 – 1.64 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.2 (d, *J* = 248.2 Hz), 134.7, 133.4 (d, *J* = 8.1 Hz), 120.4 (d, *J* = 3.6 Hz), 119.3, 115.6 (d, *J* = 22.0 Hz), 87.3, 81.3, 74.7, 59.5, 43.1, 30.4, 26.3, 23.0, 17.9. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -112.48. **HRMS** (ESI+) calculated for $[C_{19}H_{25}FNaO_2]^+$ 327.1731 m/z; found $[M + Na]^+$: 327.1722.

1-(4,4-Bis(methoxymethyl)-7-methyloct-6-en-1-yn-1-yl)-4-chlorobenzene 30l

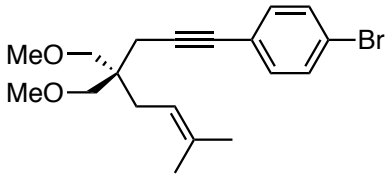


The compound was synthesized according to the general procedure **H** using $PdCl_2(PPh_3)_2$ (5 mg), copper(I) iodide (2.7 mg), 1-chloro-4-iodobenzene (187 mg) and 4,4-bis(methoxymethyl)-7-methyloct-6-en-1-yne (175 µL, 150 mg, 0.713 mmol) in NEt_3 (2.0 mL).

Purification by flash chromatography (eluent, pentane:Et_2O, 98:2) afforded to title compound (215 mg, 0.670 mmol, 94%) as a colorless oil. The obtained characterization data were in agreement with those reported in literature.[94]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.29 (m, 2H), 7.28 – 7.22 (m, 2H), 5.16 (tp, *J* = 7.8, 1.4 Hz, 1H), 3.34 (s, 6H), 3.31 – 3.25 (m, 4H), 2.38 (s, 2H), 2.14 (d, *J* = 7.9 Hz, 2H), 1.73 (s, 3H), 1.65 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 134.7, 133.6, 132.9, 128.6, 122.8, 119.3, 88.8, 81.4, 74.6, 59.5, 43.2, 30.4, 26.3, 23.1, 17.9.

1-(4,4-Bis(methoxymethyl)-7-methyloct-6-en-1-yn-1-yl)-4-bromobenzene 30m

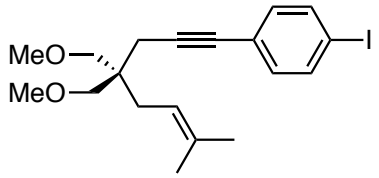


The compound was synthesized according to the general procedure **H** using $PdCl_2(PPh_3)_2$ (5 mg), copper(I) iodide (2.7 mg), 1-bromo-4-iodobenzene (212 mg) and 4,4-bis(methoxymethyl)-7-methyloct-6-en-1-yne (175 µL, 150 mg, 0.713 mmol) in NEt_3 (2.0 mL).

Purification by flash chromatography (eluent, pentane:Et_2O, 98:2) afforded to title compound (188 mg, 0.515 mmol, 72%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.38 (m, 2H), 7.29 – 7.21 (m, 2H), 5.16 (tq, *J* = 7.9, 1.4 Hz, 1H), 3.34 (s, 6H), 3.31 – 3.25 (m, 4H), 2.38 (s, 2H), 2.14 (d, *J* = 7.9 Hz, 2H), 1.73 (d, *J* = 1.4 Hz, 3H), 1.67 – 1.63 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 134.7, 133.2, 131.6, 123.3, 121.7, 119.3, 89.0, 81.4, 74.6, 59.5, 43.1, 30.4, 26.3, 23.1, 17.9. **HRMS** (ESI+) calculated for $[C_{19}H_{25}FNaO_2]^+$ 387.0930 m/z; found $[M + Na]^+$: 387.0934.

1-(4,4-Bis(methoxymethyl)-7-methyloct-6-en-1-yn-1-yl)-4-iodobenzene 30n

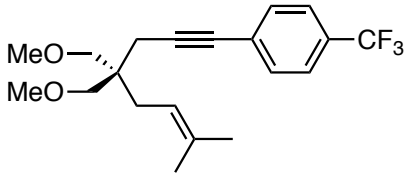


The compound was synthesized according to the general procedure **H** using $PdCl_2(PPh_3)_2$ (5 mg), copper(I) iodide (2.7 mg), 1,4-diiodobenzene (259 mg) and 4,4-bis(methoxymethyl)-7-methyloct-6-en-1-yne (175 µL, 150 mg, 0.713 mmol) in NEt_3 (2.0 mL).

Purification by flash chromatography (eluent, pentane:Et_2O, 98:2) afforded to title compound (129 mg, 0.313 mmol, 44%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.58 (m, 2H), 7.15 – 7.08 (m, 2H), 5.19 – 5.12 (m, 1H), 3.34 (s, 6H), 3.32 – 3.22 (m, 4H), 2.37 (s, 2H), 2.14 (d, *J* = 7.9 Hz, 2H), 1.73 (d, *J* = 1.3 Hz, 3H), 1.69 – 1.62 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.5, 134.7, 133.3, 123.8, 119.3, 93.2, 89.4, 81.5, 74.6, 59.5, 43.1, 30.4, 26.3, 23.2, 17.9. **HRMS** (ESI+) calculated for $[C_{19}H_{25}INaO_2]^+$ 435.0791 m/z; found $[M + Na]^+$: 435.0777.

1-(4,4-Bis(methoxymethyl)-7-methyloct-6-en-1-yn-1-yl)-4-(trifluoromethyl)benzene 30o

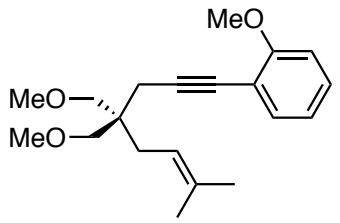


The compound was synthesized according to the general procedure **H** using $PdCl_2(PPh_3)_2$ (5 mg), copper(I) iodide (2.7 mg), 1-iodo-4-(trifluoromethyl)benzene (115 µL, 213 mg) and 4,4-bis(methoxymethyl)-7-methyloct-6-en-1-yne (175 µL, 150 mg, 0.713 mmol) in NEt_3 (2.0 mL).

Purification by flash chromatography (eluent, pentane:Et_2O, 98:2) afforded to title compound (247 mg, 0.697 mmol, 98%) as a colorless oil. The obtained characterization data were in agreement with those reported in literature.[95]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.51 (m, 2H), 7.51 – 7.46 (m, 2H), 5.21 – 5.12 (m, 1H), 3.35 (s, 6H), 3.33 – 3.24 (m, 4H), 2.42 (s, 2H), 2.15 (d, *J* = 7.9 Hz, 2H), 1.74 (d, *J* = 1.6 Hz, 3H), 1.68 – 1.63 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 134.8, 131.9, 129.4 (q, *J* = 32.5 Hz), 125.3 (q, *J* = 3.8 Hz), 124.2 (q, *J* = 272.2 Hz), 119.2, 90.7, 81.3, 74.6, 59.5, 43.2, 30.4, 26.3, 23.2, 17.9. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.45.

1-(4,4-Bis(methoxymethyl)-7-methyloct-6-en-1-yn-1-yl)-2-methoxybenzene 30p



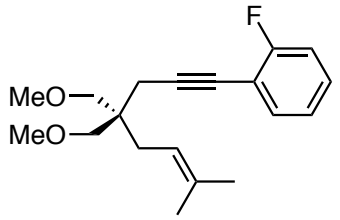
The compound was synthesized according to the general procedure **H** using $PdCl_2(PPh_3)_2$ (5 mg), copper(I) iodide (2.7 mg), 1-iodo-2-methoxybenzene (102

µL, 184 mg) and 4,4-bis(methoxymethyl)-7-methyloct-6-en-1-yne (175 µL, 150 mg, 0.713 mmol) in NEt_3 (2.0 mL).

Purification by flash chromatography (eluent, pentane:Et_2O, 92:8) afforded to title compound (207 mg, 0.654 mmol, 92%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.23 (td, *J* = 8.1, 1.6 Hz, 1H), 6.92 – 6.82 (m, 2H), 5.23 – 5.15 (m, 1H), 3.86 (s, 3H), 3.35 (s, 6H), 3.34 – 3.28 (m, 4H), 2.44 (s, 2H), 2.18 (d, *J* = 8.0 Hz, 2H), 1.73 (s, 3H), 1.66 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.2, 134.5, 133.5, 128.9, 120.5, 119.6, 113.6, 110.7, 91.9, 78.5, 74.7, 59.4, 55.8, 43.3, 30.3, 26.3, 23.4, 17.9. **HRMS** (ESI+) calculated for $[C_{20}H_{28}NaO_3]^+$ 339.1931 m/z; found $[M + Na]^+$: 339.1928.

1-(4,4-Bis(methoxymethyl)-7-methyloct-6-en-1-yn-1-yl)-2-fluorobenzene 30q



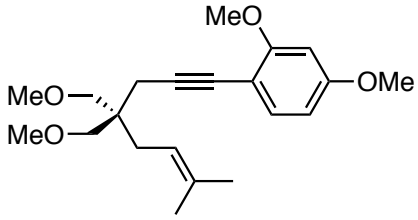
The compound was synthesized according to the general procedure **H** using $PdCl_2(PPh_3)_2$ (5 mg), copper(I) iodide (2.7 mg), 1-iodo-2-methoxybenzene (92 µL, 174 mg) and 4,4-bis(methoxymethyl)-7-methyloct-6-en-1-yne (175 µL, 150 mg, 0.713 mmol) in NEt_3 (2.0 mL).

Purification by flash chromatography (eluent, pentane:Et_2O, 97:3) afforded to title compound (195 mg, 0.641 mmol, 90%) as a colorless oil. The obtained characterization data were in agreement with those reported in literature.[95]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.35 (m, 1H), 7.29 – 7.19 (m, 1H), 7.10 – 7.00 (m, 2H), 5.22 – 5.12 (m, 1H), 3.35 (s, 6H), 3.34 – 3.27 (m, 4H), 2.44 (d, *J* = 7.9 Hz, 2H), 2.20 – 2.13 (m, 2H), 1.73 (s, 3H), 1.65 (s, 3H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.1 (d, *J* = 250.2 Hz), 134.8, 133.5 (d, *J* = 1.7 Hz), 129.2 (d, *J* = 7.9 Hz), 123.9 (d, *J* = 3.7 Hz), 119.3, 115.5 (d, *J* = 21.2 Hz), 112.8 (d, *J* = 15.9 Hz),

93.3 (d, J = 3.3 Hz), 75.7, 74.6, 59.5, 43.2, 30.3, 26.3, 23.3, 17.9. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.55.

1-(4,4-Bis(methoxymethyl)-7-methyloct-6-en-1-yn-1-yl)-2,4-dimethoxybenzene 30r

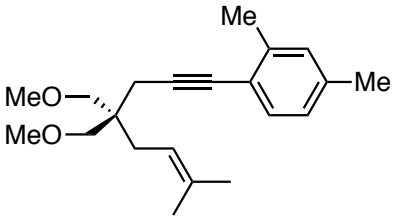


The compound was synthesized according to the general procedure **H** using $PdCl_2(PPh_3)_2$ (5 mg), copper(I) iodide (2.7 mg), 1-iodo-2,4-bis(methoxy)benzene (207 mg) and 4,4-bis(methoxymethyl)-7-methyloct-6-en-1-yne (175 µL, 150 mg, 0.713 mmol) in NEt_3 (2.0 mL).

Purification by flash chromatography (eluent, pentane:Et_2O, 90:10) afforded to title compound (230 mg, 0.664 mmol, 93%) as a colorless oil. The obtained characterization data were in agreement with those reported in literature.[95]

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.29 – 7.23 (m, 1H), 6.45 – 6.40 (m, 2H), 5.22 – 5.15 (m, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 3.32 (s, 6H), 3.31 – 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 NMR** (101 MHz, CD_2Cl_2) δ 161.7, 161.0, 134.7, 134.2, 119.9, 106.2, 105.1, 98.8, 90.1, 78.6, 74.8, 59.4, 56.0, 55.8, 43.5, 30.6, 26.2, 23.6, 17.9.

1-(4,4-Bis(methoxymethyl)-7-methyloct-6-en-1-yn-1-yl)-2,4-dimethylbenzene 30s

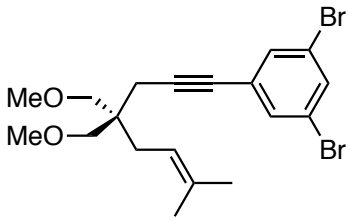


The compound was synthesized according to the general procedure **H** using $PdCl_2(PPh_3)_2$ (5 mg), copper(I) iodide (2.7 mg), 1-iodo-2,4-dimethylbenzene (107 µL, 174 mg) and 4,4-bis(methoxymethyl)-7-methyloct-6-en-1-yne (175 µL, 150 mg, 0.713 mmol) in NEt_3 (2.0 mL).

Purification by flash chromatography (eluent, pentane:Et_2O, 98:2) afforded to title compound (213 mg, 0.677 mmol, 95%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, J = 7.8 Hz, 1H), 7.00 (s, 1H), 6.92 (d, J = 7.8 Hz, 1H), 5.18 (tp, J = 7.8, 1.4 Hz, 1H), 3.34 (s, 6H), 3.33 – 3.26 (m, 4H), 2.43 (s, 2H), 2.40 (s, 3H), 2.30 (s, 3H), 2.16 (d, J = 8.0 Hz, 2H), 1.73 (s, 3H), 1.65 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 139.8, 137.5, 134.6, 132.0, 130.3, 126.3, 121.1, 119.4, 90.6, 81.3, 74.7, 59.4, 43.1, 30.3, 26.3, 23.3, 21.5, 20.9, 17.9. **HRMS** (ESI+) calculated for $[C_{21}H_{30}NaO_2]^+$ 337.2138 m/z; found $[M + Na]^+$: 337.2137.

1-(4,4-Bis(methoxymethyl)-7-methyloct-6-en-1-yn-1-yl)-3,5-dibromobenzene 30t

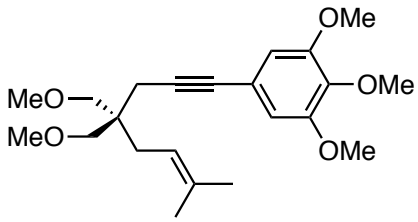


The compound was according to the general procedure **H** using $PdCl_2(PPh_3)_2$ (5 mg), copper(I) iodide (2.7 mg), 1,3-dibromo-5-iodobenzene (284 mg) and 4,4-bis(methoxymethyl)-7-methyloct-6-en-1-yne (175 µL, 150 mg, 0.713 mmol) in NEt_3 (2.0 mL).

Purification by flash chromatography (eluent, pentane:Et_2O, 98:2) afforded to title compound (257 mg, 0.579 mmol, 81%) as a colorless oil. The obtained characterization data were in agreement with those reported in literature.[95]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (t, *J* = 1.8 Hz, 1H), 7.45 (d, *J* = 1.8 Hz, 2H), 5.14 (tdd, *J* = 7.9, 2.9, 1.4 Hz, 1H), 3.34 (s, 6H), 3.26 (d, *J* = 1.1 Hz, 4H), 2.39 (s, 2H), 2.13 (d, *J* = 7.9 Hz, 2H), 1.74 (s, 3H), 1.65 (s, 3H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 134.9, 133.4, 133.2, 127.7, 122.6, 119.1, 91.0, 79.8, 74.5, 59.5, 43.2, 30.4, 26.3, 23.1, 17.9.

5-(4,4-Bis(methoxymethyl)-7-methyloct-6-en-1-yn-1-yl)-1,2,3-trimethoxybenzene 30u

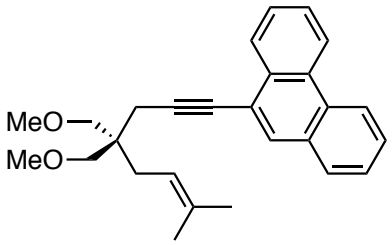


The compound was synthesized according to the general procedure **H** using $PdCl_2(PPh_3)_2$ (5 mg), copper(I) iodide (2.7 mg), 1-iodo-2,3,4-tri(methoxy)benzene (231 mg) and 4,4-bis(methoxymethyl)-7-methyloct-6-en-1-yne (175 µL, 150 mg, 0.713 mmol) in NEt_3 (2.0 mL).

Purification by flash chromatography (eluent, pentane:Et_2O, 85:15) afforded to title compound (228 mg, 0.606 mmol, 85%) as a colorless oil. The obtained characterization data were in agreement with those reported in literature.[95]

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.63 (s, 2H), 5.18 (tm, *J* = 7.9, 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* = 8.1 Hz, 2H), 1.74 (d, *J* = 1.4 Hz, 3H), 1.67 (d, *J* = 1.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.1, 134.6, 119.4, 108.9, 86.7, 82.3, 74.7, 61.1, 59.5, 56.3, 43.2, 30.4, 26.3, 23.1, 17.9.

9-(4,4-Bis(methoxymethyl)-7-methyloct-6-en-1-yn-1-yl)phenanthrene 30v

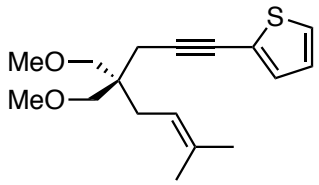


The compound was synthesized according to the general procedure **H** using $PdCl_2(PPh_3)_2$ (5 mg), copper(I) iodide (2.7 mg), 9-iodo-phenantrene (217 mg) and 4,4-bis(methoxymethyl)-7-methyloct-6-en-1-yne (175 µL, 150 mg, 0.713 mmol) in NEt_3 (2.0 mL).

Purification by flash chromatography (eluent, pentane:Et_2O, 96:4) afforded to title compound (262 mg, 0.678 mmol, 95%) as a colorless oil. The obtained characterization data were in agreement with those reported in literature.[95]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 – 8.67 (m, 1H), 8.65 (d, *J* = 8.2 Hz, 1H), 8.50 – 8.46 (m, 1H), 7.94 (s, 1H), 7.87 – 7.80 (m, 1H), 7.73 – 7.54 (m, 4H), 5.26 (tt, *J* = 7.9, 1.4 Hz, 1H), 3.46 – 3.33 (m, 10H), 2.61 (s, 2H), 2.27 (dt, *J* = 7.9, 1.0 Hz, 2H), 1.77 (d, *J* = 1.4 Hz, 3H), 1.70 (d, *J* = 1.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 134.8, 131.8, 131.5, 131.4, 130.2, 130.1, 128.4, 127.2 (d, *J* = 2.7 Hz), 127.0 (d, *J* = 1.6 Hz), 122.9, 122.7, 120.7, 119.4, 92.4, 80.6, 74.8, 59.5, 43.3, 30.6, 26.3, 23.6, 18.0.

2-(4,4-Bis(methoxymethyl)-7-methyloct-6-en-1-yn-1-yl)thiophene 30w



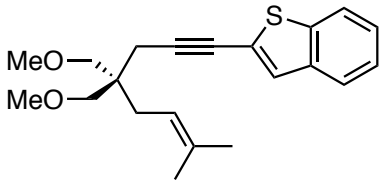
The compound was synthesized according to the general procedure **H** using $PdCl_2(PPh_3)_2$ (5 mg), copper(I) iodide (2.7 mg), 2-bromothiophene (76 µL) and

4,4-bis(methoxymethyl)-7-methyloct-6-en-1-yne (175 µL, 150 mg, 0.713 mmol) in NEt_3 (2.0 mL).

Purification by flash chromatography (eluent, pentane:Et_2O, 97:3) afforded to title compound (187 mg, 0.639 mmol, 90%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.10 (dd, *J* = 3.6, 1.2 Hz, 1H), 6.92 (dd, *J* = 5.2, 3.6 Hz, 1H), 5.14 (tp, *J* = 7.9, 1.4 Hz, 1H), 3.33 (s, 6H), 3.30 – 3.22 (m, 5H), 2.40 (s, 2H), 2.23 – 2.07 (m, 3H), 1.72 (q, *J* = 1.1 Hz, 3H), 1.64 (d, *J* = 1.3 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 134.92, 131.19, 127.08, 126.16, 124.68, 119.49, 92.10, 75.66, 74.85, 59.67, 43.47, 30.64, 26.51, 23.64, 18.15. **HRMS** (ESI+) calculated for $[C_{17}H_{25}O_2S]^+$ 293.1570 m/z; found $[M + H]^+$: 293.1569.

2-(4,4-Bis(methoxymethyl)-7-methyloct-6-en-1-yn-1-yl)benzo[*b*]thiophene 30x

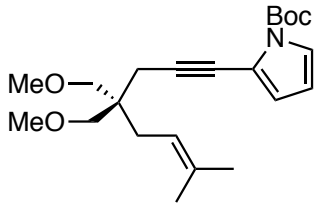


The compound was synthesized according to the general procedure **H** using $PdCl_2(PPh_3)_2$ (5 mg), copper(I) iodide (2.7 mg), 2-bromobenzo[*b*]thiophene (187 mg) and 4,4-bis(methoxymethyl)-7-methyloct-6-en-1-yne (175 µL, 150 mg, 0.713 mmol) in NEt_3 (2.0 mL).

Purification by flash chromatography (eluent, pentane:Et_2O, 97.5:2.5) afforded to title compound (237 mg, 0.692 mmol, 97%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.68 (m, 2H), 7.36 – 7.30 (m, 3H), 5.22 – 5.13 (m, 1H), 3.36 (s, 6H), 3.33 – 3.27 (m, 4H), 2.47 (s, 2H), 2.17 (d, *J* = 7.9 Hz, 2H), 1.75 (s, 3H), 1.68 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 139. 9, 139.3, 134.9, 127.7, 125.2, 124.7, 124.4, 123.6, 122.0, 119.2, 94.3, 75.9, 74.6, 59.5, 43.3, 30.5, 26.3, 23.6, 18.0. **HRMS** (ESI+) calculated for $[C_{21}H_{26}NaO_2S]^+$ 365.1546 m/z; found $[M + Na]^+$: 365.1530.

tert-Butyl-2-(4,4-bis(methoxymethyl)-7-methyloct-6-en-1-yn-1-yl)-1*H*-pyrrole-1-carboxylate 30y

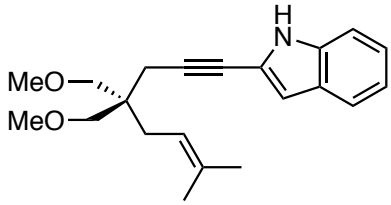


The compound was synthesized according to the general procedure **H** using $PdCl_2(PPh_3)_2$ (5 mg) and copper(I) iodide (2.7 mg) *tert*-butyl 2-iodo-1*H*-pyrrole-1-carboxylate (230 mg) and 4,4-bis(methoxymethyl)-7-methyloct-6-en-1-yne (175 µL, 150 mg, 0.713 mmol) in THF (1.6 ml) and NEt_3 (0.40 ml). The reaction was stirred 18h at 40 ºC.

