UNIVERSITAT ROVIRA I VIRGILI

DESIGN OF NEW GOLD(I) CATALYSTS: DISSECTING ELECTRONIC AND STERIC EFFECTS

Ana Arroyo Bondia

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Design of New Gold(I) Catalysts: Dissecting Electronic and Steric Effects

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Ana Arroyo Bondía

DOCTORAL THESIS

2023

Ana Arroyo Bondía

Design of New Gold(I) Catalysts: Dissecting Electronic and Steric Effects

DOCTORAL THESIS

Supervised by Prof. Antonio M. Echavarren

Institut Català d´Investigació Química (ICIQ)

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Institut
Català
d'Investigació
Química

UNIVERSITAT ROVIRA i VIRGILI

I STATE that the present study, entitled "*Design of New Gold(I) Catalysts: Dissecting Electronic and Steric Effects*", presented by Ana Arroyo Bondía to award the degree of Doctor, has been carried out under my supervision at the Institut Català d´Investigació Química (ICIQ).

Tarragona, March 29th, 2023

Doctoral Thesis Supervisor

Prof. Antonio M. Echavarren Pablos

A mis padres y a mi hermana

"En algún lugar entre el azar y el misterio se encuentra la imaginación, la única cosa que protege nuestra libertad"

Luis Buñuel (1900–1983)

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Table of Contents

Prologue

This PhD dissertation is divided into four main parts, including a general introduction, three research chapters describing the experimental results and the general conclusions. These sections are preceded by a list of abbreviations and acronyms, the abstract and general objectives, and are followed by the overall conclusions. Each research chapter contains five sections that include an introduction on the research topic, the objectives, the results and discussion, the conclusions and outlook, and the experimental section. The numbering of compounds, figures, schemes, tables and references is organized by chapters. When presenting DFT energy results, intermediates are numbered independently. In case of collaborative projects, the researchers involved are indicated in each chapter or section.

General Introduction, provides an overview of the principles of homogeneous gold(I) catalysis and the cycloisomerization of 1,*n*-enynes and summarizes the main approaches to enantioselective gold(I) catalysis.

Chapter I, '*Design and Synthesis of Chiral Pyrrolidine-Based Ligands*', describes our efforts to expand the knowledge in chiral gold(I) catalysts based on a chiral disubstituted pyrrolidine by modifications in their structures. For clarity, the results in this section have been subdivided into three parts corresponding to the different projects, that include a specific introduction to each topic and the experimental section is located at the end of the main research chapter.

Part of the results obtained was published in: Zuccarello, G.; Nanini, L.; Arroyo-Bondía, A.; Fincias, N.; Arranz, I.; Pérez-Jimeno, A. H.; Peeters, M.; Martín-Torres, I.; Sadurní, A.; García-Vázquez, V.; Wang, Y.; Kirillova, M. S.; Montesinos-Magraner, M.; Caniparoli, U.; Núñez, G. D.; Maseras, F.; Besora, M.; Escofet, I.; Echavarren A. M. Enantioselective Catalysis with Pyrrolidinyl Gold(I) Complexes: DFT and NEST Analysis of the Chiral Binding Pocket. *ChemRxiv*. (*Organic Chemistry*), **2023**, preprint. DOI: 10.26434/chemrxiv-2023-vxlcf.

Chapter II, '*Amino Acid-Phos Gold(I) Complexes*', presents our attempts to use ligands bearing amino acids to induced chirality.

Chapter III, '*Design of Gold(I) Catalysts for Targeting Senescent Cells*', describes the design and synthesis of N-heterocyclic gold(I) complexes to study their reactivity under biological conditions.

General Conclusions are provided for the research topics.

Abbreviations and Acronyms

In this manuscript, the abbreviations and acronyms most commonly used in organic and organometallic chemistry have been used following the recommendations of "*Guidelines of Authors*" of the *Journal of Organic Chemistry*.

Additional abbreviations and acronyms used in this manuscript are listed below:

APCI	atmospheric pressure chemical ionization
BAr_4^{F-}	tetrakis[3,5-bis(trifluoromethyl)phenylborate]
1,2-DCE	1,2-dichloroethane
DIPEA	Di-*iso*-propyl ethyl amine
dppm	1,1-Bis(diphenylphosphino)methane
dr	diastereomeric ratio
ee	enantiomeric excess
er	enantiomeric ratio
ESI	electrospray ionization
HRMS	High Resolution Mass Spectrometry
IPr	1,3-bis(2,4,6-trimethylphenyl)imidazole-2-ylidene
JohnPhos	(2-biphenyl)di-*tert*-butylphosphine
n/d	not detected
NTf_2^-	Bis(trifluoromethyl)imidate
L	ligand
M	metal
MW	microwave irradiation
OTf^-	Trifluoromethanesulfonate
TMEDA	*N*,*N*,*N'*,*N'*-Tetramethyl ethylenediamine
TS	transition state

Abstract

The potential of gold(I)-catalyzed transformations for the construction of molecular complexity have been studied in the last two decades. Our group has widely contributed to this field, in symmetric and asymmetric catalysis, with the preparation of gold(I) complexes, the development of new synthetic methodologies and the studies of their mechanism. In this context, this Doctoral Thesis has principally focused on expanding the knowledge in asymmetric gold(I) catalysis and the development of new gold(I) catalysts.

After the success in different transformations of a novel family of dialkylbiphenyl phosphine ligands bearing a C_2-asymmetric 2,5-disubstituted pyrrolidines developed by our group, different modifications in their structure have been carried out in order to study their reactivities and comparing them to the reactivities of the model ligand.

- The removal of one of the phenyl moieties of the biphenyl scaffold approaching the chiral information to the gold(I) metal has proved to give good enantioselectivities in different transformations. For example, in the atroposelective cyclization reaction of sulfonamides to afford 2-arylindoles, surprisingly obtaining the opposite enantiomer than the model ligand.
- The substitution of the phosphine by an N-heterocyclic carbene has been carried out to check how their reactivity changes. In this case, a similar reactivity has been observed in terms of yield compared to the model ligand. However, lower enantioselectivities have been obtained probably due to the higher angle of the gold(I).
- A third variation was the preparation of sterically hindered ligands with one, two or three chiral 2,5-disubstituted pyrrolidines. They were tested in different transformations giving in general high yields. Nevertheless, these reactions did not show good enantioselective results, this has been theoretically studied and explained by the opening of the pocket when a substrate is coordinated to the gold(I).

There have been synthesized other chiral gold(I) complexes bearing one or two amino acids to take advantage of the natural chirality of amino acids to induce enantioselectivity to the transformations. It has been studied different protecting groups, racemization issues and amide formation techniques for this synthesis. However, the asymmetry of the ligands (when only one amino acid is present) and/or the free rotation of the bonds of the amino acids have obstructed their enantioselectivity.

Other area of study has been the synthesis of a gold(I) complex active in senescent cells. These cells present high levels of associated *β*-galactosidase (SA-*β*-Gal) that could cleavage *β*-galactoses present in the gold(I) complex. The complex with *β*-galactoses would be inactive against of a prodrug or fluorophore under biological conditions, but in presence of *β*-galactosidases will be active due to the cleavage of the galactoses releasing the active gold(I) complex, allowing the reaction with the prodrug or fluorophore. To this end, it has been developed two N-heterocyclic carbene gold(I) complexes, with

and without β-galactoses. These catalysts have been tested under biological conditions in a hydroarylation reaction producing a fluorescent coumarin. Different reactivity for both complexes has been observed under several reaction conditions. Although reactivities are still modest, the differentiated reactivity might serve as *proof-of-concept* for the objective of this project.

General Objectives

The objectives of this Doctoral Thesis are the development of new gold(I) complexes and studying their reactivity in catalysis. In particular, the aims were focused on:

- The design and synthesis of new families of chiral gold(I) complexes bearing a C_2-symmetric 2,5-diaryl-substituted pyrrolidines and their application in different transformations to study their reactivities and enantioselectivities.
- The design and synthesis of gold(I) complexes bearing aminoacids as the chiral elements in a Johnphos-type scaffold.
- The design and synthesis of a gold(I) complex active in senescent cells taking advantage of the highly presence of β-galactosidase enzymes in these cells.

Each chapter of this PhD manuscript provides a more detailed description of the objectives of the corresponding chapter.

General Introduction

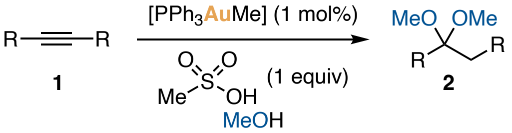
Homogeneous Gold(I) Catalysis

Gold Along History

Gold is a precious metal that is a representation of power, wealth, and beauty in the human culture. It has been highly used in jewelry, decoration, and coinage along the history (Figure 1), because of its aesthetic qualities, value, ductility, and malleability. The use of gold in jewelry data from 5000 BCE with the use of electrum (gold and silver alloy) by the Egyptians, followed by the use of gold by the Sumer civilization of Mesopotamia on 2500 BCE, to our current days.[1]

Figure 1. Some applications of gold throughout the history.

Gold is a transition metal whose symbol is Au, from Latin: *aurum*, and it has been considered to be unreactive for many years and to have a low catalytic activity.[2] The first example of a gold reaction in heterogenous catalysis was reported in 1973[3] and it was centered on this area during the 80's.[4] It was in the end of the 20th century when the homogenous gold(I)-catalyzed addition of alcohols to alkynes **1** affording acetals **2** was reported by Teles (Scheme 1).[5] Together with the work of Tanaka, applying a similar system in the hydration of alkynes[6] turned into a breakthrough in homogeneous gold(I) catalysis.



Scheme 1. Gold(I)-catalyzed reaction for the formation of acetals.

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[1] Cartwright, M. (**2014**, April 04). "Gold in Antiquity". *World History Encyclopedia*.

[2] Hashmi, A. S. K. *Gold Bull.* **2004**, *37*, 51–65.

[3] Bond, G. C.; Sermon, P. A.; Webb, G.; Buchanan, D. A.; Wells, P. B. *J. Chem. Soc., Chem. Commun.* **1973**, 444–445.

[4] (a) Hutchings, G. J. *J. Catal.* **1985**, *96*, 292–295. (b) Haruta, M.; Kobayashi, T.; Sano, H.; Yamada, N. *Chem. Lett.* **1987**, 405–408.

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

[6] Mizushima, E.; Sato, K.; Hayashi, T.; Tanaka, M. *Angew. Chem. Int. Ed.* **2002**, *41*, 4563–4565.

The use of gold(III) salts by Hashmi for the phenol synthesis[7] and the use of cationic gold(I) complexes by the groups of Hashmi,[8] Fürstner,[9] Toste[10] or our group,[11] opened a big field of study in chemistry. Since then, the homogenous gold(I) catalysis has been widely explored with the development of catalytic transformations, being established as a powerful tool for the synthesis of complex molecules under mild conditions, through the activation of unsaturated C–C bonds.

General Aspects in Gold(I) Complexes

Gold(I) complexes have the ability of being able to selectively activate π-bonds and this is the result of the relativistic effects.[12] The relativistic effects are related to the atomic number and the velocity of electrons moving around and close to a heavy nucleus. These relativistic effects increase with the atomic number because the electrons that are closest to the nucleus increase their speed, so their mass increases too. This leads to an energetic stabilization that causes a contraction of the *s* and *p* atomic orbitals. Therefore, the electrons of the *s* and *p* orbitals will have a stronger nuclear attraction, and this will shield the *d* and *f* orbitals, destabilizing and expanding them, whose electrons will show a weaker nuclear attraction. This effect becomes more significant in metals with their 4*f* and 5*d* orbitals filled. In the case of gold ([Xe] $6s^1 5d^{10}$), the relativistic effect reaches a maximum, in which the contraction of the 6*s* orbital leads to a substantial expansion of the *d* orbital that decreases the electron/electron repulsion. The high electronegativity of gold ($\chi = 2.54$), its Lewis acidic character and the aurophilic interaction can be explained by this effect. The filled 5*d* orbital can interact with the filled *p* orbitals of unsaturated bonds, which will attract the electron density towards gold so these π-bonds will be activated towards nucleophilic attack.[13]

Gold(I) complexes preferentially adopt linear dicoordinated geometry. This tendency is also justified by relativistic effects, because of the efficient hybridizations of *s*/*d* or *s*/*p* orbitals that lead to slight differences in energy gap between the *s*, *p* and *d* orbitals.[14] This dicoordinated geometry of gold(I) complexes do not easily suffer *β*-hydride elimination or oxidative addition.[15] However, examples have

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[7] Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *J. Am. Chem. Soc.* **2000**, *122*, 11553–11554.

[8] Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180–3211.

[9] Fürstner, A. *Chem. Soc. Rev.* **2009**, *38*, 3208–3221.

[10] Shapiro, N.; Toste, F. D. *Synlett* **2010**, 675–691.

[11] (a) Martín-Matute, B.; Cárdenas, D. J.; Echavarren A. M. *Angew. Chem. Int. Ed.* **2001**, *40*, 4754–4757. (b) Martín-Matute, B.; Nevado, C.; Cárdenas, D. J.; Echavarren A. M. *J. Am. Chem. Soc.* **2003**, *125*, 5757–5766. (c) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333–346. (d) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326–3350. (e) Obradors, C.; Echavarren, A. M. *Acc. Chem. Res.* **2014**, *47*, 902–912.

[12] (a) Pyykkö, P. *Angew. Chem. Int. Ed.* **2002**, *41*, 3573–3578. (b) Schwartz, H. *Angew. Chem. Int. Ed.* **2003**, *42*, 4442–4454. (c) Pyykkö, P. *Angew. Chem Int. Ed.* **2004**, *43*, 4412–4456.

[13] Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395–403.

[14] Gimeno, M. C.; Laguna, A. *Chem. Rev.* **1997**, *97*, 511–522.

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

been described in which gold(I) can promote oxidative addition.[16] On the other hand, only gold(III) complexes are known to promote *β*-hydride elimination under the right conditions.[17] Gold(III) salts (*e.g.*, AuCl$_3$ and NaAuCl$_4$) and gold(III) complexes show a square planar geometry and are able to catalyze many transformations. They can be reduced to gold(I) and gold(0) by the oxidation of some substrates.[18]

Gold(I) and gold(III) are usually used as chloride salts and the ligands employed have an important impact in the properties of the complexes. The contraction of the Au–ligand bond can tune the steric and electronic properties of the complexes affecting their reactivity and selectivity.[19] Phosphite ligands are more electrophilic than N-heterocyclic carbenes (NHC), that are more σ-donating what results in a reactivity presenting more carbene-like intermediates. Phosphine ligands show an intermediate electrophilicity (Figure 2).[20]

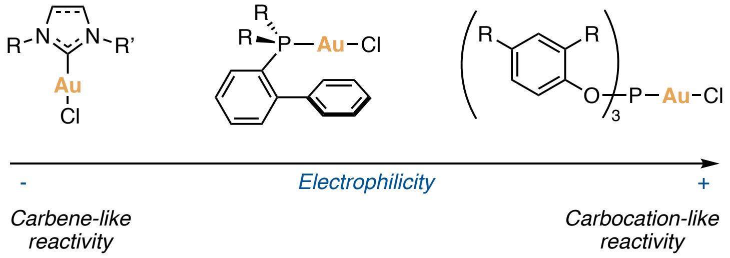

Figure 2. Ligand modification effect on gold(I) complexes.

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[16] For some examples, see: (a) Joost, M.; Zeineddine, A.; Estévez, L.; Mallet-Ladeira, S.; Miqueu, K.; Amgoune, A.; Bourissou, D. *J. Am. Chem. Soc.* **2014**, *136*, 14654–14657. (b) Guenther, J.; Mallet-Ladeira, S.; Estevez, L.; Miqueu, K.; Amgoune, A.; Bourissou, D. *J. Am. Chem. Soc.* **2014**, *136*, 1778–1781. (c) Cambeiro, X. C.; Ahlsten, N.; Larrosa, I. *J. Am. Chem. Soc.* **2015**, *137*, 15636–15639. (d) Wu, C. Y.; Horibe, T.; Jacobsen, C. B.; Toste, F. D. *Nature* **2015**, *517*, 449–454. (e) Zeineddine, A.; Estévez, L.; Mallet-Ladeira, S.; Miqueu, K.; Amgoune, A.; Bourissou, D. *Nat. Commun.* **2017**, *8*, 565–572. (f) Cadge, J. A.; Sparkes, H. A.; Bower, J. F.; Rusell, C. A. *Angew. Chem. Int. Ed.* **2020**, *59*, 6617–6621.

[17] For some examples, see: (a) Mankad, N. P.; Toste, F. D. *Chem. Sci.* **2012**, *3*, 72–76. (b) Castiñeira Reis, M.; López, C. S.; Kraka, E.; Cremer, D.; Faza, O. N. *Inorg. Chem.* **2016**, *55*, 8636–8645. (c) Rekhroukh, F.; Estevez, L.; Mallet-Ladeira, S.; Miqueu, K.; Amgoune, A.; Bourissou, D. *J. Am. Chem. Soc.* **2016**, *138*, 11920−11929. (d) Kumar, R.; Krieger, J.-P.; G.mez-Bengoa, E.; Fox, T.; Linden, A.; Nevado, C. *Angew. Chem. Int. Ed.* **2017**, *56*, 12862–12865.

[18] (a) Hashmi, A. S.; Weyrauch, J. P.; Rudolph, M.; Kurpejovi, E. Angew. *Chem. Int. Ed.* **2004**, *43*, 6545–6547 (b) Wong, M. K. *Adv. Synth. Catal.* **2013**, *355*, 2055–2070. (c) Yang, Y.; Hu, W.; Ye, X.; Wang, D.; Shi, X. *Adv. Synth. Catal.* **2016**, *358*, 2583–2588. (d) Ranieri, B.; Escofet, I.; Echavarren, A. M. *Org. Biomol. Chem.* **2015**, *13*, 7103–7118,

[19] Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351–3378.

[20] (a) Wang, Y.; Muratore, M. E.; Echavarren, A. M. *Chem. Eur. J.* **2015**, *21*, 7332–7339. (b) Zuccarello, G.; Zanini, M.; Echavarren, A. M. *Isr. J. Chem.* **2020**, *60*, 360–372.

The activation of the π-bonds of alkynes by gold(I) can be explained by the Dewar-Chatt-Duncanson model, if the bond is considered as a donor-acceptor interaction.[21] The model explains that the metal–substrate bond is formed by a combination of a σ- and a π-interaction: the donation of density from the alkyne to an empty *d*-orbital of the metal by a σ-interaction and the back donation from the filled *d*-orbital of the metal into the empty π* antibonding orbital of the alkyne (Figure 3).[22]

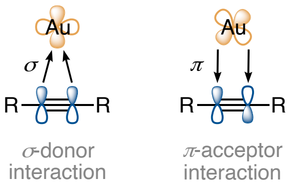
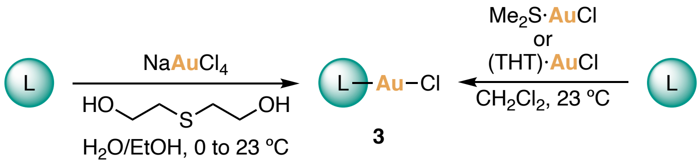


Figure 3. The Dewar-Chatt-Duncanson model for the interaction of an alkyne with gold.

The synthesis of gold(I) complexes (**3**) with formula [LAuCl] (L = ligand) can be performed by the reduction of $NaAuCl_4$ with 2,2'-thiodiethanol and the reaction with the ligand.[23] Moreover, they can be easily prepared by the direct reaction L (ligand) and $Me_2S \cdot AuCl$ or (THT)·AuCl (THT = tetrahydrothiophene) (Scheme 2).



Scheme 2. Preparation of LAuCl complexes.

These gold(I) complexes [LAuCl] are used as precatalysts and they are activated through chloride abstraction, coordinating to the substrate by an associative mechanism.[24] One approach is the activation *in situ* of **3** through the chloride abstraction using copper[25] or silver[26] salts, so the catalytically active

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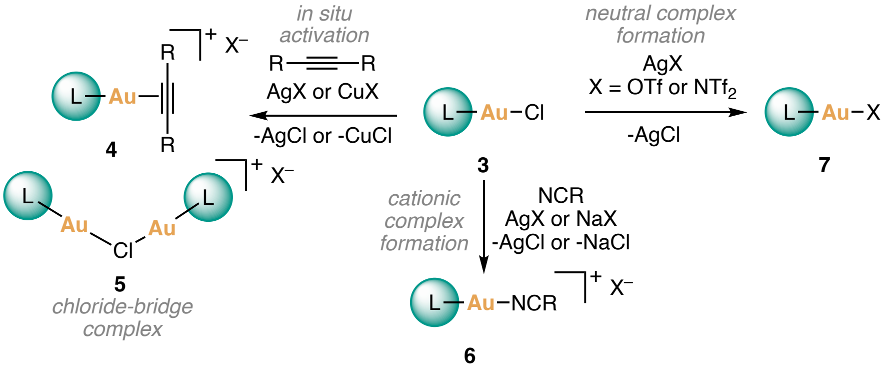
gold(I) specie is coordinated with the substrate (**4**) (Scheme 3). This strategy can promote side reactions and the formation of less reactive chloride bridged digold(I) species **5**.[27] Another approach is the formation of the air-stable cationic species **6** in which the gold(I) is coordinated to a neutral and labile ligand, such as acetonitrile and benzonitrile, and a counterion X^- (such as SbF_6^-, BF_4^-, or PF_6^-).[24a,24b,28] Alternatively, the formation of species of gold(I) directly coordinated to weakly counterions, like OTf^- or NTf_2^-, generates a neutral gold(I) complex **7**.



Scheme 3. Different strategies for the activation of LAuCl complexes.

Gold(I) complexes are able to selectively activate alkynes in the presence of other functional groups. The η^2-alkyne-gold(I) complexes **8** can be attacked by many nucleophiles in an *anti*-fashion addition, giving *trans*-alkenyl-gold species **9** (Scheme 4).[29] Many nucleophiles are used in inter- and intramolecular gold(I) catalyzed transformations, being alkenes one of the nucleophiles most commonly used in our group.[11c-e,30]

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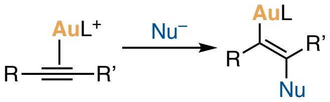


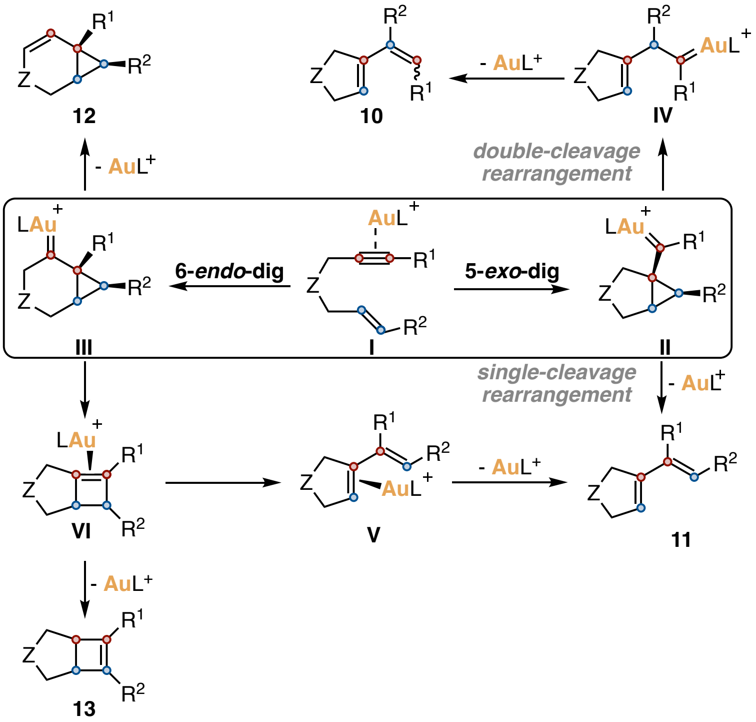
8 **9**

Scheme 4. Nucleophilic attack to η^2-alkyne-gold(I) complexes.

Cycloisomerization of 1,*n*-Enynes

In the field of gold(I)-catalyzed reactions, the cycloisomerization of 1,*n*-enynes has had a big impact in organic synthesis because it provides access to diverse and complex molecules from simple substrates.

The 1,6-enyne cycloisomerization can follow different pathways depending on the substitution at the alkyne and the alkene and depending on the catalyst employed, affording different products. The coordination of gold(I) to the alkyne forms the η^2-alkyne-gold(I) complex **I** that acts as an electrophile and it is attacked by the alkene *via* a 5-*exo*-dig or 6-*endo*-dig cyclization, generating the cyclopropyl gold(I) carbene intermediates **II** and **III** respectively (Scheme 5). The intermediate **II** can evolve through a double cleavage rearrangement, opening the cyclopropyl ring, in which the formal insertion of the terminal alkene carbon into the two carbons of the alkyne takes place (**IV**). The formation of this new carbene **IV** followed by an α-hydrogen elimination and protodeauration affords the 1,3-diene **10**. The configuration of the exocyclic alkene can be *E* or *Z*, but the *Z* configuration is more common, especially when the substituent R^2 is a proton. The cyclopropyl gold(I) carbene **II** can also evolve through a single cleavage rearrangement, where only the alkene is cleaved, and gives the 1,3-diene **11**. Alternatively, the cyclopropyl gold(I) carbene **III** can lead to the bicyclic derivative **12** through an α-hydrogen elimination and protodeauration, or to the bicycle derivative intermediate **VI** through a ring expansion, followed by a double bond isomerization affording cyclobutene **13**. The ring of the complex **VI** can also be opened (**V**) leading to the 1,3-diene **11**.



Scheme 5. Pathways for the cycloisomerization of 1,6-enynes catalyzed by gold(I).

Additionally, the direct demetallation of **VI** (Scheme 5) can also lead to a highly strained cyclobutene product, this path is not common, although there are some examples in which they have been isolated.[31] These less strained cyclobutenes are more common in 1,*n*-enynes in which n≥7, formed through a formal [2+2] cycloaddition. For example, the formation of the cyclobutene-fused products **15** and **17** by a gold(I)-catalyzed [2+2] cycloaddition of the 1,7-enyne **14**[24a,32] and 1,8-enyne **16**[31b,33] respectively (Scheme 6). Furthermore, 1,*n*-enynes with n = 10–16 can react affording cyclobutene-containing macrocycles. For example, the 1,10-enyne **18** reacts to obtain the cyclobutene-fused **19** by diastereoselective gold(I)-catalyzed [2+2] macrocyclization reaction (Scheme 6).[34] From macrocycle **19**, the total synthesis of rumphellaone A and hushinone was described, using this methodology for the construction of the cyclobutene moiety.[35]

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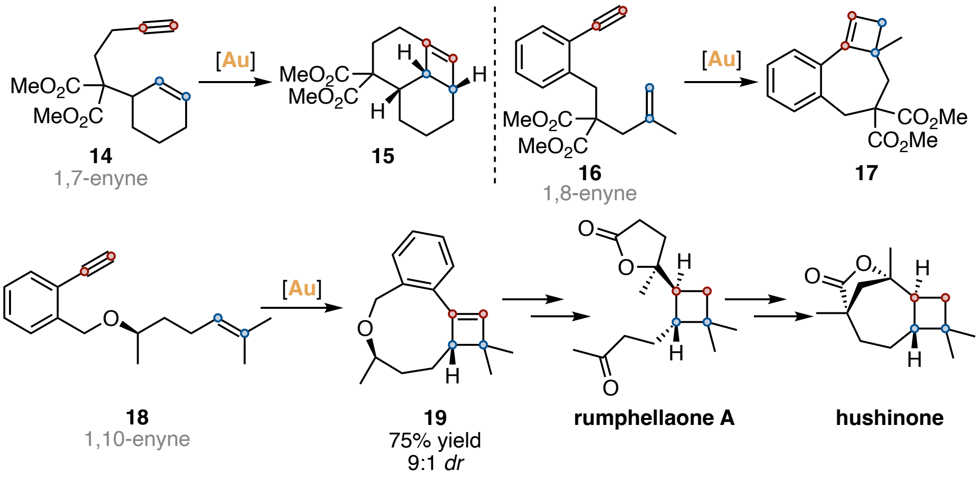

Scheme 6. Gold(I)-catalyzed cyclization of 1,*n*-enynes (n≥7).

The intermolecular gold(I) reaction of terminal alkynes with alkenes have been also studied.[36] Their development is slower since these transformations are more challenging, because there are present two unsaturated substrates that compete for coordinating to gold(I)[37] and because gold(I) can promote the polymerization of the alkenes.[38] In the last years different examples of these transformations have been developed.[30c,30f,36,39]

The cycloisomerization of 1,*n*-enynes in the presence of other nucleophiles increase the possible reaction outcomes. The presence of carbonucleophiles or heteronucleophiles can lead to a wide variety of products *via* inter- or intramolecular gold(I) catalyzed reactions, by the regioselective and stereospecific nucleophilic attack on the cyclopropyl gold(I) carbene intermediate generated.[40]

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Asymmetric Gold(I) Catalysis

Knowing the efficiency of homogeneous gold(I)-catalyzed reactions, the development of their asymmetric versions became a wide area of research, but it has been a slow process.[41] The linear dicoordination adopted by gold(I) placed the chiral source, ligand L*, on the opposite side of the reactive center, hindering the enantioinduction (Figure 4). This problem coming from the distance between the chiral information and the reactive center is extended by the attack of the nucleophile to the active π-bond in an outer-sphere mechanism.

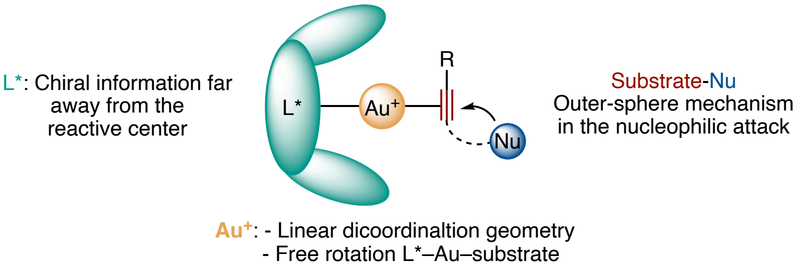
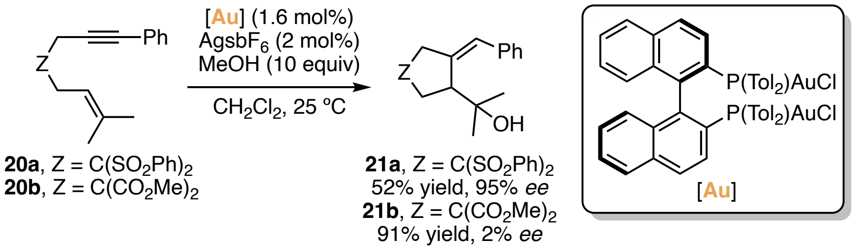


Figure 4. Main challenges that affect the enantioinduction in gold(I) catalysis.

The first example of homogenous gold(I) catalysis was developed by Hayashi and Ito, in 1986, for the synthesis of chiral oxazolines from aldehydes and isocyanoacetates, using a chiral ferrocenylphosphine gold(I) complex.[42] In 2005, twenty years later, our group reported the asymmetric alkoxycyclization of 1,6-enynes **20** catalyzed by a chiral Tol-BINAP bis-gold(I) complex (Scheme 7).[43] It was noticed that the enantioinduction was highly substrate dependent, because the system worked for sulfone derivatives **20a** but not malonates **20b**.



Scheme 7. Asymmetric alkoxycyclization of 1,6-enynes.

Since then, different strategies have been developed to overcome this challenge, based on the design of new ligands. The axially chiral digold complexes mainly supported by phosphines, such as BINAP and

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[41] (a) Widenhoefer, R. A. *Chem. Eur. J.* **2008**, *14*, 5382–5391. (b) Sengupta, S.; Shi, X. *ChemCatChem* **2010**, *2*, 609–619. (c) Pradal, A.; Toullec, P. Y.; Michelet, V. *Synthesis* **2011**, 1501–1514. (d) Wang, Y. M.; Lackner, A. D.; Toste, F. D. *Acc. Chem. Res.* **2014**, *47*, 889–901. (e) Zi, W.; Toste, F. D. *Chem. Soc. Rev.* **2016**, *45*, 4567–4589. (f) Li, Y.; Li, W.; Zhang, J. *Chem. Eur. J.* **2017**, *23*, 467–512. (g) Zuccarello, G.; Escofet, I.; Caniparoli, U.; Echavarren, A. M. *ChemPlusChem* **2021**, *86*, 1283–1296.

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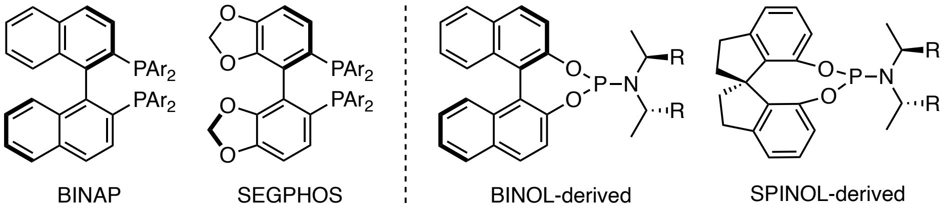
[43] Muñoz, M. P.; Adrio, J.; Carretero, J. C.; Echavarren, A. M. *Organometallics* **2005**, *24*, 1293–1300.

SEGPHOS (Figure 5, left),[44] are used in many inter- and intramolecular transformations, such as cycloisomerization of 1,*n*-enynes[43,45] and cyclopropanations.[46] The design of mononuclear gold(I) complexes with monodentate chiral phosphoramidites have been also developed, derivatives of BINOL and SPINOL for instance (Figure 5, right).[41d,47]



BINAP SEGPHOS BINOL-derived SPINOL-derived

Figure 5. Some chiral ligand-designs for enantioselective gold(I) catalysis.

In 2007, the group of Toste introduced the use of chiral binaphthol-derived phosphate counterions for inducing chirality using nonchiral gold(I) complexes. This strategy was used for the asymmetric intramolecular hydroalkoxylation, hydroamination and hydrocarboxylation transformations of allenes (Scheme 8, top).[48] However, terminal alkynes cannot be used as substrates because phosphates deprotonate the alkynyl proton, forming the inactive gold(I) acetylide complexes.[49] In this context, Marinetti and coworkers have used a cooperative bifunctional ligand, tethering the chiral phosphate counterion with the phosphine ligand. This system was successfully used in different transformations, such as the enantioselective addition of indoles (Scheme 8, bottom).[50]

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[44] (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.

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

[46] (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.

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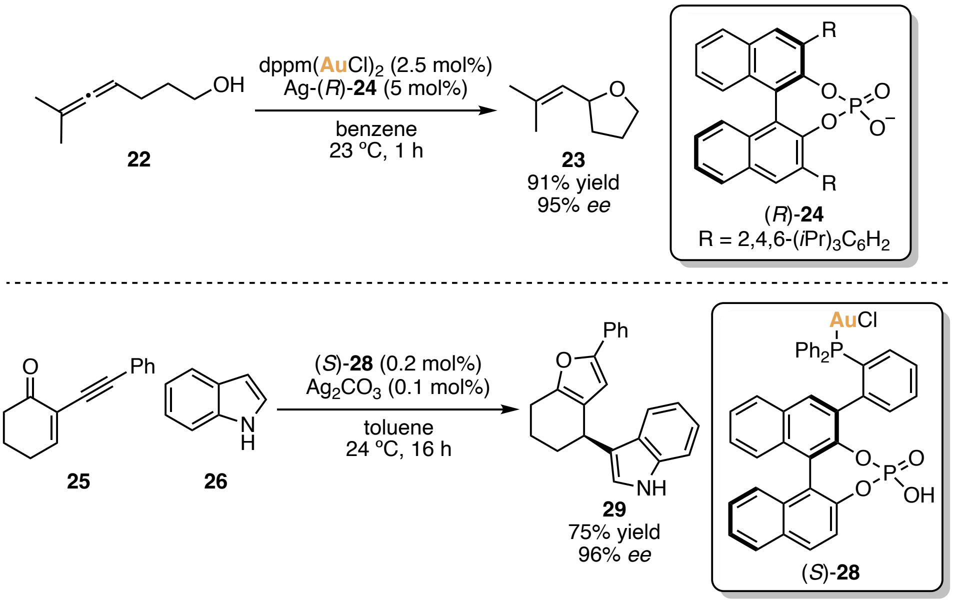
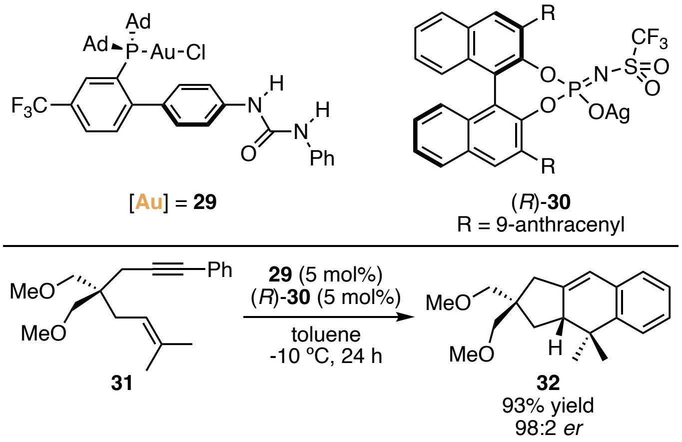


Scheme 8. Chiral phosphate counterions used in asymmetric transformations.