Purification by flash chromatography (eluent pentane: Et_2O 99:1 to 92:8) afforded to title compound (225 mg, 0.599 mmol, 84%) as a pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (dd, *J* = 3.3, 1.7 Hz, 1H), 6.42 (dd, *J* = 3.4, 1.7 Hz, 1H), 6.11 (t, *J* = 3.4 Hz, 1H), 5.21 – 5.13 (m, 1H), 3.34 (s, 6H), 3.33 – 3.27 (m, 4H), 2.42 (s, 2H), 2.16 (d, *J* = 7.9 Hz, 2H), 1.72 (s, 3H), 1.65 (s, 3H), 1.60 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.5, 134.5, 121.7, 119.7, 116.3, 110.8, 91.3, 83.9, 74.6, 59.4, 43.3, 30.4, 28.1, 26.3, 23.6, 17.9 **HRMS** (ESI+) calculated for $[C_{22}H_{33}NNaO_4]^+$ 398.2302 m/z; found $[M + Na]^+$: 398.2286.

2-(4,4-Bis(methoxymethyl)-7-methyloct-6-en-1-yn-1-yl)-1*H*-indole 30z



The compound was synthesized according to the general procedure **H** using $PdCl_2(PPh_3)_2$ (5 mg), copper(I) iodide (2.7 mg), 2-iodo-1*H*-indole (173 mg) and 4,4-bis(methoxymethyl)-7-methyloct-6-en-1-yne (175 µL, 150 mg, 0.713 mmol) in NEt_3 (2.0 mL).

Purification by flash chromatography (eluent, pentane:Et_2O 88:12) afforded to title compound (219 mg, 0.673mmol, 94%) as a pale yellow oil.

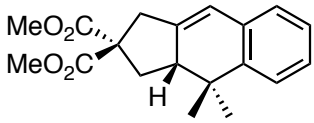
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (bs, 1H), 7.56 (d, *J* = 7.9 Hz, 1H), 7.30 (dq, *J* = 8.2, 1.0 Hz, 1H), 7.20 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.10 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 6.69 – 6.64 (m, 1H), 5.18 (tp, *J* = 7.9, 1.4 Hz, 1H), 3.36 (s, 6H), 3.34 – 3.27 (m, 4H), 2.46 (s, 2H), 2.17 (d, *J* = 7.8 Hz, 2H), 1.75 (s, 3H), 1.67 (s, 3H). **HRMS** (ESI+) calculated for $[C_{21}H_{27}NNaO_2]^+$ 348.1934 m/z; found $[M + Na]^+$: 348.1934.

Enantioselective Cyclization of 1,6-Arylenynes

General procedure I: enantioselective formal [4+2] cycloaddition reaction under optimized conditions

The corresponding 1,6-Enyne (1.0 equiv) and **(S_p)-C** (2 mol %) were dissolved in 1,2-dichloroethane (0.15 M) and cooled to –25 ºC then a solution of $AgBF_4$ (50 $mg.mL^{-1}$ in 1,2-dichloroethane, 2.2 mol %) was added. The reaction was stirred for the given time at –25 ºC unless in the dark stated otherwise. After completion the reaction was quenched by addition of 1 drop of NEt_3 and concentrated under reduced pressure. The crude was purified by flash column chromatography over silica gel using the given eluent.

Dimethyl(*R*)-4,4-dimethyl-1,3,3a,4-tetrahydro-2*H*-cyclopenta[*b*]naphthalene-2,2-dicarboxylate 31a

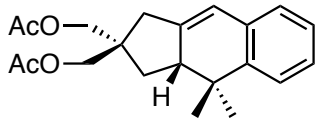


The compound was synthesized according to the general procedure **I** using 1,6-enyne **30a** (38 mg, 0.12 mmol) **(S_p)-C** (2.6 mg) in 1,2-dichloroethane (0.83 mL) and $AgBF_4$ in solution (11 µL). The reaction was stirred for 20 h.

Purification by flash column chromatography over silica gel (eluent cyclohexane:EtOAc 96:4) afforded the title compound (27 mg, 0.089 mmol, 71%) as a colorless oil in 88:12 *er.* The obtained characterization data were in agreement with those reported in literature.[95]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.27 (m, 1H), 7.17 – 7.11 (m, 2H), 7.03 – 6.97 (m, 1H), 6.32 (q, *J* = 2.4 Hz, 1H), 4.16 – 4.07 (m, 2H), 4.03 – 3.94 (m, 2H), 2.76 (ttd, *J* = 8.0, 3.2, 1.6 Hz, 1H), 2.55 (dq, *J* = 18.2, 1.6 Hz, 1H), 2.40 (dt, *J* = 18.2, 2.9 Hz, 1H), 2.09 (s, 3H), 2.07 (s, 3H), 1.87 (ddd, *J* = 12.9, 8.2, 1.4 Hz, 1H), 1.60 (dd, *J* = 13.0, 12.0 Hz, 1H), 1.39 (s, 3H), 0.91 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.2 (d, *J* = 7.6 Hz), 144.4, 144.3, 134.2, 127.0, 126.4, 126.3, 123.6, 120.0, 68.1, 65.7, 48.1, 44.9, 37.7, 36.8, 31.8, 25.7, 22.0, 21.0. $\boldsymbol{\alpha_D^{589}}$ = –19.3 deg.cm^2.g^{-1} ($CHCl_3$, c 0.1, 302 K). **HPLC** Chiralpak AD (250 × 4.6mm, 5 μm) at 25 ºC, flow 0.8 mL/min, isocratic hexane:IPA, 280 nm, t_R (minor) 5.3; t_R (major) 6.2.

(*R*)-(4,4-Dimethyl-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*b*]naphthalene-2,2-diyl)bis(methylene) diacetate 31b



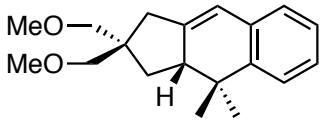
The compound was synthesized according to the general procedure **I** using 1,6-enyne **30b** (43 mg, 0.13 mmol) and **(S_p)-C** (2.7 mg) in 1,2-dichloroethane (0.83 mL) and $AgBF_4$ in solution (11 μL). The reaction was stirred for 20 h.

Purification by flash column chromatography over silica gel (eluent cyclohexane:EtOAc 92:8) afforded the title compound (41 mg, 0.12 mmol, 95%) as a colorless oil in 88:12 *er.* The obtained characterization data were in agreement with those reported in literature.[95]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.27 (m, 1H), 7.17 – 7.11 (m, 2H), 7.03 – 6.97 (m, 1H), 6.32 (q, *J* = 2.4 Hz, 1H), 4.16 – 4.07 (m, 2H), 4.03 – 3.94 (m, 2H), 2.76 (ttd, *J* = 8.0, 3.2, 1.6 Hz, 1H), 2.55 (dq, *J* = 18.2, 1.6 Hz, 1H), 2.40 (dt, *J* =

18.2, 2.9 Hz, 1H), 2.09 (s, 3H), 2.07 (s, 3H), 1.87 (ddd, *J* = 12.9, 8.2, 1.4 Hz, 1H), 1.60 (dd, *J* = 13.0, 12.0 Hz, 1H), 1.39 (s, 3H), 0.91 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.2 (d, *J* = 7.6 Hz), 144.4, 144.3, 134.2, 127.0, 126.4, 126.3, 123.6, 120.0, 68.1, 65.7, 48.1, 44.9, 37.7, 36.8, 31.8, 25.7, 22.0, 21.0. α_D^{589} = –12.3 deg.cm^2.g^{-1} ($CHCl_3$, c 0.1, 302 K). **UPC^2** Chiralpak IB (150 × 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*)-2,2-Bis(methoxymethyl)-4,4-dimethyl-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*b*]naphthalene 31c

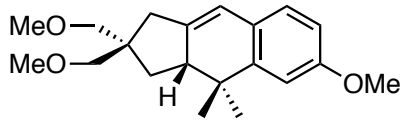


The compound was synthesized according to the general procedure **I** using 1,6-enyne **30c** (40 mg, 0.13 mmol) and **(S_p)-C** (2.7 mg) in 1,2-dichloroethane (0.83 mL) and $AgBF_4$ in solution (11 µL). The reaction was stirred for 18 h.

Purification by flash column chromatography over silica gel (eluent pentane:Et_2O 98:2) afforded the title compound (38 mg, 121 µmol, 95%) as a colorless oil in 96:4 *er*. The obtained characterization data were in agreement with those reported in literature.[95]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 1H), 7.18 – 7.08 (m, 2H), 7.03 – 6.95 (m, 1H), 6.28 (d, *J* = 2.7 Hz, 1H), 3.38 (s, 3H), 3.37 (s, 2H), 3.32 (s, 3H), 3.29 – 3.19 (m, 2H), 2.77 – 2.67 (m, 1H), 2.54 – 2.44 (m, 1H), 2.33 (dt, *J* = 18.1, 2.9 Hz, 1H), 1.89 – 1.80 (m, 1H), 1.55 (dd, *J* = 12.7, 11.7 Hz, 1H), 0.91 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.8, 144.6, 134.6, 126.6, 126.0, 123.6, 119.1, 77.4, 75.2, 59.5 (d, *J* = 2.0 Hz), 48.3, 46.8, 38.0, 36.8, 25.8, 22.0. **SFC** Chiralpak IG (100 × 3mm, 3µm) at 35 ºC, flow 1.2 mL/min, isocratic CO_2/MeOH 97:3, BPR pressure 150 bar, 280 nm, t_R (minor) 1.2; t_R (major) 1.3.

(*R*)-6-Methoxy-2,2-bis(methoxymethyl)-4,4-dimethyl-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*b*]naphthalene 31d

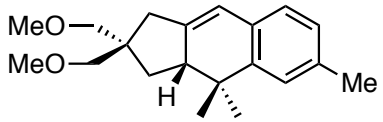


The compound was synthesized according to the general procedure **I** using 1,6-enyne **30d** (40 mg, 0.13 mmol) and **(S_p)-C** in 1,2-dichloroethane (0.83 mL) and $AgBF_4$ in solution (11 µL). The reaction was stirred for 18 h.

Purification by flash column chromatography over silica gel (eluent pentane:Et_2O 92:8) afforded the title compound (38 mg, 0.12 µmol, 95%) as a colorless oil in 93:7 *er*. The obtained characterization data were in agreement with those reported in literature.[95]

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.9 (d, *J* = 8.2 Hz, 1H), 6.9 (d, *J* = 2.6 Hz, 1H), 6.7 (dd, *J* = 8.3, 2.6 Hz, 1H), 6.2 (q, *J* = 2.5 Hz, 1H), 3.8 (s, 3H), 3.4 (s, 3H), 3.4 (s, 2H), 3.3 (s, 3H), 3.3 – 3.2 (m, 2H), 2.7 (ddtd, *J* = 11.4, 7.9, 3.1, 1.4 Hz, 1H), 2.5 (dq, *J* = 17.9, 1.6 Hz, 1H), 2.3 (dt, *J* = 18.0, 2.9 Hz, 1H), 1.9 – 1.8 (m, 1H), 1.5 (t, *J* = 12.4 Hz, 1H), 1.4 (s, 3H), 0.9 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.6, 146.6, 144.0, 128.0, 126.8, 118.4, 110.9, 110.0, 75.1, 59.5 (d, *J* = 1.8 Hz), 55.4, 48.1, 46.8, 37.8, 37.1, 31.7, 25.7, 21.9. α_D^{589} = –25.8 deg.cm^2.g^{-1} ($CHCl_3$, c 0.2, 302 K). **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, 275 nm, t_R (major) 0.73; t_R (minor) 0.84.

(*R*)-2,2-Bis(methoxymethyl)-4,4,6-trimethyl-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*b*]naphthalene 31e

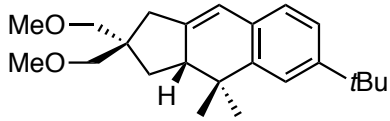


The compound was synthesized according to the general procedure **I** using 1,6-enyne **30e** (38 mg, 0.13 mol) and **(S_p)-C** (2.7 mg) in 1,2-dichloroethane (0.83 mL) and $AgBF_4$ in solution (11 μL). The reaction was stirred for 18 h.

Purification by flash column chromatography over silica gel (eluent pentane:Et_2O 98:2) afforded the title compound (35 mg, 0.12 mmol, 92%) as a colorless oil in 95:5 *er*.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (t, *J* = 1.2 Hz, 1H), 6.97 – 6.87 (m, 2H), 6.26 (q, *J* = 2.5 Hz, 1H), 3.38 (s, 3H), 3.38 – 3.37 (m, 2H), 3.32 (s, 3H), 3.28 – 3.20 (m, 2H), 2.75 – 2.65 (m, 1H), 2.52 – 2.44 (m, 1H), 2.33 (s, 4H), 1.88 – 1.80 (m, 1H), 1.53 (dd, *J* = 12.7, 11.7 Hz, 1H), 1.37 (s, 3H), 0.90 (s, 3H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.6, 144.6, 136.1, 132.0, 126.8, 125.9, 124.5, 118.8, 75.2, 59.5 (d, *J* = 1.7 Hz), 48.4, 46.8, 37.9, 36.8, 31.7, 25.7, 22.0, 21.7. **HRMS** (ESI+) calculated for $[C_{20}H_{29}O_2]^+$ 301.2162 m/z; found $[M+H]^+$: 301.2159. α_D^{589} = –8.1 deg.cm^2.g^{-1} ($CHCl_3$, c 0.2, 302 K). **HPLC** Chiralpak OD-H (250 × 4.6mm, 5 μm) at 25 ºC, flow 1.0 mL/min, isocratic hexane, 280 nm, t_R (minor) 11.2; t_R (major) 13.8.

(*R*)-2,2-Bis(methoxymethyl)-4,4,6-trimethyl-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*b*]naphthalene 31f

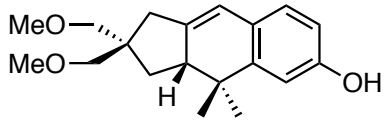


The compound was synthesized according to the general procedure **I** using 1,6-enyne **30f** (47 mg, 0.14 mol) and **(S_p)-C** (2.7 mg) in 1,2-dichloroethane (0.83 mL) and $AgBF_4$ in solution (11 μL). The reaction was stirred for 18 h.

Purification by flash column chromatography over silica gel (eluent pentane:Et_2O 96:4) afforded the title compound (43 mg, 0.14 mmol, >99%) as a colorless oil in 96:4 *er*. The obtained characterization data were in agreement with those reported in literature.[95]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 2.0 Hz, 1H), 7.16 (dd, *J* = 7.9, 2.0 Hz, 1H), 6.94 (d, *J* = 7.9 Hz, 1H), 6.30 – 6.24 (m, 1H), 3.38 (s, 3H), 3.37 (d, *J* = 1.1 Hz, 2H), 3.31 (s, 3H), 3.23 (d, *J* = 2.1 Hz, 2H), 2.72 (ddd, *J* = 9.0, 7.4, 3.9 Hz, 1H), 2.52 – 2.42 (m, 1H), 2.32 (dt, *J* = 18.0, 2.9 Hz, 1H), 1.89 – 1.79 (m, 1H), 1.54 (t, *J* = 12.2 Hz, 2H), 1.40 (s, 3H), 1.32 (s, 9H), 0.91 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.3, 145.7, 144.0, 131.9, 125.4, 122.8, 120.4, 118.6, 75.0, 59.4, 59.3, 48.3, 46.6, 37.8, 36.9, 34.8, 31.6, 31.5, 25.6, 22.0. α_D^{589} = –43.5 deg.cm^2.g^{-1} ($CHCl_3$, c 0.1, 302 K). **HPLC** Chiralpak OD-H (250 × 4.6mm, 5 µm) at 25 ºC, flow 1.0 mL/min, isocratic hexane, 280 nm, t_R (minor) 6.3; t_R (major) 7.9.

(*R*)-2,2-Bis(methoxymethyl)-4,4-dimethyl-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*b*]naphthalen-6-ol 31g

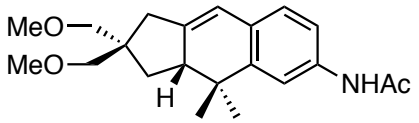


The compound was synthesized according to the general procedure **I** using 1,6-enyne **30g** (38 mg, 0.12 mmol), and **(S_p)-C** (2.7 mg) in 1,2-dichloroethane (0.83 mL) and $AgBF_4$ in solution (11 µL). The reaction was stirred for 18 h at –10 ºC. Purification by flash column chromatography over silica gel (eluent pentane:Et_2O 80:20) afforded the title compound (36 mg, 0.11 mol, 91%) as a colorless oil in 90:10 *er*.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (d, *J* = 8.1 Hz, 1H), 6.80 (d, *J* = 2.6 Hz, 1H), 6.58 (dd, *J* = 8.1, 2.6 Hz, 1H), 6.22 (q, *J* = 2.5 Hz, 1H), 4.99 (s, 1H), 3.38 (d, *J* = 0.9 Hz, 5H), 3.33 (s, 3H), 3.29 – 3.21 (m, 2H), 2.71 – 2.61 (m, 1H), 2.51 – 2.41 (m, 1H), 2.36 – 2.26 (m, 1H), 1.88 – 1.78 (m, 1H), 1.52 (d, *J* = 12.3 Hz, 1H), 1.33 (s, 3H), 0.88 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.5, 146.8, 143.8, 128.0,

127.1, 118.4, 112.5, 111.3, 77.5 (d, J = 9.3 Hz), 75.1, 59.5, 59.5, 48.0, 46.8, 37.8, 37.0, 31.7, 25.7, 21.9. **HRMS** (ESI+) calculated for $[C_{19}H_{26}NaO_3]^+$ 325.1774 m/z; found $[M+Na]^+$: 325.1772 $\boldsymbol{\alpha_D^{589}}$ = –18.2 deg.cm^2.g^{-1} ($CHCl_3$, c 0.1, 302 K). **SFC** Chiralpak IA (100 × 3mm, 3µm) at 35 ºC, flow 1.2 mL/min, isocratic CO_2/MeOH 90:10, BPR pressure 150 bar, 280 nm, t_R (minor) 1.8; t_R (major) 2.0.

(*R*)-*N*-(2,2-Bis(methoxymethyl)-4,4-dimethyl-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*b*]naphthalen-6-yl)acetamide 31i

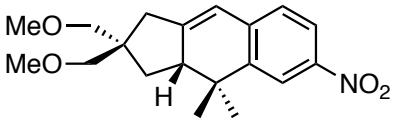


The compound was synthesized according to the general procedure **I** using 1,6-enyne **30i** (42 mg, 0.12 mmol), and **(S_p)-C** (2.7 mg) in 1,2-dichloroethane (0.83 mL) and $AgBF_4$ in solution (11 µL). The reaction was stirred for 72 h.

Purification by flash column chromatography over silica gel (eluent cyclohexane:EtOAc 40:60) afforded the title compound (38 mg, 0.11 mmol, 91%) in a 2.7:1 ratio with starting material as a colorless oil in 90:10 *er*.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (d, J = 8.1 Hz, 1H), 6.80 (d, J = 2.6 Hz, 1H), 6.58 (dd, J = 8.1, 2.6 Hz, 1H), 6.22 (q, J = 2.5 Hz, 1H), 4.99 (s, 1H), 3.38 (d, J = 0.9 Hz, 5H), 3.33 (s, 3H), 3.29 – 3.21 (m, 2H), 2.71 – 2.61 (m, 1H), 2.51 – 2.41 (m, 1H), 2.36 – 2.26 (m, 1H), 1.88 – 1.78 (m, 1H), 1.52 (d, J = 12.3 Hz, 1H), 1.33 (s, 3H), 0.88 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.1, 146.0, 145.6, 136.3, 131.2, 126.5, 118.5, 117.7, 115.6, 75.2, 59.5 (d, J = 2.3 Hz), 48.2, 46.8, 37.9, 37.0, 31.6, 25.7, 22.0. **SFC** Chiralpak IA (100 × 3mm, 3µm) at 35 ºC, flow 1.2 mL/min, isocratic CO_2/MeOH 85:15, BPR pressure 150 bar, 280 nm, t_R (minor) 1.6; t_R (major) 2.0.

(*R*)-2,2-Bis(methoxymethyl)-4,4-dimethyl-6-nitro-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*b*]naphthalene 31j

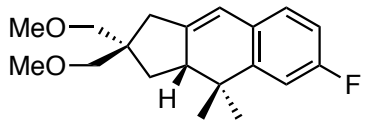


The compound was synthesized according to the general procedure **I** using 1,6-enyne **30j** (41 mg, 0.12 mmol) and **(S_p)-C** (2.7 mg) in 1,2-dichloroethane (0.83 mL) and $AgBF_4$ in solution (11 µL). The reaction was stirred for 18 h.

Purification by flash column chromatography over silica gel (eluent pentane:Et_2O 95:5) afforded the title compound (39 mg, 0.12 mmol, 95%) as a colorless oil in 95:5 *er*. The obtained characterization data were in agreement with those reported in literature.[95]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 2.3 Hz, 1H), 8.00 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.07 (d, *J* = 8.3 Hz, 1H), 6.37 (q, *J* = 2.4 Hz, 1H), 3.37 (s, 3H), 3.36 (s, 2H), 3.32 (s, 3H), 3.30 – 3.18 (m, 2H), 2.82 – 2.72 (m, 1H), 2.59 – 2.49 (m, 1H), 2.40 (dt, *J* = 18.7, 2.8 Hz, 1H), 1.93 – 1.83 (m, 1H), 1.61 (t, *J* = 12.1 Hz, 1H), 1.46 (s, 3H), 0.94 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.7, 146.3, 145.9, 141.1, 126.2, 122.2, 119.4, 118.2, 75.3, 59.5, 48.4, 46.9, 38.3, 37.3, 31.4, 25.7, 21.9. α_D^{589} = – 68.9 deg.cm^2.g^{-1} ($CHCl_3$, c 0.2, 302 K). **UPC^2** Chiralpak IG (150 × 4.6mm, 3µm) at 35 ºC, flow 2 mL/min, isocratic CO2/MeOH 95:5, ABRP pressure 2000 psi, 338 nm, t_R (minor) 4.9; t_R (major) 5.1.

(*R*)-6-Fluoro-2,2-bis(methoxymethyl)-4,4-dimethyl-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*b*]naphthalene 31k

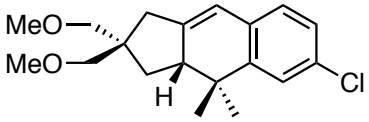


The compound was synthesized according to the general procedure **I** using 1,6-enyne **30k** (38 mg, 0.12 mmol) and **(S_p)-C** (2.7 mg) in 1,2-dichloroethane (0.83 mL) and $AgBF_4$ in solution (11 µL). The reaction was stirred for 18 h.

Purification by flash column chromatography over silica gel (eluent pentane:Et_2O 96:4) afforded the title compound (29 mg, 92 µmol, 74%) as a colorless oil in 94:6 *er*.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.98 (dd, *J* = 10.5, 2.6 Hz, 1H), 6.93 (dd, *J* = 8.3, 6.0 Hz, 1H), 6.80 (td, *J* = 8.4, 2.6 Hz, 1H), 6.25 (q, *J* = 2.5 Hz, 1H), 3.37 (s, 3H), 3.36 (s, 2H), 3.32 (s, 3H), 3.26 – 3.21 (m, 2H), 2.68 (td, *J* = 8.4, 4.2 Hz, 1H), 2.47 (dd, *J* = 18.2, 1.8 Hz, 1H), 2.36 – 2.28 (m, 1H), 1.88 – 1.80 (m, 1H), 1.54 (dd, *J* = 12.6, 11.7 Hz, 1H), 1.35 (s, 3H), 0.89 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.9 (d, *J* = 244.0 Hz), 147.2 (d, *J* = 6.3 Hz), 145.9 (d, *J* = 2.6 Hz), 130.8 (d, *J* = 3.0 Hz), 127.0 (d, *J* = 7.9 Hz), 118.1, 112.5 (d, *J* = 21.3 Hz), 111.1 (d, *J* = 22.2 Hz),77.3, 75.2, 59.5 (d, *J* = 2.2 Hz), 47.9, 46.8, 37.8, 37.1, 31.6, 25.7, 21.8. **^{19}F NMR** (471 MHz, $CDCl_3$) δ -115.7 (dt, *J* = 9.1, 5.1 Hz). **HRMS** (ESI+) calculated for $[C_{19}H_{25}FNaO_2]^+$ 327.1731 m/z; found $[M+Na]^+$: 327.1742. $\boldsymbol{\alpha_D^{589}}$ = –1.7 deg.cm^2.g^{-1} ($CHCl_3$, c 0.1, 302 K). **HPLC** Chiralpak IB-N (250 × 4.6mm, 5 µm) at 25 ºC, flow 0.5 mL/min, isocratic heptane: MTBE 98:2, 280 nm, t_R (minor) 12.9; t_R (major) 14.4.

(*R*)-6-Chloro-2,2-bis(methoxymethyl)-4,4-dimethyl-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*b*]naphthalene 31l

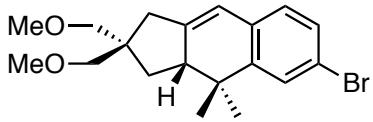


The compound was synthesized according to the general procedure **I** using 1,6-enyne **30l** (40 mg, 0.12 mmol) and **(S_p)-C** (2.7 mg) in 1,2-dichloroethane (0.83 mL) and $AgBF_4$ in solution (11 µL). The reaction was stirred for 18 h.

Purification by flash column chromatography over silica gel (eluent pentane:Et_2O 97:3) afforded the title compound (37 mg, 0.12 mmol, 92%) as a colorless oil in 95:5 *er*. The obtained characterization data were in agreement with those reported in literature.[95]

^{1}H NMR (400 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* = 8.0 Hz, 1H), 6.24 (q, *J* = 2.5 Hz, 1H), 3.37 (s, 3H), 3.36 (s, 2H), 3.32 (s, 3H), 3.27 – 3.20 (m, 2H), 2.74 – 2.64 (m, 1H), 2.48 (dq, *J* = 18.2, 1.6 Hz, 1H), 2.32 (dt, *J* = 18.2, 2.9 Hz, 1H), 1.89 – 1.80 (m, 1H), 1.54 (t, *J* = 12.4 Hz, 1H), 1.36 (s, 3H), 0.90 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.5, 146.6, 133.1, 131.8, 127.1, 126.1, 124.1, 118.2, 77.3, 75.2, 59.5, 48.1, 46.8, 37.9, 37.2, 31.5, 25.6, 21.9. $\boldsymbol{\alpha_D^{589}}$ = –24.0 deg.cm^2.g^{-1} ($CHCl_3$, c 0.1, 302 K). **HPLC** Chiralpak IB-N (250 × 4.6mm, 5 μm) at 25 ºC, flow 0.5 mL/min, isocratic heptane: MTBE 98:2, 280 nm, t_R (minor) 13.0; t_R (major) 14.7.

(*R*)-6-Bromo-2,2-bis(methoxymethyl)-4,4-dimethyl-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*b*]naphthalene 31m



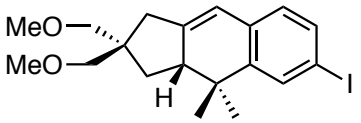
The compound was synthesized according to the general procedure **I** using 1,6-enyne **30m** (46 mg, 0.13 mmol) and **(S_p)-C** (2.7 mg) in 1,2-dichloroethane (0.83 mL) and $AgBF_4$ in solution (11 μL). The reaction was stirred for 18 h.

Purification by flash column chromatography over silica gel (eluent pentane:Et_2O 97:3) afforded the title compound (40 mg, 0.11 mmol, 87%) as a colorless oil in 95:5 *er*.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 2.0, 0.7 Hz, 1H), 7.23 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.85 (d, *J* = 8.0 Hz, 1H), 6.25 – 6.21 (m, 1H), 3.37 (s, 3H), 3.36 (d, *J* = 0.6 Hz, 2H), 3.32 (s, 3H), 3.27 – 3.19 (m, 2H), 2.68 (dddd, *J* = 10.2, 8.3, 4.9, 2.4 Hz, 1H), 2.51 – 2.43 (m, 1H), 2.31 (dt, *J* = 18.2, 2.9 Hz, 1H), 1.88 – 1.80 (m, 1H), 1.54 (dd, *J* = 12.7, 11.7 Hz, 1H), 1.35 (s, 3H), 0.90 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 147.7, 146.9, 133.6, 129.1, 127.4, 127.0, 120.0, 118.2, 77.3, 75.2, 59.5, 48.1, 46.8, 38.0, 37.1, 31.5, 25.6, 21.9. **HRMS** (ESI+) calculated for $[C_{19}H_{25}BrNaO_2]^+$ 387.0930 m/z; found $[M+Na]^+$: 387.0932. $\boldsymbol{\alpha_D^{589}}$ = –27.1 deg.cm^2.g^{-1} ($CHCl_3$, c 0.1, 302 K). **HPLC** Chiralpak IB-N (250 × 4.6mm, 5 μm) at

25 ºC, flow 0.5 mL/min, isocratic heptane: MTBE 98:2, 280 nm, t_R (minor) 13.7; t_R (major) 15.8.

(*R*)-6-Iodo-2,2-bis(methoxymethyl)-4,4-dimethyl-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*b*]naphthalene 31n

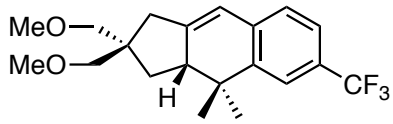


The compound was synthesized according to the general procedure **I** using 1,6-enyne **30n** (52 mg, 0.12 mmol) and **(S_p)-C** (2.7 mg) in 1,2-dichloroethane (0.83 mL) and $AgBF_4$ in solution (11 µL). The reaction was stirred for 18 h.

Purification by flash column chromatography over silica gel (eluent pentane:Et_2O 97:3) afforded the title compound (48 mg, 0.12 mmol, 92%) as a colorless oil in 96:4 *er*.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.53 (m, 1H), 7.44 (dd, *J* = 7.9, 1.8 Hz, 1H), 6.72 (d, *J* = 7.9 Hz, 1H), 6.21 (q, *J* = 2.4 Hz, 1H), 3.37 (s, 3H), 3.35 (s, 2H), 3.32 (s, 3H), 3.28 – 3.18 (m, 2H), 2.73 – 2.63 (m, 1H), 2.52 – 2.42 (m, 1H), 2.36 – 2.26 (m, 1H), 1.83 (dd, *J* = 13.3, 8.1 Hz, 1H), 1.54 (d, *J* = 12.4 Hz, 2H), 1.35 (s, 3H), 0.89 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.1, 147.1, 135.3, 134.2, 132.9, 127.8, 118.3, 91.5, 77.3, 75.2, 59.5, 48.1, 46.8, 38.0, 37.0, 31.5, 25.6, 21.9. **HRMS** (ESI+) calculated for $[C_{19}H_{26}IO_2]^+$ 413.0972 m/z; found $[M+H]^+$: 413.0967. $\boldsymbol{\alpha_D^{589}}$ = –35.4 deg.cm^2.g^{-1} ($CHCl_3$, c 0.1, 302 K). **HPLC** Chiralpak IB-N (250 × 4.6mm, 5 µm) at 25 ºC, flow 0.5 mL/min, isocratic heptane: MTBE 98:2, 280 nm, t_R (minor) 14.2; t_R (major) 16.6.

(*R*)-2,2-Bis(methoxymethyl)-4,4-dimethyl-6-(trifluoromethyl)-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*b*]naphthalene 31o

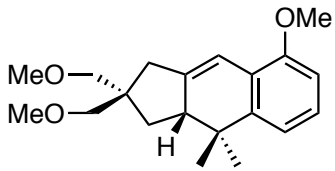


The compound was synthesized according to the general procedure **I** using 1,6-enyne **30o** (44 mg, 0.12 mmol), and **(S_p)-C** (2.7 mg) in 1,2-dichloroethane (0.83 mL) and $AgBF_4$ in solution (11 µL). The reaction was stirred for 18 h.

Purification by flash column chromatography over silica gel (eluent pentane:Et_2O 97:3) afforded the title compound (40 mg, 0.11 mol, 91%) as a colorless oil in 96:4 *er*. The obtained characterization data were in agreement with those reported in literature.[95]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.06 (d, *J* = 7.9 Hz, 1H), 6.32 (q, *J* = 2.5 Hz, 1H), 3.38 (s, 3H), 3.37 (s, 2H), 3.32 (s, 3H), 3.27 – 3.21 (m, 2H), 2.79 – 2.70 (m, 1H), 2.56 – 2.47 (m, 1H), 2.42 – 2.32 (m, 1H), 1.87 (dd, *J* = 12.8, 8.4 Hz, 1H), 1.58 (t, *J* = 12.4 Hz, 1H), 1.41 (s, 3H), 0.92 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.76. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.1, 145.1, 137.8 (d, *J* = 1.9 Hz), 128.1 (q, *J* = 31.7 Hz), 125.9 (d, *J* = 271.9 Hz), 123.1 (q, *J* = 4.0 Hz), 120.4 (q, *J* = 3.8 Hz), 118.2, 75.1, 59.3, 48.1, 46.7, 37.9, 36.9, 31.4, 25.5, 21.7. α_D^{589} = –19.7 deg.cm^2.g^{-1} ($CHCl_3$, c 0.1, 302 K). **HPLC** Chiralpak IB-N (250 × 4.6mm, 5 µm) at 25 ºC, flow 0.5 mL/min, isocratic heptane: MTBE 98:2, 280 nm, t_R (minor) 11.4; t_R (major) 12.1.

(*R*)-8-Methoxy-2,2-bis(methoxymethyl)-4,4-dimethyl-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*b*]naphthalene 31p

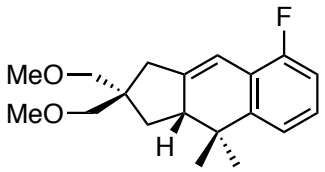


The compound was synthesized according to the general procedure **I** using 1,6-enyne **30p** (40 mg, 0.13 mmol), and **(S_p)-C** (2.7 mg) in 1,2-dichloroethane (0.83 mL) and $AgBF_4$ in solution (11 µL). The reaction was stirred for 18 h.

Purification by flash column chromatography over silica gel (eluent pentane:Et_2O 93:7) afforded the title compound (34 mg, 0.11 mol, 85%) as a colorless oil which crystallized upon standing in 95:5 *er*.

M.p = > 50 ºC (CH_2Cl_2) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.14 (t, *J* = 8.0 Hz, 1H), 6.96 (dt, *J* = 7.8, 0.8 Hz, 1H), 6.75 (dd, *J* = 8.2, 1.0 Hz, 1H), 6.70 (q, *J* = 2.6 Hz, 1H), 3.85 (s, 3H), 3.40 (d, *J* = 1.1 Hz, 6H), 3.33 (s, 3H), 3.29 – 3.22 (m, 2H), 2.77 – 2.66 (m, 1H), 2.56 (dq, *J* = 18.0, 1.6 Hz, 1H), 2.36 (dt, *J* = 18.1, 3.0 Hz, 1H), 1.92 – 1.81 (m, 1H), 1.55 (t, *J* = 12.3 Hz, 1H), 1.39 (s, 3H), 0.92 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.5, 146.2, 146.1, 127.0, 123.5, 116.3, 112.7, 108.5, 59.5, 59.4, 55.7, 47.8, 46.8, 38.3, 37.1, 31.6, 25.9, 21.5. **HRMS** (ESI+) calculated for $[C_{20}H_{29}O_3]^+$ 317.2111 m/z; found $[M + H]^+$: 317.2110. α_D^{589} = -38.8 deg.cm^2.g^{-1} ($CHCl_3$, c 0.10, 302 K). **SFC** Chiralpak IB-N (100 × 3mm, 3µm) at 35 ºC, flow 1.2 mL/min, isocratic CO_2/MeOH 85:15, BPR pressure 150 bar, 280 nm, t_R (major) 0.94; t_R (minor) 1.24.

(*R*)-8-Fluoro-2,2-bis(methoxymethyl)-4,4-dimethyl-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*b*]naphthalene 31q

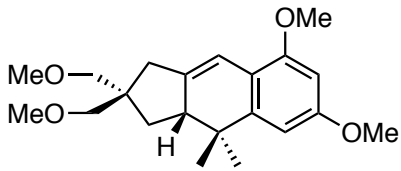


The compound was synthesized according to the general procedure **I** using 1,6-enyne **30q** (39 mg, 0.13 mmol), and **(S_p)-C** (2.7 mg) in 1,2-dichloroethane (0.83 mL) and $AgBF_4$ in solution (11 µL). The reaction was stirred for 18 h.

Purification by flash column chromatography over silica gel (eluent pentane:Et_2O 96:4) afforded the title compound (28 mg, 0.09 mol, 72%) as a colorless oil in 91:9 *er*. The obtained characterization data were in agreement with those reported in literature.[95]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 – 7.03 (m, 2H), 6.90 – 6.80 (m, 1H), 6.54 (q, *J* = 2.6 Hz, 1H), 3.38 (s, 3H), 3.37 (s, 2H), 3.32 (s, 3H), 3.28 – 3.21 (m, 2H), 2.77 – 2.65 (m, 1H), 2.52 (dq, *J* = 18.2, 1.6 Hz, 1H), 2.35 (dt, *J* = 18.2, 2.9 Hz, 1H), 1.91 – 1.80 (m, 1H), 1.55 (d, *J* = 12.5 Hz, 2H), 1.38 (s, 3H), 0.90 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.5 (d, *J* = 245.9 Hz), 147.8 (d, *J* = 1.8 Hz), 147.1 (d, *J* = 3.6 Hz), 127.0 (d, *J* = 8.5 Hz), 122.4 (d, *J* = 14.3 Hz), 119.1 (d, *J* = 2.8 Hz), 112.9 (d, *J* = 21.7 Hz), 111.0 (d, *J* = 6.3 Hz), 77.3, 75.1, 59.5 (d, *J* = 1.9 Hz), 48.0, 46.8, 38.2, 37.1 (d, *J* = 2.7 Hz), 31.6, 25.8, 21.7. **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) δ -122.84. **α_D^{589}** = –10.5 deg.cm^2.g^{-1} ($CHCl_3$, c 0.2, 302 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 (minor) 2.2.

(*R*)-6,8-Dimethoxy-2,2-bis(methoxymethyl)-4,4-dimethyl-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*b*]naphthalene 31r

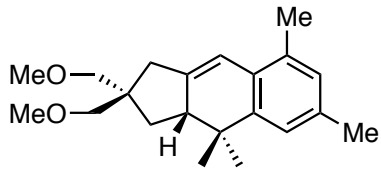


The compound was synthesized according to the general procedure **I** using 1,6-enyne **30r** (45 mg, 0.13 mmol), and **(S_p)-C** (2.7 mg) in 1,2-dichloroethane (0.83 mL) and $AgBF_4$ in solution (11 µL). The reaction was stirred for 42 h.

Purification by flash column chromatography over silica gel (eluent pentane:Et_2O 88:12) afforded the title compound (45 mg, 0.09 mol, >99%) as a colorless oil in 97:3 *er*. The obtained characterization data were in agreement with those reported in literature.[95]

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.57 (q, *J* = 2.6 Hz, 1H), 6.51 (d, *J* = 2.3 Hz, 1H), 6.31 (d, *J* = 2.3 Hz, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.37 (s, 4H), 3.31 (s, 3H), 3.28 – 3.17 (m, 2H), 2.70 – 2.60 (m, 1H), 2.50 (dq, *J* = 17.9, 1.6 Hz, 1H), 2.31 (dt, *J* = 17.9, 3.0 Hz, 1H), 1.87 – 1.77 (m, 1H), 1.50 (t, *J* = 12.3 Hz, 1H), 1.33 (s, 3H), 0.87 (s, 3H), **. ^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.3, 155.6, 147.4, 143.1, 117.0, 112.4, 101.7, 95.6, 75.0, 59.5 (d, *J* = 6.3 Hz), 55.7, 55.5, 47.8, 46.9, 38.1, 37.4, 31.7, 25.9, 21.4. α_D^{589} = –83.6 deg.cm^2.g^{-1} ($CHCl_3$, c 0.1, 302 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) 3.0; t_R (major) 3.2.

(*R*)-2,2-Bis(methoxymethyl)-4,4,6,8-tetramethyl-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*b*]naphthalene 31s

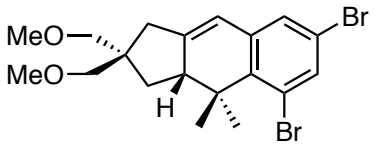


The compound was synthesized according to the general procedure **I** using 1,6-enyne **30s** (40 mg, 0.13 mmol), and **(S_p)-C** (2.7 mg) in 1,2-dichloroethane (0.83 mL) and $AgBF_4$ in solution (11 µL). The reaction was stirred for 42 h.

Purification by flash column chromatography over silica gel (eluent pentane:Et_2O 96:4) afforded the title compound (37 mg, 0.12 mol, 92%) as a colorless oil in 95:5 *er*.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.97 (d, *J* = 1.6 Hz, 1H), 6.83 – 6.79 (m, 1H), 6.45 (q, *J* = 2.5 Hz, 1H), 3.41 – 3.35 (m, 5H), 3.32 (s, 3H), 3.23 (d, *J* = 1.9 Hz, 2H), 2.69 – 2.62 (m, 1H), 2.50 (dd, *J* = 17.9, 1.7 Hz, 1H), 2.33 (dt, *J* = 18.0, 3.0 Hz, 1H), 2.29 (s, 3H), 2.28 (s, 3H), 1.87 – 1.79 (m, 1H), 1.53 (dd, *J* = 12.7, 11.6 Hz, 1H), 1.35 (s, 3H), 0.88 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 145.6, 144.8, 135.6, 132.8, 130.1, 128.8, 122.2, 115.7, 77.4, 75.1, 59.5, 59.5, 47.8, 46.8, 38.3, 37.1, 31.7, 26.0, 21.7, 21.6, 19.7. **HRMS** (ESI+) calculated for $[C_{21}H_{30}NaO_2]^+$ 337.2138 m/z; found $[M + Na]^+$: 337.2140. $\boldsymbol{\alpha_D^{589}}$ = –73.1 deg.cm^2.g^{-1} ($CHCl_3$, c 0.1, 302 K). **HPLC** Chiralpak OD-H (250 × 4.6mm, 5 µm) at 25 ºC, flow 1 mL/min, isocratic hexane, 280 nm, t_R (minor) 11.1; t_R (major) 12.4.

(*R*)-5,7-Dibromo-2,2-bis(methoxymethyl)-4,4-dimethyl-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*b*]naphthalene 31t

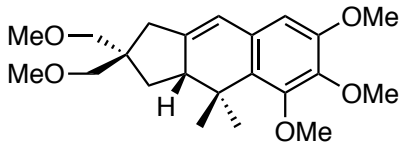


The compound was synthesized according to the general procedure **I** using 1,6-enyne **30t** (55 mg, 0.12 mmol), and **(S_p)-C** (2.7 mg) in 1,2-dichloroethane (0.83 mL) and $AgBF_4$ in solution (11 µL). The reaction was stirred for 48 h.

Purification by flash column chromatography over silica gel (eluent pentane:Et_2O 96:4) afforded the title compound (55 mg, 0.12 mol, >99%) as a colorless oil in 77:23 *er*. The obtained characterization data were in agreement with those reported in literature.[95]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 2.2 Hz, 1H), 7.03 (d, *J* = 2.2 Hz, 1H), 6.12 (q, *J* = 2.4 Hz, 1H), 3.37 (d, *J* = 0.5 Hz, 3H), 3.34 (s, 2H), 3.33 (d, *J* = 0.5 Hz, 3H), 3.29 – 3.21 (m, 2H), 2.86 – 2.74 (m, 1H), 2.55 – 2.45 (m, 1H), 2.35 (dt, *J* = 18.3, 2.9 Hz, 1H), 1.91 – 1.81 (m, 1H), 1.73 (s, 3H), 1.59 (t, *J* = 12.2 Hz, 1H), 1.03 (s, 3H). **^{13}C 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 (d, *J* = 2.3 Hz), 49.7, 46.5, 40.0, 38.0, 32.4, 27.4, 18.6. α_D^{589} = –11.5 deg.cm^2.g^{-1} ($CHCl_3$, c 0.2, 302 K). **SFC** Chiralpak IG (100 × 3mm, 3µm) at 35 ºC, flow 1.2 mL/min, isocratic CO_2/EtOH 75:25, BPR pressure 150 bar, 280 nm, t_R (major) 0.85; t_R (minor) 0.93.