Our group has been very recently contributed to this field using system with a chiral anion and an achiral gold(I) complex bearing an H-bond donor. The stereochemical information, the H-bond donor, is placed close to the reactive center which locates the chiral counterion in the optimal position for transferring enantioinduction (Scheme 9**Scheme *1***. Gold(I)-catalyzed reaction for the formation of acetals.).[51] This concept has been successfully used for different asymmetric gold(I)-catalyzed transformations.[52]



Scheme 9. Phosphino urea gold(I) complex **29** and silver(I) chiral salt (*R*)-**30**. Their use in the enantioselective formal [4+2] cycloaddition of 1,6-enyne **31**.

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[51] Franchino, A.; Martí, À.; Echavarren, A. M. *J. Am. Chem Soc.* **2022**, *144*, 3497–3509.

[52] Martí, À.; Montesinos-Magraner, M.; Echavarren, A. M.; Franchino, A. *Eur. J. Org. Chem.* **2022**, e202200518.

Other chiral ligands have been recently developed and successfully used in transformations, like the helically chiral ligands, such as HelPhos[53] and chiral sulfonamide monophosphine ligands, like the Ming-Phos, Xiang-Phos and PC-Phos (Figure 6).[54]

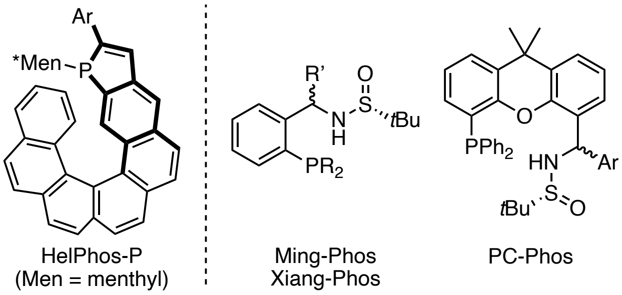

Figure 6. Other chiral ligands used in enantioselective gold(I) catalysis.

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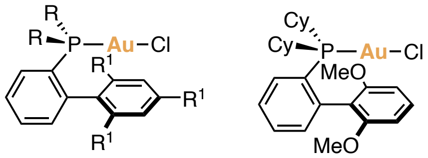
Chapter I: "Design and Synthesis of Chiral Pyrrolidine-Based Ligands"

General Introduction

Dialkylbiaryl Phosphine Ligands in Homogeneous Gold(I) Catalysis

Dialkylbiaryl phosphine ligands are highly used in homogenous catalysis because of their synthetic accessibility[1] and their resistance towards oxidation by molecular oxygen.[2] Buchwald introduced the use of these ligands in different palladium-catalyzed reactions: Suzuki-Miyaura cross-coupling reactions and amination of unactivated aryl chlorides,[3,4] and preparation of biaryl ethers.[5] Since then, many Pd-catalyzed reactions using these ligands have been reported,[6] but also with other transition metals (Ru,[7] Cu,[8] Ag,[9] Rh[10]).

In 2005, our group reported the first gold(I)-catalyzed application using this type of ligands. Different electrophilic gold(I) complexes were prepared **1a–d** (Figure 1) and, after chloride abstraction, they were active for different cyclization reactions under mild conditions.[11]



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

1d

Figure 1. Dialkylbiaryl phosphine gold(I) complexes.

Depending on the substitution of the 1,*n*-enynes, gold(I)-catalyzed reactions can follow different pathways. For example, 1,6-enynes with an aryl group in the alkyne (**2**) undergo an intramolecular formal [4+2] cycloaddition affording cyclopenta[*b*]naphthalenes (**3**). The use of dialkylbiaryl

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

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

[3] Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722–9723.

[4] Wolfe, J. P.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **1999**, *38*, 2413–2416.

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

[6] (a) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461–1473. (b) Billingsley, K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3358–3366. (c) Surry, D. S.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 6338–6361. (d) Sather, A. C.; Buchwald, S. L. *Acc. Chem. Res.* **2016**, *49*, 2146–2157. (e) Dorel, R.; Grugel, C. P.; Haydl, A. M. *Angew. Chem. Int. Ed.* **2019**, *58*, 17118–17129. (f) Ingoglia, B. T.; Wagen, C. C.; Buchwald, S. L. *Tetrahedron* **2019**, *75*, 4199–4211.

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

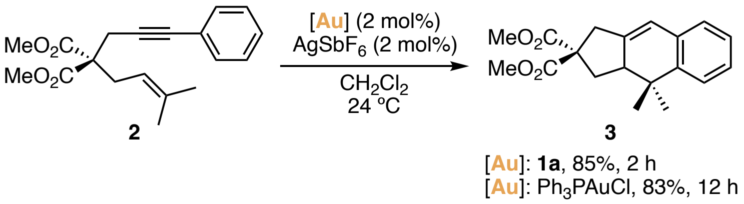
[8] Haider, J.; Kunz, K.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 717–722.

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

[10] Dhondi, P. K.; Chisholm, J. D. *Org. Lett.* **2006**, *8*, 67–69.

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

phosphine gold(I) catalyst **1a** presented faster reaction rates compared with those observed with (PPh_3)AuCl catalyst (Scheme 1).[12]



Scheme 1. Formal [4+2] cycloaddition reaction of 1,6-enynes.

Structural and Electronical Modifications of the Biaryl Scaffolds

Structures of biaryl phosphine ligands have been modified over the years, for finding new reactivities or improving already existing ones. For example, in 2014, Zhang designed a new family of ligands (**4a–h**) functionalizing the *o*-phenyl ring with different hydrogen-bond acceptors (Figure 2, **A**). With these gold(I) complexes in hand, they developed a gold(I)-catalyzed ligand-directed anti-nucleophilic attack to activated alkynes, in which the H-bond accepting carbonyl group acted as a base and also oriented the nucleophilic attack (Figure 2, **B**).[13] In the following years, the group of Zhang reported other transformations using these type of ligands and this concept.[14]

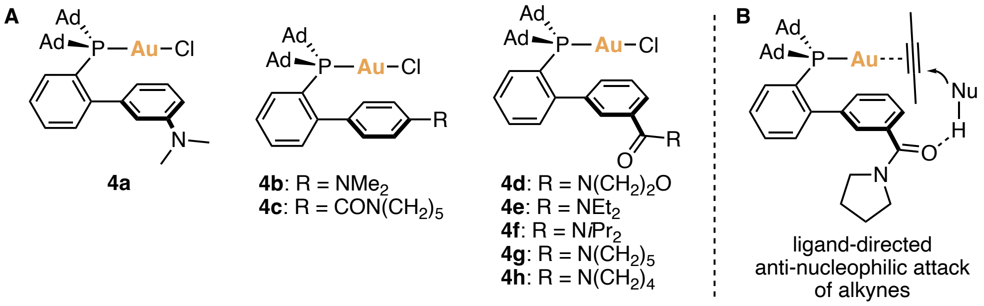


Figure 2. **A**. New functionalized biaryl phosphine gold(I) complexes. **B**. Gold(I) catalysis design for directed addition to alkynes.

To study the effect of the electronic properties of the structure and substituents at the biaryl scaffold, different structural modifications can be found in the literature. For example, it has been reported the

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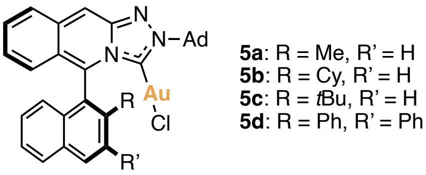
[12] Nieto-Oberhuber, C.; Pérez-Galán, P.; Herrero-Gómez, E.; Lauterbach, T.; Rodríguez, C.; López, S.; Bour, C.; Rosellón, A.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2008**, *130*, 269–279.

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

[14] (a) Wang, Z.; Wang, Y.; Zhang, L. *J. Am. Chem. Soc.* **2014**, *136*, 8887–8890. (b) Li, X.; Wang, Z.; Ma, X. Liu, P. N.; Zhang, L. *Org. Lett.* **2017**, *19*, 5744–5747. (c) Z. Wang, A. Ying, Z. Fan, C. Hervieu, L. Zhang, *ACS Catal.* **2017**, *7*, 3676–3680. (d) H. Wang, T. Li, Z. Zheng, L. Zhang, *ACS Catal.* **2019**, *9*, 10339–10342. (e) Liao, S.; Porta, A.; Cheng, X.; Ma, X.; Zanoni, G.; Zhang, L. *Angew. Chem. Int. Ed.* **2018**, *57*, 8250–8254. (f) Li, T.; Yang, Y.; Li, B.; Bao, X.; Zhang, L. *Org. Lett.* **2019**, *21*, 7791–7794. (g) Li, T.; Zhang, L. *J. Am. Chem. Soc.* **2018**, *140*, 17439–17443.

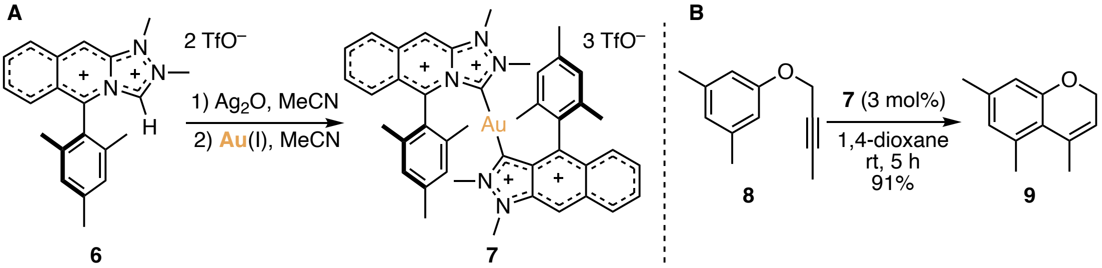
synthesis of axially chiral N-heterocyclic carbene (NHC) gold(I) complexes **5a–d** (Figure 3), with a triazoquinoline core and used for enantioselective transformations.[15]



5a: R = Me, R' = H
5b: R = Cy, R' = H
5c: R = *t*Bu, R' = H
5d: R = Ph, R' = Ph

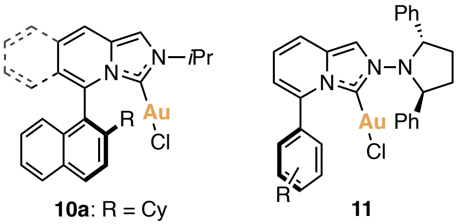
Figure 3. Axially chiral triazoquinoline-based NHC gold(I) complexes.

In 2018, it was reported the synthesis of the tricationic gold(I) complex **7** from the dicationic N-heterocyclic biaryl salt bearing a triazoquinoline biaryl core **6** (Scheme 2, **A**). This complex was catalytically used in the intramolecular hydroarylation of the propargyl aryl ether **8** to synthesize **9** in excellent yield (Scheme 2, **B**).[16]



Scheme 2. **A**. Synthesis of tricationic Au(I) complex **7**. **B**. Intramolecular hydroarylation reaction.

In 2015, two examples of chiral NHC gold(I) complexes were reported, the biaryl scaffolds were modified introducing an imidazo[1,5-*a*]pyridine-3-ylidene core **10a–b**[17] and **11**[18] (Figure 4).



10a: R = Cy
10b: R = *t*Bu
11

Figure 4. Examples of chiral N-heterocyclic carbene gold(I) complexes.

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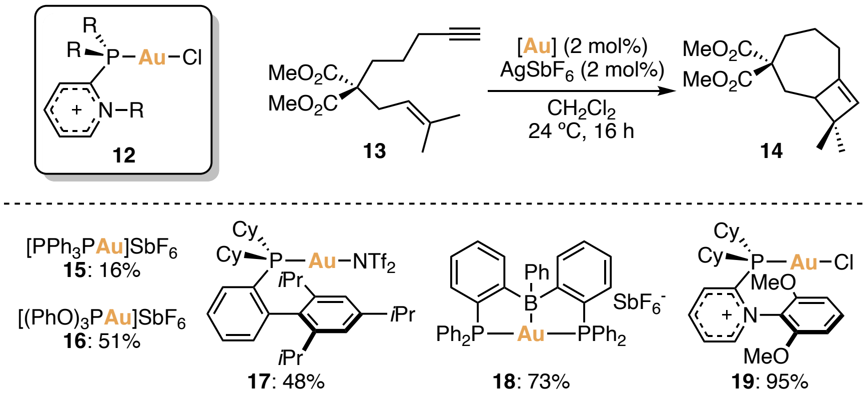
[15] (a) Francos, J.; Grande-Carmona, F.; Faustino, H.; Iglesias-Sigüenza, J.; Díez, E.; Alonso, I.; Fernández, R.; Lassaletta, J. M.; López, F.; Mascareñas, J. L. *J. Am. Chem. Soc.* **2012**, *134*, 14322–14325. (b) Varela, I.; Faustino, H.; Díez, E.; Iglesias-Sigüenza, J.; Grande-Carmona, F.; Fernández, R.; Lassaletta, J. M.; Mascareñas, J. L.; López, F. *ACS Catal.* **2017**, *7*, 2397–2402.

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

[17] Grande-Carmona, F.; Iglesias-Sigüenza, J.; Álvarez, E.; Díez, E.; Fernández, R.; Lassaletta, J. M. *Organometallics* **2015**, *34*, 5073–5080.

[18] Espina, M.; Rivilla, I.; Conde, A.; Díaz-Requejo, M. M.; Pérez, P. J.; Álvarez, E.; Fernández, R.; Lassaletta, J. M. *Organometallics* **2015**, *34*, 1328–1338.

Another example of electronically tuned biaryl phosphine gold(I) complexes was described by Alcarazo.[19] The new cationic ligands were based on a *N*-alkyl (R = Me or Et) or *N*-arylpyridiniophosphine **12**, increasing the π-acceptor ability of the ligand and allowing the activation of poorly reactive substrates. The intramolecular [2+2] gold(I)-catalyzed reaction of 1,8-enyne **13** afforded the bicyclic product **14** in 95% yield using catalyst **19**,[20] improving the result using other catalysts **15**–**18** (Scheme 3).[21]



Scheme 3. *N*-Arylpyridiniophosphine gold(I) complexes in catalysis.

In 2018, our group contributed to the synthesis of electronically tuned biaryl ligands.[22] The arsine complex **20** presented an increased π-acceptor character compared to the phosphine analogue **21**, whereas 4-arylindazole biaryl gold(I) complexes **22** presented σ-donating properties (Scheme 4, top). The catalysts were tested in the reaction of the nitrogen-tethered 1,6-enyne **23** using indole as nucleophile (Scheme 4, bottom). Arsine complex [**20**-NCMe]SbF_6 favored the formation of **24**, whereas that indazole complex **22** (R = H) favored the formation of **25**.

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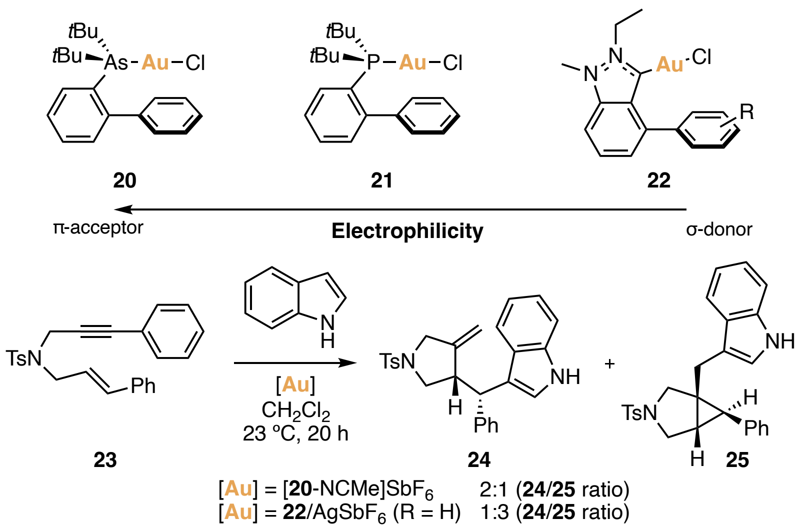
[19] Tinnermann, H.; Wille, C.; Alcarazo, M. *Angew. Chem. Int. Ed.* **2014**, *53*, 8732–8736.

[20] Tinnermann, H.; Nicholls, L. D. M.; Johannsen, T.; Wille, C.; Golz, C.; Goddard, R.; Alcarazo, M. *ACS Catal.* **2018**, *8*, 10457–10463.

[21] (a) Odabachian, Y.; Gagosz, F. *Adv. Synth. Catal.* **2009**, *351*, 379–386. (b) Inagaki, F.; Matsumoto, C.; Okada, Y.; Maruyama, N.; Mukai, C. *Angew. Chem. Int. Ed.* **2015**, *54*, 818–822.

[22] Carreras, J.; Pereira, A.; Zanini, M.; Echavarren, A. M. *Organometallics* **2018**, *37*, 3588–3597.



Scheme 4. Gold(I)-catalyzed reaction, addition of an indole to a 1,6-enyne.

Chiral Mononuclear Pyrrolidinyl-Biphenyl Phosphine Gold(I) Complexes

Design and Synthesis

In 2019, our group reported the synthesis of a new family of gold(I) complexes, based on the functionalization of the bottom phenyl ring of a JohnPhos-type ligand, with a C_2-symmetric *trans*-2,5-diarylpyrrolidines as the chiral element (Figure 5).[23] The chiral information was positioned next to the reactive center taking into consideration the outer-sphere mechanism of gold(I)-catalyzed transformations.

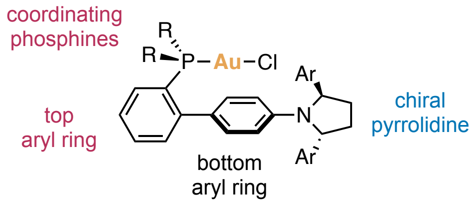


Figure 5. General design of JohnPhos-type chiral mononuclear gold(I) complexes.

The synthesis of chiral (*R*,*R*)-1,4-diol **27** was first approached by a Corey-Bakshi-Shibata reduction, following a modified reported procedure,[24] of the corresponding 1,4-dione **26** (Scheme 5).[25] It was obtained in excellent yield and enantiomeric ratio, but as a 6:1 mixture of diastereomers. Then, the formation of the chiral (*S*,*S*)-pyrrolidine bromide precursor **29** started with the *in situ* double mesylation of **27**, followed by a double S_N2 reaction with the aniline **30**, with inversion of the configuration,

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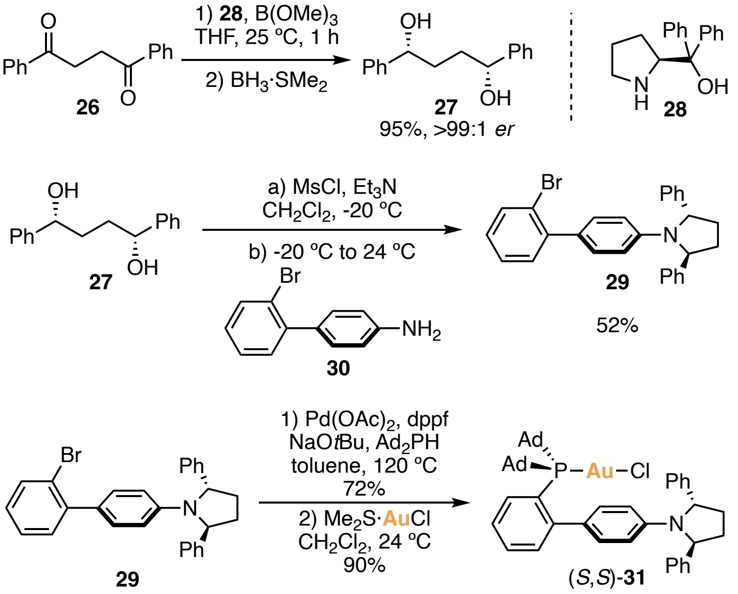
[23] Zuccarello, G.; Mayans, J. G.; Escofet, I.; Scharnagel, D.; Kirillova, M. S.; Pérez-Jimeno, A. H.; Calleja, P.; Boothe, J. R.; Echavarren, A. M. *J. Am. Chem. Soc.* **2019**, *141*, 11858–11863.

[24] Chen, H.; Sweet, J. A.; Lam, K. C.; Rheingold, A. L.; McGrath, D. V. *Tetrahedron: Asymmetry* **2009**, *20*, 1672–1682.

[25] (a) Fadeyi, O. O.; Schulte, M. L.; Lindsley, C. W. *Org. Lett.* **2010**, *12*, 3276–3278. (b) Le, N. N.; Rodriguez, A. M.; Alleyn, J. R.; Gesinski, M. R. *Synlett* **2018**, *29*, 2195–2198.

afforded **29** as a 6:1 mixture of isomers (*trans*/*meso*), separated by recrystallization. Then, the di-adamantyl phosphine was introduced, followed by the complexation of the ligand with chloro(dimethylsulfide)gold(I) afforded (*S*,*S*)-**31**.



Scheme 5. Synthesis of chiral gold(I) complex (*S*,*S*)-**31** with phenyl groups as substituents of the pyrrolidinyl scaffold.

It was noticed that, the presence of bulky substituents in the aryl groups of the pyrrolidine scaffold resulted detrimental for the reduction reaction as a result of the steric hindrance. So, a more general and uniform synthetic route was designed in order to access a family of pyrrolidinyl-biphenyl phosphine ligands (Scheme 6). The synthesis of the enantiopure aryl (*S*,*S*)-1,4-diaryl-1,4-diols **36a–c** (Ar = 3,5-$Ph_2C_6H_3$, Ar = C_6F_5 and Ar = 3,5-$(CF_3)_2C_6H_3$) started with the addition of vinylmagnesium bromide to the corresponding arylaldehyde **32a–c**, affording the allylic alcohols **33a–c**. Then, through an enzymatic kinetic resolution,[26] the enantiopure allylic alcohols **34a–c** were obtained and the alkene metathesis using Grubbs 2nd generation catalyst[27] gave the allylic alcohols **35a–c** whose alkenes were reduced through hydrogenation to afford the enantiopure aryl (*S*,*S*)-1,4-diaryl-1,4-diols **36a–c**.

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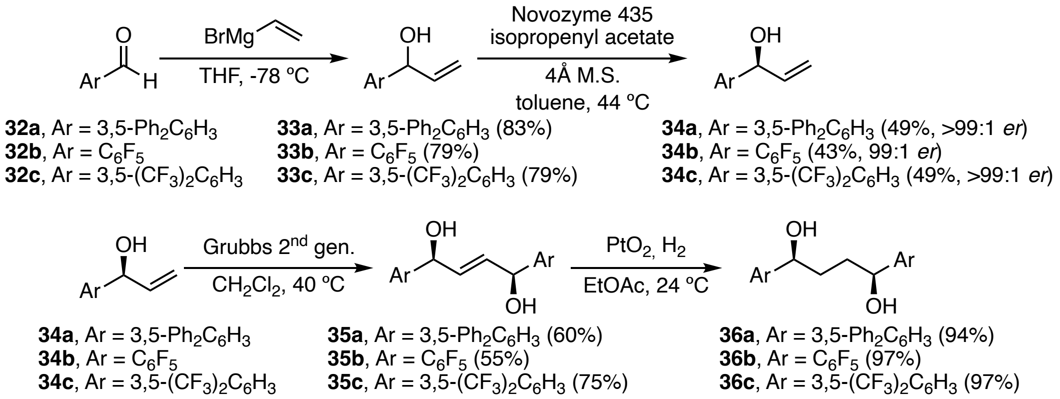
[26] (a) Štambaský, J.; Malkov, A. V.; Kočovský, P. *J. Org. Chem.* **2008**, *73*, 9148–9150. (b) Kirillova, M. S.; Muratore, M. E.; Dorel, R.; Echavarren, A. M. *J. Am. Chem. Soc.* **2016**, *138*, 3671–3674.

[27] Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.



32a, Ar = $3,5\text{-}Ph_2C_6H_3$
32b, Ar = C_6F_5
32c, Ar = $3,5\text{-}(CF_3)_2C_6H_3$

33a, Ar = $3,5\text{-}Ph_2C_6H_3$ (83%)
33b, Ar = C_6F_5 (79%)
33c, Ar = $3,5\text{-}(CF_3)_2C_6H_3$ (79%)

34a, Ar = $3,5\text{-}Ph_2C_6H_3$ (49%, >99:1 *er*)
34b, Ar = C_6F_5 (43%, 99:1 *er*)
34c, Ar = $3,5\text{-}(CF_3)_2C_6H_3$ (49%, >99:1 *er*)

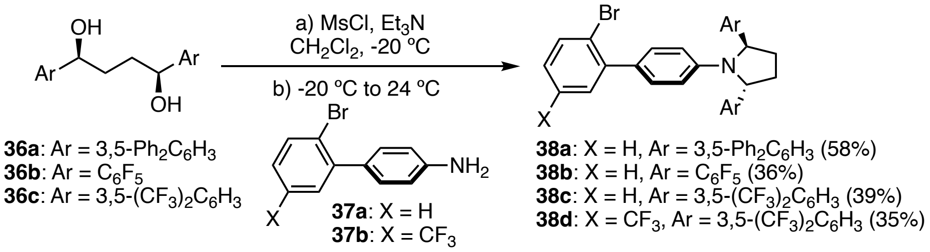
34a, Ar = $3,5\text{-}Ph_2C_6H_3$
34b, Ar = C_6F_5
34c, Ar = $3,5\text{-}(CF_3)_2C_6H_3$

35a, Ar = $3,5\text{-}Ph_2C_6H_3$ (60%)
35b, Ar = C_6F_5 (55%)
35c, Ar = $3,5\text{-}(CF_3)_2C_6H_3$ (75%)

36a, Ar = $3,5\text{-}Ph_2C_6H_3$ (94%)
36b, Ar = C_6F_5 (97%)
36c, Ar = $3,5\text{-}(CF_3)_2C_6H_3$ (97%)

Scheme 6. Synthesis of enantiopure aryl disubstituted (*S*,*S*)-1,4-diols **36a–b**.

The enantiopure (*S*,*S*)-**36a–c** were used to synthesize the new family of complexes, following the previously developed synthetic route to access (*S*,*S*)-**31** (Scheme 5). The double in situ mesylation of **36a–c**, followed by the double S_N2 reaction using the biaryl anilines **37a** and **37b**, led to pyrrolidine bromide precursors **38a–d** (Scheme 7).



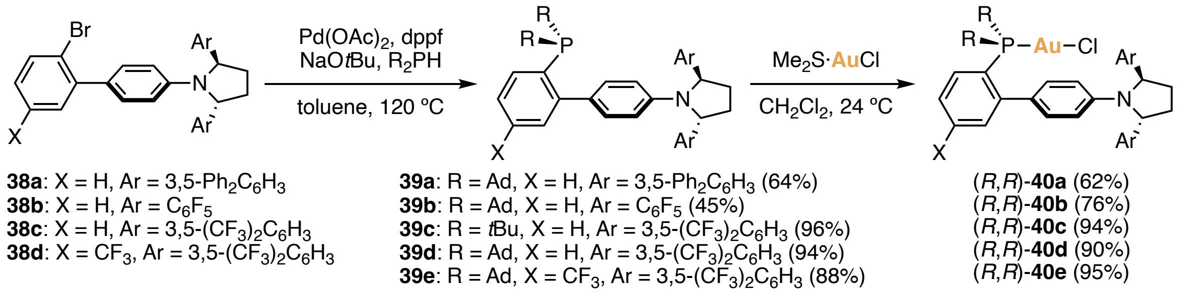
36a: Ar = $3,5\text{-}Ph_2C_6H_3$
36b: Ar = C_6F_5
36c: Ar = $3,5\text{-}(CF_3)_2C_6H_3$

37a: X = H
37b: X = CF_3

38a: X = H, Ar = $3,5\text{-}Ph_2C_6H_3$ (58%)
38b: X = H, Ar = C_6F_5 (36%)
38c: X = H, Ar = $3,5\text{-}(CF_3)_2C_6H_3$ (39%)
38d: X = CF_3, Ar = $3,5\text{-}(CF_3)_2C_6H_3$ (35%)

Scheme 7. Synthesis of pyrrolidinyl-biphenyl bromides.

Then, the introduction of di-adamantyl phosphine or di-*tert*-butyl phosphine to **38a–d** gave **39a–e**, followed by their complexation using dimethylsulfide gold(I) chloride, afforded (*R*,*R*)-**40a–e** complexes (Scheme 8).



38a: X = H, Ar = $3,5\text{-}Ph_2C_6H_3$
38b: X = H, Ar = C_6F_5
38c: X = H, Ar = $3,5\text{-}(CF_3)_2C_6H_3$
38d: X = CF_3, Ar = $3,5\text{-}(CF_3)_2C_6H_3$

39a: R = Ad, X = H, Ar = $3,5\text{-}Ph_2C_6H_3$ (64%)
39b: R = Ad, X = H, Ar = C_6F_5 (45%)
39c: R = *t*Bu, X = H, Ar = $3,5\text{-}(CF_3)_2C_6H_3$ (96%)
39d: R = Ad, X = H, Ar = $3,5\text{-}(CF_3)_2C_6H_3$ (94%)
39e: R = Ad, X = CF_3, Ar = $3,5\text{-}(CF_3)_2C_6H_3$ (88%)

(*R*,*R*)-**40a** (62%)
(*R*,*R*)-**40b** (76%)
(*R*,*R*)-**40c** (94%)
(*R*,*R*)-**40d** (90%)
(*R*,*R*)-**40e** (95%)

Scheme 8. Phosphine and gold(I) introduction reactions for the synthesis of chiral gold(I) complexes (*R*,*R*)-**40a–e**.

Complex (*R*,*R*)-**40f** bears the chiral pyrrodinyl scaffold in 3' position (Figure 6) and it was synthesized following the procedure described above yielding a 5:1 mixture of rotamers. With all these complexes in hand (Figure 6), a study of their applications was carried out.

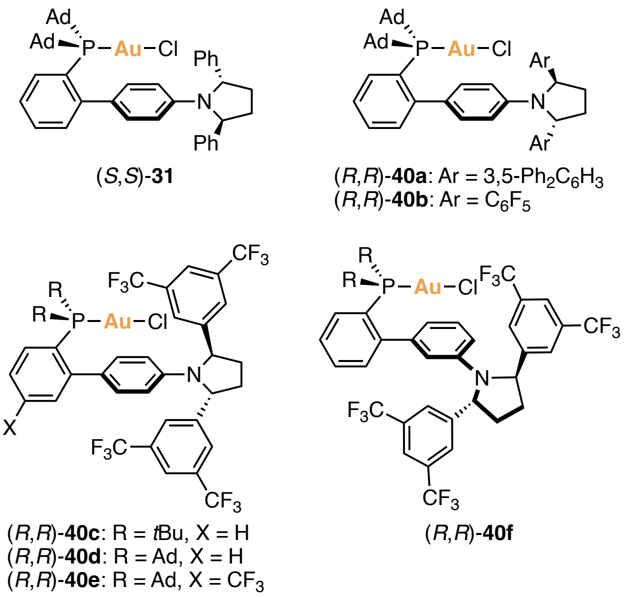
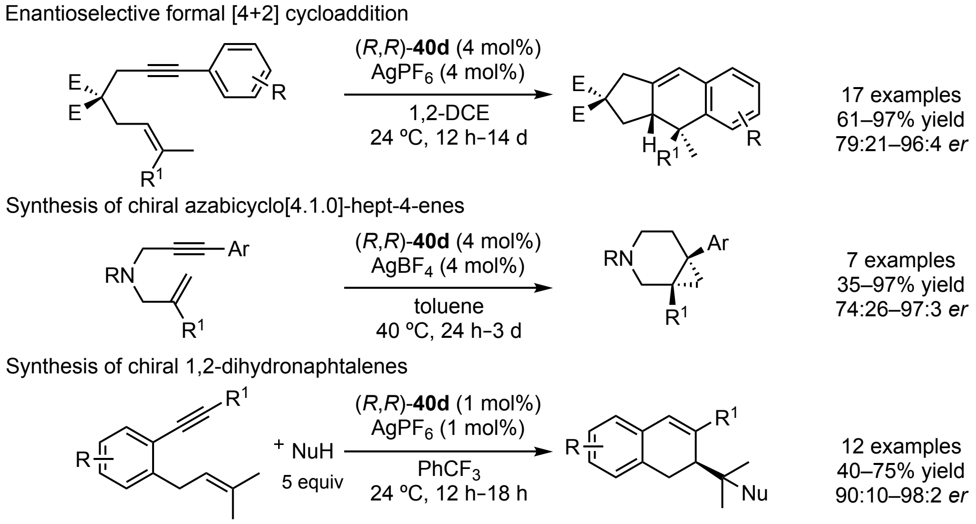


Figure 6. Family of chiral gold(I) complexes.

Applications

All the catalysts were tested in three enantioselective cyclization reactions of 1,6-arylarenes: in the enantioselective formal [4+2] cycloaddition of 1,6-arylarenes giving cyclopenta[*b*]naphthalenes; in the synthesis of azabicyclo[4.1.0]-hept-4-enes using nitrogen-tethered 1,6-enynes; and in the alkoxycyclization of aryl-tethered 1,6-enynes, giving substituted 1,2-dihydronaphtalenes. In all the cases, the best results were obtained with (*R*,*R*)-**40d** (Scheme 9). Additionally, the alkoxycyclization reaction was applied to the first total synthesis of three carexane derivatives (carexanes O, I and P).

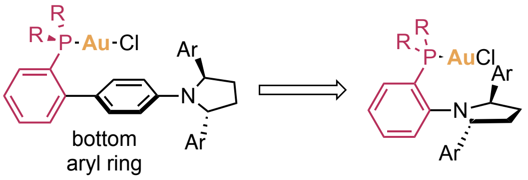


Scheme 9. Applications of (*R*,*R*)-**40d** complexes in asymmetric gold(I) catalysis.

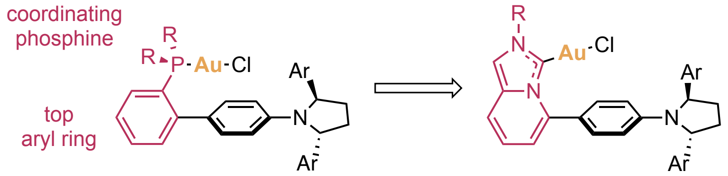
Objectives

The goal of this chapter is to synthesize three new families of chiral gold(I) complexes, based on the modification of the pyrrolidine ligands presented in 2019 by our group,23 and to study the effect of those modifications in different gold(I)-catalyzed reactions. These complexes are:

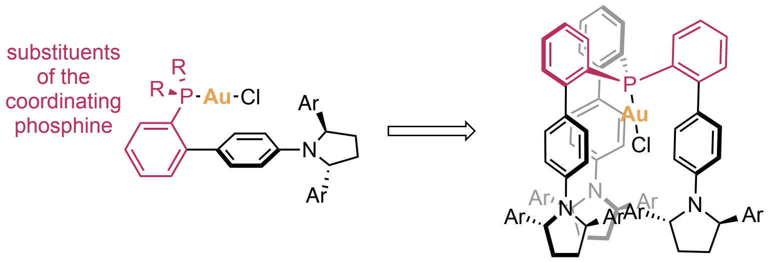
- Shorter complexes: the synthesis of smaller ligands by removing the bottom aryl ring of the biaryl scaffold, placing the pyrrolidine in *ortho* position to the phosphine.



- N-heterocyclic carbene complexes: changing the electronic properties by the substitution of the coordinating phosphine by an N-heterocyclic carbene.



- Sterically hindered complexes: the synthesis of bulkier phosphine ligands with one, two or three pyrrolidinyl-biaryl scaffolds.



Shorter Gold(I) Complexes

Introduction

The DalPhos ligands are *ortho*-(di-1-adamantylphosphino)anilines that were introduced in palladium catalysis by Stradiotto in 2010. They are air-stable chelating *N*,*P* ligands with good functional group tolerance. Two highly efficient examples are Me-DalPhos, with dimethylaniline in its structure, and Mor-DalPhos, in which the dimethylamino group is replace by a morpholine (Figure 7).[28]

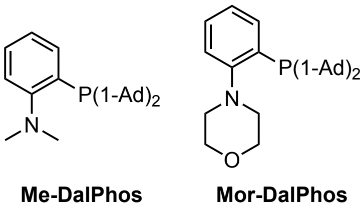
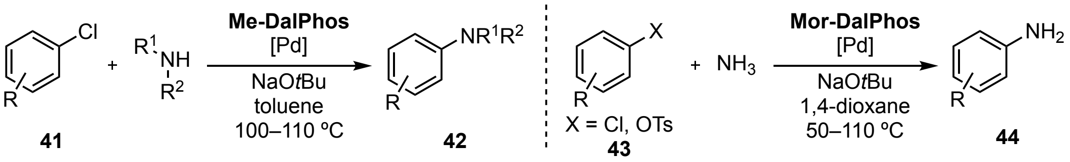


Figure 7. Examples of DalPhos ligands.

These complexes were found to be useful in Pd catalysis in C–N and C–C bond formation. Me-DalPhos has been shown to be highly reactive in cross-coupling reactions of aryl and heteroaryl chlorides **41** with ammonia, primary and secondary amines (Scheme 10, left).28[a] The Mor-DalPhos ligands showed more reactivity and chemoselectivity in cross-coupling reactions of deactivated aryl chlorides and tosylates **43** with ammonia (Scheme 10, right), achieving the first example of Pd-catalyzed cross coupling of ammonia at room temperature, using [(Mor-DalPhos)Pd(Ar)Cl] preformed as catalyst.28[b]



Scheme 10. Examples of palladium-catalyzed cross-coupling reactions using DalPhos ligands.

Other examples of palladium-catalyzed reactions using Mor-DalPhos ligands of aryl chlorides and tosylates **45** with hydrazine (Scheme 11, top)[29] and aryl chlorides, bromides and tosylates **47** with acetone (Scheme 11, bottom).[30]

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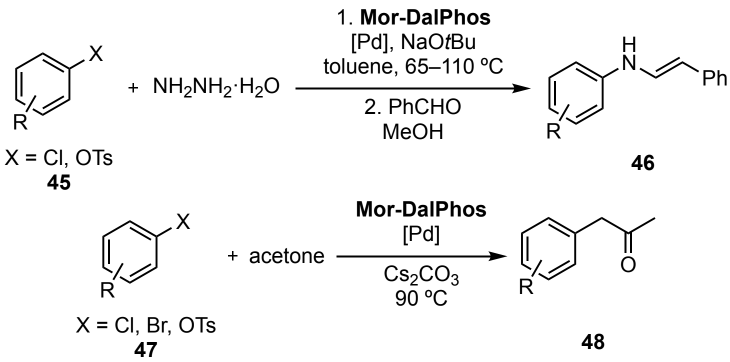
[28] (a) Lundgren, R. J.; Sappong-Kumankumah, A.; Stradiotto, M. *Chem. Eur. J.* **2010**, *16*, 1983–1991. (b) Lundgren, R. J.; Peters, B. D.; Alsabeh, P. G.; Stradiotto, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 4071–4074.

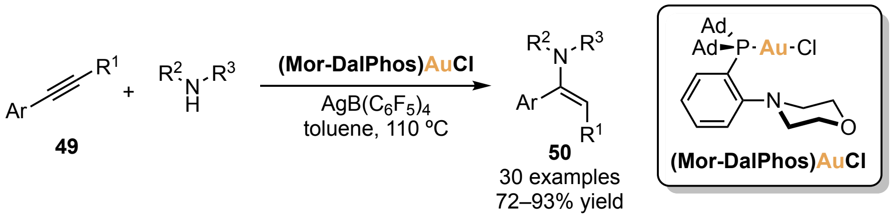
[29] Lundgren, R. J.; Stradiotto, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 8686–8690.

[30] Hesp, K. D.; Lundgren, R. J.; Stradiotto, M. *J. Am. Chem. Soc.* **2011**, *133*, 5194–5197.



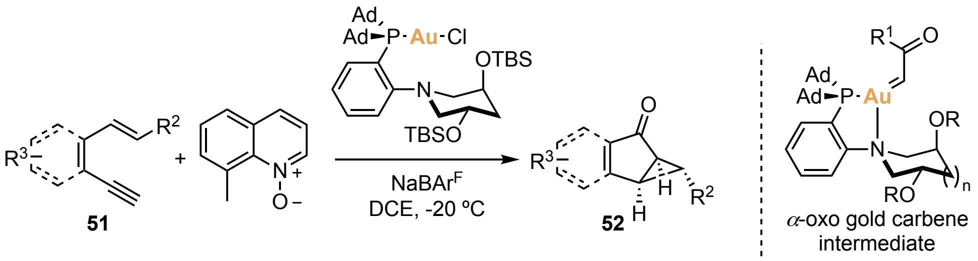
Scheme 11. Mor-DalPhos ligands used in palladium-catalyzed cross coupling reactions.

These ligands have been also used in gold(I)-catalyzed reactions. For example, in the regioselective and intermolecular hydroamination reaction of internal alkynes **49** with dialkylamines by Stradiotto in 2010, affording *E*-enamine products **50** (Scheme 12). Among the ligands tried for this reaction, most of them were *P,N*-ligand type, but also JohnPhos-type, obtaining the best result using Mor-DalPhos.[31]



Scheme 12. Gold(I) regioselective hydroamination reaction.

In 2015, Zhang developed a family of chiral *N,P*-bidentate ligands that were used in the gold(I)-catalyzed enantioselective oxidative cyclopropanation reaction of 1,5-enynes **51**.[32] The ligand allows the *in situ* generation of a highly reactive α-oxo gold(I) carbene intermediate (Scheme 13).



Scheme 13. Gold(I) enantioselective oxidative reaction.

Another application of these gold(I) complexes is in redox Au(I)/Au(III) arylation processes, described by Bourissou in 2017.[33] In the reaction, a Me-DalPhos gold(III) phenyl intermediate **53** is generated through an oxidative addition of an aryl iodide or bromide with Me-DalPhos gold(I) chloride in

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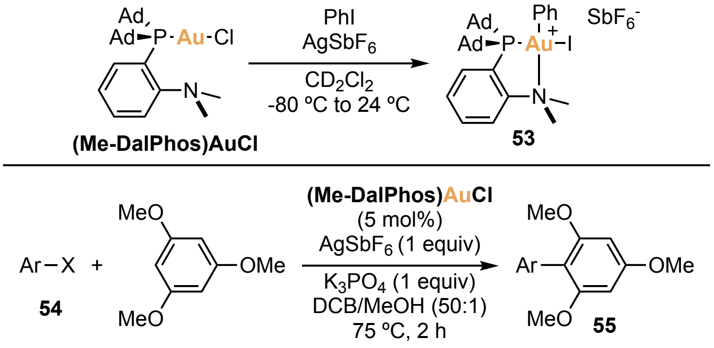
[31] Hesp, K. D.; Stradiotto, M. *J. Am. Chem. Soc.* **2010**, 132, 18026–18029.

[32] Ji, K.; Zheng, Z.; Wang, Z.; Zhang, L. *Angew. Chem. Int. Ed.* **2015**, *54*, 1245–1249.

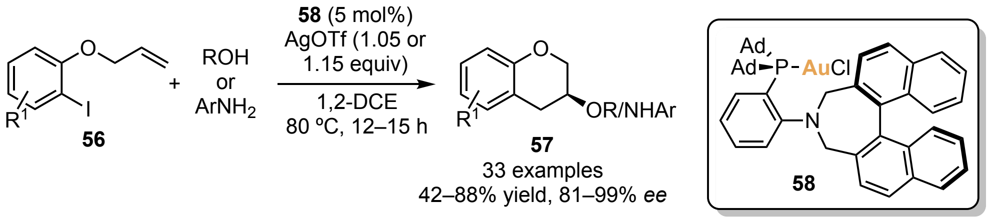
[33] Zeineddine, A.; Estévez, L.; Mallet-Ladeira, S.; Miqueu, K.; Amgoune, A.; Bourissou, D. *Nat. Commun.* **2017**, *8*, 565.

presence of $AgSbF_6$ (Scheme 14, top). This catalytic system allowed the cross-coupling reaction between aryl halides **54** with 1,3,5-trimethoxybenzene (Scheme 14, bottom).



Scheme 14. Au(I)/Au(III)-catalyzed reaction.

Since then, other Au(I)-catalyzed cross coupling reactions have been developed using this chelating *N*,*P*-catalytic system.[34] Enantioselective versions of these systems have been recently studied. In 2022, the group of Patil reported the use of chiral *N*,*P*-ligands **58** in enantioselective Au(I)/Au(III) redox catalysis for the 1,2-oxyarylation and 1,2-aminoarylation of alkenes **56** (Scheme 15).[35]



Scheme 15. Enantioselective Au(I)/Au(III) redox 1,2-oxyarylation and 1,2-aminoarylation reactions.

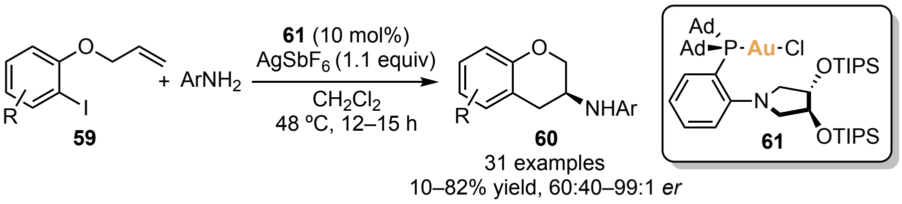
The same strategy was followed the same year using the chiral 3,4-disubstitutedpyrrolidine-based **61** catalyst. In this example, the enantioselective Au(I)/Au(III) redox intermolecular alkene arylamination of **59** was described (Scheme 16).[36]

---

[34] For some examples, see: (a) Rodriguez, J.; Zeineddine, A.; Sosa Carrizo, E. D.; Miqueu, K.; Saffon-Merceron, N.; Amgoune, A.; Bourissou, D. *Chem. Sci.* **2019**, *10*, 7183–7192. (b) Akram, M. O.; Das, A.; Chakrabarty, I.; Patil, N. T. *Org. Lett.* **2019**, *21*, 8101–8105. (c) Chintawar, C. C.; Yadav, A. K.; Patil, N. T. *Angew. Chem. Int. Ed.* **2020**, *59*, 11808–11813. (d) Rigoulet, M.; Thillaye du Boullay, O.; Amgoune, A.; Bourissou, D. *Angew. Chem. Int. Ed.* **2020**, *59*, 16625–16630. (e) Tathe, A. G.; Chintawar, C. C.; Bhoyare, V. W.; Patil, N. T. *Chem. Commun.* **2020**, *56*, 9304–9307. (f) Rodriguez, J.; Tabey, A.; Mallet-Ladeira, S.; Bourissou, D. *Chem. Sci.* **2021**, *12*, 7706–7712. (g) Tathe, A. G.; Urvashi; Yadav, A. K.; Chintawar, C. C.; Patil, N. T. *ACS Catal.* **2021**, *11*, 4576–4582. (h) Rodriguez, J.; Vesseur, D.; Tabey, A.; Mallet-Ladeira, S.; Miqueu, K.; Bourissou, D. *ACS Catal.* **2022**, *12*, 993–1003.

[35] Chintawar, C. C.; Bhoyare, V. W.; Mane, M. V.; Patil, N. T. *J. Am. Chem. Soc.* **2022**, *144*, 7089–7095.

[36] Ye, X.; Wang, C.; Zhang, S.; Tang, Q.; Wojtas, L.; Li, M.; Shi, X. *Chem. Eur. J.* **2022**, *28*, e202201018.



Scheme 16. Enantioselective Au(I)/Au(III) redox arylamination reactions.

Atropisomerism

Atropisomerism is a subclass of conformers referred to an axial dissymmetry induced by restricted rotation around a single bond occurring due to steric and/or electronic effects. It generates conformational stereoisomers with axial chirality.[37] This is mostly known between sterically hindered biaryl substituents (Figure 8), but it is also known in anilines and aromatic amides. Axially chiral biaryl and heterobiaryl scaffolds have become important in chiral privileged ligands and catalysts,[38] organocatalysis,[39] biological active natural products (e.g., (*M*)-Knipholone and (*M*)-Murrastifoline)[40] (Figure 8) and functional materials.[41] In this context, different methods for their synthesis have been developed, classified in cyclization and coupling reactions, and kinetic resolutions.40[a,42] Using gold(I) catalysis, the group of Alcarazo recently reported the atroposelective synthesis of chiral biaryls 1,1'-binaphthalene-2,3'-diols.[43]

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[37] *The IUPAC Compendium of Chemical Terminology: The Gold Book*, 4th ed.; Gold, V., Ed.; International Union of Pure and Applied Chemistry (IUPAC): Research Triangle Park, NC, **2019**.

[38] (a) Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691–1693. (b) Chen, Y.; Yekta, S.; Yudin, A. K. *Chem. Rev.* **2003**, *103*, 3155–3212. (c) Brunel, J. M. *Chem. Rev.* **2005**, *105*, 857–898.

[39] (a) Čorić, I.; List, B. *Nature* **2012**, *483*, 315–319. (b) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. *Chem. Rev.* **2014**, *114*, 9047–9153. (c) Maji, R.; Mallojjala, S. C.; Wheeler, S. E. *Chem. Soc. Rev.* **2018**, *47*, 1142–1158.

[40] (a) Bringmann, G.; Mortimer, A. J. P.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 5384–5427. (b) Clayden, J.; Moran, W. J.; Edwards, P. J.; Laplante, S. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 6398–6401. (c) Kozlowski, M. C.; Morgan, B. J.; Linton, E. C. *Chem. Soc. Rev.* **2009**, *38*, 3193–3207. (d) Laplante, S. R.; Edwards, P. J.; Fader, L. D.; Jakalian, A.; Hucke, O. *ChemMedChem* **2011**, *6*, 505–513. (e) Laplante, S. R.; Fader, L. D.; Fandrick, K. R.; Fandrick, D. R.; Hucke, O.; Kemper, R.; Miller, S. P. F.; Edwards, P. J. *J. Med. Chem.* **2011**, *54*, 7005–7022. (f) Bringmann, G.; Gulder, T.; Gulder, T. A. M.; Breuning, M. *Chem. Rev.* **2011**, *111*, 563–639.

[41] (a) Pu, L. *Chem. Rev.* **1998**, *98*, 2405–2494. (b) Pu, L. *Acc. Chem. Res.* **2012**, *45*, 150–163.

[42] Cheng, J. K.; Xiang, S.; Li, S.; Ye, L.; Tan, B. *Chem. Rev.* **2021**, *121*, 4805–4902.

[43] Zhang, J.; Simon, M.; Golz, C.; Alcarazo, M. *Angew. Chem. Int. Ed.* **2020**, *59*, 5647–5650.

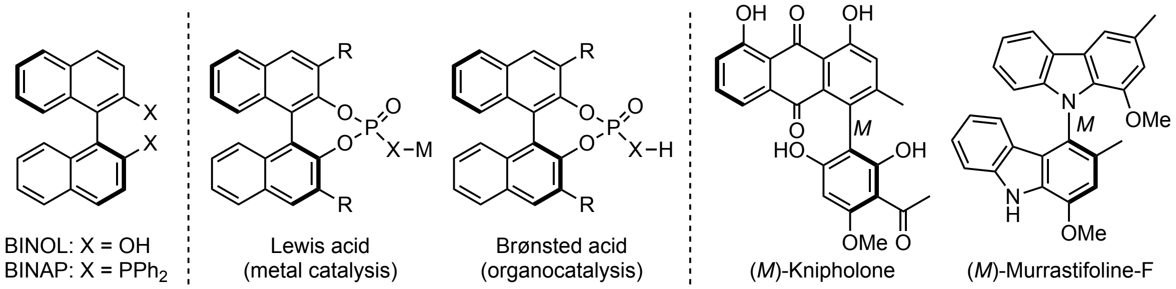
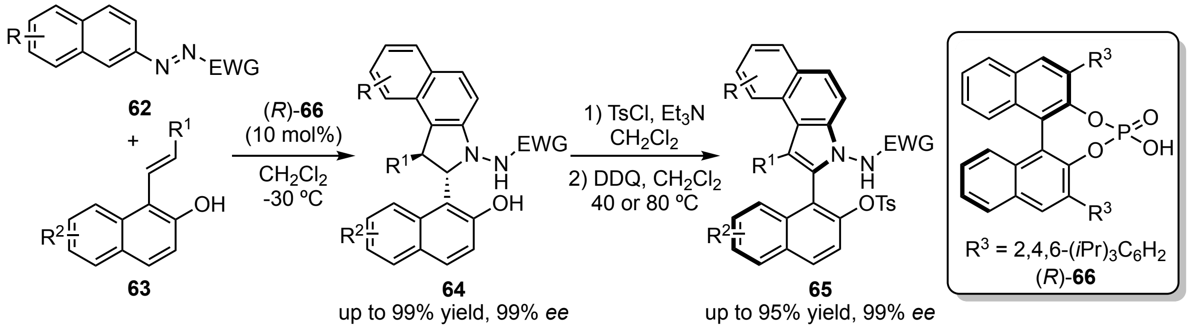


Figure 8. Selected examples of axially chiral ligands, catalysts and naturally occurring compounds.

The asymmetric synthesis of axially chiral heterobiaryl compounds that contain an indole in their structures have become an emerging area of study since they are present in ligands and natural products.[44] In 2019, the Zhou group developed a method for the synthesis of C2-arylindoles **65** using a chiral phosphoric acid (*R*)-**66**, through a (3+2) cyclization catalysis of **62** and **63** followed by an oxidation reaction (Scheme 17).[45]



Scheme 17. Synthesis of axially chiral C2-arylindoles using a chiral phosphoric acid.

The same year, the group of Yan reported a synthesis of axially chiral C2-naphtylindoles **68** via vinylidene *ortho*-quinone methide (VQM) intermediate, through an organocatalytic-asymmetric cyclization catalysis of *ortho*-alkynylanilines using the chiral bifunctional Brønsted catalyst **69** (Scheme 18).[46]

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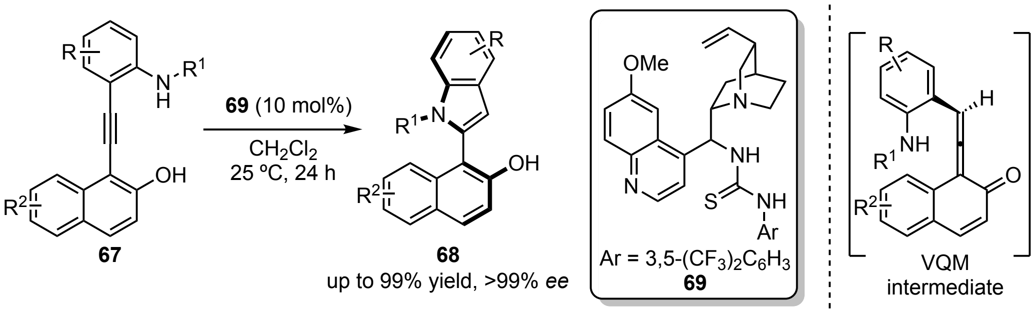
[44] Li, T.; Liu, S.; Tan, W.; Shi, F. *Chem. Eur. J.* **2020**, *26*, 15779–15792.

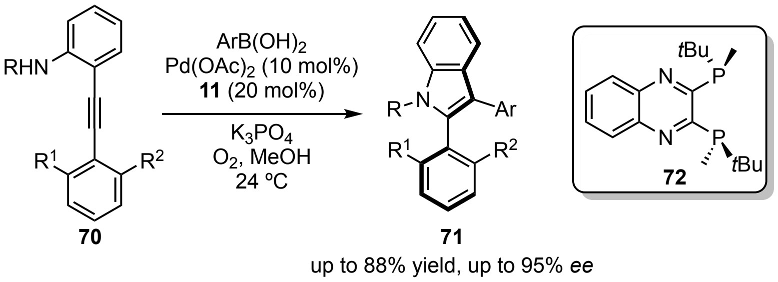
[45] Hu, Y.-L.; Wang, Z.; Yang, H.; Chen, J.; Wu, Z.-B.; Lei, Y.; Zhou, L. *Chem. Sci.* **2019**, *10*, 6777–6784.

[46] Peng, L.; Li, K.; Xie, C.; Li, S.; Xu, D.; Qin, W.; Yan, H. *Angew. Chem. Int. Ed.* **2019**, *58*, 17199–17204; *Angew. Chem.* **2019**, *131*, 17359–17364.



Scheme 18. Synthesis of axially chiral C2-arylindoles using chiral Brønsted base.

In 2020, the Zhu group designed a Pd-catalyzed enantioselective Cacchi reaction strategy to access axially chiral C2-indoles.[47] The reaction was carried out between the 2-alkynyl aniline **70** and a boronic acid under oxidative conditions using biphosphine **72** as chiral ligand, synthesizing these axially chiral C2-arylindoles 2,3-disubstituted **71** in good yields and high enantioselectivities (Scheme 19).[48]



Scheme 19. Synthesis of axially chiral C2-arylindoles via the Cacchi reaction.

Results and Discussion[49]

Design and Synthesis of Shorter Chiral Pyrrolidine Gold(I) Complexes

Inspired by the *ortho*-phosphinylaniline structures and the ligands reported in our group in 201923 we envisioned the synthesis of chiral 2-phosphine disubstituted-pyrrolidine ligands and studying their gold(I) reactivity.

The first approach was similar to the previously described in our group for the synthesis of the bromide intermediates (*R*,*R*)-**38a–d** of the chiral gold(I) complexes (Scheme 7), using (*R*,*R*)-1,4-diol **73** and 2-bromo-aniline (Scheme 20). The cyclization reaction gave a complex mixture (desired product (*S*,*S*)-**74** or an isomer observed by GC-MS), but the purification attempts were unsuccessful.

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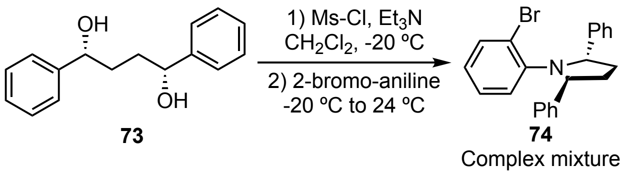
[47] Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873–2920. Update 1: Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2011**, *111*, PR215–PR283.

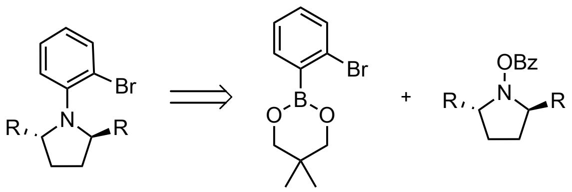
[48] He, Y. P.; Wu, H.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2020**, *59*, 2105–2109; *Angew. Chem.* **2020**, *132*, 2121–2125.

[49] Parts of the experiments described in this section were done in collaboration with Dr. Nicolás Fincias and were based upon preliminary work by Dr. Marc Montesinos and Yufei Wang.



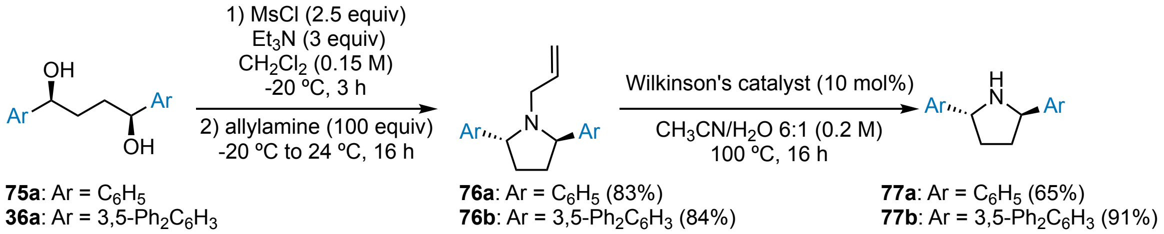
Scheme 20. First attempt for the cyclization reaction.

Other approaches were studied for the formation of C–N bonds with α,α'-disubstituted pyrrolidines and highly sterically hindered aryl groups. However, several attempts following Buchwald-Hartwig amination or Ullmann-type reactions resulted unsuccessful, certainly due to the steric crowding around the nitrogen center. Instead, other approach was carried out based on an already described procedure, a modified Chan-Lam reaction.[50] This method relies on a Cu-catalyzed coupling reaction between benzoyl hydroxylamines and a boronic ester (Scheme 21).



Scheme 21. Retrosynthetic pathway for the C-N synthesis.

After the optimization of the reaction conditions[51] the *N*-(2-bromophenyl)-pyrrolidines could be synthesized using the following synthetic sequence. The mesylation of the (*S*,*S*)-diols **75a** and **36a** followed by a double $\mathrm{S_N}2$ addition of the allylamine, allowing the synthesis of the pyrrolidines (*R*,*R*)-**76a–b** in 83 and 84% yields respectively (Scheme 22). Then, their deprotection using the Wilkinson's catalyst afforded the free pyrrolidines **77a** and **77b**.



Scheme 22. Formation of the free pyrrolidines **77a** and **77b**.

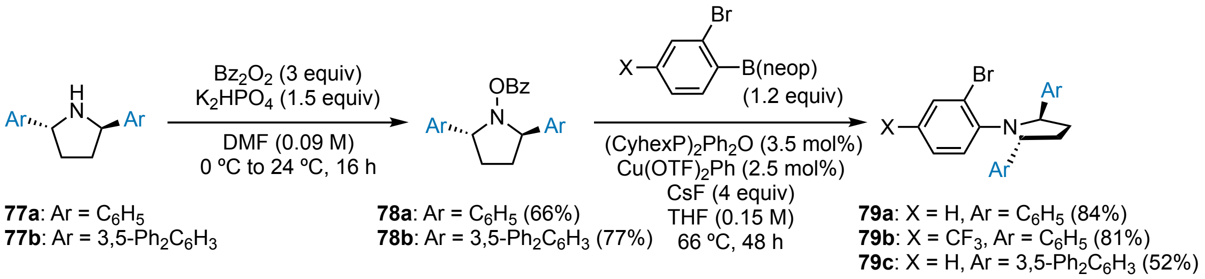
The synthesis of the benzoyl hydroxylamines **78a** and **78b** was accessed by the reaction of the amine **77a** and **77b** with dibenzoylperoxide.[52] The latter were then coupled with the corresponding boron neopentyl aryl moiety under slightly different conditions than the reported ones,50 with a proton or a CF_3 group in *para* position, affording **79a**, **79b** and **79c** (Scheme 23).

---

[50] Mailig, M.; Ruckera, R. P.; Lalic, G. *Chem. Commun.* **2015**, *51*, 11048–11051.

[51] The first attempts and the optimization of the conditions for the synthesis of these complexes were carried out by Dr. Marc Montesinos and Yufei Wang.

[52] Zhao, H.; Chen, X.; Jiang, H.; Zhang, M. *Org. Chem. Front.* **2018**, *5*, 539–543.



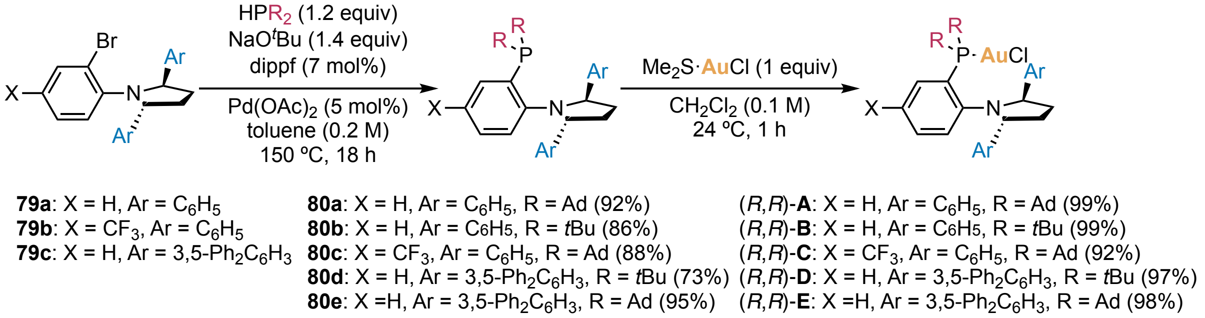
77a: Ar = C_6H_5
77b: Ar = 3,5-$Ph_2C_6H_3$

78a: Ar = C_6H_5 (66%)
78b: Ar = 3,5-$Ph_2C_6H_3$ (77%)

79a: X = H, Ar = C_6H_5 (84%)
79b: X = CF_3, Ar = C_6H_5 (81%)
79c: X = H, Ar = 3,5-$Ph_2C_6H_3$ (52%)

Scheme 23. Formation of the 2-bromoarylpyrrolidines **79a-c**.

The introduction of the corresponding dialkylphosphine to **79a-c** afforded the aryl phosphines **80a–e**, followed by the complexation of the gold(I) chloride source allowed the synthesis of five chiral complexes (*R*,*R*)-**A–E** (Scheme 24).



79a: X = H, Ar = C_6H_5
79b: X = CF_3, Ar = C_6H_5
79c: X = H, Ar = 3,5-$Ph_2C_6H_3$

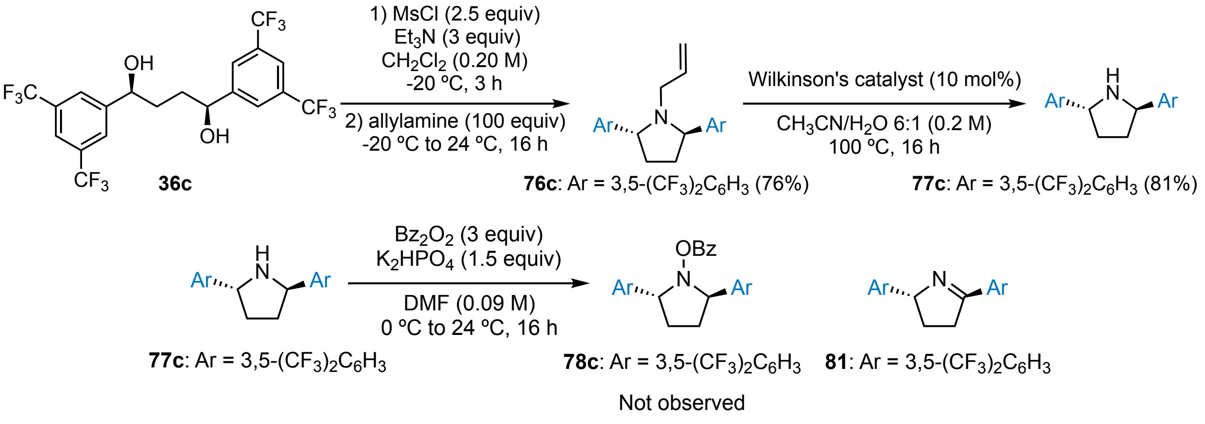
80a: X = H, Ar = C_6H_5, R = Ad (92%)
80b: X = H, Ar = C6H5, R = *t*Bu (86%)
80c: X = CF_3, Ar = C_6H_5, R = Ad (88%)
80d: X = H, Ar = 3,5-$Ph_2C_6H_3$, R = *t*Bu (73%)
80e: X =H, Ar = 3,5-$Ph_2C_6H_3$, R = Ad (95%)

(*R*,*R*)-**A**: X = H, Ar = C_6H_5, R = Ad (99%)
(*R*,*R*)-**B**: X = H, Ar = C6H5, R = *t*Bu (99%)
(*R*,*R*)-**C**: X = CF_3, Ar = C_6H_5, R = Ad (92%)
(*R*,*R*)-**D**: X = H, Ar = 3,5-$Ph_2C_6H_3$, R = *t*Bu (97%)
(*R*,*R*)-**E**: X =H, Ar = 3,5-$Ph_2C_6H_3$, R = Ad (98%)

Scheme 24. Synthesis of the chiral gold(I) complexes.

Unsuccessful Synthesis of Other Shorter Chiral Pyrrolidine Gold(I) Complexes

More ligands with other aryl substituents in the pyrrolidine were tried to be synthesized. The formation of the pyrrolidine (*R*,*R*)-**76c** using 1,4-diol (*S*,*S*)-**36c** and allylamine was successfully achieved, followed by its deprotection giving **77c** in good yields. However, its oxidation to the corresponding benzoyl hydroxylamine **78c** was not achieved, and only imine **81** was observed. Different conditions were tried (bases, solvents, temperatures and times), detecting only imine **81**.



36c

76c: Ar = 3,5-$(CF_3)_2C_6H_3$ (76%)

77c: Ar = 3,5-$(CF_3)_2C_6H_3$ (81%)

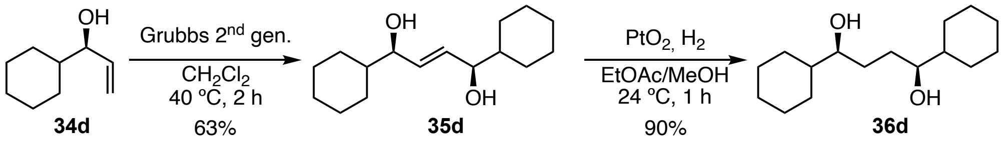
77c: Ar = 3,5-$(CF_3)_2C_6H_3$

78c: Ar = 3,5-$(CF_3)_2C_6H_3$
Not observed

81: Ar = 3,5-$(CF_3)_2C_6H_3$

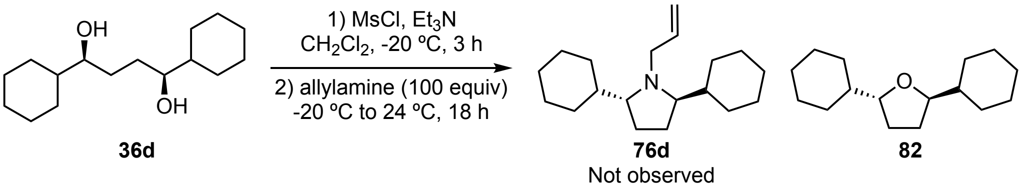
Scheme 25. Unsuccessful synthesis of a ligand with 3,5-$(CF_3)_2$-aryl groups as substituents of the pyrrolidine.

The synthesis of a ligand with α,α'-dicyclohexyl pyrrolidines was also attempted. The synthesis started with the preparation of the (*S,S*)-1,4-diol **36d** (Scheme 26). The alkene metathesis of the enantiopure allylic alcohol **34d**[53] using Grubbs 2nd generation catalyst afforded the allylic 1,4-diol **35d**. Then, the chiral (*S,S*)-1,4-diol **36d** was obtained by hydrogenation.



Scheme 26. Synthesis of (*S,S*)-1,4-diol **36d**.

After the double mesylation of (*S,S*)-**36d**, the double S_N2 with the allylamine did not lead to the formation of desired product (*R,R*)-**76d** (Scheme 27), instead, tetrahydrofuran **82** was detected as a single product by NMR and GC-MS.



Scheme 27. Unsuccessful synthesis of the allyl pyrrolidine **76d**.

As an alternative approach, the synthesis of the previously reported[54] cyclic sulfate **83** was successfully accessed in excellent yield (Scheme 28). However, the formation of pyrrolidine **79d** was not accomplished using different conditions, instead of a double S_N2 reaction, a double elimination happened leading to diene **84**.

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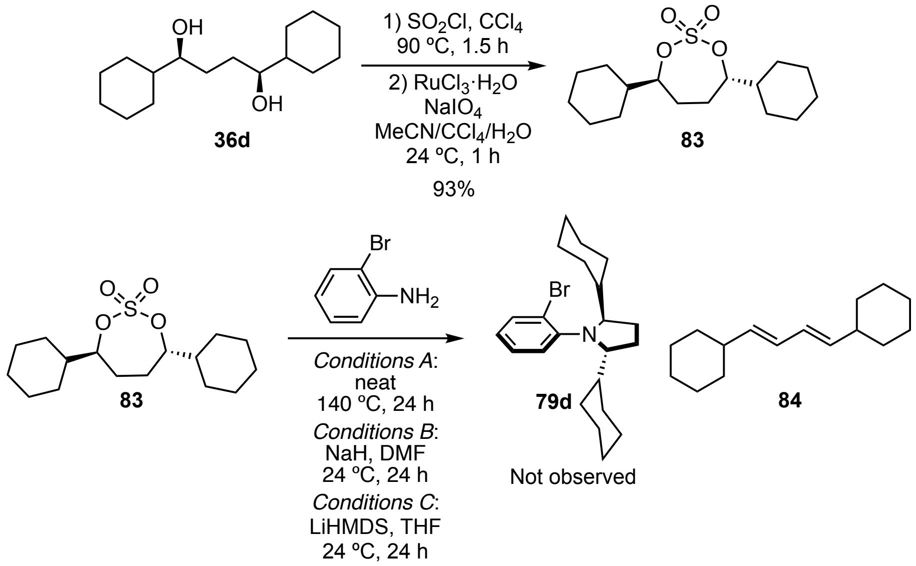
[53] Miloserdov, F. M.; Kirillova, M. S.; Muratore, M. E.; Echavarren, A. M. *J. Am. Chem. Soc.* **2018**, *140*, 5393–5400.

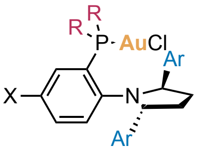
[54] Burk, M. J.; Harper, T. G. P.; Kalberg, C. S. *J. Am. Chem. Soc.* **1995**, *117*, 4423−4424.



Scheme 28. Unsuccessful synthesis of the aryl pyrrolidine **79d** through the cyclic sulfate **83**.

Study of the Reactivity in Different Transformations

We studied the reactivity of the new *ortho*-(pyrrolidinyl)phosphine aryl gold(I) complexes (*R*,*R*)-**A–E** (Figure 9) in different transformations. The results of some reactions were compared with those obtained with the chiral pyrrolidinyl-biphenyl phosphine gold(I) complexes already reported in our group, to check how the presence of the bottom aryl group can affect to the outcome of the reactions.