(*R*)-5,6,7-Trimethoxy-2,2-bis(methoxymethyl)-4,4-dimethyl-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*b*]naphthalene 31u

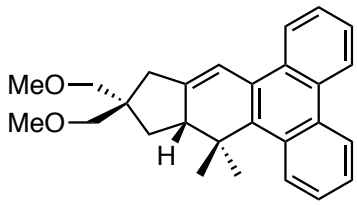


The compound was synthesized according to the general procedure **I** using 1,6-enyne **30u** (48 mg, 0.13 mmol), and **(S_p)-C** (2.7 mg) in 1,2-dichloroethane (0.83 mL) and $AgBF_4$ in solution (11 µL). The reaction was stirred for 24 h.

Purification by flash column chromatography over silica gel (eluent pentane:Et_2O 82:18) afforded the title compound (47 mg, 0.12 mol, 98%) as a colorless oil in 92:8 *er*. The obtained characterization data were in agreement with those reported in literature.[95]

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36 (s, 1H), 6.14 (q, *J* = 2.4 Hz, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.83 (s, 3H), 3.37 (s, 3H), 3.35 (d, *J* = 1.1 Hz, 2H), 3.32 (s, 3H), 3.27 – 3.21 (m, 2H), 2.72 (dddt, *J* = 10.3, 6.8, 3.3, 2.0 Hz, 1H), 2.47 (dq, *J* = 18.0, 1.6 Hz, 1H), 2.31 (dt, *J* = 18.0, 2.9 Hz, 1H), 1.90 – 1.81 (m, 1H), 1.57 (s, 3H), 1.51 (t, *J* = 12.3 Hz, 1H), 0.95 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.1, 151.5, 145.7, 141.4, 131.6, 129.5, 119.1, 105.9, 75.1, 60.9, 60.7, 59.5, 56.0, 49.7, 46.5, 37.9, 37.9, 31.9, 27.4, 20.9. $\boldsymbol{\alpha_D^{589}}$ = –75.5 deg.cm^2.g^{-1} ($CHCl_3$, c 0.1, 302 K). **UPC^2** Chiralpak OJ (150 × 4.6mm, 3µm) at 35 ºC, flow 2 mL/min, isocratic CO_2/IPA 98:2, ABRP pressure 2000 psi, 225 nm, t_R (major) 1.4; t_R (minor) 1.6.

(*R*)-11,11-Bis(methoxymethyl)-9,9-dimethyl-9a,10,11,12-tetrahydro-9*H*-cyclopenta[*b*]triphenylene 31v

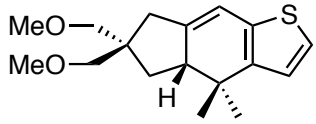


The compound was synthesized according to the general procedure **I** using 1,6-enyne **30v** (52 mg, 0.13 mmol), and **(S_p)-C** (2.7 mg) in 1,2-dichloroethane (0.83 mL) and $AgBF_4$ in solution (11 µL). The reaction was stirred for 24 h.

Purification by flash column chromatography over silica gel (eluent pentane:Et_2O 95:5) afforded the title compound (52 mg, 0.13 mol, >99%) as a colorless oil in 97:3 *er* The obtained characterization data were in agreement with those reported in literature.[95]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 – 8.69 (m, 1H), 8.69 – 8.63 (m, 1H), 8.44 – 8.38 (m, 1H), 8.21 – 8.16 (m, 1H), 7.64 – 7.57 (m, 2H), 7.57 – 7.50 (m, 2H), 7.01 (q, *J* = 2.6 Hz, 1H), 3.47 (s, 2H), 3.43 (s, 3H), 3.35 (s, 3H), 3.31 (s, 2H), 2.82 (td, *J* = 8.2, 4.1 Hz, 1H), 2.71 (dq, *J* = 17.9, 1.5 Hz, 1H), 2.52 (dt, *J* = 17.9, 3.1 Hz, 1H), 2.03 – 1.93 (m, 1H), 1.78 (t, *J* = 11.8 Hz, 1H), 1.74 (s, 3H), 1.36 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.8, 138.2, 130.8, 130.6, 130.2, 129.8, 129.5, 126.5, 126.5, 125.9, 125.1, 124.7, 124.5, 123.5, 122.6, 115.2, 74.9, 59.4, 59.4, 51.2, 46.8, 39.3, 38.4, 32.1, 29.9. **α_D^{589}** = +162.3 deg.cm^2.g^{-1} ($CHCl_3$, c 0.1, 302 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) 4.8; t_R (minor) 6.3.

(*R*)-6,6-Bis(methoxymethyl)-4,4-dimethyl-4a,5,6,7-tetrahydro-4*H*-indeno[5,6-*b*]thiophene 31w

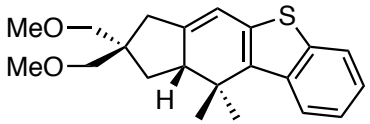


The compound was synthesized according to the general procedure **I** using 1,6-enyne **30w** (38 mg, 0.13 mmol), and **(S_p)-C** (2.7 mg) in 1,2-dichloroethane (0.83 mL) and $AgBF_4$ in solution (11 µL). The reaction was stirred for 24 h.

Purification by flash column chromatography over silica gel (eluent pentane:Et_2O 95:5) afforded the title compound (38 mg, 0.13 mol, >99%) as a colorless oil in 96:4 *er*.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, *J* = 5.0 Hz, 1H), 6.93 (dd, *J* = 5.1, 0.7 Hz, 1H), 6.31 – 6.24 (m, 1H), 3.39 – 3.36 (m, 5H), 3.32 (s, 3H), 3.27 – 3.21 (m, 2H), 2.78 (dtt, *J* = 11.7, 4.8, 2.7 Hz, 1H), 2.51 – 2.42 (m, 1H), 2.32 (dt, *J* = 18.2, 3.1 Hz, 1H), 1.86 – 1.76 (m, 1H), 1.51 (t, *J* = 12.3 Hz, 1H), 1.37 (s, 3H), 0.86 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.1, 144.6, 135.1, 124.4, 121.4, 112.4, 75.0, 59.5, 50.3, 47.1, 37.6, 36.0, 30.8, 27.0, 21.2. **HRMS** (ESI+) calculated for $[C_{17}H_{25}O_2S]^+$ 293.1570 m/z; found $[M + H]^+$: 293.1569. α_D^{589} = –99.5 deg.cm^2.g^{-1} ($CHCl_3$, c 0.1, 302 K). **HPLC** Chiralpak IA (250 × 4.6mm, 5 µm) at 25 ºC, flow 0.8 mL/min, isocratic hexane:IPA 99:1, 280 nm, t_R (minor) 4.9; t_R (major) 5.3.

(*R*)-2,2-Bis(methoxymethyl)-10,10-dimethyl-2,3,10,10a-tetrahydro-1*H*-benzo[*b*]indeno[5,6-*d*]thiophene 31x



The compound was synthesized according to the general procedure **I** using 1,6-enyne **30x** (46 mg, 0.13 mmol), and **(S_p)-C** (2.7 mg) in 1,2-dichloroethane (0.83 mL) and $AgBF_4$ in solution (11 µL). The reaction was stirred for 24 h.

Purification by flash column chromatography over silica gel (eluent pentane:Et_2O 95:5) afforded the title compound (46 mg, 0.13 mol, >99%) as a colorless oil in 95:5 *er*.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.2 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.33 – 7.27 (m, 1H), 7.21 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 6.31 (q, *J* = 2.6 Hz, 1H), 3.39 (s, 3H), 3.39 (s, 3H), 3.35 (s, 3H), 3.33 – 3.25 (m, 2H), 3.02 – 2.92 (m, 1H), 2.55 (d, *J* = 18.4 Hz, 1H), 2.40 (dt, *J* = 18.4, 3.1 Hz, 1H), 1.96 – 1.86 (m, 1H), 1.70 (s, 3H), 1.62 (d, *J* = 12.3 Hz, 1H), 1.00 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 147.3, 139.4, 138.4, 136.1, 135.8, 123.0, 122.9, 122.7, 113.1, 77.4, 75.1, 59.5, 51.4, 46.9, 37.9, 37.8, 31.0, 27.4, 19.8. **HRMS** (ESI+) calculated for $[C_{21}H_{26}NaO_2S]^+$ 365.1546 m/z; found $[M + Na]^+$: 365.1546. $\boldsymbol{\alpha_D^{589}}$ = –40.0 deg.cm^2.g^{-1} ($CHCl_3$, c 0.1, 302 K). **SFC** Chiralpak IC (100 × 3mm, 3μm) at 35 ºC, flow 1.2 mL/min, isocratic CO_2/MeOH 70:30, BPR pressure 150 bar, 280 nm, t_R (major) 0.89; t_R (minor) 1.12.

Chapter III

Gold(I)-Catalyzed Enantioselective Synthesis of Planar Chiral Ferrocenes

Introduction

Planar chirality is encountered in different scaffolds, such as metallocenes and paracyclophanes, among which ferrocenes are the most common. Planar chiral ferrocenes play an important role in organic and organometallic chemistry as ligands, catalysts or scaffolds.[173] However, these scaffolds are usually synthesized either by using chiral substituents,[100-105,174] chiral auxiliaries,[175] stoichiometric chiral reagents[107] as well as by chiral[176] or kinetic resolution, the later having been reported in an enzymatic[177] and non-enzymatic[178] fashion (Scheme 3.1).[179]

173 Urbano, A.; Hernández-Torres, G.; Del Hoyo, A. M.; Martínez-Carrión, A.; Carmen Carreño, *Chem. Commun.* **2016**, *52*, 6419–6422.

174 Selected examples: (a) Aratani, T.; Gonda, T.; Nozaki, H. *Tetrahedron Lett.* **1969**, 2265–2268. (b) Nettekoven, U.; Widhalm, M.; Kamer, P. C. J.; Van Leeuwen, P. W. N. M.; Mereiter, K.; Lutz, M.; Spek, A. L. *Organometallics* **2000**, *19*, 2299–2309. (c) Bolm, G.; Kesselgruber, M.; Muñiz, K.; Raabe, G. *Organometallics* **2000**, *19*, 1648–1651. (d) Delaye, P. O.; Ahari, M.; Vasse, J. L.; Szymoniak, J. *Tetrahedron Asymmetry* **2010**, *21*, 2505–2511.

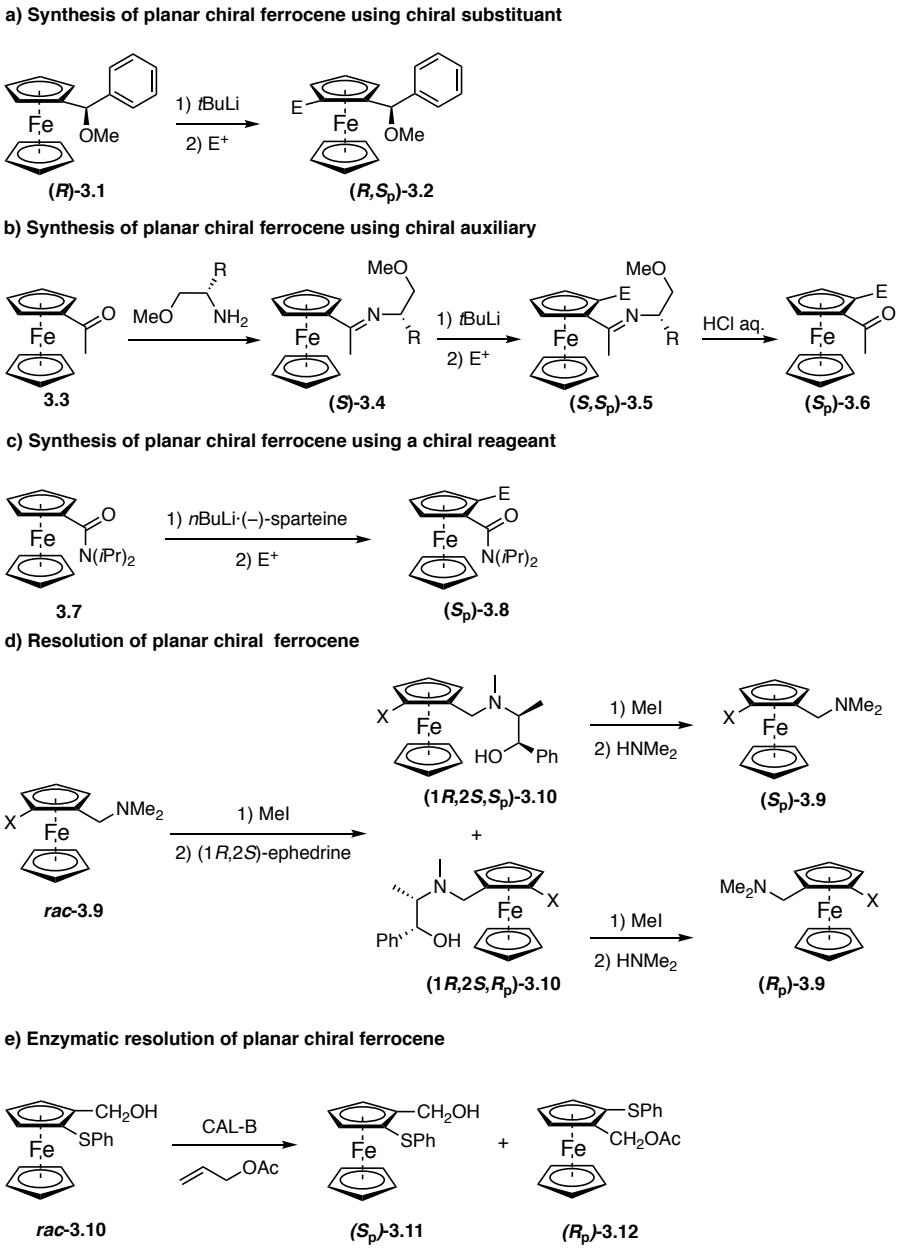
175 Selected examples: (a) Enders, D.; Peters, R.; Lochtman, R.; Runsink, J. *Eur. J. Org. Chem.* **2000**, *16*, 2839–2850. (b) Enders, D.; Klumpen, T.; Raabe, G. *Synlett* **2003**, *8*, 1198–1200. (c) Ferber, B.; Top, S.; Herson, P.; Jaouen, G. *Organometallics* **2007**, *26*, 1686–1691. (d) Enders, D.; Jonas, E. A.; Khimpen, T. *Eur. J. Org. Chem.* **2009**, *13*, 2149–2162.

176 Xiao, L.; Mereiter, K.; Weissensteiner, W. *Synthesis.* **1999**, *8*, 1354–1362.

177 selected examples: (a) Nicolosi, G.; Patti, A.; Morrone, R.; Piatelli, M. *Tetrahedron Asymmetry* **1994**, *5*, 1275–1280. (b) Izumi, T.; Aratani, S. *J. Chem. Technol. Biotechnol.* **1994**, *59*, 403–408. (c) Patti, A.; Lambusta, D.; Piattelli, M.; Nicolosi, G.; McArdle, P.; Cunningham, D.; Walsh, M. *Tetrahedron* **1997**, *53*, 1361–1368. (d) Merabet-Khellasi, M.; Aribi-Zouioueche, L.; Riant, O. *Tetrahedron Asymmetry* **2009**, *20*, 1371–1377.

178 (a) Latorre, A.; Urbano, A.; Carmen Carreño, M. *Chem. Commun.* **2011**, *47*, 8103–8105. (b) Ogasawara, M.; Arae, S.; Watanabe, S.; Nakajima, K.; Takahashi, T. *Chem. Eur. J.* **2013**, *19*, 4151–4154. (b) Liu, R.; Zhou, G.; Hall, T. H.; Clarkson, G. J.; Wills, M.; Chen, W. *Adv. Synth. Catal.* **2015**, *357*, 3453–3457.

179 For review (a) Alba, A. N. R.; Rios, R. *Molecules* **2009**, *14*, 4747–4757. (b) Schaarschmidt, D.; Lang, H. *Organometallics* **2013**, *32*, 5668–5704.



Scheme 3.1. Synthetic routes to planar chiral ferrocenes.

Despite the recognized efficiency of these methodologies, they limit the access to defined scaffolds, require additional synthetical steps and display poor atom economy. Hence, the synthesis of planar chiral ferrocenes from achiral

substrates by asymmetric catalysis is highly desirable. Over the last decade several reports appeared in this field but remain sparse to this day.

The first and most used method relies on asymmetric C–H functionalization.[180] The first example of an asymmetric synthesis of planar chiral ferrocenes was reported in 2013 by You with a chiral palladium-catalyzed C–H arylation directed by an amine group and using amino acid derivatives as ligands (Scheme 3.2a).[181] This methodology was extended to other C–H transformations such as alkynylation,[182] alkenylation[183] and acylation (Scheme 3.2a).[184] In 2014 Shibata reported an enantioselective iridium-catalyzed C–H alkylation directed by quinoline groups using a chiral diene **3.19** as ligand[185] (Scheme 3.2b). Recently Hou reported the asymmetric C–H alkynylation catalyzed by a half-sandwich scandium complex also using quinoline as directing group.[186]

180 (a) Vyhivskyi, O.; Kudashev, A.; Miyakoshi, T.; Baudoin, O. *Chem. Eur. J.* **2021**, *27*, 1231–1257. (b) Gao, D. W.; Gu, Q.; Zheng, C.; You, S. L. *Acc. Chem. Res.* **2017**, *50*, 351–365. (c) Zhu, D. Y.; Chen, P.; Xia, J. B. *ChemCatChem* **2016**, *8*, 68–73. (d) López, L. A.; López, E. *Dalt. Trans.* **2015**, *44*, 10128–10135.

181 (a) Gao, D. W.; Shi, Y. C.; Gu, Q.; Zhao, Z. Le; You, S. L. *J. Am. Chem. Soc.* **2013**, *135*, 86–89. (b) Gao, D. W.; Gu, Q.; You, S. L. *J. Am. Chem. Soc.* **2016**, *138*, 2544–2547.

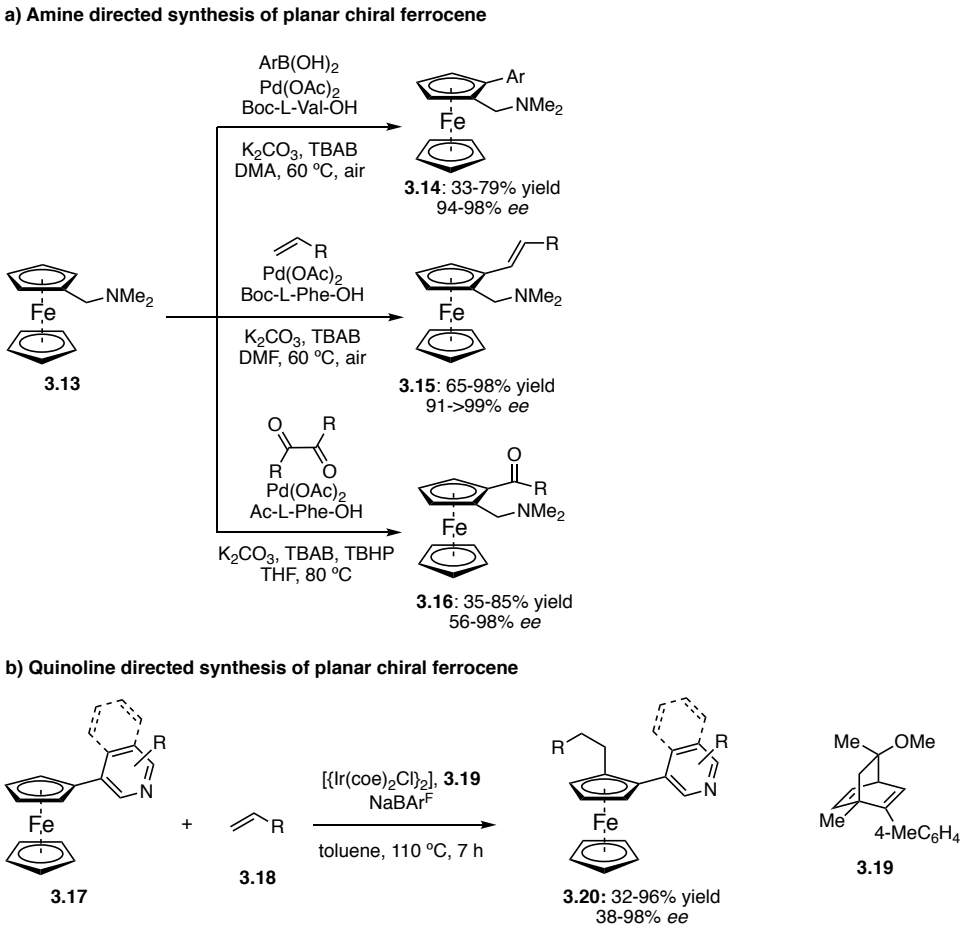
182 Shi, Y. C.; Yang, R. F.; Gao, D. W.; You, S. L. *Beilstein J. Org. Chem.* **2013**, *9*, 1891–1896.

183 Pi, C.; Cui, X.; Liu, X.; Guo, M.; Zhang, H.; Wu, Y. *Org. Lett.* **2014**, *16*, 5164–5167.

184 Pi, C.; Li, Y.; Cui X.; Zhang, H.; Han, Y.; Wu, Y. *Chem. Sci.* **2013**, *4*, 2675–2679.

185 Shibata, T.; Shizuno, T. *Angew. Chem. Int. Ed.* **2014**, *53*, 5410–5413.

186 Lou, S.; Zhuo, Q.; Nishiura, M.; Luo, G.; Hou, Z. **2020**. https://doi.org/10.1021/jacs.0c13166.

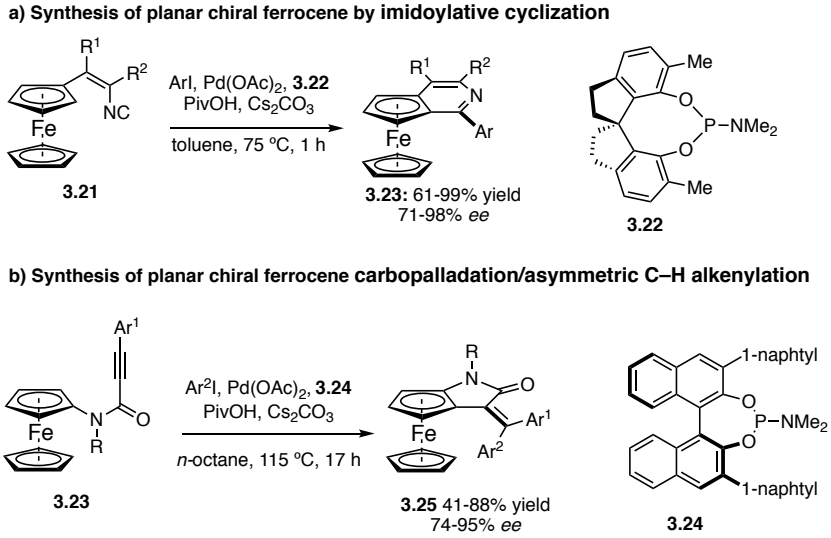


Scheme 3.2 Asymmetric C–H activation of functionalized ferrocenes.