(*R*,*R*)-**A**: X = H, Ar = C_6H_5, R = Ad
(*R*,*R*)-**B**: X = H, Ar = C_6H_5, R = *t*Bu
(*R*,*R*)-**C**: X = CF_3, Ar = C_6H_5, R = Ad
(*R*,*R*)-**D**: X = H, Ar = 3,5-$Ph_2C_6H_3$, R = *t*Bu
(*R*,*R*)-**E**: X =H, Ar = 3,5-$Ph_2C_6H_3$, R = Ad

Figure 9. Chiral gold(I) complexes.

Atroposelective Cyclization of Sulfonamides

We started the study of the atroposelective cyclization of sulfonamide **85a** (Table 1). The optimization of the reaction conditions started with a screening of the catalysts, using $AgNTf_2$ as chloride scavenger in 1,2-dichloroethane to synthesize 2-naphthylindole **86a**. Catalysts (*R*,*R*)-**40d** and (*R*,*R*)-**40g**[55] (Table 1, Entries 1 and 2) presents similar behavior, excellent yields and good enantioselectivities. Surprisingly, the opposite enantiomer was obtained with complexes (*R*,*R*)-**A**, (*R*,*R*)-**B** and (*R*,*R*)-**C** (Table 1, Entries 3–5). In all cases, compound **86a** was obtained quantitatively; however, complexes (*R*,*R*)-**A** and (*R*,*R*)-**C** showed a superior enantioinduction compared to complex (*R*,*R*)-**B**, with an *er* of 15:85 and 27:73 respectively (Table 1, Entries 3 and 5). In contrast, complexes (*R*,*R*)-**D** and (*R*,*R*)-**E** with terphenyl groups as substituents of the pyrrolidines yielded **86a** in excellent yields and with lower

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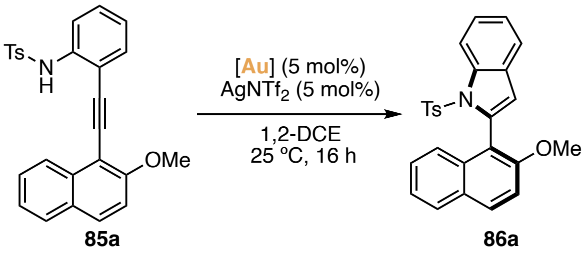
[55] Synthesized by Dr. Giuseppe Zuccarello. Synthesis described in the experimental section.

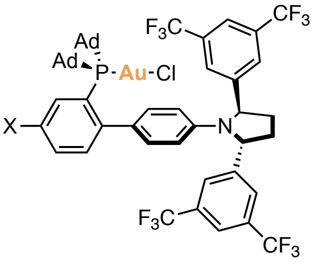
enantioselectivity, 68:32 and 71:29 *er* respectively (Table 1, Entries 6 and 7), but giving the same enantiomer that the one obtained with the complexes (*R*,*R*)-**40d** and (*R*,*R*)-**40g**.

Table 1. Catalyst screening for the atroposelective cyclization reaction.

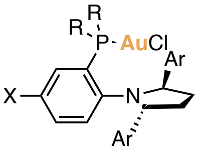


Entry	Catalyst	Conversion (%)[a]	Yield (%)[a]	*er*
1	(*R*,*R*)-**40d**	100	>99	87:13
2	(*R*,*R*)-**40g**	100	>99	88:12
3	(*R*,*R*)-**A**	100	>99	15:85
4	(*R*,*R*)-**B**	100	>99	27:73
5	(*R*,*R*)-**C**	100	>99	15:85
6	(*R*,*R*)-**D**	100	>99	68:32
7	(*R*,*R*)-**E**	100	>99	71:29

[a] Yield measured by ^{1}H NMR using diphenylmethane as internal standard.



(*R*,*R*)-**40d**: X = H
(*R*,*R*)-**40g**: X = CF_3

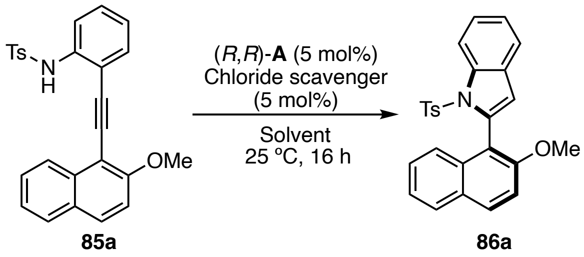


(*R*,*R*)-**A**: X = H, Ar = C_6H_5, R = Ad
(*R*,*R*)-**B**: X = H, Ar = C6H5, R = *t*Bu
(*R*,*R*)-**C**: X = CF_3, Ar = C_6H_5, R = Ad
(*R*,*R*)-**D**: X = H, Ar = 3,5-$Ph_2C_6H_3$, R = *t*Bu
(*R*,*R*)-**E**: X =H, Ar = 3,5-$Ph_2C_6H_3$, R = Ad

We continued the optimization of the reaction conditions using complex (*R*,*R*)-**A** by doing a screening of chloride scavengers (Table 2, Entries 1–5). First, the reaction was studied using $AgNTf_2$ without complex (R,R)-**A** and product **86a** was obtained in 91% yield, demonstrated that the reaction can be catalyzed by silver (Table 2, Entry 1).

$AgSbF_6$ and $AgBF_4$ silver salts were tested (Table 2, Entries 2 and 3) affording **86a** in excellent yields but the enantioselectivity was not better than the previous results using $AgNTf_2$. Using AgOTf provided the best result giving **86a** in excellent yield and slightly improved *er* of 14:86 (Table 2, Entry 4). Whereas $NaBAr_4^F$ lead to almost no conversion to the product (Table 2, Entry 5). Then, we performed a solvent screening (Table 2, Entries 6–9). Dichloromethane and ethyl acetate yielded **86a** with only small variations in terms of yields and enantioselectivities (Table 2, Entries 6 and 9), whereas aromatic solvents slightly improved the *er* to 13:87 (Table 2, Entries 7 and 8).

Table 2. Conditions screening with the catalyst (*R*,*R*)-**A**.



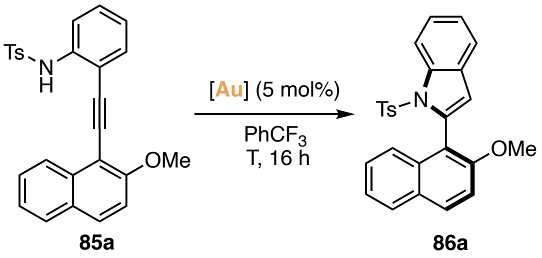
Entry	Chloride scavenger	Solvent	Conversion (%)[a]	Yield (%)[a]	*er*
1[b]	$AgNTf_2$	1,2-DCE	100	91	-
2	$AgSbF_6$	1,2-DCE	100	>99	16:84
3	$AgBF_4$	1,2-DCE	100	>99	14:86
4	AgOTf	1,2-DCE	100	96	14:86
5	$NaBAr_4^F$	1,2-DCE	7	2	n.d.
6	AgOTf	CH_2Cl_2	100	94	15:85
7	AgOTf	$PhCF_3$	100	>99	13:87
8	AgOTf	PhMe	100	>99	13:87
9	AgOTf	EtOAc	100	>99	14:86

[a] Yield measured by ^1H NMR using diphenylmethane as internal standard. [b] The reaction was carried out without (*R*,*R*)-**A**

Then, we studied the effect of the temperature, first we tested complex (*R*,*R*)-**A** at -4 ºC (Table 3, Entry 1), affording **86a** with 10:90 *er* resulting in very low conversion. We thought that at low temperature the chloride scavenger could not be operating and that we could be having solubility issues using *α*,*α*,*α*-trifluorotoluene ($PhCF_3$). To overcome this issue, we prepared the gold(I) complex (*R*,*R*)-**A1**, bearing the triflate moiety as a weakly coordinating counteranion that allows the catalyst to be active without the use of a silver scavenger. To our delight, an excellent yield and enantioselectivity (>99% yield, 8:92 *er*) was observed when the reaction was carried out with this complex (*R*,*R*)-**A1** at -4 ºC (Table 3, Entry 2). The enantioselectivity could be further improved by decreasing the temperature to -20 ºC (Table 3, Entry 3). In order to access to lower temperatures, toluene was used as solvent, and similar results were observed when the reaction was performed at -20 ºC and -40 ºC (Table 3, Entries 4 and 5 respectively).

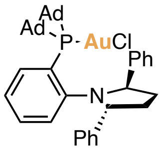
So finally, (*R*,*R*)-**A1** complex in *α*,*α*,*α*-trifluorotoluene at -20 ºC were the optimized conditions selected to study the reaction scope.

Table 3. Screening of temperatures.

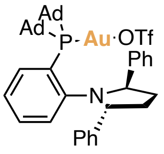


Entry	[Au]	T (ºC)	Conversion (%)	Yield (%)[a]	*er*
1[B]	(*R*,*R*)-**A**	–4	22	11	10:90
2	(*R*,*R*)-**A1**	-4	100	>99	8:92
3	(*R*,*R*)-**A1**	-20	100	>99	6:94
4[C]	(*R*,*R*)-**A1**	-20	100	>99	7:93
5[C]	(*R*,*R*)-**A1**	-40	100	>99	5:95

[a] Yield measured by ^{1}H NMR using diphenylmethane as internal standard. [b] AgOTf (5 mol%). [c] Toluene.

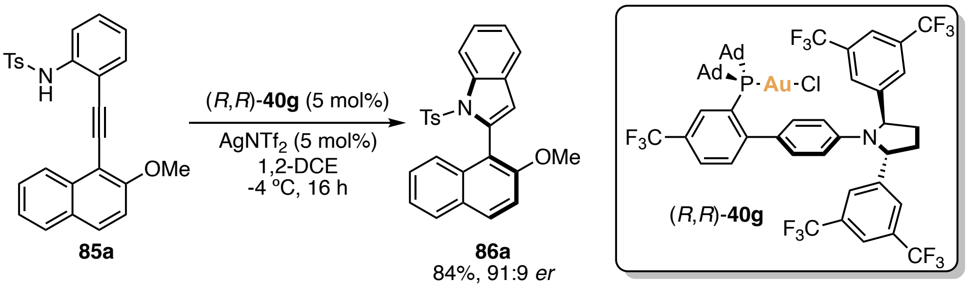


(*R*,*R*)-**A**



(*R*,*R*)-**A1**

The optimization of the reaction conditions using (*R*,*R*)-**40g** was also carried out,[56] obtaining the best results with AgNTf$_2$ in 1,2-dichloromethane at -4 ºC in 16 h, product **86a** was afforded in 84% yield with 91:9 *er* (Scheme 29).



Scheme 29. Optimal conditions using chiral gold(I) complex (*R*,*R*)-**40g**.

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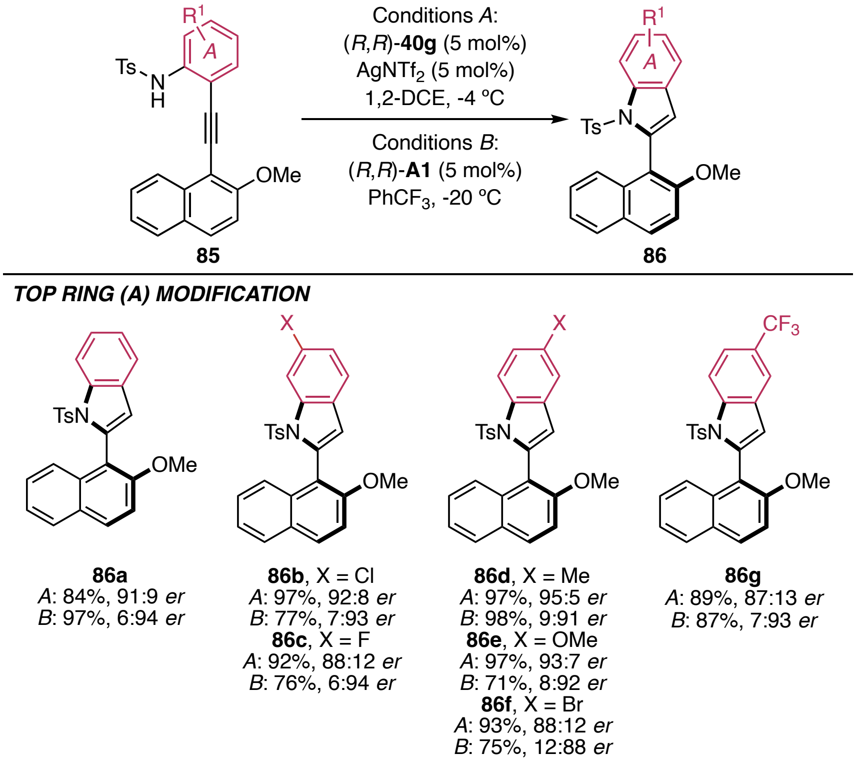
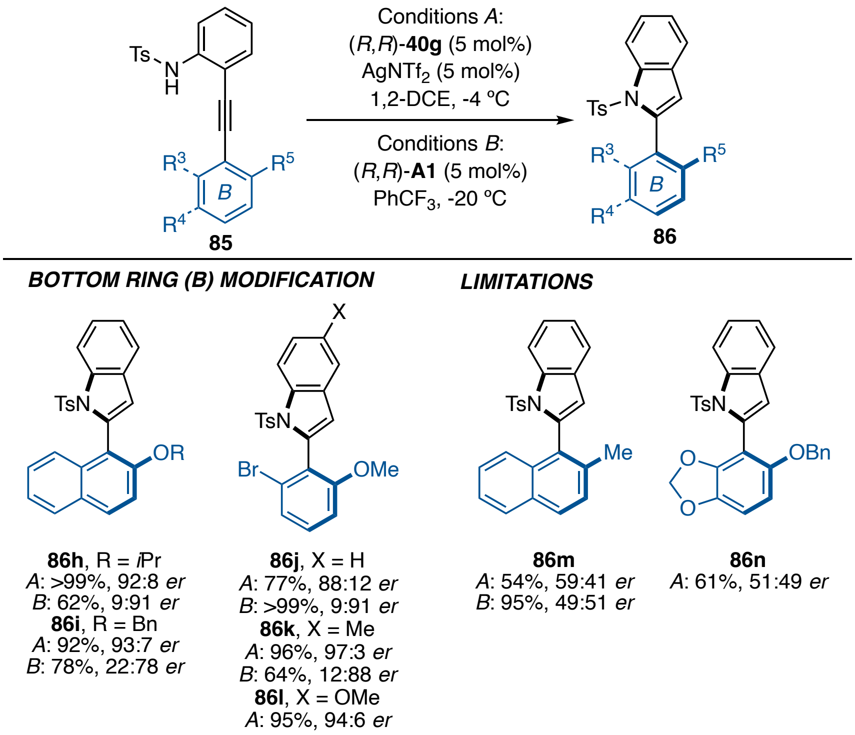
[56] The optimization and scope of this reaction with gold(I) complex (*R*,*R*)-**40g** have been done in our group by Dr. Leonardo Nannini, Dr. Giuseppe Zuccarello and Matthias Peeters.

With the optimal conditions in hand, we investigated the scope of the reaction using both catalysts (*R*,*R*)-**40g** and (*R*,*R*)-**A1**, obtaining opposite enantiomers in all the examples. We started modifying the top ring (*A*) by introducing different functionalizations (Scheme 30). Modifications in the substituents at *meta* position to the aniline gave 2-aryl indoles **86b** and **86c** in good yields with the same enantioselectivities than without substituents (**86a**), except when there was a fluor as substituent using (*R*,*R*)-**40g** that the enantioselectivity was slightly lower. Analogous results were obtained when the substituents were present in *ortho* position, affording **86d–g**.



Scheme 30. Scope with top ring (*A*) modifications.

We followed the study of the scope introducing modifications in the bottom aryl group (*B*) (Scheme 31). The substitution of the methoxy group by a bulkier substituent, an isopropoxy group, did not affect the enantioselectivity, obtaining **86h** in 92:8 using (*R*,*R*)-**40g** and 9:91 *er* using (*R*,*R*)-**A1**. When it was changed by a benzyloxy group **86i** was obtained with a moderate enantioselectivity. Changing the naphthyl by a phenyl *ortho*-disubstituted with a methoxy and a bromide gave **86j** and **86k**, adding a methyl group as a substituent at *para* position to the aniline, from moderate to excellent yields and enantioselectivities. It was also added a methoxy group at *para* position and the reaction was tested using (*R*,*R*)-**40g** affording **86l** in excellent yield and enantioselectivity. Surprisingly, when the methoxy was replaced by a methyl group there was no enantioinduction (**86m**). The same result was observed when the dioxolane-substituted substrate was tested using (*R*,*R*)-**40g**, the indole **86n** was obtained in a racemic manner.



86h, R = *i*Pr
A: >99%, 92:8 *er*
B: 62%, 9:91 *er*
86i, R = Bn
A: 92%, 93:7 *er*
B: 78%, 22:78 *er*

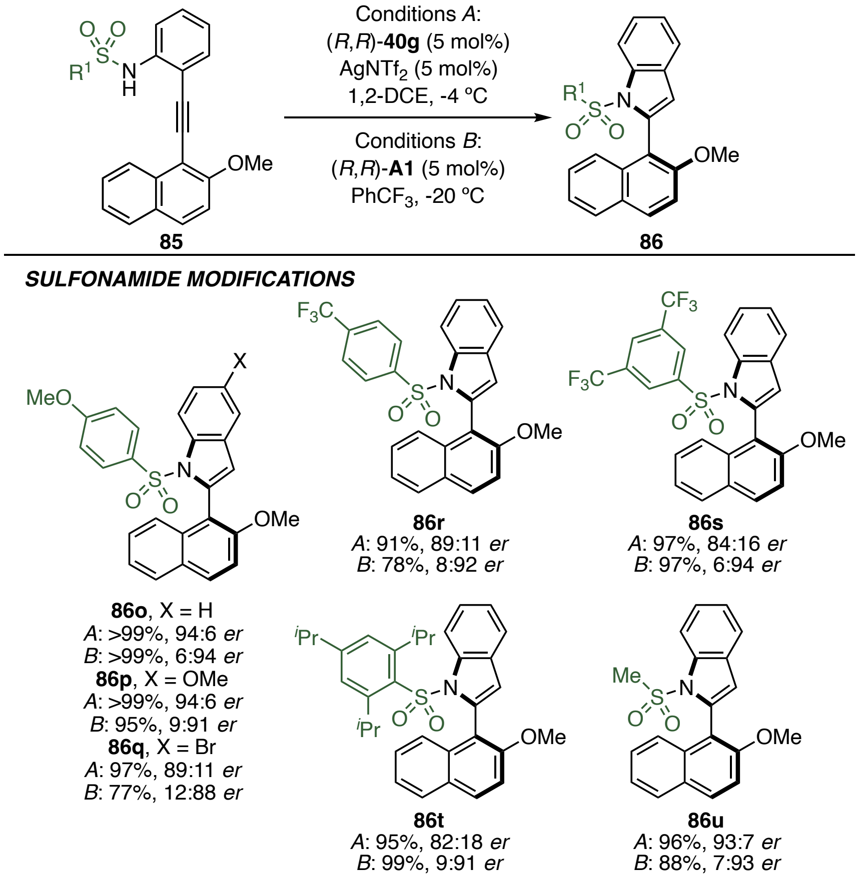
86j, X = H
A: 77%, 88:12 *er*
B: >99%, 9:91 *er*
86k, X = Me
A: 96%, 97:3 *er*
B: 64%, 12:88 *er*
86l, X = OMe
A: 95%, 94:6 *er*

86m
A: 54%, 59:41 *er*
B: 95%, 49:51 *er*

86n
A: 61%, 51:49 *er*

Scheme 31. Scope with bottom ring (*B*) modifications.

Finally, anilines with modifications in the electronic properties of the sulfonamide were synthesized **85o–u**, obtaining 2-aryl indoles **86o–u** mostly in good yields and enantioselectivities using (*R*,*R*)-**40g** and (*R*,*R*)-**A1** (Scheme 32).



Scheme 32. Scope with sulfonamide modifications.

Crystals of products **86a** and **86l** were obtained when the reaction was carried out with complex (*R*,*R*)-**40g** and they were measured by X-ray diffraction (Figure 10). The configuration observed in these X-ray structures will sustain that the configuration obtained using complex (*R*,*R*)-**40g** is *M* or R_a, therefore the configuration obtained using complex (*R*,*R*)-**A1** is *P* or S_a.

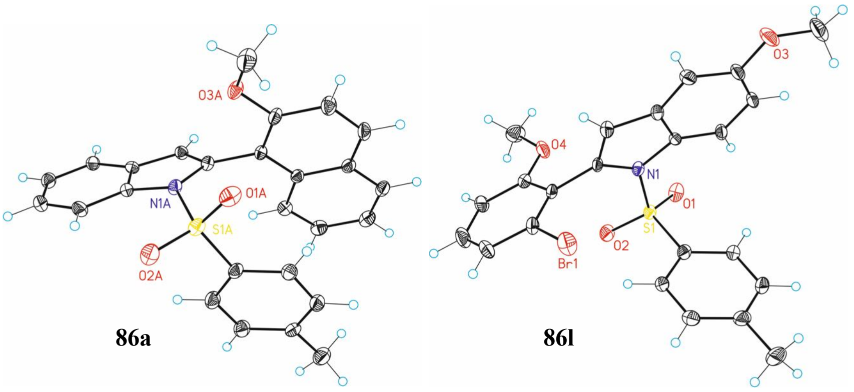


Figure 10. X-ray structure **86a** and **86l** synthesized using (*R*,*R*)-**40g**.

DFT calculations

The recognition of **85a** with the catalysts has been theoretically studied by DFT calculations (BP86-D3/6-31G(d) (C, H, P, O, F, N) and SDD (Au), PCM = CH_2Cl_2).[57] Complex (*R*,*R*)-**40h** has been simplified as (*R*,*R*)-**40h'** with *tert*-butyl instead of adamantyl groups. Two possible binding orientations *A* and *B* of the alkyne of the substrate coordinated to gold(I) have been considered, with the two possible prochiral faces of the *proR* and *proS* faces for sulfonamide **85a**. Orientation *A* corresponds to the one with the methoxynaphthyl **85a** closer with the aryl C2-substituent of the pyrrolidine (Scheme 33). This orientation was favored in both catalysts (*R*,*R*)-**40h'** and (*R*,*R*)-**S** by non-covalent interactions. For catalyst (*R*,*R*)- **40h'**, the lowest transition state ***A*-TS$_{\mathbf{Int1c\text{-}2c}}$** is stabilized by non-covalent interactions between the chiral pocket of the catalyst and the sulfonamide **85a**, preferentially forming intermediate ***A*-Int1c** and leading to product (*R*)-**86a** ($\Delta G^{\ddagger} = 2.2$ kcal/mol) (Scheme 33, a). This result is in agreement with the experimental result obtained with the analogue (*R*,*R*)-**40h** catalyst (91:9 *er*). For catalyst (*R*,*R*)-**S**, two possible pathways from orientation *A* can compete (Scheme 33, b). The *proS* transition state ***A*-TS$_{\mathbf{Int3a\text{-}4a}}$**, is lower in energy ($\Delta G^{\ddagger} = 1.1$ kcal/mol) than the *proR* ***A*-TS$_{\mathbf{Int3c\text{-}4c}}$** in a Curtin-Hammett scenario. In consequence, the major product comes from the intermediate *proS* (***A*-Int3a**), in spite of the intermediate *proR* (***A*-Int3c**) is 1.9 kcal/mol more stable.

The NCI plots[58] revealed the size and shape of the surfaces generated from the interactions present in both systems (Scheme 33). Thus, the chiral folding of sulfonamide **85a** and the stabilization of the corresponding transition states are favored by the T-shape π-π interactions between the naphthyl ring of the substrate **85a** and aryl substituent of the pyrrolidine of the corresponding catalyst.

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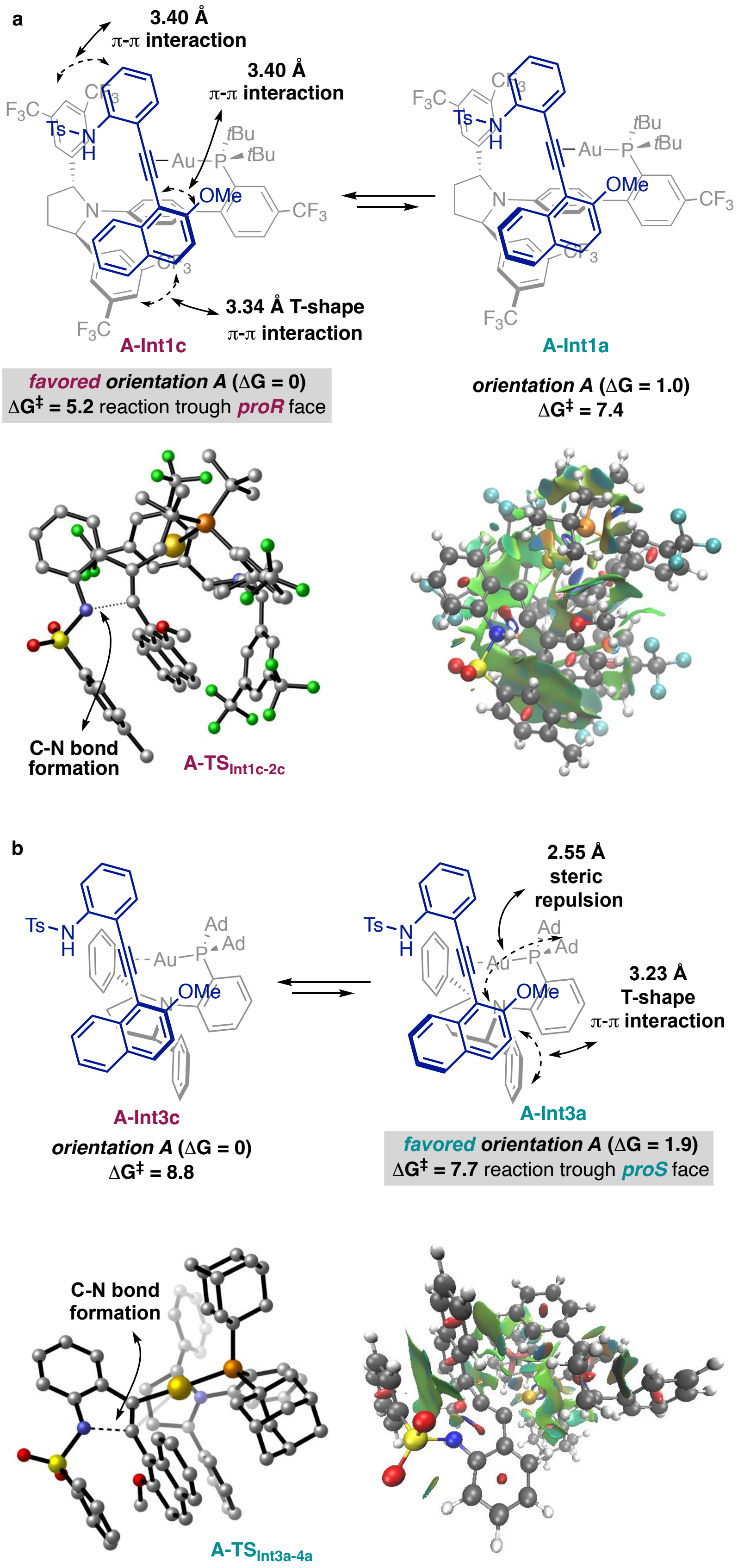
[57] The DFT calculations have been performed by Dr. Imma Escofet and Dr. Nicolás Fincias.

[58] (a) Johnson, E. R.; Keinan, S.; Mori-Sánchez, P.; Contreras-García, J.; Cohen, A. J.; Yang, W. *J. Am. Chem. Soc.* **2010**, *132*, 6498–6506. (b) Contreras-García, J.; Johnson, E. R.; Keinan, S.; Chaudret, R.; Piquemal, J.-P.; Beratan, D. N.; Yang, W. *J. Chem. Theory Comput.* **2011**, *7*, 625–632.

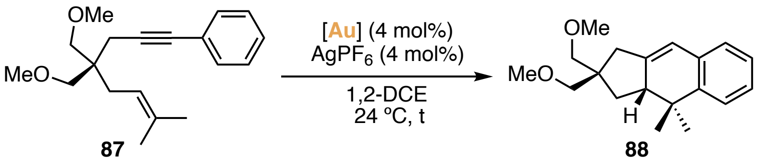


Scheme 33. Lowest energy intermediates and transition states of sulfonamide **85a** coordinated to catalysts (*R*,*R*)-**40h’** and (*R*,*R*)-**S**, 3D molecular representations and NCI plots.

Other Reactions

In order to compare the reactivity with the complex (*R*,*R*)-**40d**, the formal [4+2] cycloaddition of 1,6-arylenyne **87** was tried with these complexes to obtain cyclopenta[b]naphthalene **88** (Table 4). Complex (*R*,*R*)-**40d** gave the product in 92% yield and 94:6 *er* (Table 4, Entry 1). Complexes (*R*,*R*)-**A**–**E** lead to the opposite enantiomer of **88** also in excellent yields but with lower enantioselectivities (Table 4, Entries 2–6).

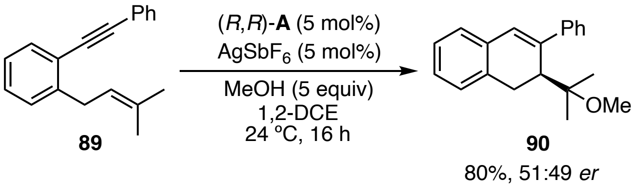
Table 4. Formal [4+2] cycloaddition reaction.



Entry	[Au]	t	Yield (%)[a]	*er*
1	(*R*,*R*)-**40d**	16 h	92	94:6
2	(*R*,*R*)-**A**	20 min	>99	15:85
3	(*R*,*R*)-**B**	40 min	98	20:80
4	(*R*,*R*)-**C**	20 min	98	14:86
5	(*R*,*R*)-**D**	40 min	>99	30:70
6	(*R*,*R*)-**E**	40 min	>99	22:78

[a] Yield measured by ^{1}H NMR using diphenylmethane as internal standard.

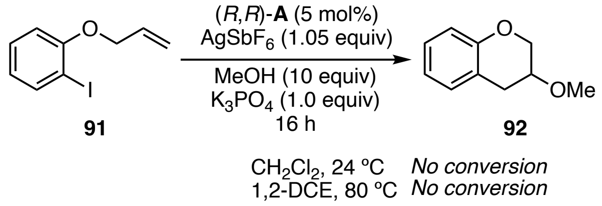
The alkoxycyclization reaction was also studied using the aryl-tethered 1,6-arylenyne **89**, methanol as nucleophile and complex (*R*,*R*)-**A** to afford 1,2-dihydronaphthalene **90** in 80% yield. These conditions did not show any enantioinduction for this reaction (Scheme 34).



Scheme 34. Asymmetric synthesis of 1,2-dihydronaphthalene **90**.

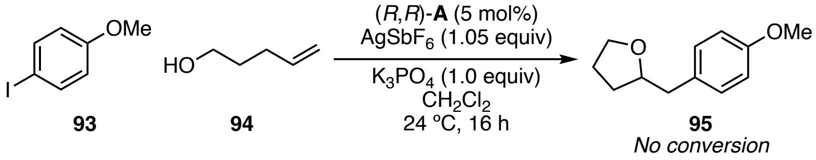
Au(I)/Au(III) Catalyzed Transformations

We also tested a Au(I)/Au(III) arylation process with this type of ligands, using (*R*,*R*)-**A** complex. We tried to perform an already reported reaction in racemic and enantioselective form, the 1,2-oxyarylation of alkene **91** using methanol (Scheme 35).35 However, no conversion was observed trying the reaction at 24 ºC and at 80 ºC.



Scheme 35. Gold-catalyzed 1,2-oxyarylation of alkene **91** reaction using (*R*,*R*)-**A** complex.

The gold(I)-catalyzed oxy-arylation using aryliodide **93** and alkenol **94** was previously reported in its racemic version using Me-DalPhos as ligand.[59] We did not observe any conversion to **95** when (*R,R*)-**A** was tested under the same reaction conditions (Scheme 36).



Scheme 36. Gold-catalyzed oxyarylation.

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[59] Rigoulet, M.; Thillaye du Boullay, O.; Amgoune, A.; Bourissou, D. *Angew. Chem. Int. Ed.* **2020**, *59*, 16625–16630.

N-Heterocyclic Carbenes Gold(I) Complexes

Introduction

N-Heterocyclic Carbenes in Gold(I) Catalysis

N-heterocyclic carbenes (NHC) have had a big impact in organometallic chemistry,[60] due to their high stability and reactivity enhancement.[61] In gold(I) chemistry, the first NHC-Au(I) complex was isolated in 1973[62] and since then, these complexes have become popular thanks to their reactivity and their applications in different areas, such as catalysis and medicine.[63] [(NHC)AuCl] complexes have the structure presented in Figure 11 and IMes, SIMes and IPr are examples of ligands frequently used in this type of complexes.

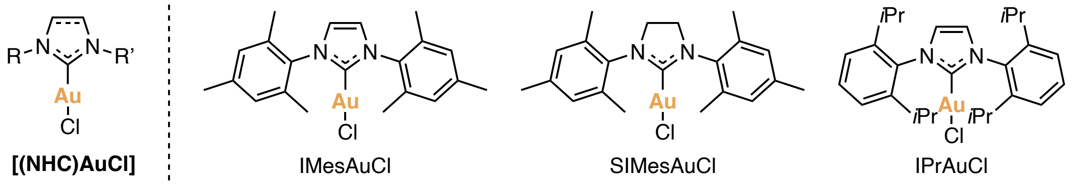

Figure 11. N-heterocyclic carbene gold(I) complexes.

Different methods have been developed for the synthesis of NHC-gold(I) complexes (Scheme 37). One of them is the direct metalation of the NHC salt precursor using a gold(I) source, commonly used tht·AuCl and Me_2S·AuCl, and a base, such as K_2CO_3.[64] Moreover, other method frequently used is the transmetalation, using silver or copper as the first metal source.[65]

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[60] Díez-González, S.; Marion, N.; Nolan, S. P. *Chem. Rev.* **2009**, *109*, 8, 3612–3676.

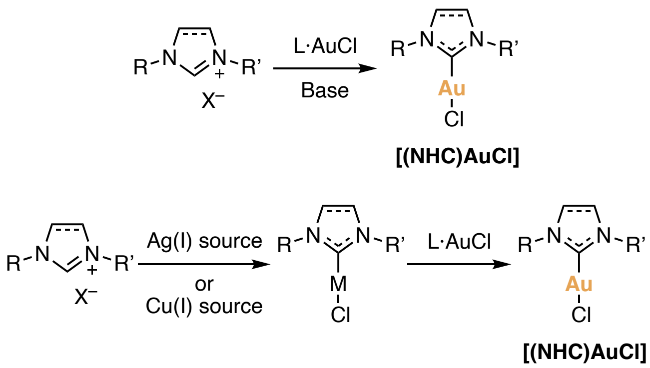
[61] Díez-González, S.; Nolan, S. P. *Coord. Chem. Rev.* **2007**, *251*, 874–883.

[62] Minghetti, G.; Bonati, F. *Journal of Organometallic Chemistry* **1973**, *54*, C62–C63.

[63] For reviews, see: (a) Lin, I. J. B.; Vasam, C. S. *Can. J. Chem.* **2005**, *83*, 812–825. (b) Raubenheimer, H. G.; Cronje, S. *Chem. Soc. Rev.* **2008**, *37*, 1998–2011. (c) Marion, N.; Nolan, S. P. *Chem. Soc. Rev.* **2008**, *37*, 1776–1782. (d) Nolan, S. P. *Acc. Chem. Res.* **2011**, *44*, 91–100.

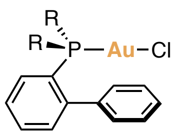
[64] For some examples see: (a) Fèvre, M.; Pinaud, J.; Leteneur, A.; Gnanou, Y.; Vignolle, J.; Taton, D.; Miqueu, K.; Sotiropoulos, J.-M. *J. Am. Chem. Soc.* **2012**, *134*, 6776–6784. (b) Collado, A.; Gómez-Suárez, A.; Martin, A. R.; Slawin, A. M. Z.; Nolan, S. P. *Chem. Commun.* **2013**, *49*, 5541–5543. (c) Visbal, R.; Laguna, A.; Gimeno, M. C. *Chem. Commun.* **2013**, *49*, 5642–5644. (d) Johnson, A.; Gimeno, M.C. *Chem. Commun.* **2016**, *52*, 9664–9667.

[65] (a) Wang, H. M. J.; Lin, I. J. B. *Organometallics* **1998**, *17*, 972–975. (b) de Frémont, P.; Scott, N.M.; Stevens, E.D.; Nolan, S.P. *Organometallics* **2005**, *24*, 2411–2418.

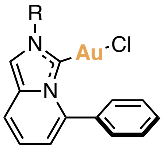


Scheme 37. Common strategies for the synthesis of NHC gold(I) complexes.

A subtype of electronically modified biaryl phosphine scaffolds **96** are the NHC-type biaryl ligands **97** (Figure 12), that present different properties and sometimes different reactivity. In general, N-heterocyclic carbenes are more rigid, removing issues associated with C–P rotation, and are also more σ-donating what results in the formation of carbene-like intermediates.[66] However, the gold(I) orientation is different, the angle between gold and the aryl group in NHC is higher, increasing the separation between the participating groups.



96



97

Figure 12. General structures of phosphinyl and NHC gold(I) complexes.

Reactivity of N-Heterocyclic Carbenes in Gold(I) Catalysis

The reactivity and selectivity of NHC-gold(I) catalysts has been studied and compared with other ligands. The IPr ligands have been used in different transformations, such as in the synthesis of substituted 1,2-dihydroquinolines and quinolines catalyzed by IPrAuCl[67] and synthesis of 1,3-disubstituted allenes using IPrAuNTf$_2$ as catalyst.[68] But also biaryl ligands have been used in other transformations such as olefin cyclopropanations, alkynylbenzaldehyde alkoxycyclizations[69] and hydrocarboxylation of allenes.[70]

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[66] (a) Wang, Y.; Muratore, M. E.; Echavarren, A. M. *Chem. Eur. J.* **2015**, *21*, 7332–7339. (b) Zuccarello, G.; Zanini, M.; Echavarren, A. M. *Isr. J. Chem.* **2020**, *60*, 360–372.

[67] Liu, X.-Y.; Ding, P.; Huang, J.-S.; Che, C.-M. *Org. Lett.* **2007**, *9*, 2645–2648.

[68] Lustosa, D. M.; Clemens, S.; Rudolph, M.; Hashmi, A. S. K. *Adv. Synth. Catal.* **2019**, *361*, 5050–5056.

[69] Pedrazzani, R.; Pintus, A.; De Ventura, R.; Marchini, M.; Ceroni, P.; Silva López, C.; Monari, M.; Bandini, M. *ACS Org. Inorg. Au* **2022**, *2*, 229–235.

[70] Pedrazzani, R.; Pinosa, E.; Bertuzzi, G.; Monari, M.; Lauzon, S.; Ollevier, T.; Bandini, M. *Chem. Commun.* **2022**, *58*, 8698–8701.

The reactivity of alkynes has also been studied in oxidation, amination and cycloaddition reactions using NHC-gold(I) catalysts (Figure 13).[71] For example, Toste and coworkers reported the synthesis of cyclopropyl aldehydes **98** by oxidative NHC gold(I)-catalyzed transformations of 1,6-enynes using sulfoxides as oxidants.[72] Other oxidation reaction was reported by Liu and coworkers, for the synthesis of cyclopentenone derivatives **99** from *cis*-substituted 3-en-1-ynes using a quinoline *N*-oxide as oxidant.[73] An example of NHC gold(I)-catalyzed alkyne amination was reported by Gagosz in 2011, for the synthesis of indolin-3-ones **100** through the amination cyclization reaction of 2-alkynyl arylazides with allyl alcohols.[74] NHC gold(I) catalysts have been also used in intermolecular [4+2] cycloaddition reaction of enynes with alkenes leading to 2-aminonaphatlenes **101**, reported by Liu and coworkers.[75] Similar catalysts have been used in the [2+2] intermolecular reaction of alkynes with alkenes allowing the synthesis of cyclobutenes **102** reported by Zhang in 2018.[76]

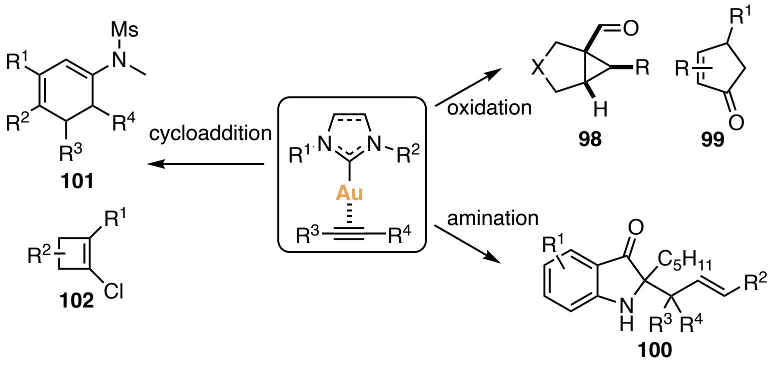

Figure 13. N-heterocyclic carbene gold(I)-catalyzed reactions.

Reactivity of N-heterocyclic Carbenes in Asymmetric Gold(I) Catalysis

The synthesis of some chiral NHC gold(I) complexes have been also reported and their reactivity and enantioselectivity studied. In 2010, the group of Tomioka reported the first asymmetric NHC gold(I) catalyzed alkoxyciclization of 1,6 enynes **103** using complex **105**, but giving products **104** only with moderate enantioselectivities (Table 5, Entries 1 and 2).[77] In 2016, other two examples of chiral NHC

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[71] Review: Tang, X.-T.; Yang, F.; Zhang, T.-T.; Liu, Y.-F.; Liu, S.-Y.; Su, T.-F.; Lv, D.-C.; Shen, W.-B. *Catalysts* **2020**, *10*, 350.

[72] Witham, C.A.; Mauleón, P.; Shapiro, N.D.; Sherry, B.D.; Toste, F.D. *J. Am. Chem. Soc.* **2007**, *129*, 5838–5839.

[73] Bhunia, S.; Ghorpade, S.; Huple, D.B.; Liu, R.-S. *Angew. Chem. Int. Ed.* **2012**, *51*, 2939–2942.

[74] Wetzel, A.; Gagosz, F. *Angew. Chem. Int. Ed.* **2011**, *50*, 7354–7358.

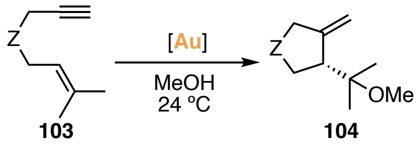
[75] Dateer, R.B.; Shaibu, B.S.; Liu, R.-S. *Angew. Chem. Int. Ed.* **2012**, *51*, 113–117.

[76] Bai, Y.-B.; Luo, Z.; Wang, Y.; Gao, J.-M.; Zhang, L. *J. Am. Chem. Soc.* **2018**, *140*, 5860–5865.

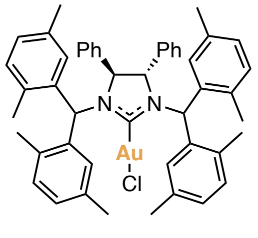
[77] Matsumoto, Y.; Selim, K. B.; Nakanishi, H.; Yamada, K.; Yamamoto, Y.; Tomioka, K. *Tetrahedron Letters* **2010**, *51*, 404–406.

gold(I) complexes were reported (**106**[78] and **107**[79]) and used for this kind of transformations improving significantly the enantioselectivity (Table 5, Entry 3 and 4 respectively).

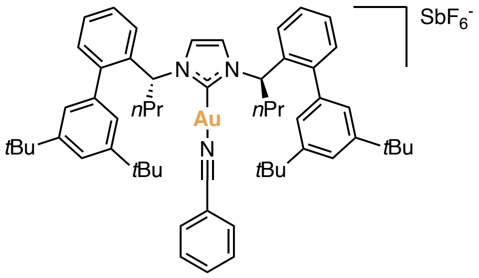
Table 5. Alkoxycyclization reaction using different NHC gold(I) complexes.



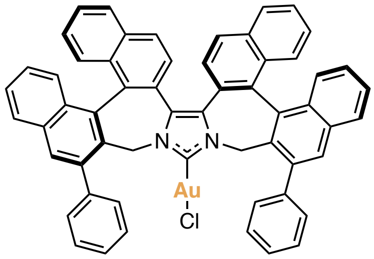
Entry	[Au] (mol%)	Chloride scavenger (mol%)	Z	Yield (%)	*ee* (%)
1	**105** (6)	$AgSbF_6$ (6)	$C(CO_2Me)_2$	95	56
2	**105** (6)	$AgSbF_6$ (6)	$C(SO_2Ph)_2$	93	52
3	**106** (6)	-	$C(CO_2Me)_2$	67	75
4	**107** (5)	$AgNTf_2$ (5)	$C(SO_2Ph)_2$	>99	78



105

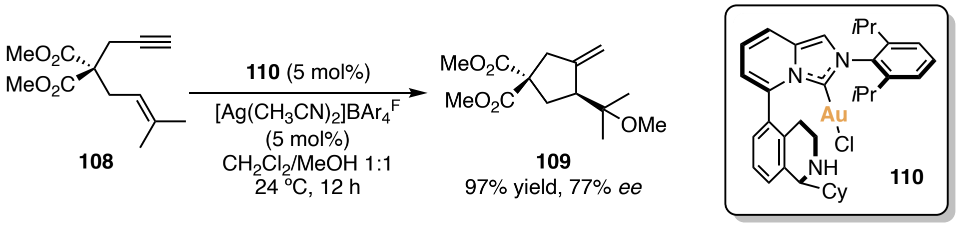


106



107

It has been reported the synthesis of chiral bifunctional NHC gold(I) complexes **110** (Scheme 38) and their chirality induction in gold(I)-catalyzed reactions has been studied. For example, in the alkoxycyclization reaction of the 1,6-enyne **108**.[80]



Scheme 38. Gold(I)-catalyzed alkoxycyclization of 1,6-enyne **108**.

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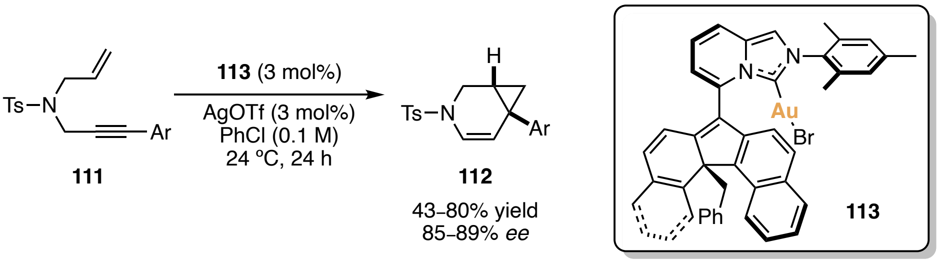
[78] Gung, B. W.; Holmes, M. R.; Jones, C. A.; Ma, R.; Barnes, C. L. *Tetrahedron Letters* **2016**, *57*, 3912–3915.

[79] Okitsu, N.; Yoshida, T.; Usui, K.; Nakada, M. *Heterocycles* **2016**, *92*, 720–732.

[80] Zhang, J.-Q.; Liu, Y.; Wang, X.-W.; Zhang, L. *Organometallics* **2019**, *38*, 3931–3938.

It has been also recently reported another example of chiral helical NHC gold(I) complexes **113** and their application in the cycloisomerization of nitrogen-tethered 1,6-enynes **111** for the synthesis of bicyclic products **112** (Scheme 39).[81]



Scheme 39. Gold(I)-catalyzed cycloisomerization of *N*-tethered 1,6-enynes.

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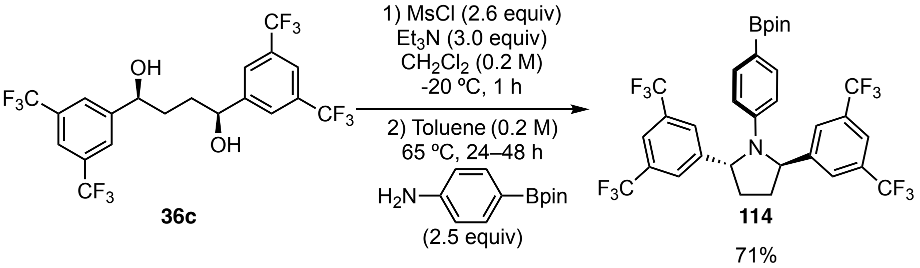
[81] Pallova, L.; Abella, L.; Jean, M.; Vanthuyne, N.; Barthes, C.; Vendier, L.; Autschbach, J.; Crassous, J.; Bastin, S.; César, V. *Chem. Eur. J.* **2022**, *28*, e202200166.

Results and Discussion[82]

Design and Synthesis of New Chiral N-Heterocyclic Carbene Gold(I) Complexes

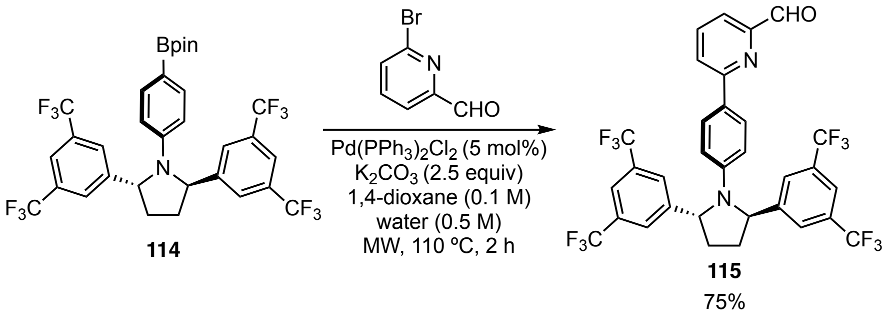
Inspired by the results with chiral N-heterocyclic carbenes structures described above, and the ligands previously reported in our group in 201923 the objective of this part of the project is: synthesizing NHC ligands with a chiral pyrrolidine moiety and study their reactivity in gold(I) transformations.

Pyrrolidine (*R*,*R*)-**114** was synthesized from diol (*S*,*S*)-**36c**23 that served as a building block for the synthesis of the N-heterocyclic gold(I) carbenes through a double mesylation and followed by a double S_N2 reaction with the *para*-(boronpinacolate)aniline (Scheme 40). The second step of this reaction was carried out in toluene instead of dichloromethane as used before, since it was needed to heat up the reaction to improve the yield. Therefore, toluene was used and the reaction was heated at 65 ºC. The formation of **114** and the isomer *meso* product were observed in a diastereomeric ratio of 7:1, that could be easily separated by column chromatography.



Scheme 40. Formation of pyrrolidine **114**.

Then, through a Suzuki-Miyaura cross-coupling reaction the pyridine moiety was introduced to **114**, affording the 2-pyridine aldehyde **115** in 75% yield, the common scaffold for the synthesis of the three gold(I) complexes targeted (Scheme 41).



Scheme 41. Introduction of the pyridine moiety.

With the aldehyde of the pyridine **115** and the corresponding amine (R-NH_2) the imine was preformed, followed by the addition of chloromethyl methyl ether, the corresponding N-heterocyclic carbene chloride salt precursors **116a–c** were synthesized (Scheme 42).

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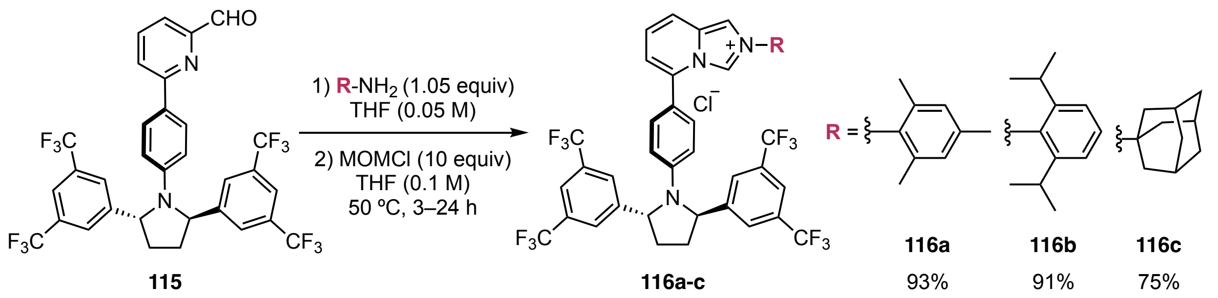
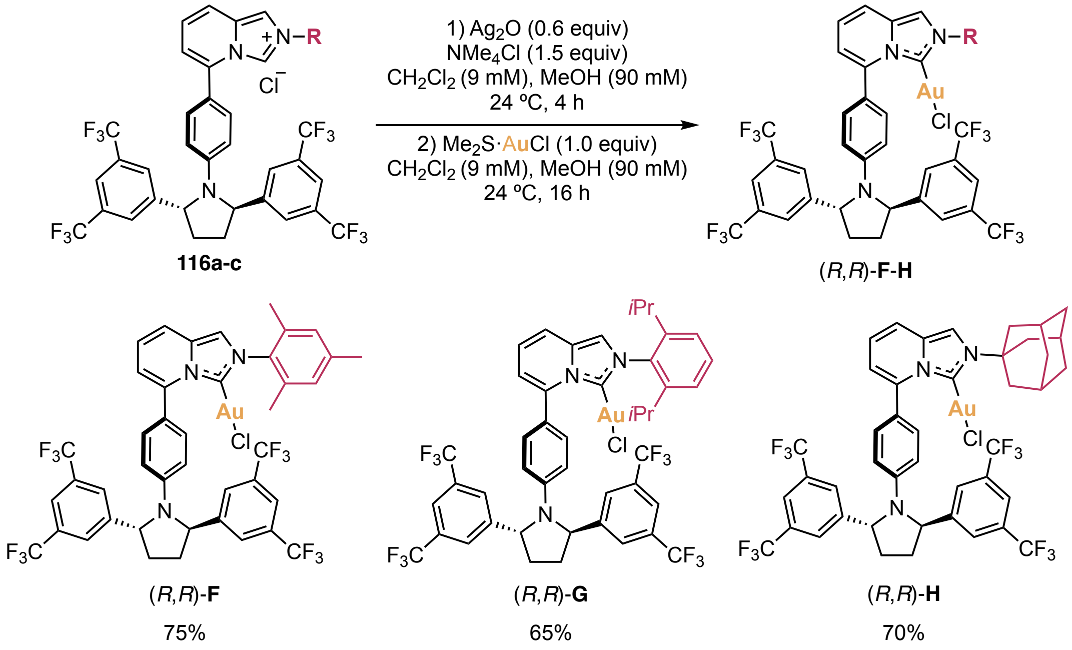
[82] These experiments were based upon preliminary work done by Dr. Leonardo Nannini.



Scheme 42. Synthesis of the N-heterocyclic carbene chloride salt precursors.

Finally, the introduction of silver to **116a–c** using Ag_2O as silver source, and its transmetalation with dimethylsulfide gold(I) chloride allowed the synthesis of the chiral complexes (*R*,*R*)-**F**, (*R*,*R*)-**G** and (*R*,*R*)-**H** (Scheme 43).

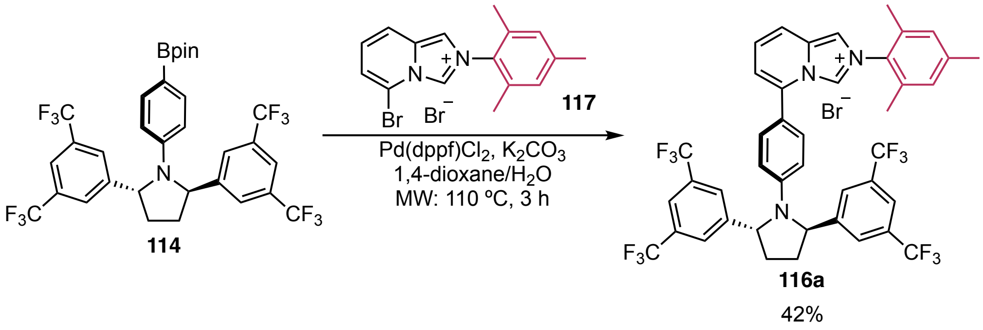


Scheme 43. Synthesis of the chiral gold(I) complexes (*R*,*R*)-**F**–**H**.

Other less linear pathway for the synthesis of this complexes was tested as shown in Scheme 44. With the already salt precursor formed **117**[83] and the boronic ester **114**, a Suzuki-Miyaura coupling reaction was performed obtaining **116a**, but the overall yield was lower, so this pathway was discarded.

---

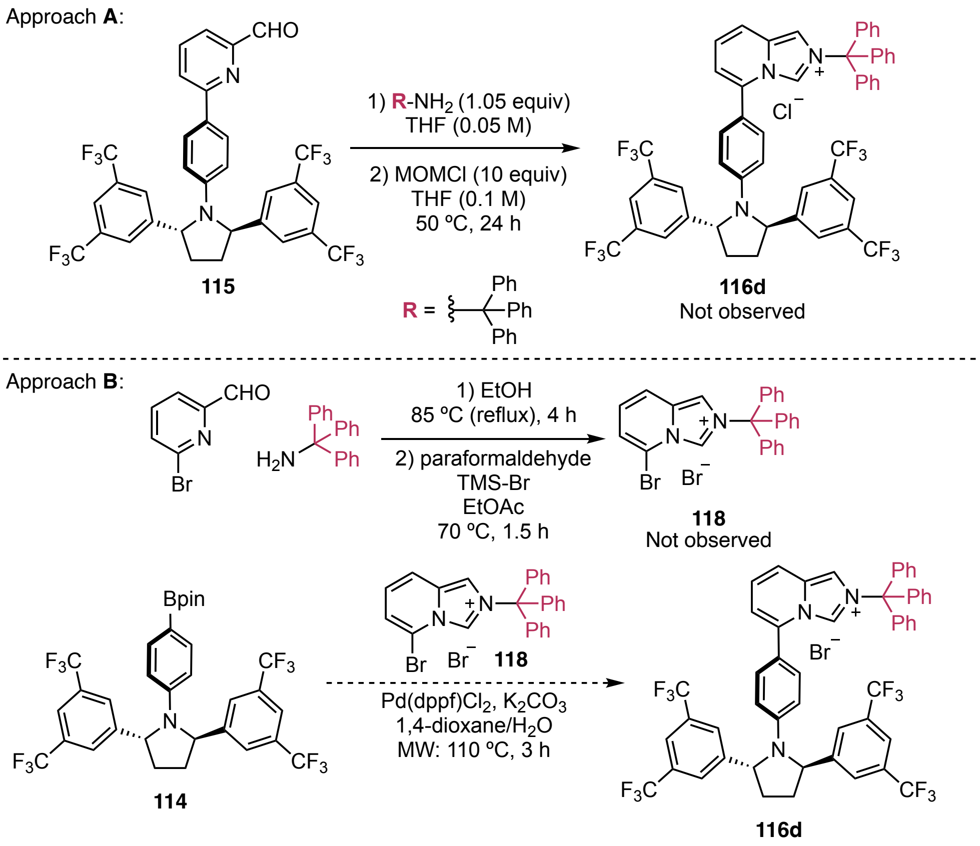
[83] Azouzi, K.; Duhayon, C.; Benaissa, I.; Lugan, N.; Canac, Y.; Bastin, S.; César, V. *Organometallics* **2018**, *37*, 4726–4735.



Scheme 44. Other pathway for the synthesis of the NHC chloride salt precursor **116a**.

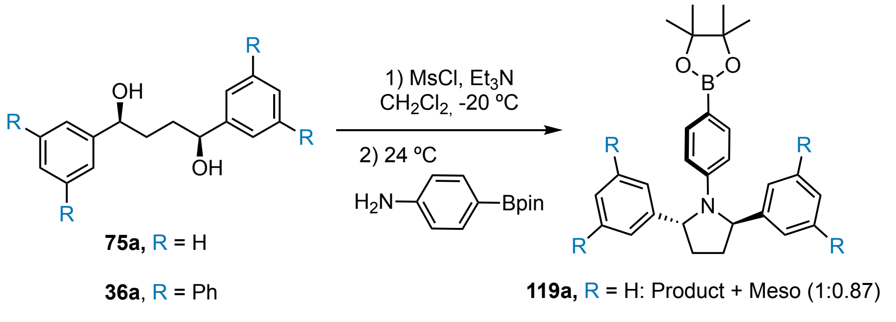
Unsuccessful Synthesis of Other NHC-Gold(I) Complexes

The synthesis of the NHC salt precursor with a triphenyl methyl group was also attempted and none of the two previously presented pathways was successful (Scheme 45). Following approach **A**, it seemed that the imine was being formed but not the NHC salt precursor **116d**. And the same happened with approach **B**, product **118** was not observed, and therefore the Suzuki cross-coupling reaction was not tested.



Scheme 45. Unsuccessful attempt for the synthesis of NHC salt precursor **116d**.

Since only different substituents in the nitrogen of the imidazo[1,5-*a*]pyridinium were changed, also other substituents in the pyrrolidine were tried starting from 1,4-diols (*S*,*S*)-**75a** and (*S*,*S*)-**36a**. But after the double S_N2 addition the *R*,*R* product and the *meso* product **119a** and **119b** were obtained and were not possible to be separated trying different techniques (Scheme 46). Although it was possible to continue with the designed synthetic routes, separation of the desired product and the *meso* compounds was not achieved at any step, and the synthesis of the corresponding NHC-gold(I) catalysts was discarded.



75a, R = H

36a, R = Ph

119a, R = H: Product + Meso (1:0.87)

119b, R = Ph: Product + Meso (1:0.51)

Scheme 46. Attempts for the synthesis of pyrrolidines with other substituents (R^1 = H, Ph).

Study of the Reactivity in Different Transformations

In order to know how the chiral NHC gold(I) complexes (*R*,*R*)-**F**, (*R*,*R*)-**G** and (*R*,*R*)-**H** (Figure 14) behave in asymmetric catalysis, we tested them in different transformations.

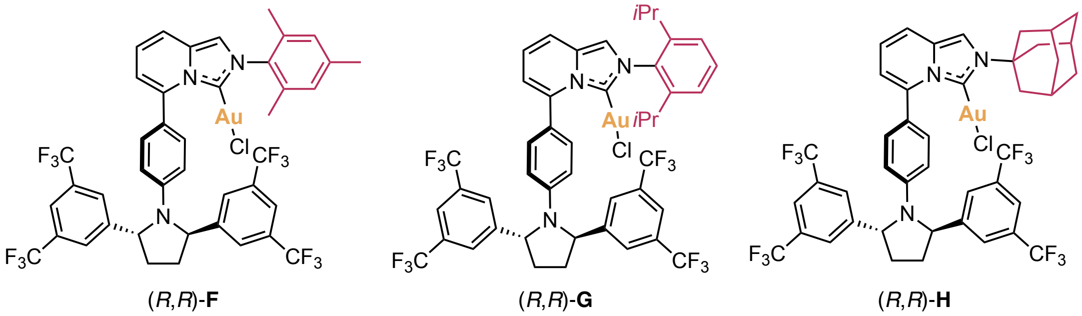
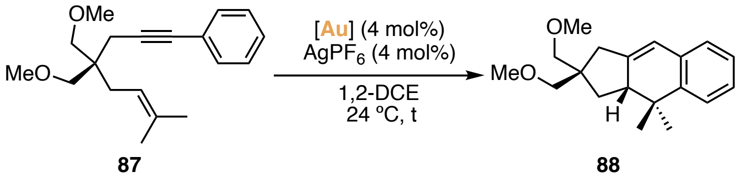


Figure 14. Chiral N-heterocyclic gold(I) complexes.

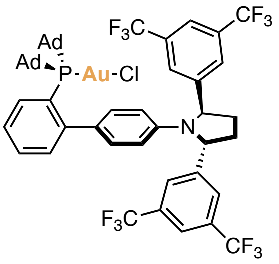
In the formal [4+2] cycloaddition of 1,6-arylenyne **87**, we observed the formation of **88** in high yields and enantioselectivities using (*R*,*R*)-**F**, (*R*,*R*)-**G** and (*R*,*R*)-**H** (Table 6, Entries 1–3), but lower than those obtained with complex (*R*,*R*)-**40d** (Table 6, Entry 4). However, there is room for improvement of the results after an optimization of the reaction conditions with this type of catalysts.

Table 6. Formal [4+2] cycloaddition reaction.



Entry	[Au]	t (h)	Yield (%)[a]	*er*
1	(*R*,*R*)-**F**	2	83	89:11
2	(*R*,*R*)-**G**	2	88	88:12
3	(*R*,*R*)-**H**	6	>99	87:13
4	(*R*,*R*)-**40d**	16	92	94:6

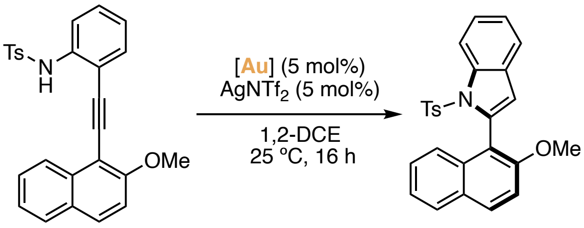
[a] Yield measured by ^{1}H NMR using diphenylmethane as internal standard.



(*R*,*R*)-**40d**: X = H

The atroposelective reaction for the formation of C2-arylindoles was also tried with complexes (*R*,*R*)-**F**, (*R*,*R*)-**G** and (*R*,*R*)-**H**, although the yields were excellent, indole **86a** was obtained with moderate enantioselectivity (Table 7, Entries 3–5). The results were significantly worse than using (*R*,*R*)-**40d** or (*R*,*R*)-**40g** (Table 7, Entries 1 and 2 respectively) and that with the new chiral *ortho*-pyrodinyl phosphine gold(I) catalyst described before (*R*,*R*)-**A**.

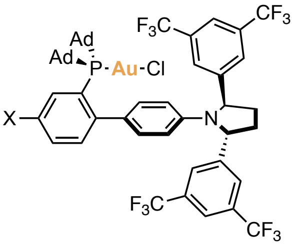
Table 7. Atroposelective cyclization reaction.



85a **86a**

Entry	[Au]	Conversion (%)	Yield (%)[a]	*er*
1	(*R*,*R*)-**40d**	100	>99	87:13
2	(*R*,*R*)-**40g**	100	>99	88:12
3	(*R*,*R*)-**F**	100	96	67:33
4	(*R*,*R*)-**G**	97	97	73:27
5	(*R*,*R*)-**H**	100	97	69:31

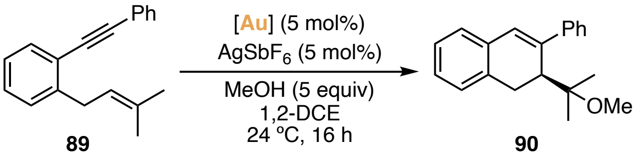
[a] Yield measured by ^{1}H NMR using diphenylmethane as internal standard.



(*R*,*R*)-**40d**: X = H
(*R*,*R*)-**40g**: X = CF_3

The alkoxycyclization reaction using phenyl-tethered 1,6-arylenyne **89** and the complexes (*R*,*R*)-**F**, (*R*,*R*)-**G** and (*R*,*R*)-**H** gave product **90** in good yields and enantioselectivities (Table 8, Entries 2–4), but again results were not better than using (*R*,*R*)-**40d** (Table 8, Entry 1).

Table 8. Alkoxycyclization of aryl-tethered 1,6-arylenyne **89**.

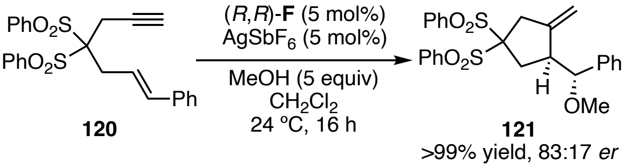


89 **90**

Entry	[Au]	Yield (%)	*er*
1	(*R*,*R*)-**40d**	81	94:6
2	(*R*,*R*)-**F**	64	86:14
3	(*R*,*R*)-**G**	73	83:17
4	(*R*,*R*)-**H**	62	84:16

[a] Yield measured by ^{1}H NMR using diphenylmethane as internal standard.

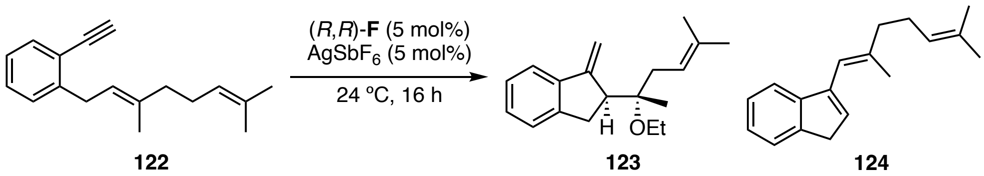
Then, the complex (*R*,*R*)-**F** was tested in other transformations. The alkoxycyclization reaction of the 1,6-enyne **120** using methanol as nucleophile yielded product **121**[84] in excellent yield and high enantioselectivity (Scheme 47).



Scheme 47. Alkoxycyclization reaction of 1,6-enyne **120**.

Other alkoxycyclization that was tried was with the aryl-tethered 1,6-enyne **122** (Table 9). With a mixture of dichloromethane and ethanol 1:1, product **123** was obtained in 25% yield with 83:17 er, but the side-product **124** was mainly obtained (Table 9, Entry 1). When only 10 equivalents of ethanol were used only the side product **124** was obtained (Table 9, Entry 2).

Table 9. Alkoxycyclization reaction of aryl-tethered 1,6-enyne **122**.



Entry	Solvents mixture	123 yield (%)[a]	*er*	124 (%)[a]
1	EtOH/CH_2Cl_2 1:1 (0.1 M)	25	83:17	57
2	EtOH (10 equiv), CH_2Cl_2 (0.1 M)	-	-	60[b]

[a] Yield measured by ^{1}H NMR using diphenylmethane as internal standard.
[b] Also 22% of an unidentified product.

Moreover, other reactions were studied using complex (*R*,*R*)-**F** (Scheme 48). The cyclopropanation reaction using **125** and **126**[85] afforded cyclopropane **127** in excellent yield but with low enantioselectivity. However, the retro Buchner reaction using **128** and **129**[86] did not result in the

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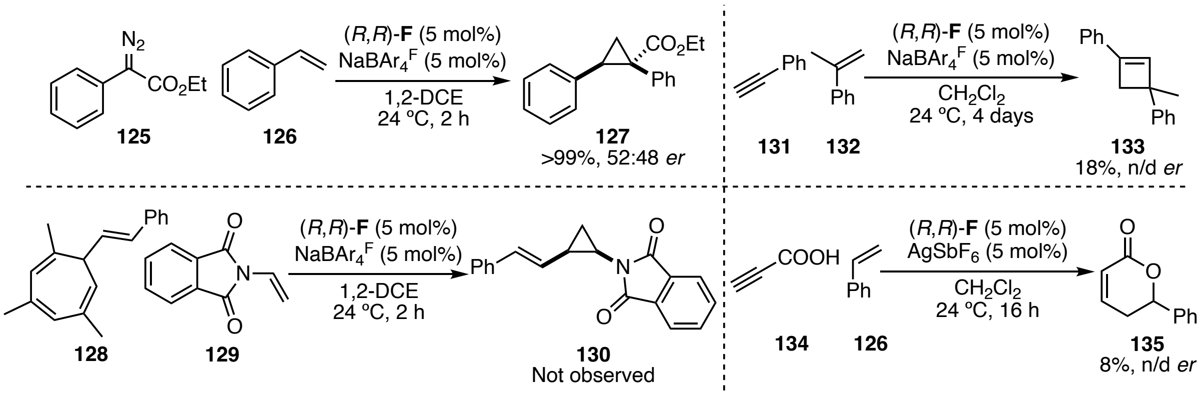
[84] (a) Méndez, M.; Muñoz, M. P.; Echavarren, A. M. *J. Am. Chem. Soc.* **2000**, *122*, 11549–11550. (b) Muñoz, M. P.; Adrio, J.; Carretero, J. C.; Echavarren, A. M. *Organometallics* **2005**, *24*, 1293–1300.

[85] Xu, Z.-H.; Zhu, S.-N.; Sun, X.-L.; Tang, Y.; Dai, L.-X. *Chem. Commun.* **2007**, *19*, 1960–1962.

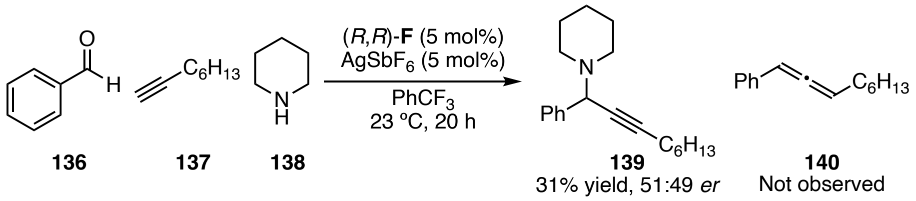
[86] (a) Herlé, B.; Holstein, P. M.; Echavarren, A. M. *ACS Catal.* **2017**, *7*, 3668–3675. (b) Mato, M.; Herlé, B.; Echavarren, A. M. *Org. Lett.* **2018**, *20*, 4341–4345. (c) Mato, M.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2019**, *58*, 2088–2092.

formation of cyclopropane **130**. The [2+2] cycloaddition reaction[87] to obtain the cyclobutene **133** and the formation of the lactone **135**[88] were also unsuccessful under the tested reaction conditions.



Scheme 48. Unsuccessful asymmetric transformations. Yields were measured by ^{1}H NMR using diphenylmethane as internal standard.

The formation of the propargylic amine **139** was accomplished in 31% yield and low enantioselectivity by a three-component coupling reaction catalyzed by (*R*,*R*)-**F**, the formation of the allene **140** was not observed (Scheme 49).[89]



Scheme 49. Synthesis of the propargylic amine **139**.