In 2018 Luo and Zhu reported an asymmetric palladium-catalyzed C–H imidoylation protocol through domino reaction yielding the formation of the pyridoferrocene **3.23** from an aryl iodide and the substrate **3.21** (Scheme 3.3a).[187] Recently Liu disclosed another palladium-catalyzed domino reaction forming the lactam fused ferrocene **3.25** through carbopalladation/C–H alkenylation in

187 Luo, S.; Xiong, Z.; Lu, Y.; Zhu, Q. *Org. Lett.* **2018**, *20*, 1837–1840.

presence of an aryl iodide (Scheme 3.3b).[188] Similarly, You reported one example of rhodium(III)-catalyzed C–H bond functionalization/annulation of ferrocenyl carboxamides[189] and rhodium(III)-catalyzed amidation of ferrocenylpyridines and analogues[190] using a chiral Cp ligand with low enantiocontrol. Mitsui reported one example of asymmetric synthesis of a pyrane-fused ferrocene by C–H activation/cyclization of alkynylferrocenylethers with alkynes.[191] These methodologies provide access to complex planar chiral ferrocenes in good yield and enantioselectivity employing chiral phosphoramidite ligands.



Scheme 3.3. Asymmetric synthesis of planar chiral ferrocene by tandem reactions.

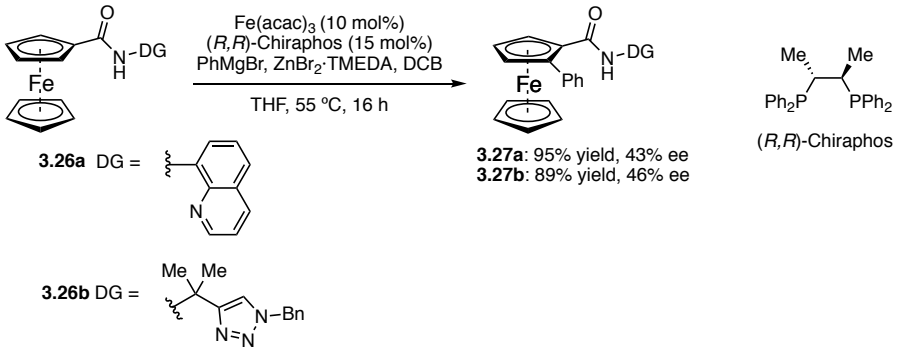
188 Jia, L.; Liu, X.; Zhang, A. A.; Wang, T.; Hua, Y.; Li, H.; Liu, L. *Chem. Commun.* **2020**, *56*, 1737–1740.

189 Wang, S. B.; Zheng, J.; You, S. L. *Organometallics* **2016**, *35*, 1420–1425.

190 Wang, S. B.; Gu, Q.; You, S. L. *Organometallics* **2017**, *36*, 4359–4362.

191 Mitsui, T.; Tokoro, Y.; Haraguchi, R.; Sugita, K.; Harada, M.; Fukuzawa, S. I.; Minami, Y.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **2018**, *91*, 839–845.

Butenshön reported in 2017 an iron-catalyzed *ortho*-alkylation and arylation of ferrocenes **3.26** directed by amide-branched directing groups and demonstrated the feasibility of achieving this reaction in an enantioselective manner using the chiral ligand (*R,R*)-Chiraphos (Scheme 3.4).[192]



Scheme 3.4. Asymmetric *ortho*-arylation of ferrocenylamide **3.26**.

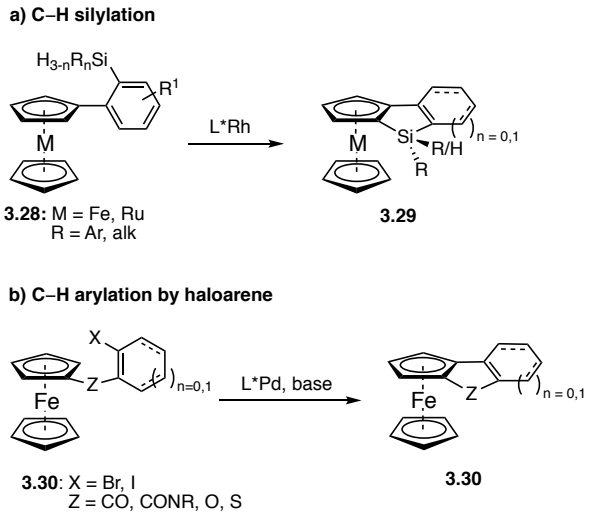
In addition to these intermolecular transformations several intramolecular enantioselective C–H activation reactions were reported such as the copper-catalyzed carbene C–H insertion of diazoketone-ferrocenes disclosed in a pioneering work of Schmaltz in 1997[193] and several examples of rhodium-catalyzed C–H silylation (Scheme 3.5).[194] Yet, palladium-catalyzed C–H arylation using haloarene remains the most explored approach.[195]

192 Schmiel, D.; Butenschön, H. *Organometallics* **2017**, *36*, 4979–4989.

193 Schmalz, H. G.; Spiegel, S. *Angew. Chem. Int. Ed. English* **1997**, *36*, 2456–2458.

194 (a) Zhang, Q. W.; An, K.; Liu, L. C.; Yue, Y.; He, W. *Angew. Chem. Int. Ed.* **2015**, *54*, 6918–6921. (b) Murai, M.; Matsumoto, K.; Takeuchi, Y.; Takai, K. *Org. Lett.* **2015**, *17*, 3102–3105. (c) Yuan, W.; You, L.; Lin, W.; Ke, J.; Li, Y.; He, C. *Org. Lett.* **2021**. https://doi.org/10.1021/acs.orglett.1c00029.

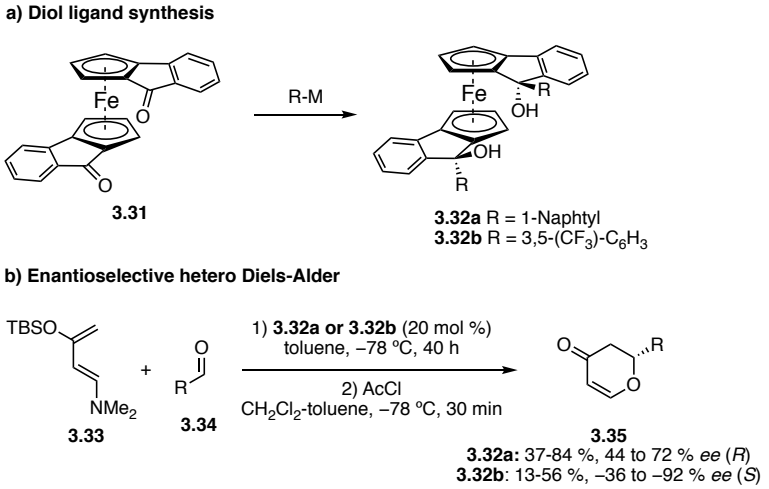
195 (a) Deng, R.; Huang, Y.; Ma, X.; Li, G.; Zhu, R.; Wang, B.; Kang, Y. B.; Gu, Z. *J. Am. Chem. Soc.* **2014**, *136*, 4472–4475. (b) Ma, X.; Gu, Z. *RSC Adv.* **2014**, *4*, 36241–36244. (c) Liu, L.; Zhang, A. A.; Zhao, R. J.; Li, F.; Meng, T. J.; Ishida, N.; Murakami, M.; Zhao, W. X. *Org. Lett.* **2014**, *16*, 5336–5338. (d) Gao, D. W.; Yin, Q.; Gu, Q.; You, S. L. *J. Am. Chem. Soc.* **2014**, *136*, 4841–4844. (e) Zhang, S.; Lu, J.; Ye, J.; Duan, W. L. *Chinese J. Org. Chem.* **2016**, *36*, 752–759. (f) Nottingham,



Scheme 3.5. Asymmetric synthesis of planar chiral ferrocenes.

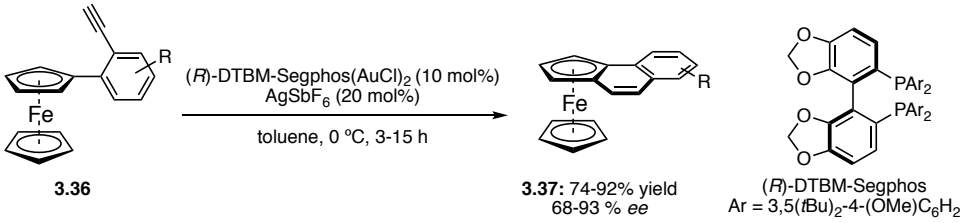
An interesting application of this methodology was reported by Guiry with the synthesis of the diol ligands **3.32a** and **3.32b** for the asymmetric catalysis of hetero Diels-Alder reaction (Scheme 3.6). Derived from the same enantiomer of the planar chiral keto-ferrocene **3.31**, the ligand **3.32a** yields **(*R*)-3.35**, while **3.32b** furnishes **(*S*)-3.35**. The ketone **3.31** is synthesized by C–H arylation followed by the addition of the corresponding organometallic reagent providing **3.32a** and **3.32b**.

C.; Müller-Bunz, H.; Guiry, P. J. *Angew. Chem.* **2016**, *128*, 11281–11285. (g) Wang, S. B.; Zheng, J.; You, S. L. *Organometallics* **2016**, *35*, 1420–1425. (h) Xu, B. B.; Ye, J.; Yuan, Y.; Duan, W. L. *ACS Catal.* **2018**, *8*, 11735–11740.



Scheme 3.6. Ferrocene-based ligands for asymmetric catalysis of hetero Diels-Alder reactions.

Ferrocene reacts 3.10^6 time faster than benzene, reacting readily as nucleophile toward activated alkynes. In 2016 Urbano reported the asymmetric synthesis of the tricyclic ferrocene **3.37** by cycloisomerization of 2-alkynearyl ferrocene **3.36** catalyzed by the digold(I) complex of the axially chiral bisphosphine ligand DTBM-Segphos (Scheme 3.7).[173] This transformation was based on the work reported by Fürstner on the synthesis of phenantrenes by intramolecular hydroarylation of 2-alkynyl biphenyls.[196]

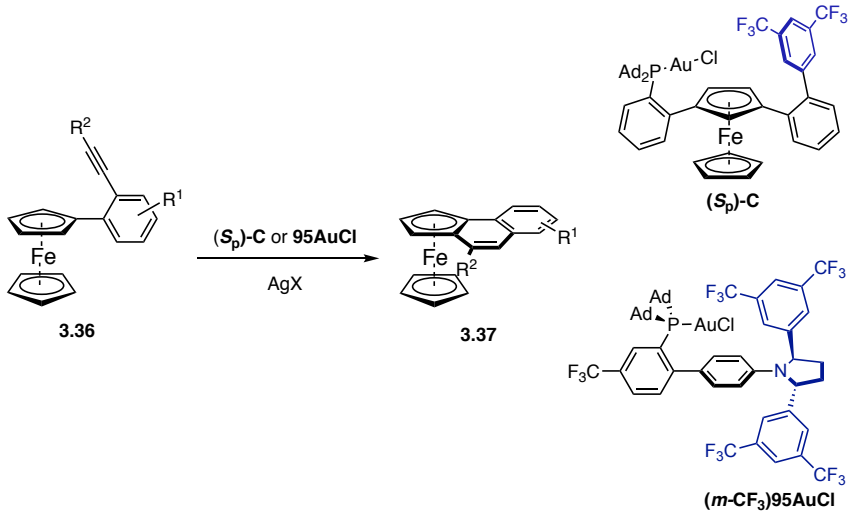


Scheme 3.7. Gold(I)-catalyzed synthesis of planar chiral ferrocenes.

196 Mamane, V.; Hannen, P.; Fürstner, A. *Chem. Eur. J.* **2004**, *10*, 4556–4575.

Objective

We envisioned that the complexes **(*m*-CF$_3$)95AuCl** or **(*S*$_p$)-C**, newly developed by our group for asymmetric gold(I) catalysis, could offer an additional tool to the previously reported cycloisomerization of the terminal or substituted 2-alkynylaryl ferrocenes. Therefore, we decided to test the possible application of these gold(I) complexes in the enantioselective synthesis of planar chiral ferrocenes **3.37** by cycloisomerization reaction of **3.36** (Scheme 3.8). Additionally, we aimed at enlarging the scope of gold(I)-catalyzed cycloisomerization reactions to new 1,*n*-alkyne ferrocenes to access unprecedented scaffolds.

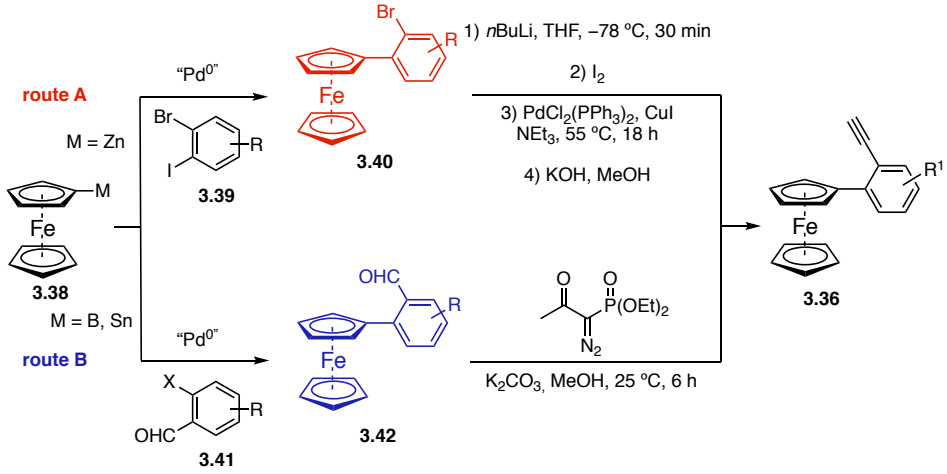


Scheme 3.8. Gold(I)-catalyzed cycloisomerization of 2-alkynylaryl ferrocenes.

Results and discussion

Synthesis of 2-Alkynylaryl Metallocenes

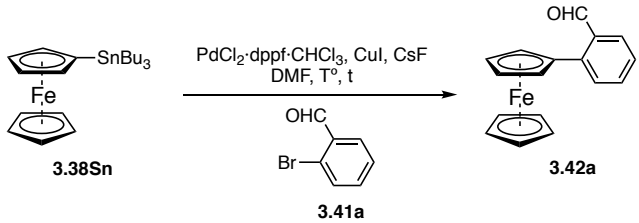
After encouraging preliminary results, we commenced our investigation by the synthesis of a small family of substrates **3.36**. The synthesis begins with a cross-coupling reaction between ferrocene and the aryl moieties. It can be achieved by Negishi cross-coupling (Scheme 3.9, route A) implying preparation of the ferrocenyl-zinc chloride **3.38Zn** that cannot be stored. In addition, the Sonogashira cross-coupling between the aryl bromide **3.40** does not occur. Furthermore, the purification of these compounds proved to be challenging because their polarity are very similar. The overall route is longer than starting from ferrocenyl-boronic acid **3.38B** or tributylstannyl ferrocene **3.38Sn** (Scheme 3.9, route B). Although the palladium-catalyzed Suzuki-Miyaura cross-coupling between the ferrocenyl-boronic acid **3.38B** and 2-bromoarylcarboxaldehyde **3.41** has been reported,[173] we decided to use the readily available tributylstannyl ferrocene in a palladium-catalyzed Stille cross-coupling.



Scheme 3.9. Synthetic pathways toward substrates **3.36**.

Inspired by the work of Kagan[149] and Konopelski,[197] we investigated the palladium/copper-catalyzed Stille cross-coupling using $PdCl_2 \cdot dppf \cdot CHCl_3$ as palladium precatalyst and CuI as copper source in presence of CsF.[198] Gratifyingly, this method provided the desired product **3.41a** in good yield (Table 3.1 entry 1). Optimization of the reaction conditions showed that the catalyst loading could be decreased to 0.1 mol % without noticeable impact on the reaction (Table 3.1 entries 2 and 6). Similarly, the amount of CuI could be decreased to 1 mol % (Table 3.1, entry 5). In the absence of copper(I) or palladium no product was observed (Table 3.1 entries 3 and 4). The aryl bromide remains unreacted when the reaction was carried below 90 ºC (Table 3.1, entry 5).

Table 3.1. Optimization of Stille cross-coupling reaction[a].



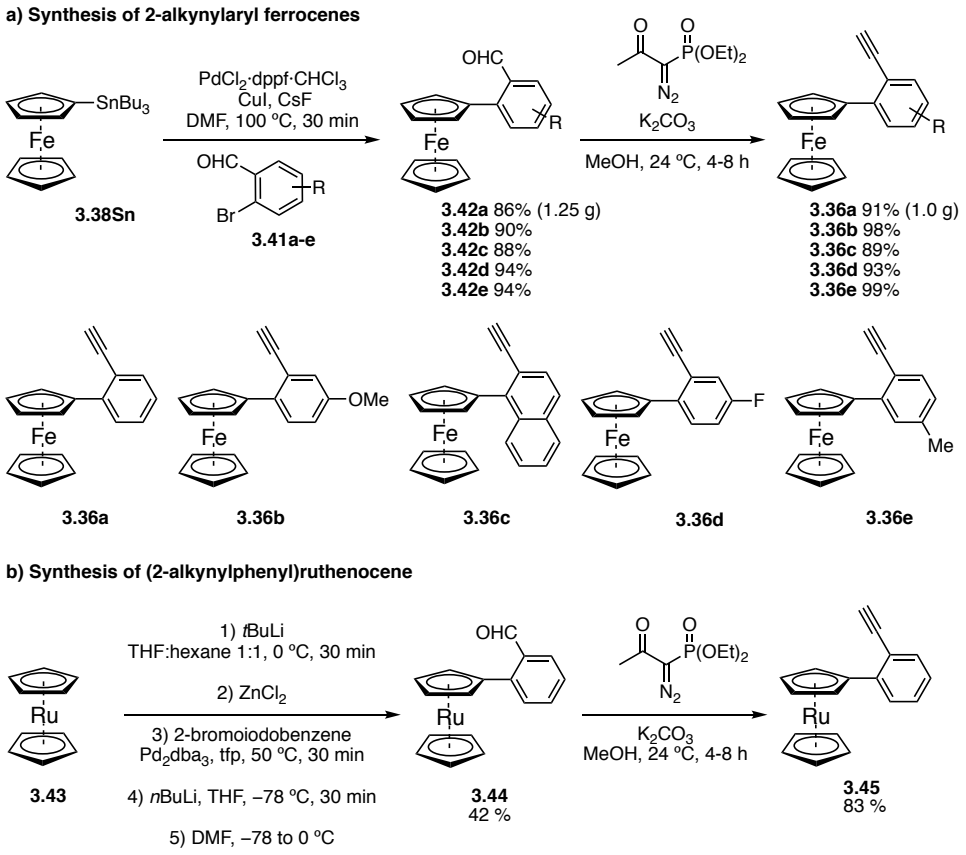
entry	Pd mol % (Pd/Cu)	T (ºC)	t (min)	yield (%)
1	5 mol % (1/1)	100	10	96
2	1 mol % (1/1)	100	30	95
3	1 mol % (1/0)	100	30	0
4	1 mol % (0/1)	100	30	0
5	1 mol % (1/1)	85	30	0
6	0.1 mol % (1/10)	100	30	97

[a]0.1mmol scale

197 Zuckerman, N. B.; Kang, X.; Chen, S.; Konopelski, J. P. *Tetrahedron Lett.* **2013**, *54*, 1482–1485.

198 (a) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905–5911. (b) Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748–2749. (c) Mee, S. P. H.; Lee, V.; Baldwin, J. E. *Angew. Chem. Int. Ed.* **2004**, *43*, 1132–1136. (d) Lee, V. *Org. Biomol. Chem.* **2019**, *17*, 9095–9123.

With these conditions in hand, we synthesized arylcarboxaldehydes **3.42a-e**. Upon treatment with Bestman-Ohira reagent, aldehydes **3.42a-e** undergo Seyferth-Gilbert rearrangements to deliver the desired alkynes products **3.36a-e** in excellent yields (Scheme 3.10).[173] The 2-alkynearyl ruthenocene **3.43** was also synthesized.



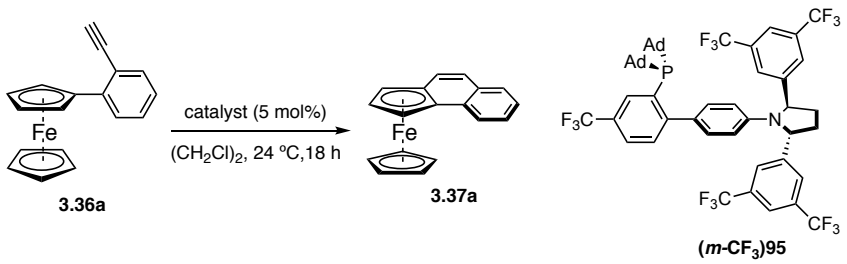
Scheme 3.10. Synthesis of the 2-alkynearyl metallocenes.

Enantioselective Cyclization of 2-Alkynylaryl Metallocenes

We investigated conditions for the cycloisomerization reaction using **3.36a** as model substrate. Catalyst **(S_p)-C** furnished the desired product **3.37a** in good yield but only 59:41 *er* (Table 3.2, entry 1), whereas **(*m*-CF_3)95AuNTf_2** afforded

3.37a in 90:10 *er* but only 12% yield (Table 3.2, entry 2). With this encouraging result we aimed to optimize reaction conditions using **(*m*-CF$_3$)95AuCl**. Addition of silver salts led to the preferential oxidation of the ferrocene substrate **3.36a** rather than chloride abstraction of the gold(I) complex. Thus, premixing of the silver salt with the precatalyst followed by a filtration to remove the Ag(I) salts prior to the addition of the solution on the substrate was required to achieve chloride abstraction. On the course of the reaction, we noted in several cases the formation of a precipitate after what the reaction stopped. While undergoing the screening of chloride scavengers we identified that this phenomenon was minimized by the use of $AgPF_6$. With this silver(I) salt, higher yields were obtained and the reaction proceeded to full conversion (Table 3.2, entry 4).