Finally, the cyclization reaction of the *O*-tethered 1,6-enynes[90] **141a–e** was also tested but there was almost no conversion, affording the corresponding products **142a–e** in very low yield (Scheme 50).

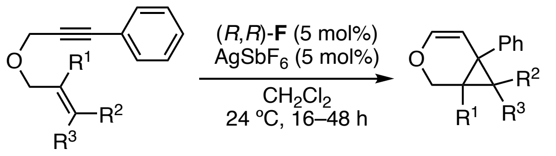
---

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

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

[89] Xiao, J.; Cui, Y.; Li, C.; Xu, H.; Zhai, Y.; Zhang, X.; Ma, S. *Angew. Chem. Int. Ed.* **2021**, *60*, 25708–25713.

[90] (a) Laher, R.; Marin, C.; Michelet, V. *Org. Lett.* **2020**, *22*, 4058–4062. (b) Chao, C.-M.; Beltrami, D.; Toullec, P. Y.; Michelet, V. *Chem. Commun.* **2009**, *45*, 6988–6990.



141a, R^1 = H, R^2 = Ph, R^3 = H — **142a**, 10%
141b, R^1 = H, R^2 = Me, R^3 = Me — **142b**, 13%
141c, R^1 = H, R^2 = H, R^3 = H — **142c**, 11%
141d, R^1 = H, R^2 = $(CH_2)_2CH{=}C(CH_3)_2$, R^3 = Me — **142d**, >5%
141e, R^1 = Me, R^2 = H, R^3 = H — **142e**, 28%

Scheme 50. Cyclization reaction of *O*-tethered 1,6-enynes. Yields were measured by ^{1}H NMR using diphenylmethane as internal standard.

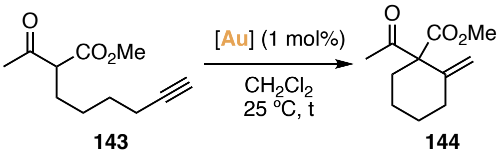
Sterically Hindered Gold(I) Catalysts

Introduction

In homogenous gold(I) catalysis, the reactive site of the catalyst has been sometimes related to the encapsulation of gold(I), using ligands that create a specific structure environment around it. In this context, sterically hindered ligands have shown to be able to change the outcome of some reactions.

The group of Sawamura reported the synthesis of gold(I) complexes that have a tri-alkynylphosphine with bulky end caps in the alkynes, such as **149** (Table 10) to create a pocket in the catalytic environment. They found that this catalyst **149** applied to the 6-*exo*-dig gold(I)-catalyzed cyclization of acetylenic keto esters **143** gave better result (Table 10, Entry 5) than those obtained with more conventional ligands **145–148** (Table 10, Entries 1–4).[91] Since then, other advantages of highly sterically hindered ligands have been observed in cyclization reactions using that kind of gold(I) complexes.[92]

Table 10. Gold(I)-catalyzed 6-*exo*-dig cyclization reaction.



Entry	[Au]	t (h)	Yield (%)[a]
1	**145**	1.5	3
2	**146**	1.5	<1
3	**147**	6	21
4	**148**	6	28
5	**149**	1.5	100

[a] Yield measured by ^{1}H NMR against an internal standard.

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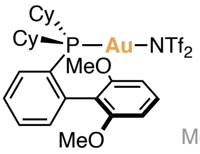
[91] Ochida, A.; Ito, H.; Sawamura, M. *J. Am. Chem. Soc.* **2006**, 128, 16486–16487.

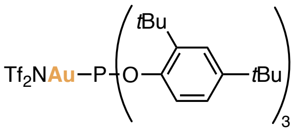
[92] (a) Iwai, T.; Sawamura, M. *Bull. Chem. Soc. Jpn.* **2014**, *87*, 1147–1160. (b) Ito, H.; Ohmiya, H.; Sawamura, M. *Org. Lett.* **2010**, *12*, 4380–4383. (c) Ito, H.; Harada, T.; Ohmiya, H.; Sawamura, M. *Beilstein J. Org. Chem.* **2011**, *7*, 951–959. (d) Ito, H.; Harada, A.; Ohmiya, H.; Sawamura, M. *Adv. Synth. Catal.* **2013**, *355*, 647–652. (e) Iwai, T.; Okochi, H.; Ito, H.; Sawamura, M. *Angew. Chem.* **2013**, *125*, 4333–4336; *Angew. Chem. Int. Ed.* **2013**, *52*, 4239–4242. (f) Iwai, T.; Ueno, M.; Okochi, H.; Sawamura, M. *Adv. Synth. Catal.* **2018**, *360*, 670–675. (g) Iwai, T.; Goto, Y.; Yu, Z.; Sawamura, M. *Chem. Lett.* **2021**, *50*, 1236–1239.

145: PPh_3AuNTf_2

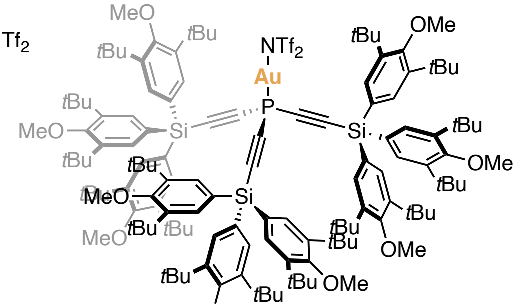
146: $P(OPh_3)AuNTf_2$



147

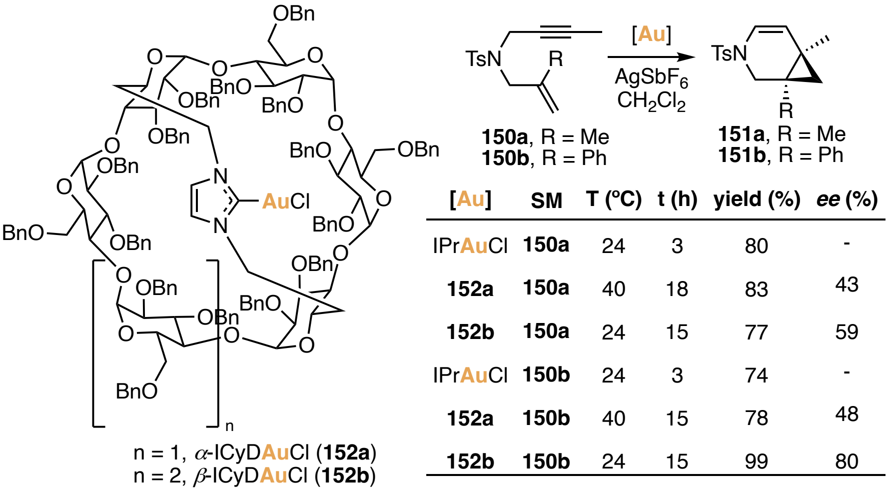


148



149

In 2013, the synthesis of a new family of chiral N-heterocyclic carbene-capped cyclodextrin gold(I) complexes α-ICyDAuCl (**152a**) and β-ICyDAuCl (**152b**) was described and the reactivity of the catalysts was studied (Scheme 51). For example, the cycloisomerization of enyne **150a** to obtain the bicyclic product **151a** was achieved in good yields and moderate enantioselectivities using α-ICyDAuCl (**152a**), the enantioselectivity was slightly enhanced when **152b** was used.[93] Later, the reaction was also tried with **150b** bearing a phenyl substituent and the enantioselectivity was specially improved when complex **152b** was used.[94]



[Au]	SM	T (°C)	t (h)	yield (%)	*ee* (%)
IPrAuCl	**150a**	24	3	80	-
152a	**150a**	40	18	83	43
152b	**150a**	24	15	77	59
IPrAuCl	**150b**	24	3	74	-
152a	**150b**	40	15	78	48
152b	**150b**	24	15	99	80

Scheme 51. Gold(I)-catalyzed cycloisomerization reaction of **150** using cyclodextrin ligands.

Since then, their chiral induction and product selectivity in cycloisomerization reactions have been studied using these complexes.[95] One of these examples is the alkoxycyclization reaction of the 1,6-

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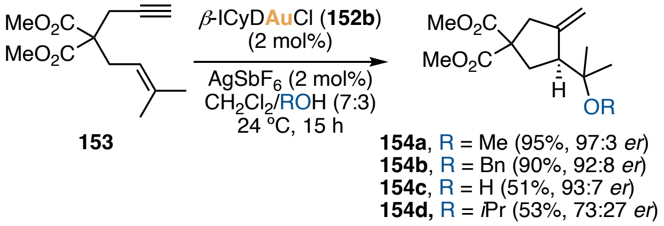
[93] Guitet, M.; Zhang, P.; Marcelo, F.; Tugny, C.; Jiménez-Barbero, J.; Buriez, O.; Amatore, C.; Mouriès-Mansuy, V.; Goddard, J.-P.; Fensterbank, L.; Zhang, Y.; Roland, S.; Ménand, M.; Sollogoub, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 7213–7218; *Angew. Chem.* **2013**, *125*, 7354–7359.

[94] 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.

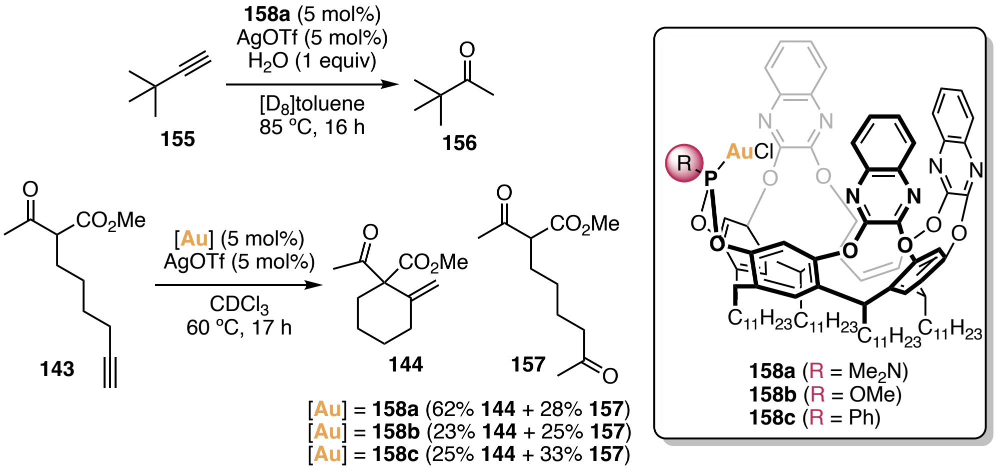
[95] (a) Kaya, Z.; Andna, L.; Matt, D.; Bentouhami, E.; Djukic, J.; Armspach, D. *Chem. Eur. J.* **2018**, *24*, 17921–17926. (b) Kaya, Z.; Andna, L.; Matt, D.; Bentouhami, E.; Djukic, J.-P.; Armspach, D. *Eur. J. Org. Chem.* **2019**, 4528–4537. (c) Zhu, X.; Xu, G.; Chamoreau, L.-M.; Zhang, Y.; Mouriès-Mansuy, V.; Fensterbank, L.; Bistri-Aslanoff, O.; Roland, S.; Sollogoub, M. *Chem. Eur. J.* **2020**, *26*, 15901–15909.

enyne **153** in presence of different alcohol nucleophiles using complex *β*-ICyDAuCl (**152b**) led to the corresponding products **154a–c** in moderate to high yields and with high enantioselectivities, decreasing the enantiomeric excess when isopropanol was used (**154d**) (Scheme 52).[96]



Scheme 52. Enantioselective alkoxycyclization using *β*-ICyDAuCl.

In 2016, Iwasawa group presented the design and synthesis of a resorcin[4]arene phosphoramidite **158a**, phosphite **158b** and phosphonite **158c** gold(I)-cavitand complexes, locating the metal inside the cavity (Scheme 53). The hydration reaction of terminal alkynes **155** and the Conia-ene reaction of *β*-keto ester alkyne **143** were successfully achieved.[97] The product and substrate selectivities for this type of complexes have been later studied in other reactions by Iwasawa and Schramm.[98]



Scheme 53. Gold(I)-cavitand complexes and their application in hydration of terminal alkynes and in the Conia-ene reaction.

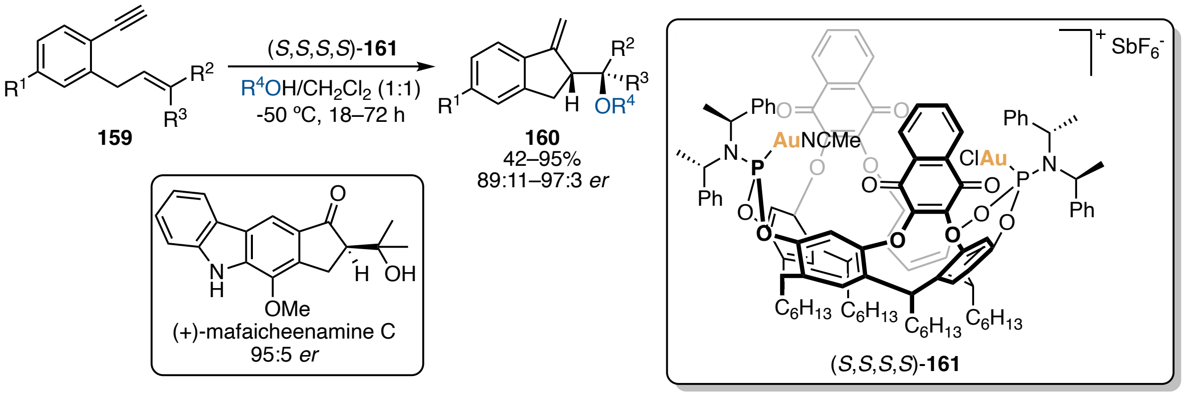
---

[96] 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.

[97] Schramm, M. P.; Kanaura, M.; Ito, K.; Ide, M.; Iwasawa, T. *Eur. J. Org. Chem.* **2016**, 813–820.

[98] (a) Endo, N.; Kanaura, M.; Schramm, M. P.; Iwasawa, T. *Eur. J. Org. Chem.* **2016**, 2514–2521. (b) Kanaura, M.; Endo, N.; Schramm, M. P.; Iwasawa, T. *Eur. J. Org. Chem.* **2016**, 4970–4975. (c) Endo, N.; Inoue, M.; Iwasawa, T. *Eur. J. Org. Chem.* **2018**, 1136–1140. (d) Inoue, M.; Ugawa, K.; Maruyama, T.; Iwasawa, T. *Eur. J. Org. Chem.* **2018**, 5304–5311. (e) Ho, T. D.; Schramm, M. P. *Eur. J. Org. Chem.* **2019**, 5678–5684. (f) Rusali, L. E.; Schramm, M. P. *Tetrahedron Lett.* **2020**, *61*, 152333–152337.

Our group have recently developed a synthesis of a new family of gold(I)-cavitand complexes, discovering new selectivity in the cycloisomerization of 1,6-enynes (Scheme 54).[99] A chiral version of those gold(I)-cavitands were also developed and they were applied in the alkoxyciclization of 1,6-enynes **159** using complex (*S*,*S*,*S*,*S*)-**161**, affording 1-methylene-2,3-dihydro-1*H*-indenes **160** in good to excellent yields and enantioselectivities. The utility of this method was demonstrated in the total synthesis of (+)-mafaicheenamine C.



Scheme 54. Enantioselective alkoxycyclization of 1,6-enynes **159** using the chiral gold(I)-cavitand (*S*,*S*,*S*,*S*)-**161**.

In 2021, the group of Campos reported the synthesis and characterization of the first dicoordinate gold(I)-ethylene complex **163**, stabilizing the coordination of ethylene with the cavity formed by bulky tris-biaryl phosphine ligand **162** (Scheme 55, left).[100] They have also reported the synthesis of other unusual dicoordinate gold(I)-ethylene complexes with bulky ligands and their stability was studied. Those complexes were used for the gold(I)-catalyzed hydroamination of ethylene by imidazolidine-2-one **164**, for example the one showed in Scheme 55 (right).[101]

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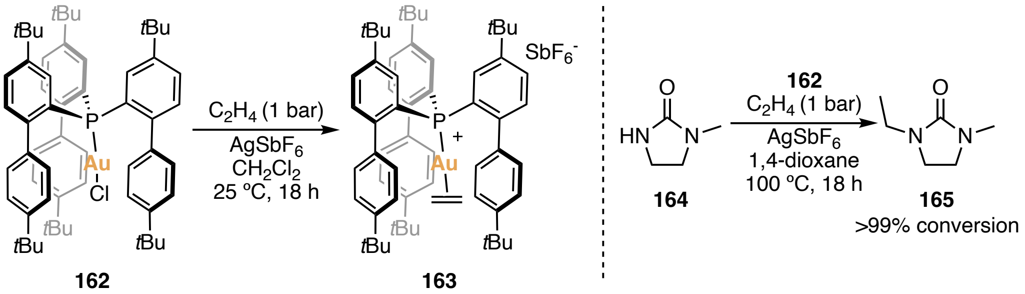
[99] Martín-Torres, I.; Ogalla, G.; Yang, J.-M.; Rinaldi, A.; Echavarren, A. M. *Angew. Chem.* **2021**, *133*, 9425–9430; *Angew. Chem. Int. Ed.* **2021**, *60*, 9339–9344.

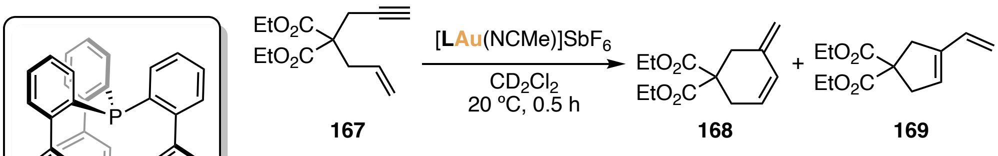
[100] Navarro, M.; Miranda-Pizarro, J.; Moreno, J. J.; Navarro-Gilabert, C.; Fernández, I.; Campos, J. *Chem. Commun.*, **2021**, *57*, 9280–9283.

[101] Navarro, M.; Alférez, M. G.; de Sousa, M.; Miranda-Pizarro, J.; Campos, J. *ACS Catal.* **2022**, *12*, 4227−4241.



Scheme 55. Synthesis of gold(I)-ethylene complex **163** (left) and example of a gold(I)-catalyzed hydroamination of ethylene (right).

In 2022, Gagosz group synthesized a family of sterically hindered gold(I) complexes using tris-(*ortho*-biaryl) phosphine ligands **166** (Scheme 56). The catalytic activity showed unusual selectivities in different cycloisomerization gold(I)-catalyzed reactions. For example, in the cycloisomerization of 1,6-enynes **167**,[102] common ligands such as PPh_3, JohnPhos or IPr afforded mainly the endocyclic product **168**. However, the sterically hindered ligands **166** favored the synthesis of the exocyclic product **169**.



L	**yield (%)**	**selectivity 168**:**169**
PPh_3	63	4.7:1
JohnPhos	97	2.4:1
IPr	77	2.8:1
166a (R = H)	99	1:>30
166b (R = 3-*t*Bu)	98	1:19

Scheme 56. Bulky ligands used for inducing selectivity in gold(I) catalysis.

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[102] Muratov, K.; Gagosz, F. *Angew. Chem. Int. Ed.* **2022**, e202203452.

Results and Discussion[103]

Design and Synthesis of the New Chiral Gold(I) Complexes

Thinking about the new developments in the synthesis of sterically hindered gold(I) complexes and their synthetic applications, we contemplated the possibility of the design and synthesis of chiral sterically hindered ligands, based on the pyrrolidinyl-biphenylphosphine ligands already reported in our group.23 These new chiral gold(I) complexes $(R,R)_3$-**I**, $(R,R)_2$-**J** and (R,R)-**K** (Figure 15) would be synthesized from the common scaffold **38c** and they could change the reactivity of known reactions or help in the development and improvement of reactions using small molecules, such as acetylene.

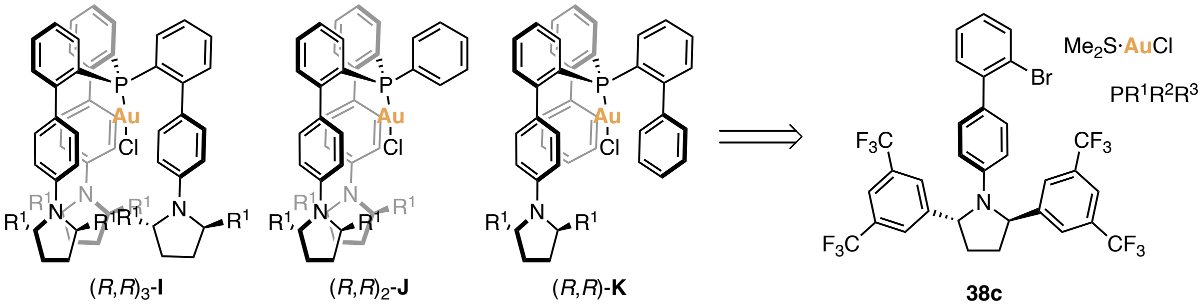
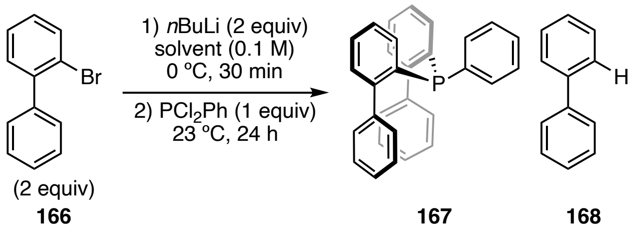


Figure 15. Sterically hindered gold(I) catalysts synthesized. (R^1 = 3,5-$(CF_3)_2C_6H_3$)

Instead of using compound **38c** for the optimization for the synthesis of these complexes, we have been using 2-bromobiphenyl **166** to find the optimal conditions for the aryl lithiation and the phosphine introduction. For the synthesis of ligand **167**, the use of TMEDA[104] improved the lithiation of **166** but resulted to be unfavorable for the introduction of the phosphine (Table 11, entries 1 and 2). However, in THF only starting material was observed (Table 11, entry 3).

Table 11. Optimization of the reaction conditions with a model substrate.



Entry	Solvent	Additive	Products
1	Et_2O	-	**166** + **167** + **168**

---

[103] The experiments presented in this section were performed in collaboration with Dr. Anna Sadurní and Dr. Víctor García.

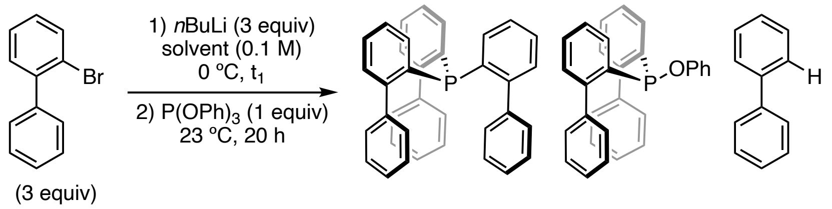
[104] Initial conditions without TMEDA from: Griebel, C.; Hodges, D. D.; Yager, B. R.; Liu, F. L.; Zhou, W.; Makaravage, K. J.; Zhu, Y.; Norman, S. G.; Lan, R.; Day, C. S.; Jones, A. C. *Organometallics* **2020**, *39*, 2665–2671.

2	Et_2O	TMEDA	**167** + **168**
3	THF	TMEDA	**166**

[a] Products detected by GC-MS.

Similar results were obtained in the case of the synthesis of ligand **169**[105] (Table 12). We started using $P(OPh)_3$ as phosphorous source.[106] Without TMEDA lithiation did not finished but the introduction of the phosphine worked better than with TMEDA (Table 12, entries 1 and 2). Again, THF inhibited completely the reaction (Table 12, entry 3).

Table 12. Optimization of the reaction conditions with a model substrate.

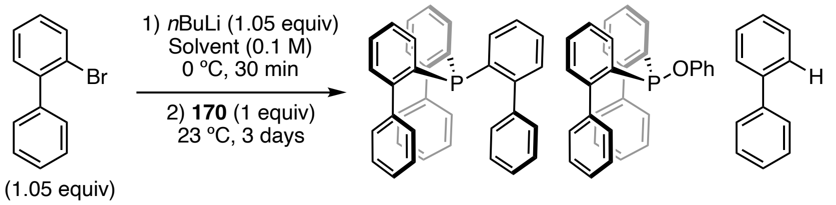


166 **169** **170** **168**

Entry	Solvent	Additive	Observations
1	Et_2O	-	1) t_1 = 2h: not finished: **166** + **168**[a] 2) **169**/**170** (1:1.5)[b]
2	Et_2O	TMEDA	1) t_1 = 30 min: finished: **168**[a] 2) **169**/**170** (1:30)[b]
3	THF	TMEDA	**166**

[a] Observations by GC-MS. [b] Observations by ^{31}P NMR.

We observed that **169** and **170** are difficult to separate by column chromatography, so we thought about adding more Li-phenyl preformed to **170**. We used a test reaction in which only **170** was formed, but not **169**, and after purification we set up the reaction showed in Scheme 57 and we obtained **169**/**170** in a 1:4.5 *ratio*. Still, the reaction did not achieve completion.



166 **169** **170** **168**

Scheme 57. Synthesis of **169** using **170**.

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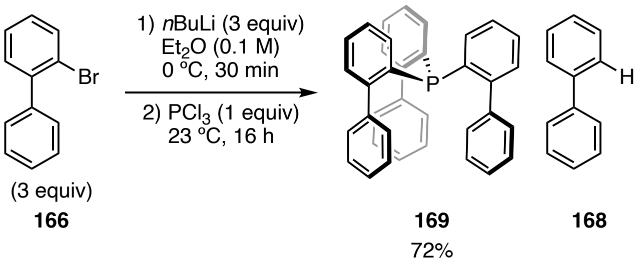
[105] Malhotra, D.; Mashuta, M. S.; Hammond, G. B.; Xu, B. *Angew. Chem. Int. Ed.* **2014**, *53*, 4456–4459.

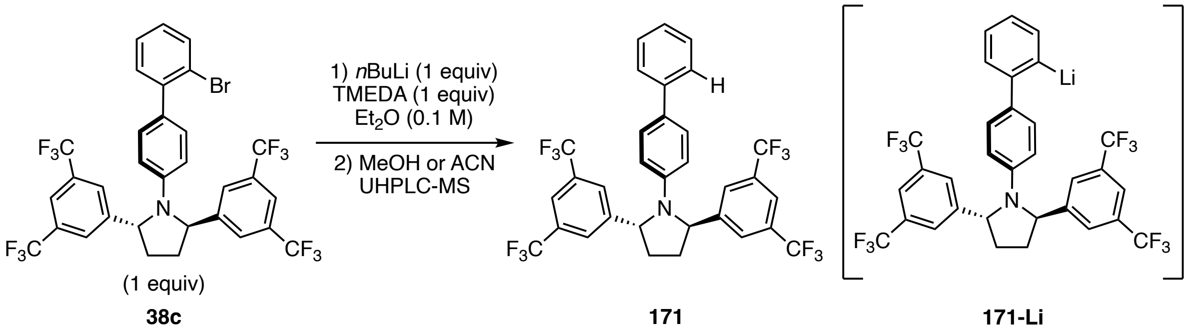
[106] (a) Jeganathan, S.; Tsukarmoto, M.; Schlosser, M. *Synthesis* **1990**, *1990*, 109–111. (b) Keller, J.; Schlierf, C.; Nolte, C.; Mayer, P.; Straub, B. F. *Synthesis* **2006**, No. 2, 354–365.

Since the reaction using $P(OPh)_3$ was not working with the desired results, we tried the reaction using PCl_3 (Scheme 58).[107] At the ^{31}P NMR of the crude, we only observed the signal of the desired product **169**, which could be isolated in 72% yield.



Scheme 58. Synthesis of **169** using PCl_3.

Using the corresponding pyrrolidine biphenyl bromide **38c**, we followed the lithiation step by UHPLC-MS, observing **171**, formed by protonation of **171-Li**.



Scheme 59. Test reaction of the lithiation of **38c**.

Synthesis of complex (*R*,*R*)$_3$-**I**

Complex (*R*,*R*)$_3$-**I** was synthesized by the lithiation of three equivalents of **38c** followed by the trisubstitution of PCl_3 giving ligand **172** in 61% yield (Scheme 60). We observed two signals by ^{31}P NMR that overlapped at some temperatures in a temperature slope NMR experiment, suggesting the presence of rotamers. Then, using dimethylsulfide gold(I) chloride, complex (*R*,*R*)$_3$-**I** was afforded in 86% yield.

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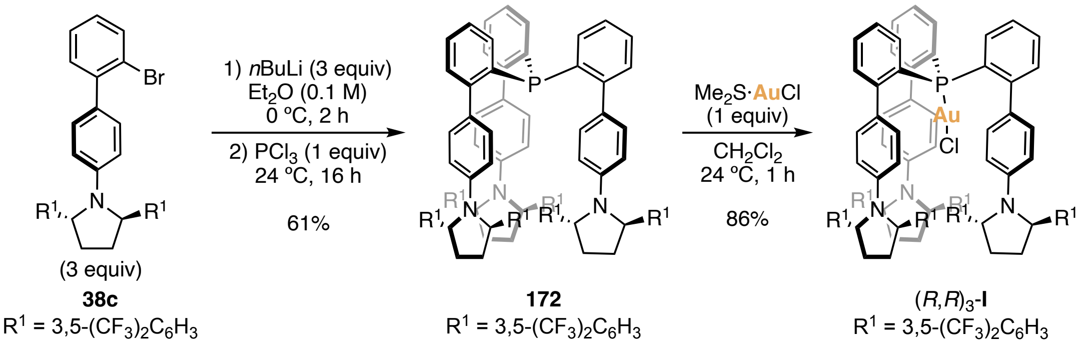
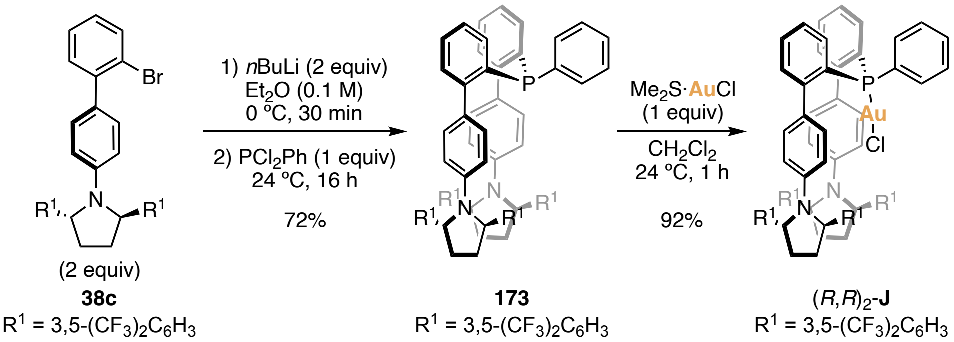
[107] (a) Dupré, J.; Gaumont, A.-C.; Lakhdar, S. *Org. Lett.* **2017**, *19*, 694–697. (b) Niyomura, O.; Iwasawa, T.; Sawada, N.; Tokunaga, M.; Obora, Y.; Tsuji, Y. *Organometallics* **2005**, *24*, 3468–3475.



Scheme 60. Synthesis of gold(I) complex (*R*,*R*)$_3$-**I**.

Synthesis of complex (*R*,*R*)$_2$-**J**

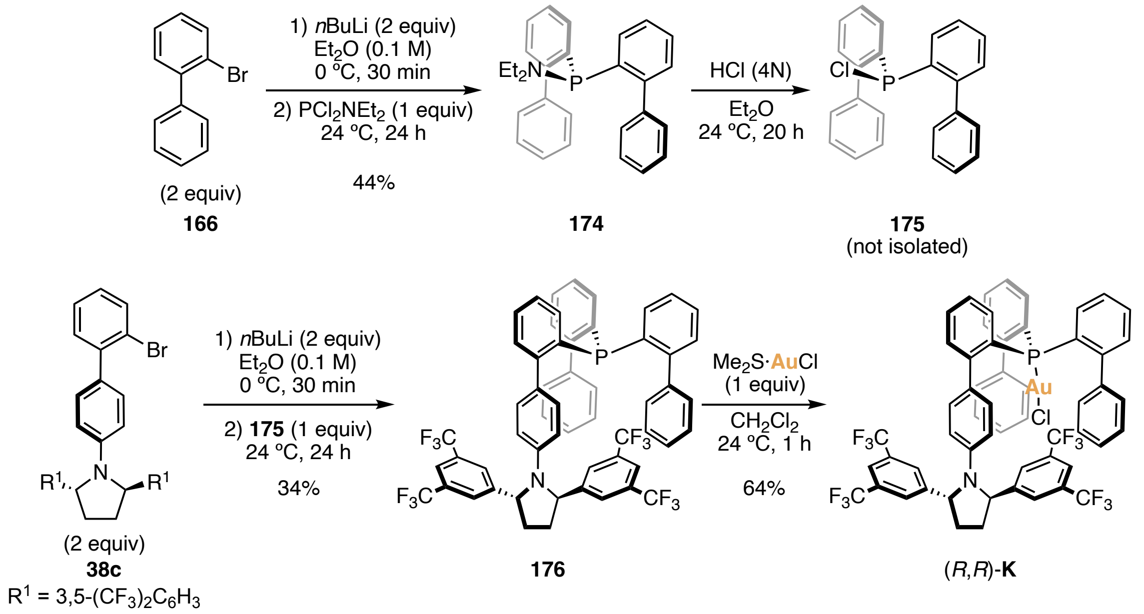
A similar synthetic route was applied for the synthesis of gold(I) complex (*R*,*R*)$_2$-**J**. After the lithiation of two equivalents of **38c**, disubstitution of phenylphosphine dichloride afforded ligand **173** in 72% yield. Its reaction with dimethylsulfide gold(I) chloride gave complex (*R*,*R*)$_2$-**J** in 92% yield (Scheme 61).



Scheme 61. Synthesis of gold(I) complex (*R*,*R*)$_2$-**J**.

Synthesis of complex (*R*,*R*)-**K**

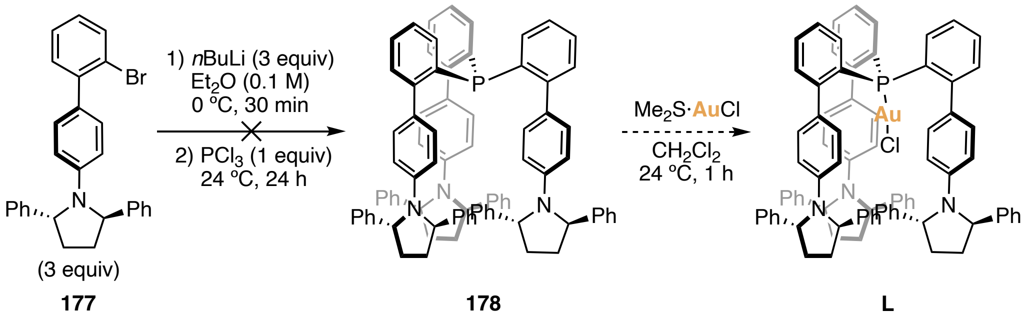
A slightly different route was designed for the synthesis of gold(I) complex (*R*,*R*)-**K**. Previously lithiated 2-bromobiphenyl **166** was reacted with diethylaminephosphine dichloride giving compound **174** in 44% yield. Chlorination using HCl in Et$_2$O yielded intermediate **175** which was not isolated and directly used for the substitution reaction. After addition of the lithiated **38c**, ligand **176** was formed in 34% yield, leading to complex (*R*,*R*)-**K** in 64% yield after complexation with dimethylsulfide gold(I) chloride (Scheme 62).



Scheme 62. Synthesis of gold(I) complex (*R*,*R*)-**K**.

Unsuccessful Synthesis of Other Gold(I) Complexes

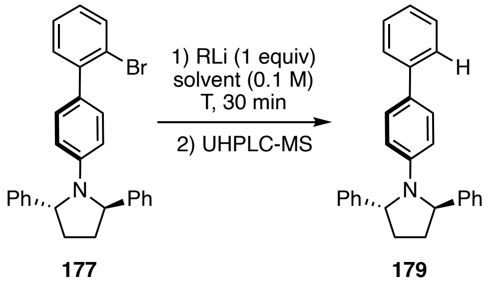
Other family of these gold(I) complexes was tried to be synthesized, without the CF_3 substituents on the aryl groups of the pyrrolidines, in order to study their structures and reactivities. But when we tried to synthesize complex (*R*,*R*)$_3$-**L** (Scheme 63), the reaction did not work. By UHPLC-MS, phosphine **178** was not observed, only **177**, so the lithiation step did not work.



Scheme 63. Attempt to synthesize gold(I) complex **L**.

In an attempt to understand the limitations of the lithiation, we tested the initial conditions (Table 13, Entry 1) several times but only starting material **177** was observed by UHPLC-MS: using diethyl ether from the glovebox and from the Solvent Purification System and after different *n*BuLi titrations. We tried same conditions than Entry 1 but at 24 ºC with the same outcome (Table 13, Entry 2). We thought that the reason that lithiation step was not working could be the poor solubility of **177** in diethyl ether at 0 ºC or 24 ºC, and we observed that solubility was better using a mixture of solvents, toluene and diethyl ether. Using a mixture Et_2O/toluene 1:2 (Table 13, Entry 3) both **177** and **179** were observed after 30 min and two hours later the reaction had not evolved. However, reproducibility issues were observed with these conditions (Table 13, Entry 4), when only **177** was observed. Other Et_2O/toluene ratios (1:4) at 0 and 24 ºC or only toluene as solvent at 0 ºC (Table 13, Entries 5, 6 and 7 respectively) did not lead to the desired product. Using *t*BuLi as lithiation reagent did not show a significant effect in the formation of **179** (Table 13, Entry 8).

Table 13. Different conditions for the lithiation step.



Entries	RLi	solvent	T (ºC)	Observations[a]
1	*n*BuLi	Et_2O	0	**177**
2	*n*BuLi	Et_2O	24	**177**
3	*n*BuLi	Et_2O/toluene 1:2	0	**177 and 179**
4	*n*BuLi	Et_2O/toluene 1:2	0	**177**
5	*n*BuLi	Et_2O/toluene 1:4	0	**177**
6	*n*BuLi	Et_2O/toluene 1:4	24	**177**
7	*n*BuLi	toluene	0	**177**
8	*t*BuLi[b]	Et_2O	-78	**177**

[a] Observations by UHPLC-MS. [b] 2 equivalents of *t*BuLi were added.

As a latter approach, preformation of the corresponding Grignard reagent using Mg and I_2 in THF was attempted, but the product **179** was not either detected by UHPLC-MS or NMR.

Study of the Reactivity in Different Transformations

The reactivity of the synthesized sterically hindered chiral gold(I) complexes $(R,R)_3$-**I**, $(R,R)_2$-**J** and (*R*,*R*)-**K** and the achiral one **M**[108] (Figure 16) was studied.

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[108] Complex **M** was delivered by Dr. Jesús Campos's research group.

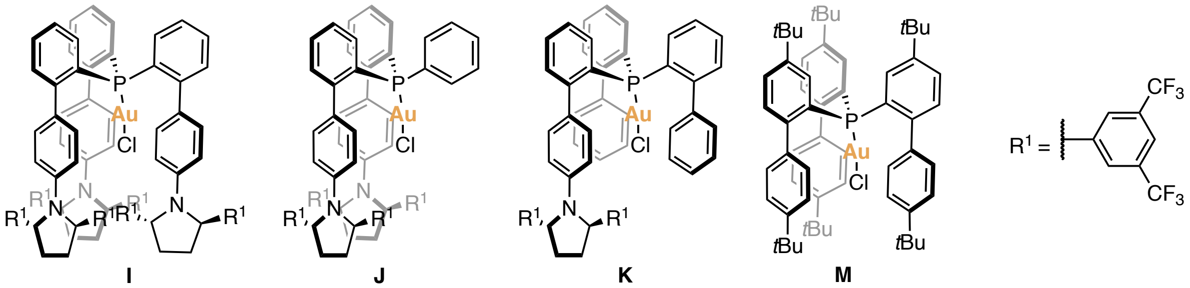
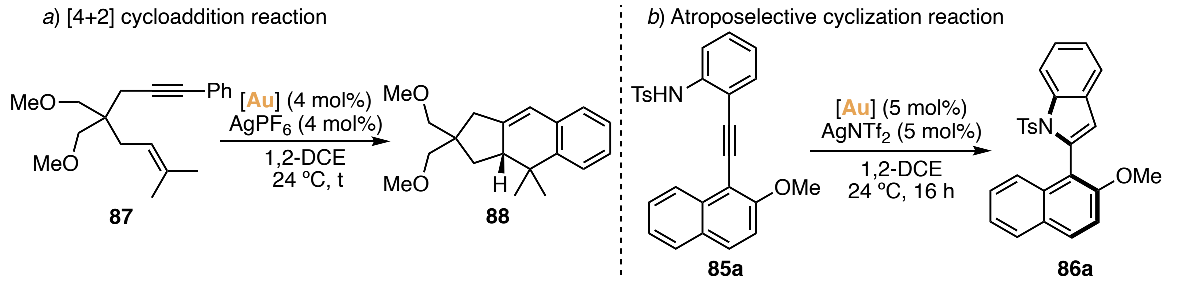


Figure 16. Sterically hindered gold(I) complexes

We tested these complexes in the [4+2] cycloaddition of 1,6-enyne **87**, though all the complexes yielded the desired product **88** with high efficacy, the enantioselectivity was very low (Table 14, Entries 1–3, Reaction *a*). All the complexes were also tested in the atroposelective cyclization of **85a** (Table 14, Entries 4–6, Reaction *b*). Complex (*R*,*R*)$_3$-**I** only gave product **86a** in 8% yield (Table 14, Entry 4), so the enantioselectivity was not measured; with complex (*R*,*R*)$_2$-**J** the yield was improved for this reaction but the enantioselectivity was low (Table 14, Entry 5); and complex (*R*,*R*)-**K** lead to the same outcome of enantioselectivity, but with excellent yields (Table 14, Entry 6).

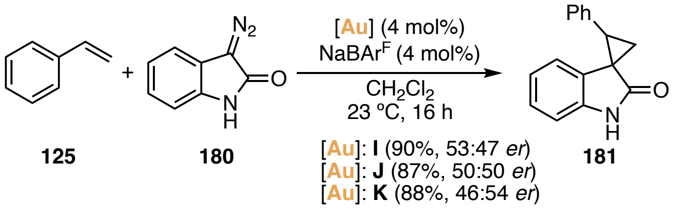
Table 14. [4+2] cycloaddition and atroposelective cyclization reactions.



Entry	Reaction	[Au]	Yield (%)[a]	*er*
1	*a*	(*R*,*R*)$_3$-**I**	87	57:43
2	*a*	(*R*,*R*)$_2$-**J**	95	49:51
3	*a*	(*R*,*R*)-**K**	95	50:50
4	*b*	(*R*,*R*)$_3$-**I**	8	n.d.
5	*b*	(*R*,*R*)$_2$-**J**	65	52:48
6	*b*	(*R*,*R*)-**K**	>99	51:49

[a] Yield was measured by ^{1}H NMR using 1,1,2,2-tetrachloroethane as internal standard.

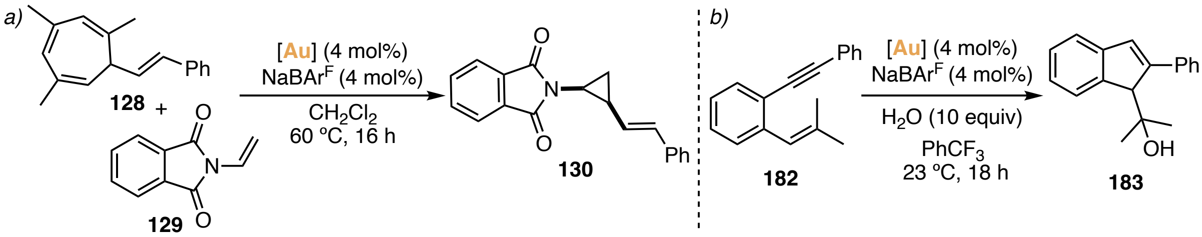
Other reaction that was also tried was the cyclopropanation reaction using styrene **125** and **180**,[109] all the complexes gave the product **181** in high yields but poor enantioselectivity (Scheme 64).



Scheme 64. Cyclopropanation reaction.

To know more about the reactivity of sterically hindered gold(I) catalysts, we carried out some reactions using achiral complex **M** as a model complex. We tried the Retro-Buchner reaction86 of *N*-vinylphthalimide **129** and 7-styryl-1,3,5-cycloheptatriene **128** and with complex **M** obtaining cyclopropane **130** in 55% yield (Table 15, Entry 1). However, when complexes (*R*,*R*)$_3$-**I**, (*R*,*R*)$_2$-**J** and (*R*,*R*)-**K** were used under the same reaction conditions, the yields were very low and also the enantiomeric ratios (Table 15, Entries 2–4). On the other hand, the 5-*endo*-dig cyclization of the 1,5-arylenyne **182**[110] with complex **M** afforded the desired 1*H*-indene **183** in excellent yield by ^{1}H NMR (Table 15, Entry 5). So, this reaction using complexes (*R*,*R*)$_2$-**J** and (*R*,*R*)-**K** was also studied, again in excellent yields but with low enantioselectivities (Table 15, Entries 6 and 7).

Table 15. Retro-Buchner reaction and 5-*endo*-dig cyclization of 1,5-arylenyne **183**.



Entry	Reaction	[Au]	Yield (%)[a]	*er*
1	*a*	**M**	55	-
2	*a*	(*R*,*R*)$_3$-**I**	8	51:49
3	*a*	(*R*,*R*)$_2$-**J**	12	50:50
4	*a*	(*R*,*R*)-**K**	21	49:51
5	*b*	**M**	>99[a]	-

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[109] (a) Cao, Z.-Y.; Zhou, F.; Yu, Y.-H.; Zhou, J. *Org. Lett.* **2013**, *15*, 42–45. (b) Cao, Z.-Y.; Wang, X.; Tan, C.; Zhao, X.-L.; Zhou, J.; Ding, K. *J. Am. Chem. Soc.* **2013**, *135*, 8197–8200.

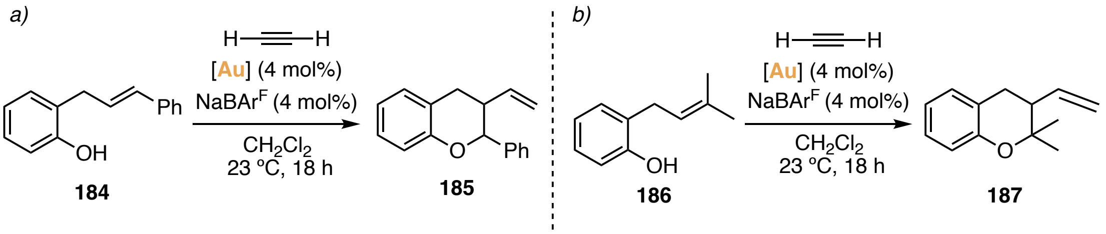
[110] (a) Martínez, A.; García-García, P.; Fernández-Rodríguez, M. A.; Rodríguez, F.; Sanz, R. *Angew. Chem. Int. Ed.* **2010**, *49*, 4633–4637. (b) Sanjuán, A. M.; Rashid, M. A.; García-García, P.; Martínez-Cuezva, A.; Fernández-Rodríguez, M. A.; Rodríguez, F.; Sanz, R. *Chem. Eur. J.* **2015**, *21*,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

6	*b*	(*R*,*R*)$_2$-**J**	>99[a]	57:43
7	*b*	(*R*,*R*)-**K**	>99[a]	47:53

[a] Yield measured by ^{1}H NMR using diphenylmethane as internal standard.

Since one of the goals of synthesizing sterically hindered catalysts was to study the activation of small molecules, such as acetylene gas, we attempted the reaction of acetylene with compounds **184** and **186** (reaction currently being studied in our group) in the presence of the achiral complex **M** for the formation of phenyl substituted chromane **185** and dimethyl substituted chromane **187**, leading to the desired products in 70% and 89% yields respectively (Table 16, Entries 1 and 5). With these results in hand, we carried out the reactions with complexes (*R*,*R*)$_3$-**I**, (*R*,*R*)$_2$-**J** and (*R*,*R*)-**K**. Complex (*R*,*R*)$_3$-**I**, the most sterically hindered, yielded only 10% yield of **185** (Table 16, Entry 2), but it afforded chromane **187** in very high yield (Table 16, Entry 6). However, enantioselectivities were very low in both examples. Complexes (*R*,*R*)$_2$-**J** and (*R*,*R*)-**K** successfully afforded both chromanes, but they showed similar levels of enantioselectivity (Table 16, Entries 3, 4, 7 and 8).

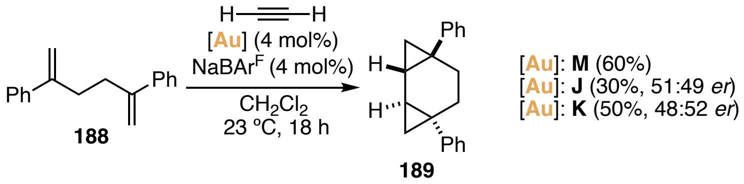
Table 16. Reactions with acetylene gas for the formation of chromanes.



Entry	Reaction	Gold(I) catalyst	Yield (%)[a]	*er*
1	*a*	**M**	70	-
2	*a*	(*R*,*R*)$_3$-**I**	10	57:43
3	*a*	(*R*,*R*)$_2$-**J**	77	56:44
4	*a*	(*R*,*R*)-**K**	83	47:53
5	*b*	**M**	89	-
6	*b*	(*R*,*R*)$_3$-**I**	95	55:45
7	*b*	(*R*,*R*)$_2$-**J**	83	56:44
8	*b*	(*R*,*R*)-**K**	-[b]	48:52

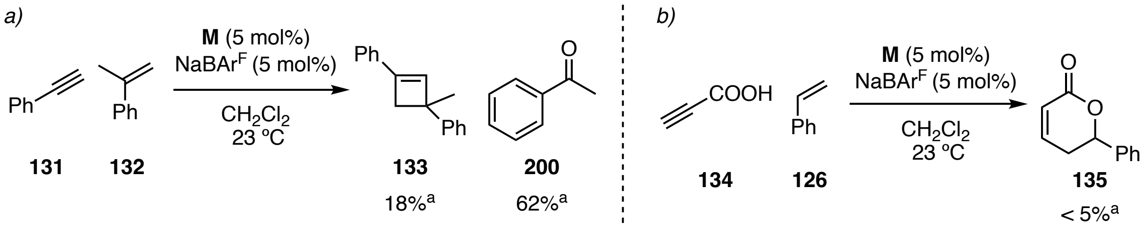
[a] Yield was measured by ^{1}H NMR using 1,1,2,2-tetrachloroethane as internal standard. [b] NMR yield not measured, although high conversion was observed.

The reaction **188** with acetylene gas[111] using complexes **M**, (*R*,*R*)2-**J** and (*R*,*R*)-**K**, afforded the tricyclic product **189** in moderates yields and very low enantioselectivity when the chiral complexes (*R*,*R*)2-**J** and (*R*,*R*)-**K** were used (Scheme 65).



Scheme 65. Reaction with acetylene gas for the synthesis of the tricyclic compound **187**.

The [2+2] cycloaddition reaction87 was also tested with complex **M**. Reaction between phenylacetylene **131** and α-methyl styrene **132** gave the desired cyclobutene **133** in only 18% yield, obtaining 62% of acetophenone **200** (Scheme 66, Reaction *a*). The reaction between propiolic acid **134** and styrene **126** form the corresponding lactone **135**88 but in very low yield (Scheme 66, Reaction *b*).



Scheme 66. [2+2] cycloaddition reaction and formation of lactone **135**. ᵃ Yield was measured by ^{1}H NMR using 1,1,2,2-tetrachloroethane as internal standard.

Finally, we wanted to study to use a chiral silver salts as chloride scavengers in the formal [4+2] cycloaddition of **87**.[112] Unfortunately, no reaction was observed using complexes (*R*,*R*)3-**I** and **M** with any of the chiral silver salts (*R*,*R*)-**201** and (*R*,*R*)-**202** (Scheme 67).

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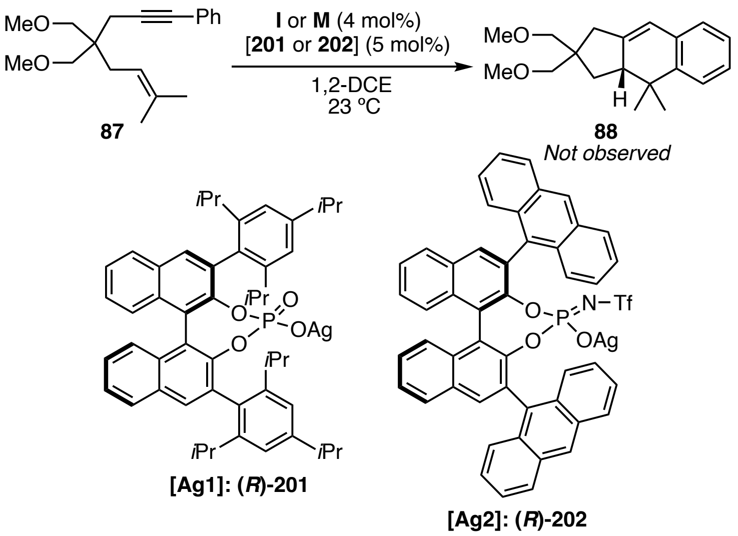
[111] Scharnagel, D.; Escofet, I.; Armengol-Relats, H.; de Orbe, M. E.; Korber, J. N.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2020**, *59*, 4888-4891.

[112] Franchino, A.; Martí, À.; Echavarren, A. M. *J. Am. Chem. Soc.* **2022**, *144*, 3497–3509.



Scheme 67. Formal [4+2] cycloaddition using chiral silver salts.

The explanation for the lack of enantioselectivity using these chiral gold(I) complexes has been theoretically studied by conformational sampling performed with semiempirical CREST based on xTB methods.[113,114] The studies were performed with the bulky $(R,R)_3$-**I**, $(R,R)_2$-**J** and (R,R)-**K** complexes and the corresponding **Int1** ($[\mathrm{LAu}(\eta^2\text{-alkyne})]^+$ complexes with 1,6-enyne **87** (Figure 17).[115] The bond distances have been calculated between the gold(I) atom and the *o*-aryl centroid of each aryl ring. For all the complexes, the coordination of the alkyne to the gold(I) center generates an intermediate that reorganize the complexes opening the catalytic pocket and showing the high flexibility of these systems. The chiral information provided by the C_2-symmetric pyrrolidines finishes far away from the reaction center, losing the enantioinduction. These results match the experimental information obtained with the formation of the almost racemic product **88** and could explain the absence of enantioselectivity obtained in other transformations.

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[113] The CREST conformational analysis have been performed by Dr. Imma Escofet.

[114] Pracht, P.; Bohle, F.; Grimme, S. *Phys. Chem. Chem. Phys.* **2020**, *22*, 7169–7192.

[115] In each example the lowest energy conformer was reoptimized at DFT level, see in the Computational Details of the Supporting Information. Zuccarello, G.; Nanini, L.; Arroyo-Bondía, A.; Fincias, N.; Arranz, I.; Pérez-Jimeno, A. H.; Peeters, M.; Martín-Torres, I.; Sadurní, A.; García-Vázquez, V.; Wang, Y.; Kirillova, M. S.; Montesinos-Magraner, M.; Caniparoli, U.; Núñez, G. D.; Maseras, F.; Besora, M.; Escofet, I.; Echavarren A. M. Enantioselective Catalysis with Pyrrolidinyl Gold(I) Complexes: DFT and NEST Analysis of the Chiral Binding Pocket. *ChemRxiv*. (*Organic Chemistry*), **2023**, preprint. DOI: 10.26434/chemrxiv-2023-vxlcf.

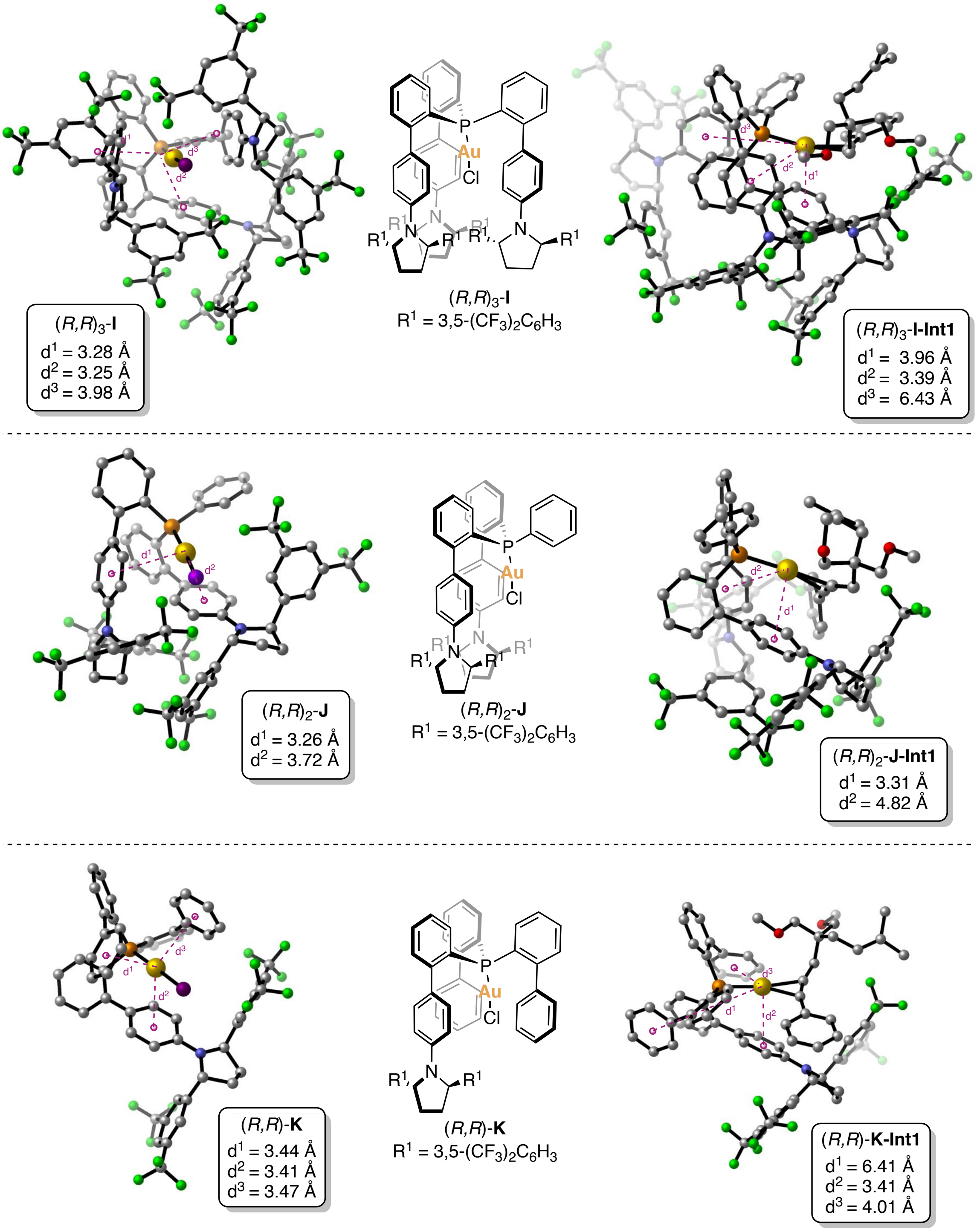
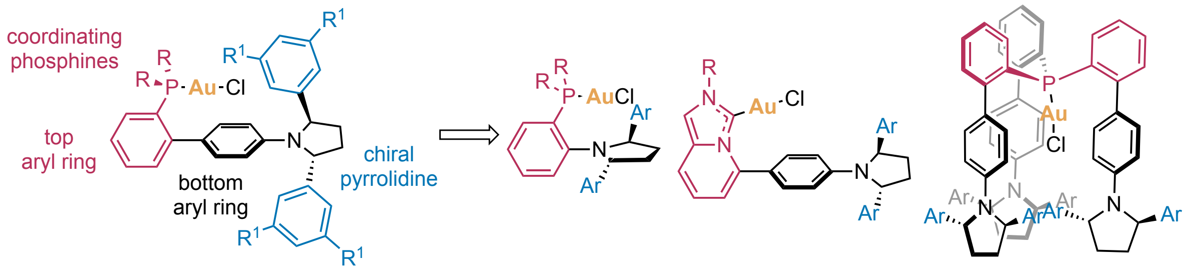


Figure 17. CREST conformational analysis.

Conclusions and Outlook

In summary, three families of chiral pyrrolidine-based gold(I) complexes have been synthesized and their reactivities in different transformations have been studied.



- Shorter complexes: the synthesis of complexes (*R*,*R*)-**A–E** has been successfully achieved and their reactivity have been studied. They have been used in the atroposelective formation of C2-arylindoles in good yields and enantioselectivities. The use of these complexes in Au(I)/Au(III) redox catalysis has been tried but it seems that the 2,5-diaryl substituted pyrrolidine do not work for these systems. A new design with this kind of complexes is being currently developed using 3,4-diaryl substituted pyrrolidines.
- N-heterocyclic carbene complexes: it has been changed the top aryl ring with a coordinated phosphine by a NHC moiety and complexes (*R*,*R*)-**F–H** have been successfully prepared. Their reactivity has been studied and it has been showed good results in terms of yields and enantioselectivities. However, the enantioselectivity is not improved compared to the previously reported results for the tested reactions. Therefore, the ligands are being currently tested in other gold(I) catalyzed transformations.
- Sterically hindered complexes: three new sterically hindered chiral gold(I) complexes $(R,R)_3$-**I**, $(R,R)_2$-**J** and (*R*,*R*)-**K** have been successfully prepared. They have been tested in different gold(I)-catalyzed reactions giving in most of them high yields. However, none of these reactions showed good results in terms of enantioselectivity. Their behavior has been studied by DFT calculations and a new subclass of ligands is being planned to be prepared bearing substituents in the top aryl ring, expecting to close the environment of the Au(I) atom.

Experimental Section

General Information

Unless otherwise stated, all the reactions reported herein were carried out under argon or nitrogen atmosphere. Reactions were carried out in solvents dried by passing through an activated alumina column on a PureSolv^{TM} Solvent Purification System (SPS, Innovative Technologies, Inc., MA), in commercially available anhydrous solvents purchased from ACROS Organics or in HPLC-grade solvents. Yields refer to chromatographically and spectroscopically pure (^{1}H NMR) homogeneous material, unless otherwise stated. Reactions were monitored by TLC (thin layer chromatography), UHPLC-MS, NMR analysis and/or GC-MS. Thin layer chromatography was carried out using TLC aluminum sheets coated with 0.2 mm of silica gel (Merck 60 F_{254}) using short-wave UV light as visualizing agent and acidic solution of vanillin in ethanol or a basic solution of $KMnO_4$ in water as stain followed by heat as developing agents. UHPLC-MS was performed in Agilent Technologies 1290 Infinity II, LC-MS with single-squad detector InfinityLab (APCI ionization source). Chromatographic purifications were carried out using flash grade silica gel (SDS Chromatogel 60 ACC, 40-60 μm) as the stationary phase manually, or using a CombiFlash® R_f instrument with normal phase disposable columns of different sizes (Teledyne Isco). Preparative TLC was performed on 20 cm x 20 cm silica gel plates (2.0 mm thick, catalogue number 02015, Analtech or 1.0 mm thick, catalogue number P02013 Analtech). NMR spectra were recorded at 298 K on a Bruker Avance 300 Ultrashield, a Bruker Avance 400 Ultrashield (400 MHz for ^{1}H and 101 MHz for ^{13}C) or a Bruker Avance 500 Ultrashield (500 MHz for ^{1}H and 126 MHz for ^{13}C) spectrometers. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane, using as reference residual solvent (^{1}H NMR: $CDCl_3$ at 7.26 ppm, CD_2Cl_2 at 5.31 ppm, CD_3OD at 3.31 ppm, $(CD_3)_2SO$ at 2.50 ppm, TCE-d_2 at 6.0 ppm; for $^{13}C\{^1H\}$ NMR: $CDCl_3$ at 77.16 ppm, CD_2Cl_2 at 54.00 ppm, CD_3OD at 49.00 ppm, $(CD_3)_2SO$ at 39.52 ppm, TCE-d_2 at 73.78 ppm) or tetramethylsilane. Coupling constants (*J*) are reported in hertz (*Hz*). The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintuplet, m = multiplet, br s = broad singlet. Mass spectra were recorded on MicroTOF Focus or Maxis Impact spectrometers (both from Bruker Daltonics). Melting points were determined using a MP70 Melting Point System (Mettler Toledo). Single-crystal X-ray diffraction data were collected at 100 K on a Rigaku MicroMax-007HF, Mo *Kα* rotating anode, equipped with a Pilatus 200 K detector or on a Bruker APEX DUO, Mo *Kα* Microfocus source E025 IuS anode, equipped with an APEX DUO detector using omega scans. Chiral HPLC analyses were performed on an Agilent Technologies 1200 series. SFC analyses were performed on an Agilent Technologies 1260 Infinity II, a Waters ACQUITY UPC2 System with diode array detector and by Chiral Technologies Europe analytical service. 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 2 mL (100 mm pathlength) cells.

Reagents were obtained from commercial sources and used without further purification. The preparation of the following compounds has been previously described: **36a**,23 **36c**,23 **87**,23 **88**,23 **89**,23 **91**,35 **117**,83 **120**,84 **121**,84 **122**,99 **123**,99 **125**,85 **127**,85 **128**,86[b] **130**,86 **133**,87 **135**,88 **139**,89 **141a-e**,90 **142a-e**,90 **167**,104 **169**,105 **170**,104 **181**,109 **182**,110 **183**,110 **201**,[116] **202**.112

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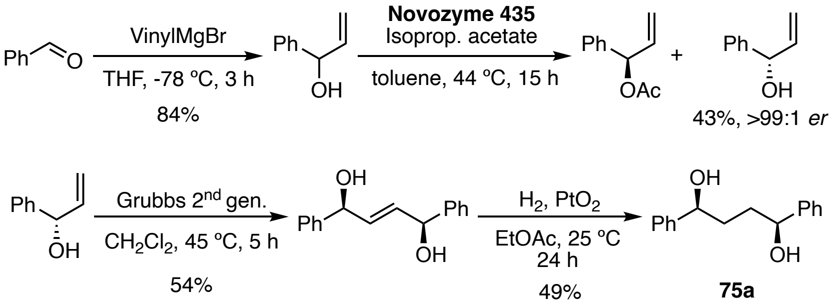
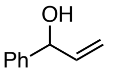
[116] Raducan, M.; Moreno, M.; Bour, C.; Echavarren, A. M. *Chem. Commun.* **2012**, *48*, 52–54.

Synthetic Procedures and Analytical Data

Synthetic route for (1*S*,4*S*)-1,4-diphenylbutane-1,4-diol, (*S*,*S*)-75a



1-Phenylprop-2-en-1-ol

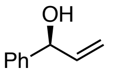


1-phenylprop-2-en-1-ol was synthesized according to the reported procedure.[117] Vinylmagnesium bromide (1.0 M in THF, 56.5 mL, 56.5 mmol, 1.2 equiv) was added dropwise to a solution of benzaldehyde (4.8 mL, 47.1 mmol, 1.0 equiv) at -78 ºC. The mixture was stirred at -78 ºC for 3h. Then, an aqueous saturated solution of NH_4Cl was added to the mixture and the aqueous phase was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc from 0 to 40% of EtOAc) to provide the title compound (5.3 g, 39.6 mmol, 84% yield) as a clear oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.27 (m, 5H), 6.06 (ddd, *J* = 17.2, 10.2, 6.0 Hz, 1H), 5.36 (dt, *J* = 17.2, 1.4 Hz, 1H), 5.26 – 5.16 (m, 2H), 1.91 (br s, 1H).

The characterization data were fully consistent with those previously reported.117

(*S*)-1-Phenylprop-2-en-1-ol



The synthesis of (*S*)-1-phenylprop-2-en-1-ol was performed following an analogous procedure to the one previously reported for other enantioenriched aryl substituted allylic alcohols.117 A two-necked round bottom flask equipped with a stirring bar was charged with powdered 4 Å molecular sieves (8.3 g) and heated to 200 ºC under high vacuum (ca 0.1 mbar) during 40 min. The flask was allowed to cool to 24 ºC under argon and Novozyme 435 resin (1.82 g, >5000 U/g) was added. The solids were suspended in anhydrous toluene (700.0 mL). Isopropenyl acetate (47.5 mL, 436.4 mmol, 4.6 equiv) was added followed by the addition of 1-phenylprop-2-en-1-ol (12.9 g, 95.9 mmol, 1.0 equiv) in toluene (100.0 mL), and the mixture was stirred at 44 ºC for 15 h. The reaction progress was tracked by chiral HPLC and upon completion, was cooled to 23 ºC then filtered through celite, and concentrated under reduced pressure. The crude material was purified by flash silica gel column

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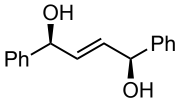
[117] Yung-Son, H.; Ying-Chieh, W.; Kuo-Jui, W. *J. Chin. Chem. Soc.*, **2008**, *55*, 896–914.

chromatography (SiO_2, cyclohexane/EtOAc from 0 to 30% of EtOAc), affording the title compound (5.6 g, 41.7 mmol, 43% yield, >99:1 *er*) as a light-yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.26 (m, 5H), 6.13 – 5.99 (m, 1H), 5.36 (dt, *J* = 17.2, 1.4 Hz, 1H), 5.24 – 5.17 (m, 2H), 1.94 (dd, *J* = 3.9, 1.8 Hz, 1H). **α_D^{589}** = +163.7 deg·cm^2·g^{-1} ($CHCl_3$, c 0.089, 301 K). **HPLC** Chiralcel OJ-H (250 x 4.6 mm, 5 μm) at 25 ºC, flow 1.0 mL/min, isocratic hexane/iPrOH 98:2, 220 nm; t_{R1}= 28.6 min, t_{R2}= 35.8 min.

All other experimental data were in agreement with the literature.[118]

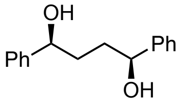
(1*S*,4*S*,*E*)-1,4-Diphenylbut-2-ene-1,4-diol



The synthesis of (1*S*,4*S*)-1,4-Diphenylbut-2-ene-1,4-diol was performed following an analogous procedure to the one previously reported for other enantioenriched aryl substituted allylic diols.23 Grubbs 2nd gen. catalyst (354.1 mg, 417.1 mmol, 10 mol%) was added to a solution of (*S*)-1-phenylprop-2-en-1-ol (5.6 g, 41.7 mmol, 1.0 equiv) in dichloromethane (41.7 mL, 1.0 M). The mixture was stirred for 5 h at 40 ºC. The crude material was purified by flash column chromatography using Combiflash (SiO_2, cyclohexane/EtOAc from 0 to 70% of EtOAc), affording the title compound (5.4 g, 22.6 mmol, 54% yield) as a beige solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 10H), 6.03 (dd, *J* = 3.3, 1.5 Hz, 2H), 5.26 (td, *J* = 3.5, 1.5 Hz, 2H), 1.92 (d, *J* = 3.8 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 142.7, 133.3, 128.8, 127.9, 126.4, 74.5. **M.p. =** >70 ºC (decomposition). **α_D^{589}** = +12.5 deg·cm^2·g^{-1} ($CHCl_3$, c 0.1, 296 K).

(1*S*,4*S*)-1,4-Diphenylbutane-1,4-diol, (*S,S*)-75a



The synthesis of (*S,S*)-**75a** was performed following an analogous procedure to the one previously reported for other enantioenriched aryl substituted diols.23 A flask was charged with PtO_2 (257.0 mg, 173.0 mmol, 5 mol%), then evacuated and back-filled with argon three times. Then, (1*S*,4*S*,*E*)-1,4-diphenylbut-2-ene-1,4-diol (5.4 g, 22.6 mmol, 1.0 equiv) was dissolved in EtOAc (226.0 mL, 0.1 M) and the solution was added to the flask. Subsequently, the reaction mixture was evacuated and back-filled with hydrogen. The reaction was stirred at 24 ºC for 24 h under hydrogen atmosphere (1 atm), then filtered over Celite and concentrated in vacuo. The crude material was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc from 0 to 70% of EtOAc), affording the title compound (*S,S*)-**75a** (2.7 g, 22.6 mmol, 49% yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 4.4 Hz, 8H), 7.29 – 7.26 (m, 2H), 4.76 – 4.69 (m, 2H), 2.52 (br s, 2H), 1.99 – 1.89 (m, 2H), 1.88 – 1.78 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.8, 128.6, 127.7, 126.0, 74.8, 36.0. **M.p. =** 72–73 ºC. **α_D^{589}** = –44.6 deg·cm^2·g^{-1} ($CHCl_3$, c 0.1, 302 K).

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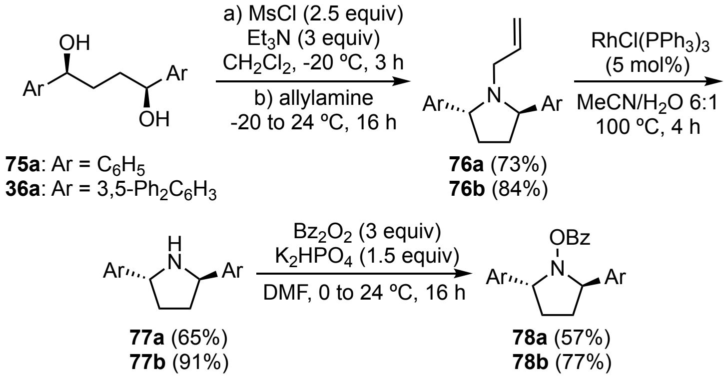
[118] Lyothier, I.; Defieber, C.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 6204–6207.