Table 3.2. Cycloisomerization, counter anion screening[a]



3.36a **3.37a** **(*m*-CF$_3$)95**

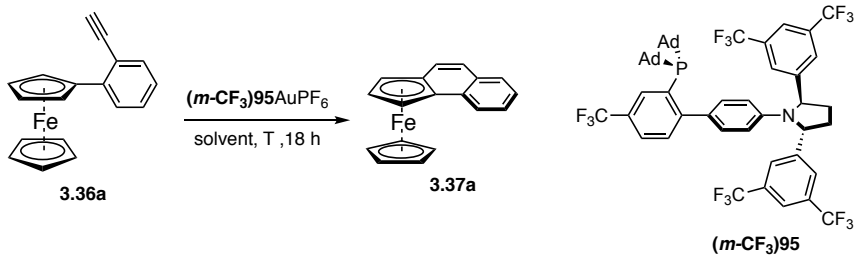
entry	catalyst	yield (%)	*er*[b]
1	**(*S*$_p$)-C**/$AgBF_4$	94	59:41
2	**(*m*-CF$_3$)95AuNTf$_2$**	12	90:10
3	**(*m*-CF$_3$)95AuCl**/$AgBF_4$	67	89:11
4	**(*m*-CF$_3$)95AuCl**/$AgPF_6$	91	87:13
5	**(*m*-CF$_3$)95AuCl**/$AgSbF_6$	54	88:12
6	**(*m*-CF$_3$)95AuCl**/$AgNTf_2$	50	88:12

[a]0.06mmol scale. [b]0.06mmol scale. [b]Determined by HPLC on chiral stationary phase.

The enantioinduction slightly increased by decreasing the temperature to –10 ºC but no formation of the product was observed at –20 ºC (Table 3.3, entries 6 and 7). We carried out a screening of solvents and noticed a strong influence on

the outcome of the reaction. The use of CH_2Cl_2 prevents the apparition of the previously observed solid and allowed the reaction to proceed with good reproducibility. Under these conditions, the desired product was obtained in high yield with good enantioselectivity (Table 3.3, entry 8). In addition, the enantioselectivity of the reaction is strongly dependent of the employed solvent. Indeed, performing the reaction in 1,2-dichloroethane with the cationic gold(I) complex formed from **(*m*-CF$_3$)95AuCl**/$AgPF_6$ afforded product **(*S*)-3.37a** in 90:10 *er* (Table 3.3, entry 8) but in mesitylene the formation of the opposite enantiomer was favored delivering **(*R*)-3.37a** as major product (Table 3.3, entry 1).

Table 3.3. Cycloisomerization, solvent-temperature screening[a].

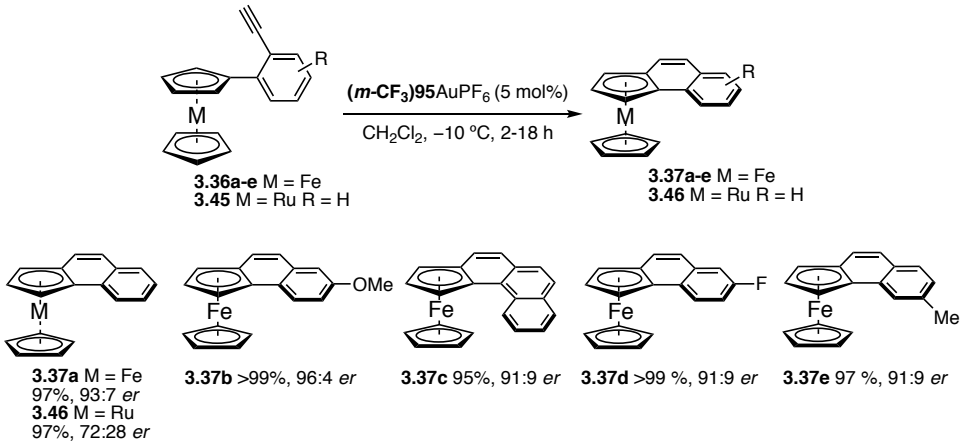


entry	solvent	T (ºC)	yield (%)	*er*[b]
1	mesitylene	0	12	28:72
2	anisole	0	15	42:58
3	toluene	0	55	34:66
4	$PhCF_3$	0	34	68:32
5	PhCl	0	68	48:52
6	$(CH_2Cl)_2$	0	61	90:10
7	$(CH_2Cl)_2$	–10	50	92:8
8	CH_2Cl_2	–10	95	91:9
9	CH_2Cl_2	–25	-	-

[a]0.06mmol scale. [b]0.06mmol scale. [b]Determined by HPLC on chiral stationary phase

With those conditions in hand, we synthesized a small series of planar chiral ferrocenes (Scheme 3.11) in good yields and enantioselectivity. Additionally we applied those conditions to the cyclization of 2-alkynylaryl ruthenocene,

desired product **3.46** was obtained in high yield but low enantioselectivity (72:28 *er*). Although no substantial improvement of the enantioselectivity was noted compared to the previous report,[173] this is an interesting new application of complex **(*m*-CF_3)95AuCl** as well as decreasing the catalyst loading of gold(I) complex to 5 mol %.



Scheme 3.11. Scope of gold(I)-catalyzed cycloisomerization of 2-alkynylaryl metallocene.

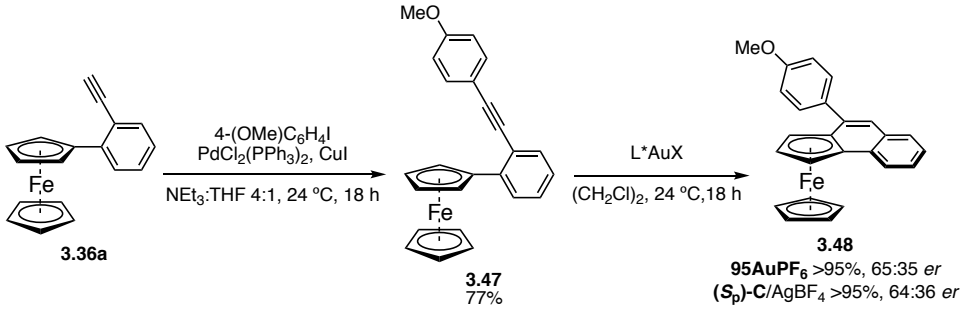
The absolute configuration of **3.37b** was determined by X-ray diffraction and those of **3.37a**, **3.37a-e** by correlation with reported optical rotations. The absolute configuration of **3.46** was determined by comparison with its ferrocene analogue.

Unsuccessful Transformations

We also attempted the cyclization of non-terminal alkynes. Zhang reported the non-enantioselective synthesis of the naphthyl-fused ferrocene **3.48** by gold(I)-catalyzed cycloisomerization of **3.47** (Scheme 3.12).[199] The substrate **3.47** was

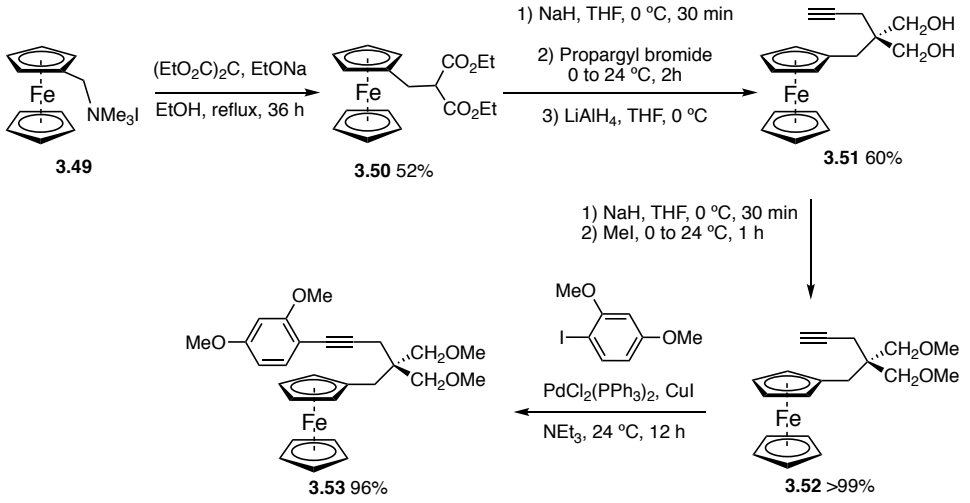
199 Zhang, P. C.; Wang, Y.; Qian, D.; Li, W.; Zhang, J. *Chinese J. Chem.* **2017**, *35*, 849–852.

synthesized by palladium-catalyzed Sonogashira cross-coupling between the alkyne **3.36** and *p*-iodoanisole. However, complexes **(*m*-CF$_3$)95AuCl** and **(*S*$_p$)-C** yielded the desired product **3.48** in only 65:35 *er* and 64:36 *er*, respectively.



Scheme 3.12. Synthesis and cycloisomerization of substituted 2-alkynylaryl ferrocene.

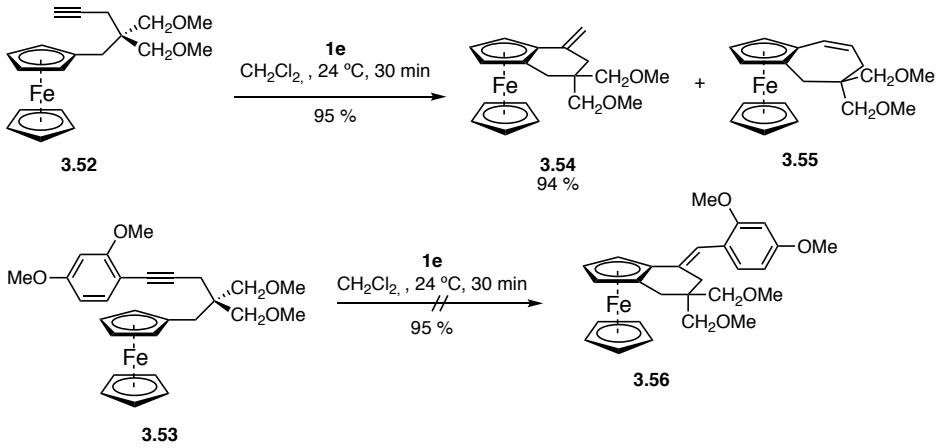
We then proceeded to synthesize 1,5-alkynyl ferrocenes **3.52** and **3.53**, following the synthetic pathway described in Scheme 3.13.



Scheme 3.13. Synthesis of 1,5-alkynyl ferrocene.

In presence of the cationic complex **1e** at 24 ºC in 1,2-dichloroethane, substrate **3.52** gave a mixture of two inseparable products detected by GC-MS

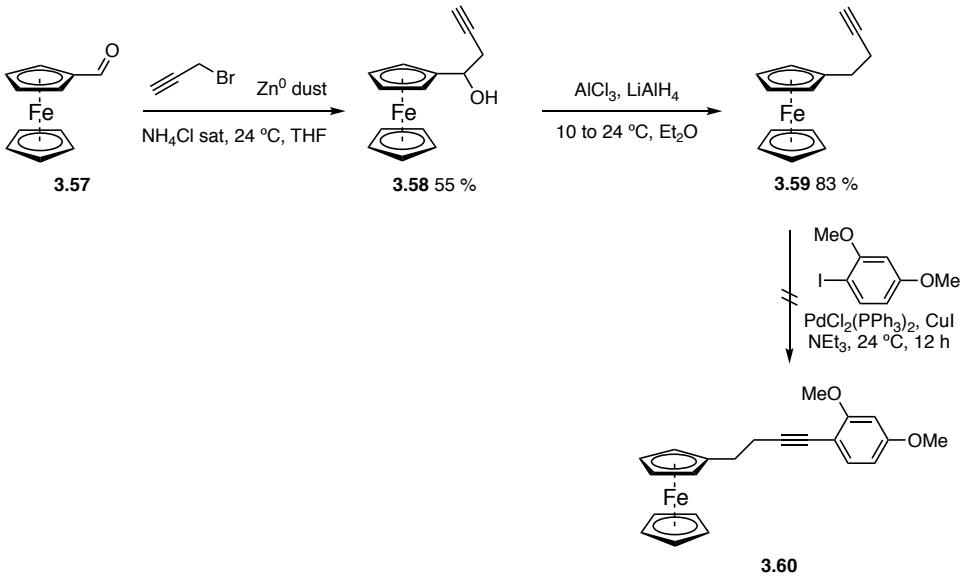
assigned as the regioisomers **3.54** and **3.55** in a 1:2 ratio, resulting respectively from 6-*exo* and 7-e*ndo*-cyclization (Scheme 3.14). Carrying out the reaction in CH_2Cl_2 gave **3.54** in approximately 94% yield along with an unknow product. Unfortunately, substrate **3.53** was unchanged in presence of cationic gold(I) complex **1e** even after 4 d at 80 ºC.



Scheme 3.14. Gold(I)-catalyzed cycloisomerization of 1,5-alkynyl ferrocenes.

In addition, we attempted the synthesis of the 1,4-alkyne ferrocene **3.60** for asymmetric gold(I)-catalyzed cycloisomerization reaction (Scheme 3.15). Following the literature,[200] ferrocene carboxaldehyde **3.57** underwent a Barbier-type reaction with propargyl bromide delivering alcohol **3.58**. Deoxygenation of intermediate **3.58** provided alkyne ferrocene **3.59**. Under the conditions required for the Sonogashira cross-coupling step from **3.59** to **3.60** only decomposition of the starting material was observed and product **3.60** was not detected.

200 Guk, D. A.; Krasnovskaya, O. O.; Dashkova, N. S.; Skvortsov, D. A.; Rubtsova, M. P.; Dyadchenko, V. P.; Yudina, E. S.; Kosarev, M. A.; Soldatov, A. V.; Shapovalov, V. V.; et al. *Dalt. Trans.* **2018**, *47*, 17357–17366.

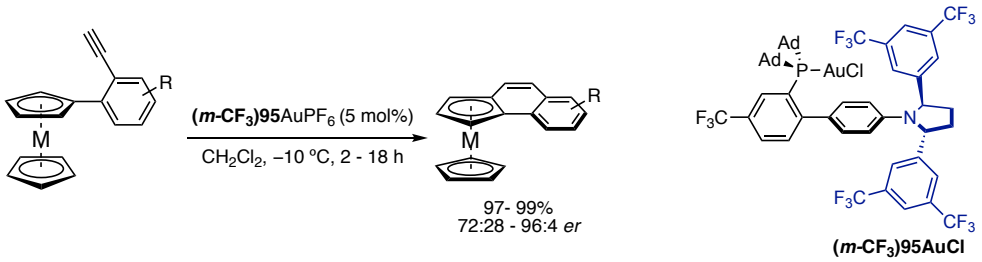


3.57 **3.58** 55 % **3.59** 83 % **3.60**

Scheme 3.15. Synthesis of 1,4-alkynyl ferrocene.

Conclusion

We developed a catalytic system suitable for the enantioselective synthesis of 1,2-disubstitued metallocenes in excellent yields and moderate to high enantioselectivities by cyclization of 2-alkynylaryl metallocenes using gold complex **(*m*-CF$_3$)95AuCl** (Scheme 3.16).



Scheme 3.16. Enantioselective synthesis 1,2-disubstitued metallocenes.

Experimental section

General information

General information are provided in the Experimental Section of **Chapter 1**.

Synthetic Procedures and Characterizations of Compounds

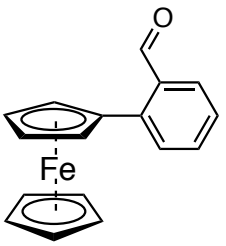
Synthesis of 2-Formylaryl Metallocenes

General procedure J: Stille coupling

A flask was charged with ferrocenyl tributylstannane (1 equiv), CsF (2 equiv), $PdCl_2 \cdot dppf \cdot CH_2Cl_2$ (0.2 mol %), the corresponding aryl halide (1.1 equiv) and DMF (0.33 M, 1 volume). The mixture was stirred for 5 min at 24 ºC. CuI (1 mol %) was added and the atmosphere was evacuated and backfilled with Argon (2x). The mixture was stirred for 30 min in an oil bath preheated to 100 ºC. The reaction was monitored by TLC analysis.

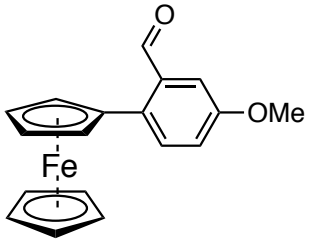
After completion of the reaction the crude mixture was cooled down to room temperature, diluted with Et_2O (4 volumes) and water (10 volumes), and filtered over a pad of celite. Phases were separated and the aqueous layer was extracted with Et_2O (2x). The reunited organic layer was washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography over silica gel using the indicated eluent.

(2-Formylphenyl)ferrocene 3.42a



The compound was synthesized according to the general **J** procedure using ferrocenyl tributylstannane (2.38g, 5.00 mmol), 2-bromo-benzaldehyde (925 mg), CsF (1.5 g), $PdCl_2 \cdot dppf \cdot CH_2Cl_2$ (30 mg) and CuI (10 mg) in DMF (15 mL).
Purification by flash column chromatography over silica gel (eluent pentane:Et_2O 97:3) afforded the title compound (1.25 g, 4.31 mmol, 86%) as a red oil which crystallized upon storage in the fridge. The obtained characterization data were in agreement with those reported in literature.[173]
^{1}H NMR (500 MHz, $CDCl_3$) δ 10.42 (s, 1H), 7.87 – 7.79 (m, 2H), 7.54 (td, *J* = 7.5, 1.5 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 4.56 (s, 2H), 4.44 (s, 2H), 4.18 (s, 5H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 192.76, 143.21, 134.31, 133.10, 131.77, 127.46, 126.56, 83.69, 71.18, 70.08, 69.41.

(2-Formyl-4-methoxyphenyl)ferrocene 3.42b

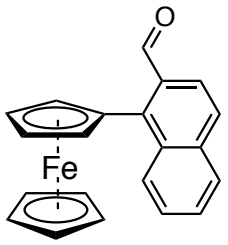


The compound was synthesized according to the general procedure **J** using ferrocenyl tributylstannane (475 mg, 1.00 mmol), 2-bromo-5-methoxybenzaldehyde (215 mg), CsF (0.30 g), $PdCl_2 \cdot dppf \cdot CH_2Cl_2$ (2 mg) and CuI (2 mg) in DMF (3.0 mL).

Purification by flash column chromatography over silica gel (eluent pentane: Et_2O 95:5) afforded the title compound (289 mg, 0.90 mmol, 90%) as a red oil which crystallized upon standing. The obtained characterization data were in agreement with those reported in literature.[173]

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.38 (s, 1H), 7.78 (d, *J* = 8.6 Hz, 1H), 7.34 (d, *J* = 2.9 Hz, 1H), 7.13 (dd, *J* = 8.6, 2.9 Hz, 1H), 4.47 (t, *J* = 1.8 Hz, 2H), 4.37 (t, *J* = 1.9 Hz, 2H), 4.14 (s, 5H), 3.87 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 192.44, 158.29, 135.92, 134.92, 133.26, 121.50, 109.26, 83.82, 70.93, 69.93, 69.11, 55.69.

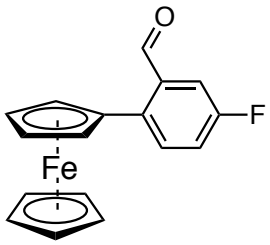
(2-Formylnaphtyl)ferrocene 3.42c



The compound was synthesized according to the general procedure **J** using ferrocenyl tributylstannane (475 mg, 1.00 mmol), 1-bromo-2-naphthaldehyde (235 mg), CsF (0.30 g), $PdCl_2 \cdot dppf \cdot CH_2Cl_2$ (2 mg) and CuI (2 mg) in DMF (3.0 mL).
Purification by flash column chromatography over silica gel (eluent pentane: Et_2O 95:5) afforded the title compound (300 mg, 0.88 mmol, 88%) as a red a red oil which crystallized upon standing. The obtained characterization data were in agreement with those reported in literature.[173]

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.47 (s, 1H), 9.58 – 9.51 (m, 1H), 7.95 – 7.86 (m, 2H), 7.83 (d, *J* = 8.6 Hz, 1H), 7.70 – 7.57 (m, 2H), 4.66 (t, *J* = 1.9 Hz, 2H), 4.57 (t, *J* = 1.9 Hz, 2H), 4.20 (s, 5H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 193.69, 142.00, 136.17, 133.78, 132.27, 128.70, 128.55, 128.32, 127.80, 125.64, 123.34, 81.37, 73.64, 70.15, 69.10.

(2-Formyl-4-fluorophenyl)ferrocene 3.42d

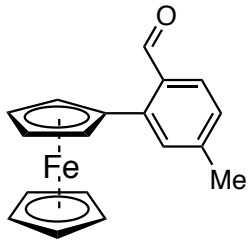


The compound was synthesized according to the general procedure **J** using ferrocenyl tributylstannane (475 mg, 1.00 mmol), 2-bromo-5-fluorobenzaldehyde (203 mg), CsF (0.30 g), $PdCl_2 \cdot dppf \cdot CH_2Cl_2$ (2 mg) and CuI (2 mg) in DMF (3.0 mL).

Purification by flash column chromatography over silica gel (eluent pentane: Et_2O 98:2) afforded the title compound (290 mg, 0.94 mmol, 94%) as a red oil which crystallized upon standing. The obtained characterization data were in agreement with those reported in literature.[173]

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.35 (d, *J* = 3.3 Hz, 1H), 7.85 (dd, *J* = 8.6, 5.2 Hz, 1H), 7.52 (dd, *J* = 9.0, 2.9 Hz, 1H), 7.25 (td, *J* = 7.8, 2.9 Hz, 1H), 4.49 (t, *J* = 1.8 Hz, 2H), 4.43 – 4.38 (m, 2H), 4.15 (s, 5H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 191.43 (d, *J* = 1.9 Hz), 161.39 (d, *J* = 248.3 Hz), 139.24 (d, *J* = 3.1 Hz), 135.59 (d, *J* = 6.1 Hz), 133.86 (d, *J* = 7.2 Hz), 120.58 (d, *J* = 22.3 Hz), 113.26 (d, *J* = 22.1 Hz), 83.02, 71.08, 70.03, 69.44. ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.63.

(2-Formyl-4-methyphenyl)ferrocene 3.42e



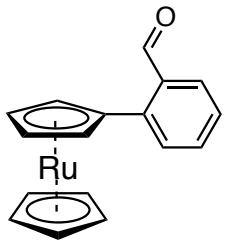
The compound was synthesized according to the general procedure **J** using Ferrocenyl tributylstannane (475 mg, 1.00 mmol), 2-bromo-4-methylbenzaldehyde

(199 mg), CsF (0.30 g), $PdCl_2 \cdot dppf \cdot CH_2Cl_2$ (2 mg) and CuI (2 mg) in DMF (3.0 mL).

Purification by flash column chromatography over silica gel (eluent pentane: Et_2O 98:2) afforded the title compound (285 mg, 0.94 mmol, 94%) as a red oil which crystallized upon standing. The obtained characterization data were in agreement with those reported in literature.[173]

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.43 (d, *J* = 0.9 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.65 – 7.60 (m, 1H), 7.15 (ddt, *J* = 8.1, 1.7, 0.8 Hz, 1H), 4.51 (t, *J* = 1.9 Hz, 2H), 4.40 (t, *J* = 1.9 Hz, 2H), 4.15 (s, 5H), 2.46 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 192.38, 143.84, 143.18, 132.16, 132.05, 127.65 (d, *J* = 1.9 Hz), 83.79, 71.12, 70.02, 69.26, 22.00.

(2-Phenylcarboxaldehyde)ruthenocene 3.44



An oven dried flask wash charged with ruthenocene (463 mg, 2.00 mmol, 1 equiv) suspended in THF/hexane 1:1 (15 mL) and cooled to 0º C in an ice bath. To the suspension was added a solution of *t*BuLi (1.7 M, 1.3 mL, 1.1 equiv) and the mixture was stirred at the same temperature for 30 min before a solution of $ZnCl_2$ (0.20 $g.mL^{-1}$ in 2-MeTHF, 2.0 mL, 2.4 mmol, 1.2 equiv) was added dropwise at 0 ºC. The resulting cloudy mixture was allowed to warm up to 24 ºC and stirred for 30 min. Pd_2dba_3 (36 mg, 2 mol %) and tri-furylphosphine (37 mg, 8 mol %) were stirred in THF (0.4 mL) at 24 ºC for 30 min yielding a bright yellow solution that was added to the previously former organo-zinc compound followed by 1-bromo-2-iodobenzene (280 µL, 622 mg, 2.20 mmol, 1.1 equiv) and brown precipitate

immediately formed. The reaction mixture was stirred for 30 min at 50 ºC. The reaction was monitored by TLC and GC-MS analysis.

The reaction was quenched by addition of 5% aq. citric acid, EtOAc was added and the mixture was stirred for 30 min then filtered over pad of celite. Phases were separated and the aqueous layer was extracted with EtOAc (2x). The reunited organic layer was washed with 5% aq. citric acid, water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was eluted over a pad of silica gel with pentane:CH_2Cl_2 9:1 allowing (2-bromophenyl)ruthenocene () mixed with ruthenocene as light yellow solid used without further purification.

The crude solid (150 mg, 0.39 mmol) was dissolved in THF (1.8 mL), cooled to –78 ºC in a dry ice/acetone bath and a solution *n*BuLi (2.5 M, 155 µL, 0.39 mmol, 1 equiv) was added dropwise. The solution was stirred for 30 min at the same temperature before DMF (60 µL, 0.78 mmol, 2 equiv) was added. The reaction mixture was stirred for 10 min at –78 ºC, allowed to warm up to 24 ºC and stirred for 30 min.

The reaction was quenched by addition of sat. NH_4Cl, EtOAc was added and the mixture was stirred for 30 min. Phases were separated and the aqueous layer was extracted with EtOAc (2x). The reunited organic layer was washed with 5% aq. citric acid, water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by flash column chromatography over silica gel (eluent pentane:CH_2Cl_2 90:10) to afford the title compound (102 mg, 0.31 mmol, 42% over 2 steps) as a pale-yellow solid.

M.p. = 92 – 94 ºC ($CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.60 (d, *J* = 0.8 Hz, 1H), 7.83 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.59 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.44 (ddd, *J* = 7.8, 7.2, 1.5 Hz, 1H), 7.36 – 7.28 (m, 1H), 4.87 (t, *J* = 1.9 Hz, 2H), 4.72 (t, *J* = 1.9 Hz, 2H), 4.57 (s, 5H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 192.8, 141.8, 134.0, 133.1, 133.0, 127.2, 127.0, 88.7, 73.9, 72.1, 71.3. **HRMS** (ESI+) calculated for $[C_{17}H_{14}NaORu]^+$ 358.9985 m/z; found $[M + H]^+$: 358.9972.

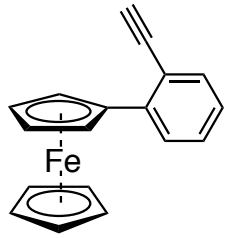
Synthesis of 2-Alkynylaryl Metallocenes

General procedure K: Seyferth-Gilbert homologation

To the corresponding aldehyde (1 equiv) was dissolved in THF (0.16 M, 1 volume) at 24 ºC then MeOH (1 volume) was added followed by powdered K_2CO_3 (1.8 equiv) with vigorous stirring and the reaction mixture was cooled to 0 ºC in an ice bath. Bestman-Ohira reagent (1.2 equiv) was added to the suspension and the mixture was stirred 10 min at 0 ºC then allowed to warm up to 24 ºC and stirred for 4 h. The reaction was monitored by TLC analysis. If starting material remains, K_2CO_3 (1 equiv) and Bestman-Ohira reagent (0.6 equiv) were added and the reaction mixture was stirred for an additional 2 h at 24 ºC.

After completion, the reaction mixture was filtered and concentrated under reduced pressure. The residue was redissolved in Et_2O and water and phases were separated. The organic layer was washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography over silica gel using the indicated eluent.

(2-Ethynylphenyl)ferrocene 3.36a

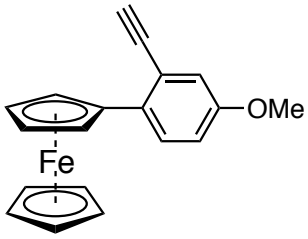


The compound was synthesized according to the general procedure **K** using aldehyde **3.42a** (192 mg, 0.60 mmol), K_2CO_3 (149 mg) and Bestman-Ohira reagent (108 µL, 138 mg) in THF (3.7 mL) MeOH (3.7 mL).

Purification by flash column chromatography over silica gel (eluent pentane: Et_2O 99:1) afforded the title compound (186 mg, 0.059 mmol, 98%) as a red oil which crystallized upon standing. The obtained characterization data were in agreement with those reported in literature.[173]

M.p. = <50 ºC (CH_2Cl_2) **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.61 (ddd, *J* = 8.0, 1.3, 0.6 Hz, 1H), 7.49 (ddd, *J* = 7.7, 1.5, 0.5 Hz, 1H), 7.29 (ddd, *J* = 8.0, 7.3, 1.5 Hz, 1H), 7.16 (td, *J* = 7.5, 1.3 Hz, 1H), 4.98 – 4.94 (m, 2H), 4.34 (p, *J* = 2.0 Hz, 2H), 3.32 (s, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 141.4, 134.6, 129.0, 128.6, 125.6, 119.5, 84.5, 81.2, 69.8, 69.1, 68.7.

(2-Ethynyl-4-mehtoxyphenyl)ferrocene 3.36b

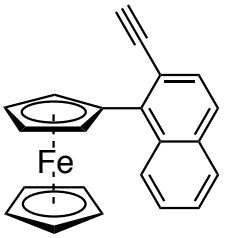


The compound was synthesized according to the general procedure **K** using using aldehyde **3.42b** (192 mg, 0.60 mmol), K_2CO_3 (149 mg) and Bestman-Ohira reagent (108 µL, 138 mg) in THF (3.7 mL) and MeOH (3.7 mL).

Purification by flash column chromatography over silica gel (eluent pentane: Et_2O 99:1) afforded the title compound (186 mg, 0.059 mmol, 98%) as a red oil which crystallized upon standing. The obtained characterization data were in agreement with those reported in literature.[173]

M.p. = 80 – 81 ºC (CH_2Cl_2). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.52 (dd, *J* = 8.7, 0.4 Hz, 1H), 7.00 (d, *J* = 2.8 Hz, 1H), 6.88 (dd, *J* = 8.7, 2.8 Hz, 1H), 4.87 (p, *J* = 2.0 Hz, 2H), 4.32 – 4.26 (m, 2H), 4.10 (s, 5H), 3.82 (s, 3H), 3.30 (s, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 157.3, 133.9, 130.4, 120.3, 118.4, 116.1, 84.8, 84.3, 81.1, 69.7, 68.8, 68.4, 55.5.

(2-Ethynylnaphtyl)ferrocene 3.36c

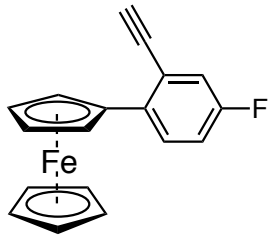


The compound was synthesized according to the general procedure **K** using aldehyde **3.42c** (204 mg, 0.60 mmol), K_2CO_3 (149 mg) and Bestman-Ohira reagent (108 µL, 138 mg) in THF (3.7 mL) and MeOH (3.7 mL).

Purification by flash column chromatography over silica gel (eluent pentane: Et_2O 95:5) afforded the title compound (179 mg, 0.053 mmol, 89%) as a red gum. The obtained characterization data were in agreement with those reported in literature.[173]

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.47 – 9.41 (m, 1H), 7.85 – 7.79 (m, 1H), 7.68 (dt, *J* = 8.4, 0.7 Hz, 1H), 7.57 (ddd, *J* = 8.6, 6.7, 1.5 Hz, 1H), 7.53 (d, *J* = 8.5 Hz, 1H), 7.51 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1H), 4.96 (p, *J* = 2.1 Hz, 2H), 4.48 (p, *J* = 2.0 Hz, 2H), 4.21 (s, 5H), 3.33 (s, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 138.9, 133.9, 131.8, 130.9, 128.4, 127.7, 126.9, 126.6, 125.4, 119.7, 85.9, 83.4, 82.2, 72.3, 70.0, 68.0.

(2-Ethynyl-4-fluorophenyl)ferrocene 3.36d

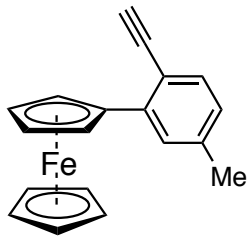


The compound was synthesized according to the general procedure **K** using aldehyde **3.42d** (185 mg, 0.60 mmol), K_2CO_3 (149 mg) and Bestman-Ohira reagent (108 µL, 138 mg) in THF (3.7 mL) and MeOH (3.7 mL).

Purification by flash column chromatography over silica gel (eluent pentane: Et_2O 99:1) afforded the title compound (170 mg, 0.056 mmol, 93%) as a red oil which crystallized upon standing. The obtained characterization data were in agreement with those reported in literature.[173]

M.p. = 73 – 75 ºC (CH_2Cl_2) **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.47 – 9.41 (m, 1H), 7.85 – 7.79 (m, 1H), 7.68 (dt, *J* = 8.4, 0.7 Hz, 1H), 7.57 (ddd, *J* = 8.6, 6.7, 1.5 Hz, 1H), 7.56 – 7.47 (m, 2H), 4.96 (p, *J* = 2.1 Hz, 2H), 4.48 (p, *J* = 2.0 Hz, 2H), 4.21 (s, 5H), 3.33 (s, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.4 (d, *J* = 245.9 Hz), 137.8 (d, *J* = 3.1 Hz), 130.8 (d, *J* = 8.2 Hz), 123.0 – 118.6 (m), 116.4 (d, *J* = 21.2 Hz), 84.0, 83.2 (d, *J* = 2.8 Hz), 82.1, 69.9, 69.1, 68.8. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -117.39.

(2-Ethynyl-4-methylphenyl)ferrocene 3.36e

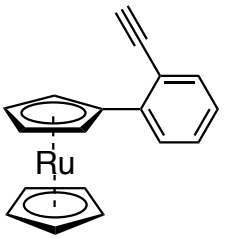


The compound was synthesized according to the general procedure **K** using aldehyde **3.42e** (183 mg, 0.60 mmol), K_2CO_3 (149 mg) and Bestman-Ohira reagent (108 µL, 138 mg) in THF (3.7 mL) and MeOH (3.7 mL).

Purification by flash column chromatography over silica gel (eluent pentane: Et_2O 98:2) afforded the title compound (179 mg, 0.060 mmol, >99%) as a red oil which crystallized upon standing. The obtained characterization data were in agreement with those reported in literature.[173]

M.p. = 109 – 111 ºC ($CHCl_3$). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41 – 7.36 (m, 2H), 7.00 – 6.94 (m, 1H), 4.94 (p, *J* = 2.1 Hz, 2H), 4.32 (p, *J* = 2.0 Hz, 2H), 4.11 (s, 5H), 3.29 (s, 1H), 2.38 (d, *J* = 0.8 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 141.3, 138.7, 134.7, 129.7, 126.8, 116.8, 84.7, 84.7, 80.7, 69.9, 69.0, 68.7, 30.5, 21.7.

(2-Ethynylphenyl)ruthenocene 3.45



The compound was synthesized according to the general procedure **K** using aldehyde **3.44** (80 mg, 0.24 mmol), K_2CO_3 (59 mg) and Bestman-Ohira reagent (43 µL, 138 mg) in THF (1.5 mL) MeOH (1.5 mL).

Purification by flash column chromatography over silica gel (eluent pentane:CH_2Cl_2 90:10) afforded the title compound (66 mg, 0.20 mmol, 83%) as a pale-yellow oil which crystallized upon standing.

M.p. = 121 – 122 ºC ($CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.44 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.21 (td, *J* = 7.6, 1.5 Hz, 1H), 7.12 (td, *J* = 7.5, 1.4 Hz, 1H), 5.23 (p, *J* = 1.9 Hz, 2H), 4.67 (p, *J* = 1.8 Hz, 2H), 4.52 (s, 5H), 3.27 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.7, 134.1, 130.1, 128.5, 126.0, 120.0, 89.7, 84.0, 81.4, 72.1, 71.7, 70.6. **HRMS** (ESI+) calculated for $[C_{18}H_{15}Ru]^+$ 333.0217 m/z; found $[M + H]^+$: 333.0209.

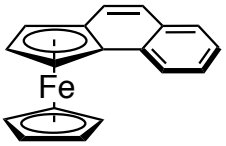
Enantioselective Cyclization of 2-Alkynylaryl Metallocenes

General procedure L: Enantioselective cycloisomerization

To a solution of **(*m*-CF_3)95AuCl** (5 mol %) in dry CH_2Cl_2 (1.0 mL) at 0 ºC under argon atmosphere was added a solution of $AgPF_6$ (0.10 g.mL^{-1} in dry CH_2Cl_2) and the solution was stirred in the dark for 10 min. The solution was transferred with filtration on PTFE filter to a microwave vial precooled at –10 ºC containing the corresponding alkyne under argon atmosphere and the mixture was stirred for the indicated time at –10 ºC. The reaction was monitored by TLC and GC-MS analysis. The reaction was quenched by addition of 3 drops of NEt_3 and concentrated under reduced pressure.

The crude product was purified by flash column chromatography over silica gel using the indicated eluent.

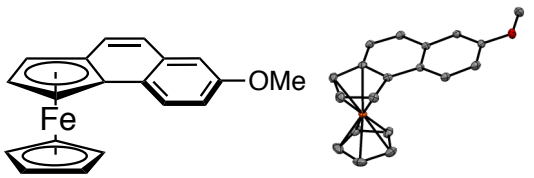
(S_p)-Ferrocene[3]helicene 3.37a



The compound was synthesized using the general procedure **L** using alkyne **3.36a** (29 mg, 0.10 mmol). The reaction was stirred for 4 h. Purification by flash column chromatography over silica gel afforded (pentane) the title compound (28 mg, 97 µmol, 97%) as a red oil in 93:7 *er*. The obtained characterization data were in agreement with those reported in literature.[173]

M.p. = 72 – 74 ºC ($CHCl_3$). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.03 – 7.97 (m, 1H), 7.66 – 7.60 (m, 1H), 7.47 (td, *J* = 7.5, 1.4 Hz, 1H), 7.42 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.39 (dd, *J* = 9.1, 0.9 Hz, 1H), 7.17 (d, *J* = 9.1 Hz, 1H), 5.26 (dd, *J* = 2.3, 1.2 Hz, 1H), 4.82 (dd, *J* = 2.5, 1.1 Hz, 1H), 4.23 (t, *J* = 2.5 Hz, 1H), 3.74 (s, 5H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 135.2, 132.0, 128.7, 127.6, 126.7, 125.3, 123.4, 84.1, 83.1, 69.4 (d, *J* = 13.2 Hz), 64.1, 61.2. **α_D^{589}** = –1765 deg.cm^2.g^{-1} ($CHCl_3$, c 0.05, 302 K). **HPLC** Chiralpak IB (250 × 4.6mm, 5 µm) at 25 ºC, flow 0.8 mL/min, isocratic hexane:IPA 99:1, 280 nm, t_R (minor) 8.0; t_R (major) 8.9.

(S_p)-7-Methoxyferrocene[3]helicene 3.37b

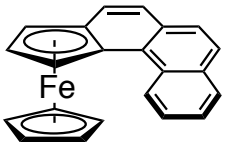


The compound was synthesized using the general procedure **L** using alkyne **3.36b** (32 mg, 0.10 mmol). The reaction was stirred for 2 h. Purification by flash column chromatography over silica gel afforded (pentane:Et_2O 97:3) the title compound

(32 mg, 0.10 mmol, >99%) as a red oil which solidified upon standing in 95.5:4.5 *er*. The obtained characterization data were in agreement with those reported in literature.[173]

M.p. = 143 – 145 ºC ($CHCl_3$). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.4 Hz, 1H), 7.39 (d, *J* = 9.1 Hz, 1H), 7.18 – 7.02 (m, 3H), 5.21 (d, *J* = 2.5 Hz, 1H), 4.79 – 4.75 (m, 1H), 4.18 (t, *J* = 2.6 Hz, 1H), 3.92 (s, 3H), 3.73 (s, 5H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 157.6, 133.3, 128.5, 128.2, 125.1, 124.7, 115.3, 84.0, 83.1, 69.3, 68.9, 63.8, 60.7, 55.5. $\boldsymbol{\alpha_D^{589}}$ = –1458 deg.cm^2.g^{-1} ($CHCl_3$, c 0.05, 302 K). **SFC** Chiralpak IG (100 × 3mm, 3µm) at 35 ºC, flow 1.2 mL/min, isocratic CO_2/MeOH 85:15, BPR pressure 150 bar, 280 nm, t_R (minor) 2.5 ; t_R (major) 3.0.

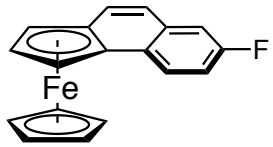
(S_p)-Ferrocene-[4]helicene 3.37c



The compound was synthesized using the general procedure **L** using alkyne **3.36c** (34 mg, 0.10 mmol). The reaction was stirred for 18 h. Purification by flash column chromatography over silica gel afforded (pentane:Et_2O 99:1) the title compound (32 mg, 95 µmol, 95%) as a red oil which solidified upon standing in 91:9 *er*. The obtained characterization data were in agreement with those reported in literature.[173]

M.p. = 105 – 108 ºC ($CHCl_3$) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.17 (d, *J* = 8.5 Hz, 1H), 8.01 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.78 (ddd, *J* = 8.5, 6.8, 1.5 Hz, 1H), 7.71 (d, *J* = 8.5 Hz, 1H), 7.66 – 7.60 (m, 2H), 7.37 (d, *J* = 8.9 Hz, 1H), 5.79 (dd, *J* = 2.6, 1.3 Hz, 1H), 5.03 (dd, *J* = 2.6, 1.1 Hz, 1H), 4.34 (t, *J* = 2.6 Hz, 1H), 3.76 (s, 5H). $\boldsymbol{\alpha_D^{589}}$ = –1580 deg.cm^2.g^{-1} ($CHCl_3$, c 0.05, 302 K). **SFC** Chiralpak IC (100 × 3mm, 3µm) at 35 ºC, flow 1.2 mL/min, isocratic CO_2/IPA 70:30, BPR pressure 150 bar, 280 nm, t_R (major) 2.5; t_R (minor) 2.8.

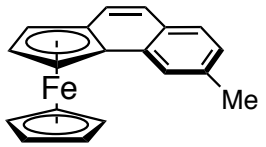
(S_p)-7-Fluoroferrocene-[3]-helicene 3.37d



The compound was synthesized using the general procedure **L** using alkyne **3.36d** (30 mg, 0.10 mmol). The reaction was stirred for 18 h. Purification by flash column chromatography over silica gel afforded (pentane:Et_2O 99:1) the title compound (30 mg, 0.10 μmol, >99%) as a red oil which solidified upon standing in 91:9 *er*. The obtained characterization data were in agreement with those reported in literature.[173]

M.p. = 61 – 62 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 8.6, 5.5 Hz, 1H), 7.43 (d, *J* = 9.1 Hz, 1H), 7.30 (dd, *J* = 9.8, 2.7 Hz, 1H), 7.20 (td, *J* = 8.6, 2.7 Hz, 1H), 7.10 (d, *J* = 9.1 Hz, 1H), 5.26 – 5.22 (m, 1H), 4.83 – 4.79 (m, 1H), 4.22 (t, *J* = 2.5 Hz, 1H), 3.74 (s, 5H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.9 (d, *J* = 242.9 Hz), 133.5 (d, *J* = 8.2 Hz), 131.2, 129.4, 125.0 (d, *J* = 8.4 Hz), 124.4 (d, *J* = 3.2 Hz), 114.7 (d, *J* = 22.9 Hz), 113.8 (d, *J* = 21.0 Hz), 83.3 (d, *J* = 30.9 Hz), 69.5 (d, *J* = 3.2 Hz), 64.2, 61.2. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -117.34. **α_D^{589}** = –2085 deg.cm^2.g^{-1} ($CHCl_3$, c 0.05, 302 K). **SFC** Chiralpak IA (100 × 3mm, 3μm) at 35 ºC, flow 1.2 mL/min, isocratic CO_2/MeOH 90:10, BPR pressure 150 bar, 280 nm, t_R (minor) 1.8; t_R (major) 2.0.

(S_p)-8-Methylferrocene-[3]-helicene 3.37e

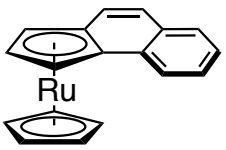


The compound was synthesized using the general procedure **L** using alkyne **3.36e** (30 mg, 0.10 mmol). The reaction was stirred for 18 h. Purification by flash column chromatography over silica gel afforded (pentane) the title compound (29 mg, 97

μmol, 97%) as a red oil which solidified upon standing in 91:9 *er*. The obtained characterization data were in agreement with those reported in literature.[173]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.52 (d, *J* = 7.9 Hz, 1H), 7.30 (d, *J* = 9.1 Hz, 1H), 7.26 – 7.20 (m, 1H), 7.13 (d, *J* = 9.1 Hz, 1H), 5.23 (d, *J* = 2.5 Hz, 1H), 4.79 (dd, *J* = 2.4, 1.1 Hz, 1H), 4.21 (t, *J* = 2.5 Hz, 1H), 3.73 (s, 5H), 2.55 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 136.5, 135.2, 129.7, 128.5, 126.7, 126.4, 125.2, 123.5, 84.3, 83.1, 69.4, 69.2, 64.0, 61.1, 29.9, 22.0. $\boldsymbol{\alpha_D^{589}}$ = –2036 deg.cm^2.g^{-1} ($CHCl_3$, c 0.05, 302 K). **HPLC** Chiralpak IB (250 × 4.6mm, 5 μm) at 25 ºC, flow 0.3 mL/min, isocratic hexane:IPA 97:3, 280 nm, t_R (minor) 14.7; t_R (major) 18.5.

(S_p)-Ruthenocene[3]helicene 3.46

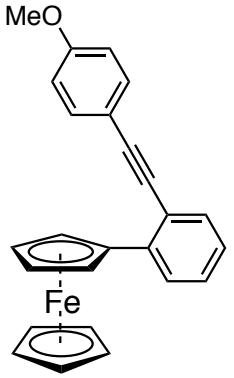


The compound was synthesized using the general procedure **L** using alkyne **3.45** (33 mg, 0.10 mmol). The reaction was stirred for 2 h. Purification by flash column chromatography over silica gel afforded (pentane) the title compound (32 mg, 97 μmol, 97%) as a pale-yellow oil which solidified upon standing in 72:28 *er*.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.89 (m, 1H), 7.58 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.46 – 7.31 (m, 2H), 7.27 (dd, *J* = 9.2, 0.8 Hz, 1H), 7.07 – 7.00 (m, 1H), 5.64 (dt, *J* = 2.4, 0.9 Hz, 1H), 5.16 (dd, *J* = 2.4, 1.0 Hz, 1H), 4.70 (t, *J* = 2.4 Hz, 1H), 4.18 (s, 5H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 134.2, 132.0, 129.2, 127.3, 126.4, 126.0, 125.3, 123.9, 88.8, 88.1, 72.3, 71.6, 68.1, 65.3. **HRMS** (ESI+) calculated for $[C_{18}H_{15}Ru]^+$ 333.0217 m/z; found $[M+H]^+$: 333.0214. $\boldsymbol{\alpha_D^{589}}$ = –759.5 deg.cm^2.g^{-1} ($CHCl_3$, c 0.05, 302 K). **SFC** Chiralpak IA (100 × 3mm, 3μm) at 35 ºC, flow 1.2 mL/min, isocratic CO_2/EtOH 80:20, BPR pressure 150 bar, 280 nm, t_R (minor) 1.5; t_R (major) 1.7.

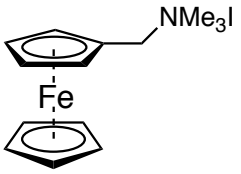
Synthesis of Additional Ferrocene Substrates

1-Ferrocenyl-2-((4-methoxyphenyl)ethynyl)benzene 3.47



A microwave tube was charged with $PdCl_2(PPh_3)_2$ (9.8 mg, 2.0 mol %) and copper(I) iodide (2.6 mg, 2 mol %) and 1-iodo-4-methoxybenzene (180 mg, 1.1 equiv, 0.49 mmol) and **3.36a** (200 mg, 0.70 mmol) then evacuated/backfilled with Argon. NEt_3 (1.6 mL) was added and the solution was stirred at 25 ºC for 18 h. *i*PrOH:H_2O 4:1 (1.2 mL) and cysteine was added (*ca.* equal mass of $PdCl_2(PPh_3)_2$) were added to the reaction mixture and stirred for 30 min then filtered over a pad of Celite®. The pad of Celite® was washed with Et_2O, 5% aq. citric acid (10 mL) was added to the filtrate and phases were separated. The aqueous layer was extracted with Et_2O (2x). The reunited organic layer was washed with NH_4Cl sat. water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography over silica gel (eluant pentane: Et_2O 95:5) afforded the title compound (210 g, 0.43 mmol, 77%) as a red solid. The obtained characterization data were in agreement with those reported in literature.[199]

Trimethylferrocenyl(methyl)ammonium iodide 3.49

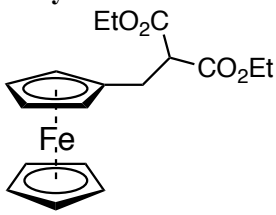


In a flask charged with phosphoric acid (80 %, 1.8 mL) in acetic acid (30 mL) N,N,N',N'-tetramethylmethanediamine (4.0 mL, 1.7 equiv, 32mmol) was added dropwise at 0 ºC. The solution was stirred for 5 min at the same temperature then allowed to warm up to 24 ºC. Ferrocene (3.5 g, 19 mmol) was added to the solution, the flask was evacuated and back-filled with argon (x2) and the suspension was refluxed for 4 h before being cooled to room temperature. The solution was diluted with 50 mL of water and the aqueous phase was extracted with small portions of Et_2O until the organic phase came colorless. The aqueous phase was basified with NaOH aq. 20 %w keeping the solution below 10 ºC with an ice bath. The mixture was extracted with Et_2O (3x100 mL) allowing the dimethylaminoferrocene (4.17 g, 17 mmol, 90%) as a dark red oil used with further purification.

The dimethylaminoferrocene (4.0 g, 1.0 equiv, 16 mmol) was diluted with MeOH (3.3 mL) then MeI (3.3 mL, 3.2 equiv 53 mmol) was added to the solution was refluxed for 10 min then cooled to room temperature. Under vigorous stirring 50 mL of Et_2O were added to the crude mixture causing the precipitation of the product. The suspension was filtered and the solid was washed this Et_2O then dried under reduced pressure yielding the pure trimethylammonium ferrocene iodide (6.2g, 16 mmol, 98%) as a yellow powder. The obtained characterization data were in agreement with those reported in literature.[201]

201 (a) Hauser, C. R.; Lindsay, J. K. *J. Org. Chem.* **1957**, *22*, 355–358. (b) Forgie, J. C.; El Khakani, S.; MacNeil, D. D.; Rochefort, D. *Phys. Chem. Chem. Phys.* **2013**, *15*, 7713–7721.

Ferrocenylmethylmalonic diethylester 3.50

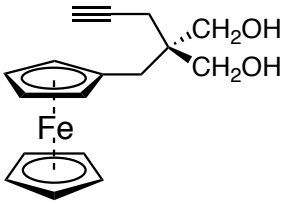


A flask equipped with a condenser under N_2 stream was charged with ethanol (16 mL) at 24 ºC and was added Na^0 (0.41 g. 1.1 equiv, 18 mmol). The mixture was stirred until full consumption of the metal then diethyl malonate (2.85 g, 2.71 mL, 1.1 equiv, 17.8 mmol) in ethanol (8 mL) was added at 24 ºC. After complete addition ferrocenylmethyltrimethylammonium (6.2g, 16 mmol) was added and the mixture was heated to reflux for 36 h. The reaction was monitored by TLC analysis. The crude mixture was diluted with water (200 mL) and Et_2O (20 mL), acidified with HCl aq. To pH 7 and phases were separated. The aqueous layer was extracted with Et_2O (2x), reunited organic layers were washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography over silica gel (eluent cyclohexane:EtOAc 95:5) afforded the title compound (3.3 g, 9.2 mmol, 57%) as a red oil mixed with a small amount of inseparable impurity. The obtained characterization data were in agreement with those reported in literature.[202]

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.16 (qd, *J* = 7.2, 0.8 Hz, 4H), 4.12 (s, 5H), 4.11 – 4.04 (m, 4H), 3.45 (t, *J* = 7.5 Hz, 1H), 2.96 (d, *J* = 7.5 Hz, 2H), 1.24 (t, *J* = 7.1 Hz, 6H).

202 Anne, A.; Blanc, B.; Moiroux, J. *Bioconjug. Chem.* **2001**, *12*, 396–405.

2-Ferrocenyl-2-(prop-2-yn-1-yl)propane-1,3-diol 3.51



In flask under argon charged with (2.8 g, 7.8 mmol) in THF (15 mL) at 0 ºC, NaH (60 % Wt, 38 mg, 1.2 equiv, 9.4 mmol) was added and the mixture was stirred for 30 min at the same temperature then 3-bromoprop-1-yne (0.77 mL, 1.0 g, 1.1 equiv, 8.6 mmol) was added. The mixture was stirred 5 min at the same temperature then allowed to warm up to 24 ºC and stirred for 2 h. The reaction was monitored by TLC analysis.

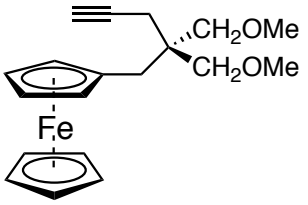
The crude mixture was diluted with citric acid aq. (150 mL) and Et_2O (20 mL) and phases were separated. The aqueous layer was extracted with Et_2O (2x), reunited organic layers were washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was filtered over a plug of silica (eluant cyclohexane:EtOAc 90:10) concentrated under reduced pressure.

The residue was dissolved in THF (16 mL) and the solution was cooled to 0 ºC then $LiAlH_4$ (0.62 g, 2.1 equiv, 16 mmol) was added portion-wise. The mixture was stirred for 15 min at the same tempature then allowed to warm up to 24 ºC and stirred 1 h. The reaction was monitored by TLC analysis.

20 %wt KOH aq. was slowly added to the mixture until no gas evolution was observed. The suspension was stirred for 30 min at room temperature then filtered over a pad of Celite® washed with Et_2O until the filtrate was colorless. The filtrate was diluted with water (200 mL) and phases were separated. The aqueous layer was extracted with Et_2O (2x), reunited organic layers were washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography over silica gel (eluant cyclohexane:EtOAc 90:10) afforded the title compound (1.47 g, 4.7 mmol, 60%) as an orange oil which crystallized upon standing.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23 – 4.06 (m, 9H), 3.64 – 3.53 (m, 4H), 2.45 (s, 2H), 2.15 (p, *J* = 3.5, 2.9 Hz, 4H), 2.08 (t, *J* = 2.6 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 81.4, 71.2, 70.3, 69.1, 68.8, 68.2, 67.4, 43.0, 32.4, 21.6. **HRMS** (ESI+) calculated for $[C_{17}H_{20}NaO_2{}^{54}Fe]^+$ 333.0752 m/z; found $[M + Na]^+$: 333.0754.

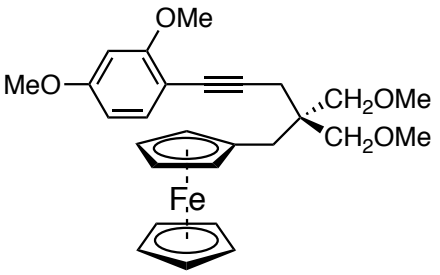
(2,2-Bis(methoxymethyl)pent-4-yn-1-yl)ferrocene 3.52



In flask under argon charged with (1.10 g, 3.52 mmol) in THF (7 mL) at 0 ºC, NaH (60 %wt, 325 mg, 2.3 equiv, 8.1 mmol) was added and the mixture was stirred for 30 min at the same temperature then MeI (0.51 mL, 1.2 g, 2.3 equiv, 8.1 mmol) was added. The mixture was stirred 5 min a the same temperature then allowed to warm up to 24 ºC and stirred for 2 h. The reaction was monitored by TLC analysis. The crude mixture was diluted with citric acid aq. (100 mL) and Et_2O (20 mL) and phases were separated. The aqueous layer was extracted with Et_2O (2x), reunited organic layers were washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography over silica gel (eluant cyclohexane:EtOAc 95:5) afforded the title compound (1.20 g, 3.52 mmol, >99%) as a red oil which crystallized upon storage at 5 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.14 (s, 2H), 4.11 (s, 4H), 4.07 (s, 2H), 3.32 (s, 6H), 3.19 – 3.09 (m, 4H), 2.48 (s, 2H), 2.09 (d, *J* = 2.7 Hz, 2H), 2.01 (t, *J* = 2.7 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 81.6, 73.8, 70.3, 69.0, 67.9, 59.2, 42.6, 32.0, 21.9. **HRMS** (ESI+) calculated for $[C_{19}H_{24}NaO_2{}^{54}Fe]^+$ 361.1065 m/z; found $[M + Na]^+$: 361.1071.

1-(4-Ferrocenyl-5-methoxy-4-(methoxymethyl)pent-1-yn-1-yl)-2,4-dimethoxybenzene 3.53

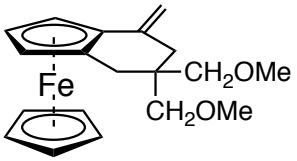


A microwave tube was charged with $PdCl_2(PPh_3)_2$ (1.0 mol %) and copper(I) iodide (2.0 mol %) and 1-iodo-2,4-bis(methoxy)benzene (128 mg, 1.1 equiv, 0.49 mmol) then evacuated/backfilled with Argon. NEt_3 (1.2 mL) were added and the solution was stirred 10 min at room temperature. Alkyne **3.52** (150 mg, 0.44 mmol) was added and the mixture was stirred at 25 ºC for 12 h.

*i*PrOH:H_2O 4:1 (1.2 mL) and cysteine was added (*ca.* equal mass of $PdCl_2(PPh_3)_2$) were added to the reaction mixture and stirred for 30 min then filtered over a pad of Celite®. The pad of Celite® was washed with Et_2O, 5% aq. citric acid (10 mL) was added to the filtrate and phases were separated. The aqueous layer was extracted with Et_2O (2x). The reunited organic layer was washed with NH_4Cl sat. water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography over silica gel (eluant pentane: Et_2O 80:20) afforded the title compound (205 g, 0.43 mmol, 98%) as a red oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.30 (m, 1H), 6.45 (dq, J = 5.1, 2.4 Hz, 2H), 4.23 – 4.19 (m, 2H), 4.10 (s, 5H), 4.08 – 4.03 (m, 2H), 3.89 (s, 3H), 3.82 (s, 3H), 3.35 (s, 6H), 3.26 – 3.18 (m, 4H), 2.56 (s, 2H), 2.30 (s, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.4, 160.6, 134.1, 106.2, 104.7, 98.7, 89.9, 83.6, 78.7, 74.2, 70.5, 68.8, 67.7, 59.3, 55.9, 55.6, 43.4, 32.2, 23.2. **HRMS** (ESI+) calculated for $[C_{27}H_{33}FeO_4]^+$ 477.1723 m/z; found $[M + H]^+$: 477.1729.

1,2-[1-[1,1-Bis(4-hydroxyphenyl)methylidene]-3-3'-[methoxynethyl]tetramethylene]ferrocene 3.54

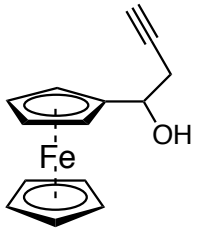


(2,2-bis(methoxymethyl)pent-4-yn-1-yl)ferrocene **3.52** (16 mg, 0.05 mmol) and **1e** (1.8 mg, 5 mol%) were dissolved in CH_2Cl_2 (0.3 mL). The solution was stirred for 1 h at 25 ºC. The reaction was quenched by addition of 1 drop of NEt_3, filtered over neutral alumina and concentrated under reduced pressure. The crude product was dissolved in $CDCl_3$ (*ca* 1 mL) and 1,1,2 trichloroethane (0.200 $mg.mL^{-1}$ in $CDCl_3$, 31.3 µL) was added and the solution was swirled.

94% yield was determined by ^1H NMR using 1,1,2 trichloroethane as internal standard.

^1H NMR (500 MHz, $CDCl_3$) δ 5.08 (t, *J* = 2.0 Hz, 1H), 4.82 (t, *J* = 1.9 Hz, 1H), 4.40 (s, 1H), 4.21 (s, 1H), 4.02 (s, 5H), 3.40 (s, 3H), 3.36 – 3.31 (m, 3H), 3.20 (s, 3H), 3.03 (d, *J* = 1.4 Hz, 2H), 2.73 (t, *J* = 14.8 Hz, 2H), 2.37 (q, *J* = 1.6 Hz, 1H), 2.34 (dd, *J* = 5.5, 1.7 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 141.5, 116.8, 106.4, 78.3, 73.5, 70.7 (bs), 67.7, 60.8, 59.6, 59.4, 40.8, 37.5, 29.0.

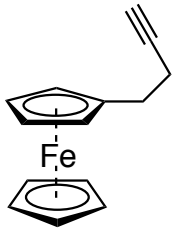
1-Ferrocenyl-3-butin-1-ol 3.58



A flask under argon was charged with ferrocene-carboxaldehyde (0.54 g, 3.52 mmol) and Zn dust (0.59 g, 3.6 equiv, 9.0 mmol) in THF (1.7 mL) at 10 ºC. 3-bromoprop-1-yne (0.57 mL, 0.89 g, 3 equiv, 7.5 mmol) was added then aq. NH_4Cl sat. (1.3 mL) was added dropwise. the mixture was stirred for 6 h. The reaction was monitored by TLC and GC-MS analysis.

The mixture was filtered over a pad of Celite®. The pad of Celite® was washed with Et_2O, 5% aq. citric acid (10 mL) was added to the filtrate and phases were separated. The aqueous layer was extracted with Et_2O (2x). The reunited organic layer was washed with NH_4Cl sat. water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography over silica gel (eluent cyclohexane:EtOAc 80:20) afforded the title compound (350 mg, 1.38 mmol, 55%) as a red oil which crystallized upon standing. The obtained characterization data were in agreement with those reported in literature.[200]

1-Ferrocenyl-3-butyne 3.59



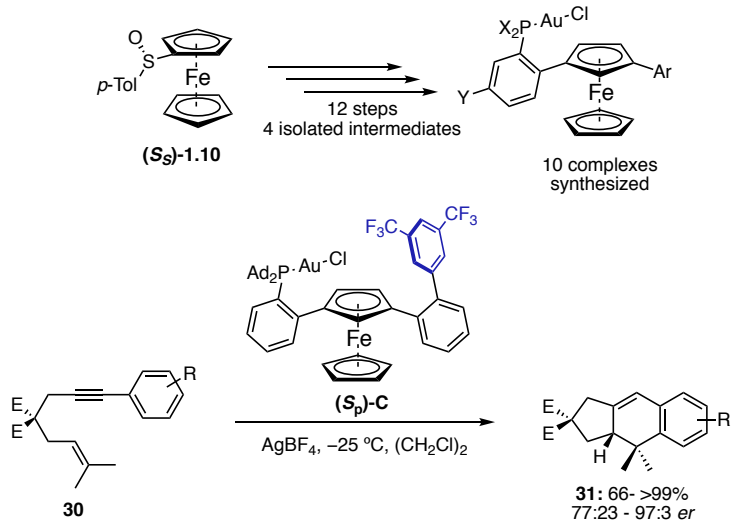
To flask charged with $LiAlH_4$ (0.26 g, 1.0 mmol,) in Et_2O (1.0 mL) at 0 ºC was added a solution of $AlCl_3$ (0.14 g, 1 equiv, 1.0 mmol) in Et_2O (2.2 mL). After completion of the addition the ice bath was removed and 1-ferrocenyl-3-butin-1-ol (0.26 g, 1 mmol) in Et_2O (4.0 mL) was added dropwise to the mixture. The mixture was stirred for 30 min then poured over ice (10 mL). The reaction was monitored by TLC and GC-MS analysis.

The crude mixture was diluted with Et_2O (10 mL) and phases were separated. The aqueous layer was extracted with Et_2O (2x), reunited organic layers were washed with water $NaHCO_3$ sat. and brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography over silica gel (eluant cyclohexane) afforded the title compound (0.202 g, 0.85 mmol, 83%) as a red oil. The obtained characterization data were in agreement with those reported in literature.[200]

General Conclusions

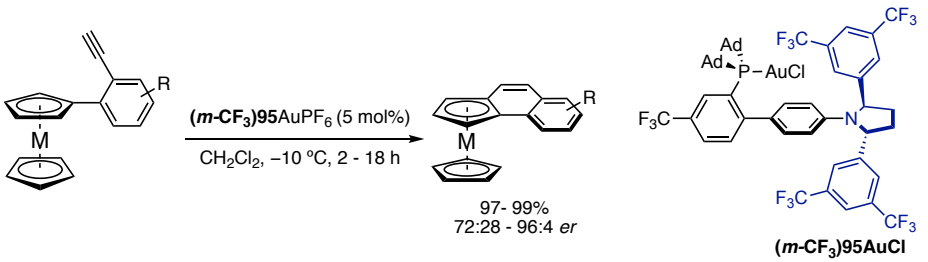
This Doctoral Thesis presents the design and synthesis of a new class of chiral ferrocene-based ligands and the application of their corresponding gold(I) complexes in enantioselective catalysis. In addition, the enantioselective synthesis of planar chiral metallocenes was achieved using a chiral mononuclear phosphine gold(I) complex.

Our ligand design is based on well-defined dialkylbiaryl phosphine ligands in which the monosubstituted aryl ring was replaced by a planar chiral disubstituted ferrocene. Considering the linear dicoordination of gold(I) and the outer sphere mechanism, a 1,3-disubstitution pattern of the ferrocene core was selected for our design. In this design, the ferrocene core acts as the source of chirality in the ligand and as a spacer between the phosphine binding point and a biaryl group, creating a chiral environment proximal to the reactive site. The new catalysts allowed the synthesis of enantioenriched 1,2-dihydronaphtalenes by formal [4+2] cycloaddition of 1,6-arylenynes.



Computational studies on the mode of action of our catalysts demonstrate the crucial roles of attractive interactions between the biaryl moiety of the ligand and the aromatic substituent of the substrate. Tethers of 1,6-arylenynes also play an important role in the orientation of the substrate with respect to the catalyst. Combination of these two factors induce a favored folding of the substrate in the chiral environment of the catalyst resulting in the observed enantioselectivity of the transformation. The developed theoretical model shows a good correlation with the experimental results.

In addition, we extended the range of applications of the chiral JohnPhos-type ligand (***m*-CF$_3$)95** containing a C_2-symmetric element to the synthesis of planar chiral metallocenes. The gold(I)-catalyzed intramolecular hydroarylation reaction of 2-alkynylaryl metallocenes allowed to access naphtyl-fused chiral metallocenes in high yield and good enantioselectivity.



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FERROCENE-BASED CHIRAL CATALYST DESIGN FOR ENANTIOSELECTIVE CYCLOADDITIONS REACTIONS
Ulysse Caniparoli

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