The characterization data were fully consistent with those previously reported.117

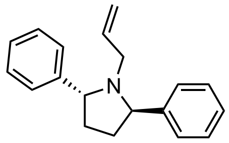
Synthesis of (2*R*,5*R*)-78a and (2*R*,5*R*)-78b



General procedure A: for the synthesis of *N*-allylpyrrolidines

A flamed-dried round bottom flask equipped with a stirring bar was charged with the corresponding 1,4-diol (1.0 equiv) and dichloromethane (0.1 M). The solution was cooled down to -20 ºC and triethylamine (3.0 equiv) and methanesulfonyl chloride (2.5 equiv) were added under argon atmosphere. The mixture was stirred at -20 ºC for 3 h. Then, at -20 ºC, allylamine (100 equiv) was added. The reaction was left to warm up to room temperature and then stirred at 25 ºC for 16 h. The reaction was checked by TLC and concentrated under reduced pressure. Residue was diluted with Et_2O, washed with a saturated solution of $NaHCO_3$ (3x), brine, dried over Na_2SO_4 and concentrated. The crude product was purified by flash SiO_2 column chromatography.

(2*R*,5*R*)-1-Allyl-2,5-diphenylpyrrolidine, 76a



The title compound **76a** (796.0 mg, 3.0 mmol, 73% yield) was obtained as a colorless oil according to general procedure **A**, using (*S,S*)-**75a** (1.0 g, 4.1 mmol). It was purified by flash column chromatography (SiO_2, cyclohexane/CH_2Cl_2 from 10:1 to 1:1).

The spectral data are consistent with the literature.[119]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 –7.22 (m, 10H), 5.64 (dddd, *J* = 17.0, 10.4, 7.4, 4.5 Hz, 1H), 4.97 – 4.87 (m, 2H), 4.33 (ddd, *J* = 7.4, 4.0, 1.5 Hz, 2H), 3.02 – 2.95 (m, 1H), 2.71 (dd, *J* = 14.7, 7.4 Hz, 1H), 2.59 – 2.47 (m, 2H), 1.97 – 1.86 (m, 2H).

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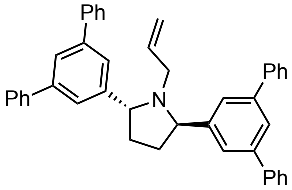
[119] Chong, J. M.; Clarke, I. S.; Koch, I.; Olbach, P.C.; Taylor, N. J. *Tetrahedron: Asymmetry,* **1995**, 6, 2, 409–418.

(2*R*,5*R*)-2,5-Di([1,1':3',1''-terphenyl]-5'-yl)-1-allylpyrrolidine, 76b



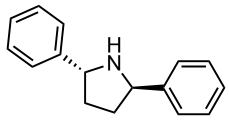
The title compound **76b** (684.0 mg, 1.2 mmol, 84% yield) was obtained as a pale-yellow solid according to general procedure **A**, using (1*S*,4*S*)-1,4-di([1,1':3',1''-terphenyl]-5'-yl) butane-1,4-diol (*S,S*)-**36a**23 (780.0 mg, 1.4 mmol) and after purification by flash column chromatography (SiO_2, pentane/Et_2O from 1:0 to 20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.67 (m, 10H), 7.58 (d, J = 1.7 Hz, 4H), 7.52 – 7.47 (m, 8H), 7.42 – 7.37 (m, 4H), 5.79 (dddd, J = 17.9, 9.5, 7.3, 4.3 Hz, 1H), 5.09 – 5.04 (m, 1H), 5.04 – 5.00 (m, 1H), 4.62 – 4.53 (m, 2H), 3.22 (ddt, J = 14.9, 4.3, 2.0 Hz, 1H), 2.97 (dd, J = 14.8, 7.3 Hz, 1H), 2.77 – 2.56 (m, 2H), 2.08 (qt, J = 7.0, 3.2 Hz, 2H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 145.5, 141.9, 141.5, 137.1, 128.9, 127.5, 127.5, 125.9, 124.9, 115.9, 66.0, 50.3, 33.6. **HRMS** (ESI+) calculated for $[C_{40}H_{38}N]^+$ 568.2999 *m/z*; found $[M + H]^+$ 568.3006 *m/z*. **M.p.** = 66–68 ºC. **α_D^{589}**= 101.9 deg·cm^2·g^{-1} (CH_2Cl_2, c 0.1, 303 K).

General procedure B: for the deallylation of *N*-allylpyrrolidines

A round bottom flask equipped with a stirring bar was evacuated and backfilled with argon. The flask was charged with the corresponding *N*-allylpyrrolidine (1.0 equiv) and solid was dissolved in 84:16 mixture of $MeCN/H_2O$ (68.6 mM). Wilkinson's catalyst (5 mol%) was added, the solution was purged with argon for 10 minutes and the reaction was heated to reflux over 4 hours. The reaction was followed by TLC (cyclohexane/EtOAc, 3:1) until completion. Reaction was cooled down to room temperature and diluted with diethyl ether and brine. Aqueous phase was extracted with diethyl ether (3x), combined organic fractions were dried over Na_2SO_4 and concentrated. Crude product was purified by flash SiO_2 column chromatography.

(2*R*,5*R*)-2,5-Diphenylpyrrolidine, 77a

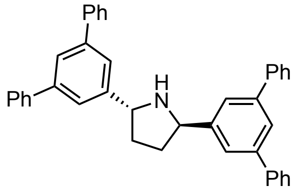


The title compound **77a** (425.0 mg, 1.9 mmol, 65% yield) was obtained as a white solid according to general procedure **B**, using **76a** (770.0 mg, 2.9 mmol). It was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc, 4:1).

The characterization data were fully consistent with those previously reported.119

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.39 (m, 4H), 7.37 – 7.32 (m, 4H), 7.26 – 7.22 (m, 2H), 4.58 – 4.53 (m, 2H), 2.45 – 2.37 (m, 2H), 1.96 – 1.87 (m, 2H). **α_D^{589}** = +138.7 deg·cm^2·g^{-1} ($CHCl_3$, c 0.1, 301K).

(2*R*,5*R*)-2,5-Di([1,1':3',1''-terphenyl]-5'-yl)pyrrolidine, 77b



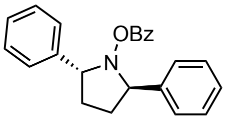
The title compound **77b** (747.0 mg, 1.4 mmol, 91% yield) was obtained as a pale-yellow solid according to general procedure **B**, using **76b** (880.0 mg, 1.55 mmol). It was purified by flash column chromatography (SiO_2, pentane/Et_2O from 100:0 to 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 – 7.57 (m, 14H), 7.57 – 7.43 (m, 8H), 7.43 – 7.35 (m, 4H), 4.77 (t, *J* = 6.9 Hz, 2H), 2.64 – 2.41 (m, 2H), 2.19 – 1.98 (m, 2H), 1.89 (s, 1H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 142.2, 141.4, 128.9, 127.8, 127.6, 127.5, 125.0, 124.5, 62.6, 35.8. **HRMS** (ESI+) calculated for $[C_{40}H_{34}N]^+$ 528.2686 *m/z*; found $[M + H]^+$ 528.2696 *m/z*. **M.p.** = 129–130 ºC. **α_D^{589}**= 78.0 deg·cm^2·g^{-1} (CH_2Cl_2, c 0.1, 303 K).

General procedure C: for the oxidation of 2,5-diarylpyrrolidines[120]

A round-bottom flask equipped with stirring bar was charged with K_2HPO_4 (1.5 equiv) and benzoic peroxyanhydride (70% Wt, 3.0 equiv), the vial was purged with argon and DMF (0.15 M) was added. The vial was placed in an ice-water bath and a solution of the corresponding 2,5-diarylpyrrolidines (1.0 equiv) in DMF was added dropwise (final concentration 0.09 M). The reaction was allowed to reach room temperature slowly, inside the ice-water bath. Reaction was stirred during 18 h at 25 ºC and followed by ^{1}H NMR. When starting material was consumed, reaction was quenched with deionized water and stirred vigorously over 5 minutes. The reaction mixture was extracted with dichloromethane (3x). The organic phases were collected, washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash SiO_2 column chromatography.

(2*R*,5*R*)-2,5-Diphenylpyrrolidin-1-yl benzoate, 78a



The title compound **78a** (360.0 mg, 1.1 mmol, 57% yield) was obtained as a colorless oil according to general procedure **C**, using **77a** (410 mg, 1.8 mmol). It was purified by flash column chromatography (SiO_2, cyclohexane/CH_2Cl_2 from 100:0 to 75:25).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 – 7.51 (m, 2H), 7.48 – 7.44 (m, 4H), 7.43 – 7.38 (m, 1H), 7.31 (tt, *J* = 6.7, 0.9 Hz, 4H), 7.26 – 7.21 (m, 4H), 4.84 (t, *J* = 7.0 Hz, 2H), 2.64 – 2.54 (m, 2H), 2.33 – 2.21(m, 2H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 165.3, 132.8, 130.3, 129.4, 129.3, 128.6, 128.4, 128.2, 128.1, 127.6, 126.7, 68.0, 28.8. **HRMS** (ESI+) calculated for $[C_{23}H_{21}NNaO_2]^+$ 366.1464 *m/z*; found $[M + Na]^+$ 366.1465 *m/z*. **α_D^{589}** = +68.5 deg·cm^2·g^{-1}(CH_2Cl_2, c 0.10, 299 K).

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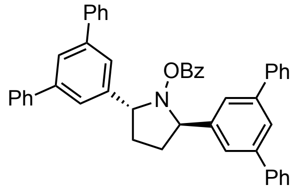
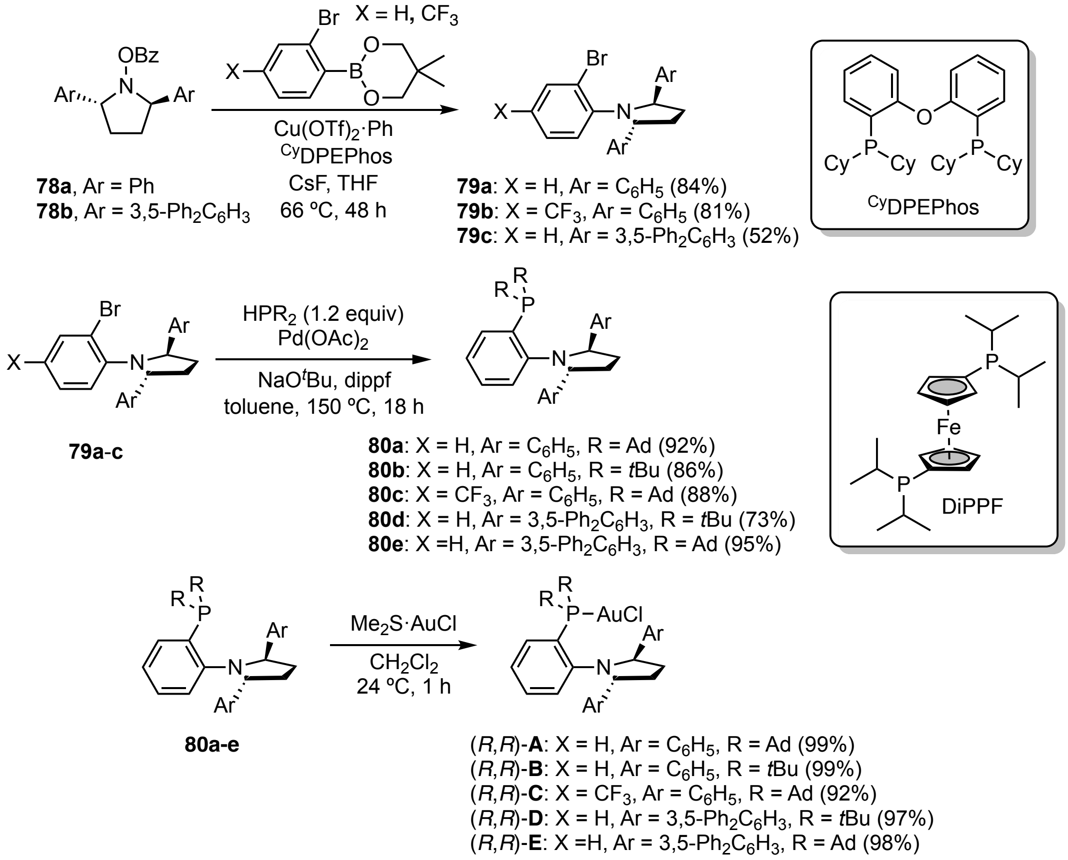
[120] The procedure was adapted from: *J. Org. Chem.* **2006**, *71*, 1, 219–224 and *Org. Synth.* **2015**, *92*, 356.

(2*R*,5*R*)-2,5-Di([1,1':3',1''-terphenyl]-5'-yl)pyrrolidin-1-yl benzoate, 78b

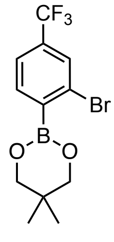


The title compound **78b** (331.0 mg, 0.46 mmol, 90% purity, 77% yield) was obtained according to general procedure **C**, using **77b** (317.0 mg, 600.0 µmol). It was purified by flash column chromatography (SiO_2, pentane/Et_2O from 100:0 to 85:15). The *N*-benzoyloxypyrrolidine **78b** could not be separated from the corresponding imine and the mixture was engaged in next step without further purification.

Synthesis of the chiral complexes (*R*,*R*)-A, (*R*,*R*)-B, (*R*,*R*)-C, (*R*,*R*)-D, (*R*,*R*)-E, (*R*,*R*)-A1



Synthesis of 2-(2-bromo-4-(trifluoromethyl)phenyl)-5,5-dimethyl-1,3,2-dioxaborinane



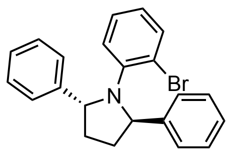
2,2-Dimethyl-1,3-propanediol (2.32 g, 22.3 mmol, 1.20 equiv) was added to a solution of 2-(2-bromo-4-(trifluoromethyl)phenyl)-5,5-dimethyl-1,3,2-dioxaborinane (5.00 g, 18.6 mmol, 1.00 equiv) in CH_2Cl_2 (0.5 M) and the mixture was stirred at 25 ºC for 3.5 h. The reaction was quenched with H_2O and the mixture was extracted with CH_2Cl_2 (2x). The combined organic phase was washed with brine and dried over $MgSO_4$. The organic phase was filtered and concentrated under reduced pressure to afford 2-(2-bromo-4-(trifluoromethyl)phenyl)-5,5-dimethyl-1,3,2-dioxaborinane (6.25 g, 18.6 mmol, >99% yield) as a colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.75 (m, 1H), 7.68 (d, J = 7.7 Hz, 1H), 7.51 (ddt, J = 7.8, 1.5, 0.8 Hz, 1H), 3.81 (s, 4H), 1.07 (s, 4H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 135.9, 133.0 (q, J = 32.9 Hz), 129.4 (q, J = 3.8 Hz), 127.2, 123.3 (q, J = 273.4 Hz), 123.1 (q, J = 3.7 Hz), 72.7, 31.9, 22.0. **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) δ –63.2. **HRMS** (ESI+) the exact mass calculated for $[C_{12}H_{13}BrF_3O_2B]^+$ is 336.0139 *m/z*; found $[M + H]^+$ 336.0146 *m/z*.

General procedure D: for the Cham Lam-type coupling reaction[121]

A flame-dried round bottom flask was charged with the corresponding *N*-benzoyloxy-pyrrolidine (1.0 equiv), the corresponding boronic ester (1.2 equiv), CsF (4.0 equiv), the phosphine ^{Cy}DPEPPhos (5.0 mol%) and $Cu(OTf)_2$ benzene complex (2.5 mol%). The round bottom flask was evacuated and backfilled with argon 3 times. Anhydrous THF (0.15 M) was added and the solution was stirred 10 min at 23 ºC (the solution became blue and progressively turned green). After 10 min stirring, the solution was refluxed for 16 h. Upon completion, the solution was filtered over a plug of Celite®, evaporated and purified by flash column chromatography (SiO_2, pentane/Et_2O from 100:0 to 96:4) affording the corresponding aniline.

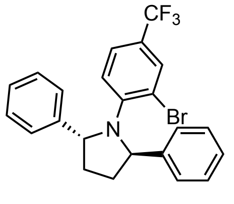
(2*R*,5*R*)-1-(2-Bromophenyl)-2,5-diphenylpyrrolidine, 79a



The title compound **79a** (138 mg, 365 µmol, 84% yield) was obtained as a pale-yellow gum according to general procedure **D**, using **78a** (150 mg, 437 µmol) and 2-(2-bromophenyl)-5,5-dimethyl-1,3,2-dioxaborinane (141 mg, 524 µmol).

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.45 – 7.37 (m, 2H), 7.27 (t J = 7.6 Hz, 2H), 7.25 – 7.14 (m, 6H), 7.14 – 7.06 (m, 1H), 6.93 (ddd, J = 8.5, 7.0, 1.5 Hz, 1H), 6.88 (dd, J = 8.2, 1.8 Hz, 1H), 6.55 (ddd, J = 8.7, 7.1, 1.7 Hz, 1H), 5.75 (t, J = 7.6 Hz, 1H), 5.24 (dd, J = 9.9, 5.5 Hz, 1H), 2.66 (dtd, J = 12.1, 7.1, 1.7 Hz, 1H), 2.56 – 2.47 (m, 1H), 2.08 (tdd, J = 12.1, 8.0, 6.5 Hz, 1H), 1.98 (tdd, J = 11.9, 9.8, 7.0 Hz, 1H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 145.3, 144.3, 143.4, 133.4, 128.5, 128.1, 127.9, 127.1, 126.9, 126.9, 126.7, 123.9, 122.4, 117.8, 66.0, 65.2, 37.6, 36.9. **HRMS** (ESI+) calculated for $[C_{22}H_{21}BrN]^+$ 378.0852 *m/z*; found $[M + H]^+$ 378.0851 *m/z*. **α_D^{589}**= –34.7 deg·cm^2·g^{-1} (CH_2Cl_2, c 0.1, 303 K).

(2*R*,5*R*)-1-(2-Bromo-4-(trifluoromethyl)phenyl)-2,5-diphenylpyrrolidine, 79b



The title compound **79b** (152 mg, 341 µmol, 81% yield) was obtained as a pale-yellow gum according to general procedure **D**, using **78a** (145 mg, 422 µmol) and 2-(2-bromo-4-(trifluoromethyl)phenyl)-5,5-dimethyl-1,3,2-dioxaborinane (171 mg, 507 µmol).

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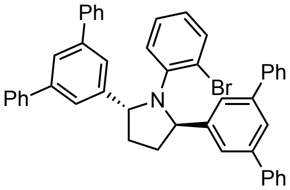
[121] Mailig, M.; Rucker, R. P.; Lalic G. *Chem. Commun.,* **2015**, *51*, 11048–11051.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.44 (d, *J* = 2.2 Hz, 1H), 7.40 – 7.34 (m, 2H), 7.28 (t, *J* = 7.6 Hz, 2H), 7.23 – 7.14 (m, 6H), 7.16 – 7.09 (m, 1H), 6.92 (d, *J* = 8.6 Hz, 1H), 5.87 (t, *J* = 7.4 Hz, 1H), 5.25 (dd, *J* = 9.4, 5.4 Hz, 1H), 2.69 – 2.61 (m, 1H), 2.55 – 2.49 (m, 1H), 2.07 – 1.95 (m, 2H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 148.8, 143.9, 142.6, 130.9 (q, *J* = 3.8 Hz), 128.7, 128.1, 127.8, 127.4, 126.9, 126.7, 123.8 (q, *J* = 270.2 Hz), 124.0 (q, *J* = 3.6 Hz), 122.9, 122.7 (q, *J* = 33.1 Hz), 115.6, 66.6, 65.8, 37.7, 37.6. **^{19}F{^{1}H} NMR** (376 MHz, CD_2Cl_2) *δ* –62.3. **HRMS** (ESI+) calculated for $[C_{23}H_{20}BrF_3N]^+$ 446.0726 *m/z*; found $[M + H]^+$ 446.0719 *m/z*. **α_D^{589}**= –64.5 deg·cm^2·g^{-1} (CH_2Cl_2, c 0.1, 303 K).

(2*R*,5*R*)-2,5-Di([1,1':3',1''-terphenyl]-5'-yl)-1-(2-bromophenyl)pyrrolidine, 79c



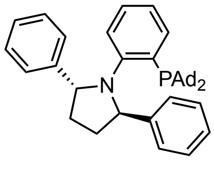
The title compound **79c** (214 mg, 313 μmol, 52% yield over two steps) was obtained as a pale-yellow solid according to general procedure **D**, using **78b** (318 mg, 600 μmol) and 2-(2-bromophenyl)-5,5-dimethyl-1,3,2-dioxaborinane (194 mg, 720 μmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 – 7.66 (m, 2H), 7.66 – 7.61 (m, 5H), 7.56 – 7.42 (m, 13H), 7.42 – 7.34 (m, 6H), 7.34 – 7.27 (m, 1H), 7.13 – 7.00 (m, 2H), 6.66 – 6.55 (m, 1H), 5.89 (t, *J* = 7.3 Hz, 1H), 5.40 (dd, *J* = 9.3, 5.7 Hz, 1H), 2.75 (dq, *J* = 13.1, 6.8 Hz, 1H), 2.63 (dt, *J* = 12.9, 6.0 Hz, 1H), 2.28 – 2.06 (m, 2H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 145.0, 144.7, 144.6, 141.7, 141.2, 141.1, 141.0, 133.7, 128.9, 128.8, 127.4, 127.4, 127.3, 127.3, 127.2, 126.0, 124.9, 124.8, 124.6, 123.9, 123.0, 118.2, 65.8, 65.5, 37.4, 36.6. **HRMS** (ESI+) calculated for $[C_{46}H_{37}BrN]^+$ 682.2104 *m/z*; found $[M + H]^+$ 682.2077 *m/z*. **M.p.**= 95–97 ºC. **α_D^{589}**= –30.9 deg·cm^2·g^{-1} (CH_2Cl_2, c 0.1, 303 K).

General procedure E: for the phosphine coupling reaction

A MW vial was charged with $Pd(OAc)_2$ (5 mol%), DiPPF (7 mol%) and the corresponding pyrrolidine (1.0 equiv) and it was entered into a glovebox. Toluene (0.1 M) was added and the solution was stirred for 5 min at 23 ºC. Then, the corresponding phosphine (1.2 equiv) was added followed by NaO*t*Bu (1.4 equiv). The MW vial was sealed, removed from the glovebox and the reaction was stirred overnight at 150 ºC (14 h approx.). Reaction was then filtered through a plug of Celite®, evaporated and purified by flash column chromatography (SiO_2, pentane/Et_2O from 100:0 to 95:5) affording the desired phosphine.

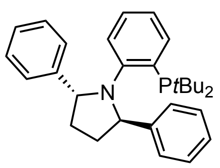
Ligand 80a



The title compound **80a** (105.0 mg, 180.0 μmol, 92% yield) was obtained as a pale-yellow solid according to general procedure **E**, using **79a** (72.0 mg, 190.0 μmol).

^{1}H NMR (400 MHz, CD_2Cl_2) *δ* 7.44 (d, *J* = 7.5 Hz, 2H), 7.42 – 7.35 (m, 1H), 7.27 – 7.01 (m, 10H), 6.95 (dd, *J* = 8.5, 4.2 Hz, 1H), 6.63 (t, *J* = 7.2 Hz, 1H), 5.25 (dd, *J* = 8.8, 3.6 Hz, 1H), 2.74 – 2.56 (m, 1H), 2.51 – 2.36 (m, 1H), 1.94 – 1.70 (m, 17H), 1.67 – 1.53 (m, 15H). **^{13}C{^{1}H} NMR** (101 MHz, CD_2Cl_2) *δ* 153.0 (d, *J* = 21.2 Hz), 146.0, 145.5, 139.8, 129.1, 128.4, 128.2, 127.9, 127.8, 127.1, 126.1, 122.8 (d, *J* = 34.4 Hz), 120.5 (d, *J* = 5.9 Hz), 117.4, 66.7 (d, *J* = 36.4 Hz), 64.9, 42.5 (d, *J* = 13.8 Hz), 42.0 (d, *J* = 13.3 Hz), 38.4 (d, *J* = 25.0 Hz), 37.5, 37.3, 37.2 (d, *J* = 28.8 Hz), 34.1, 33.4, 29.7 (d, *J* = 8.9 Hz), 29.4 (d, *J* = 8.8 Hz). **^{31}P{^{1}H} NMR** (162 MHz, CD_2Cl_2) *δ* 29.9. **HRMS** (ESI+) calculated for $[C_{42}H_{51}NP]^+$ 600.3754 *m/z*; found $[M + H]^+$ 600.3762 *m/z*. **M.p.** = 121–124 ºC. α_D^{589} = –5.8 deg·cm^2·g^{-1} (CH_2Cl_2, c 0.1, 303 K).

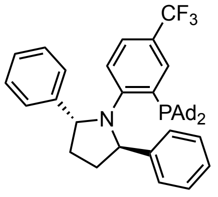
Ligand 80b



The title compound **80b** (130.9 mg, 290.0 μmol, 86% yield) was obtained as a pale-yellow solid according to general procedure **E**, using **79b** (130.0 mg, 340.0 μmol).

^{1}H NMR (500 MHz, CD_2Cl_2) *δ* 7.46 – 7.37 (m, 3H), 7.28 – 7.16 (m, 5H), 7.11 – 7.01 (m, 5H), 6.93 (ddd, *J* = 8.5, 4.3, 1.2 Hz, 1H), 6.64 (ddd, *J* = 7.9, 7.2, 1.2 Hz, 1H), 5.23 (d, *J* = 8.6 Hz, 1H), 2.76 – 2.58 (m, 1H), 2.53 – 2.36 (m, 1H), 1.87 (p, *J* = 8.3 Hz, 2H), 1.08 (d, *J* = 11.8 Hz, 9H), 0.95 (d, *J* = 11.9 Hz, 9H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 152.5 (d, *J* = 21.4 Hz), 145.7, 145.5, 138.6, 129.3, 128.5, 128.2, 127.8, 127.6, 127.1, 126.2, 125.4 (d, *J* = 34.4 Hz), 120.2 (d, *J* = 5.8 Hz), 117.8, 66.8 (d, *J* = 36.5 Hz), 64.8, 34.0 (d, *J* = 24.6 Hz), 33.8, 33.3, 32.4 (d, *J* = 28.1 Hz), 31.5 (d, *J* = 16.0 Hz), 30.4 (d, *J* = 15.8 Hz). **^{31}P{^{1}H} NMR** (202 MHz, CD_2Cl_2) δ 25.6. **HRMS** (ESI+) calculated for $[C_{30}H_{39}NP]^+$ 444.2815 *m/z*; found $[M + H]^+$ 444.2822 *m/z*. **M.p.** = 141–143 ºC. α_D^{589}= +9.2 deg·cm^2·g^{-1} (CH_2Cl_2, c 0.1, 303 K).

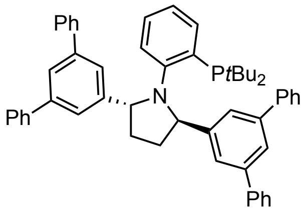
Ligand 80c



The title compound **80c** (172.0 mg, 260.0 μmol, 88% yield) was obtained as a light orange solid according to general procedure **E**, using **79a** (130.0 mg, 290.0 μmol).

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.64 (s, 1H), 7.44 – 7.32 (m, 3H), 7.32 – 7.17 (m, 6H), 7.12 (t, *J* = 7.4 Hz, 1H), 7.05 (d, *J* = 7.6 Hz, 2H), 6.89 (dd, *J* = 9.0, 4.0 Hz, 1H), 5.30 (dd, *J* = 9.0, 2.7 Hz, 1H), 2.72 – 2.59 (m, 1H), 2.50 – 2.37 (m, 1H), 1.95 – 1.84 (m, 7H), 1.81 (dtd, *J* = 11.8, 4.5, 2.5 Hz, 4H), 1.79 – 1.66 (m, 10H), 1.64 (d, *J* = 11.6 Hz, 3H), 1.61 – 1.50 (m, 8H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 155.1 (d, *J* = 19.8 Hz), 145.1, 144.7, 137.2 (q, *J* = 3.7 Hz), 128.8, 128.5, 128.0, 127.4, 127.2, 126.4, 125.9 (q, *J* = 3.5 Hz), 125.6 (q, *J* = 270.6 Hz), 120.3 (d, *J* = 40.3 Hz), 118.5 (d, *J* = 5.3 Hz), 117.2 (q, *J* = 32.0 Hz), 66.1 (d, *J* = 40.6 Hz), 65.9, 42.3 (d, *J* = 14.0 Hz), 41.9 (d, *J* = 13.2 Hz), 38.9 (d, *J* = 25.7 Hz), 37.4 (d, *J* = 30.6 Hz), 37.4, 37.1, 33.9, 32.7, 29.6 (d, *J* = 9.1 Hz), 29.4 (d, *J* = 8.7 Hz). **^{31}P{^{1}H} NMR** (162 MHz, CD_2Cl_2) *δ* 31.4. **^{19}F{^{1}H} NMR** (282 MHz, CD_2Cl_2) *δ* –61.5. **HRMS** (ESI+) calculated for $[C_{43}H_{50}F_3NP]^+$ 668.3627 *m/z*; found $[M + H]^+$ 668.3643 *m/z*. **M.p.** = >155 ºC (decomposition). α_D^{589}= –1.5 deg·cm^2·g^{-1} (CH_2Cl_2, c 0.1, 303 K).

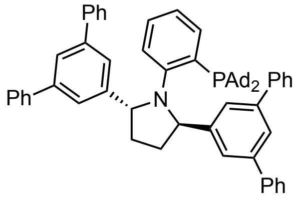
Ligand 80d



The title compound **80d** (97.3 mg, 110.0 μmol, 73% yield) was obtained as a white solid according to general procedure **E**, using **79c** (100.0 mg, 150.0 μmol).

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.69 (s, 3H), 7.67 – 7.59 (m, 4H), 7.56 (s, 1H), 7.54 – 7.40 (m, 13H), 7.40 – 7.30 (m, 6H), 7.25 (dd, *J* = 13.5, 7.6 Hz, 1H), 7.19 (ddd, *J* = 8.5, 6.9, 1.6 Hz, 1H), 7.12 (ddd, *J* = 8.6, 4.2, 1.3 Hz, 1H), 6.74 (td, *J* = 7.3, 1.3 Hz, 1H), 5.42 (dd, *J* = 9.1, 3.5 Hz, 1H), 2.97 – 2.73 (m, 1H), 2.67 – 2.52 (m, 1H), 2.17 – 1.97 (m, 2H), 1.02 (d, *J* = 11.8 Hz, 9H), 0.94 (d, *J* = 11.9 Hz, 9H). **^{13}C{^{1}H} NMR** (101 MHz, CD_2Cl_2) δ 152.7 (d, *J* = 21.3 Hz), 146.7, 146.6, 142.2, 141.8, 141.8, 141.5, 138.9, 129.5, 129.1, 127.7 (d, *J* = 11.9 Hz), 127.6 (d, *J* = 10.9 Hz), 126.1, 125.3, 125.3 (d, *J* = 35.0 Hz), 125.0, 124.0, 120.1 (d, *J* = 5.8 Hz), 118.0, 66.9 (d, *J* = 36.6 Hz), 65.4, 34.1, 34.0 (d, *J* = 24.1 Hz), 33.8, 32.5 (d, *J* = 28.5 Hz), 31.5 (d, *J* = 16.1 Hz), 30.4 (d, *J* = 15.7 Hz). **^{31}P{^{1}H} NMR** (202 MHz, CD_2Cl_2) δ 26.7. **HRMS** (ESI+) calculated for $[C_{54}H_{55}NP]^+$ 748.4067 *m/z*; found $[M + H]^+$ 748.4068 *m/z*. **M.p.** = 113–115 ºC. **α_D^{589}**= –56.8 deg·cm^{2}·g^{-1} (CH_2Cl_2, c 0.1, 303 K).

Ligand 80e



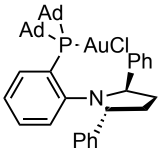
The title compound **80e** (169.0 mg, 190.0 μmol, 95% yield) was obtained as a white solid according to general procedure **E**, using **79c** (135.0 mg, 200.0 μmol).

^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.82 – 7.62 (m, 7H), 7.66 – 7.53 (m, 5H), 7.54 – 7.40 (m, 10H), 7.39 (d, *J* = 6.6 Hz, 6H), 7.29 – 7.07 (m, 2H), 6.75 (t, *J* = 7.1 Hz, 1H), 5.55 – 5.41 (m, 1H), 3.00 – 2.86 (m, 1H), 2.74 – 2.51 (m, 1H), 2.21 – 1.97 (m, 2H), 1.95 – 1.38 (m, 30H). **^{13}C{^{1}H} NMR** (75 MHz, CD_2Cl_2) δ 153.0 (d, *J* = 20.8 Hz), 147.1, 146.8, 142.3, 141.8, 141.7, 140.3, 129.4 (d, *J* = 17.8 Hz), 129.1, 127.7 (d, *J* = 6.6 Hz), 127.6 (d, *J* = 8.7 Hz), 126.1, 125.2, 125.1, 123.8, 121.6 (d, *J* = 34.9 Hz), 119.7 (d, *J* = 5.8 Hz), 117.3, 67.0 (d, *J* = 38.4 Hz), 65.1, 42.7 (d, *J* = 14.0 Hz), 41.8 (d, *J* = 13.1 Hz), 38.5 (d, *J* = 24.8 Hz), 37.3, 37.3 (d, *J* = 29.3 Hz), 37.2, 33.8, 33.2, 29.7 (d, *J* = 8.9 Hz), 29.1 (d, *J* = 8.7 Hz). **^{31}P{^{1}H} NMR** (202 MHz, CD_2Cl_2) δ 27.8. **HRMS** (ESI+) calculated for $[C_{66}H_{67}NP]^+$ 904.5006 *m/z*; found $[M + H]^+$ 904.5021 *m/z*. **M.p.** = 151–153 ºC. **α_D^{589}**= –47.1 deg·cm^{2}·g^{-1} (CH_2Cl_2, c 0.1, 303 K).

General procedure F: for the Au(I) complex synthesis.

To a solution of the corresponding phosphine (1.0 equiv) in CH_2Cl_2 (0.25 M) was added $Me_2S{\cdot}AuCl$ (1.0 equiv). The resulting solution was stirred for 1 h at 23 ºC, filtered over a pad of neutral alumina and the solvent was removed under vacuum, affording the corresponding gold(I) complex.

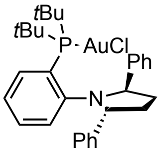
Complex (*R*,*R*)-A



The title complex (*R*,*R*)-**A** (66.5 mg, 79.9 µmol, 99% yield) was obtained as a white solid according to general procedure **F**, using **80a** (48.5 mg, 80.9 µmol).

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.75 – 7.69 (m, 2H), 7.56 (td, *J* = 7.5, 2.2 Hz, 1H), 7.20 – 7.16 (m, 3H), 7.17 – 7.10 (m, 2H), 7.09 – 7.01 (m, 1H), 7.04 – 6.95 (m, 2H), 6.95 – 6.88 (m, 2H), 6.67 (ddd, *J* = 7.5, 4.8, 1.9 Hz, 1H), 4.94 – 4.85 (m, 2H), 3.55 – 3.39 (m, 1H), 2.84 – 2.72 (m, 1H), 2.68 – 2.56 (m, 1H), 2.42 (t, *J* = 8.0 Hz, 3H), 2.34 – 2.26 (m, 3H), 2.18 (dddd, *J* = 13.1, 9.9, 5.1, 1.5 Hz, 1H), 2.09 (q, *J* = 3.1 Hz, 3H), 1.82 – 1.71 (m, 12H), 1.68 – 1.60 (m, 3H), 1.52 (q, *J* = 12.7 Hz, 6H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 152.8 (d, *J* = 6.5 Hz), 141.9, 141.3, 135.9 (d, *J* = 1.8 Hz), 130.7, 130.6 (d, *J* = 2.1 Hz), 129.3 (d, *J* = 5.3 Hz), 128.9, 128.1, 128.1, 127.6, 127.3, 123.6 (d, *J* = 7.2 Hz), 123.3 (d, *J* = 44.7 Hz), 72.3, 64.7, 43.4 (d, *J* = 2.8 Hz), 43.3 (d, *J* = 24.2 Hz), 43.0 (d, *J* = 24.5 Hz), 42.1 (d, *J* = 2.7 Hz), 36.7 (d, *J* = 32.2 Hz), 36.7 (d, *J* = 32.0 Hz), 33.3, 29.9, 29.2 (d, *J* = 9.7 Hz), 29.2 (d, *J* = 10.1 Hz). **^{31}P{^{1}H} NMR** (202 MHz, CD_2Cl_2) δ 59.8. **HRMS** (ESI+) calculated for $[C_{42}H_{51}AuClNP]^+$ 832.3108 *m/z*; found $[M + H]^+$ 832.3093 *m/z*. **M.p.** = >250 ºC (decomposition). **α_D^{589}**= +96.5 deg·cm^2·g^{-1} (CH_2Cl_2, c 0.1, 303 K).

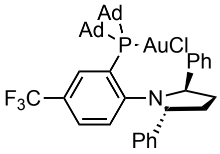
Complex (*R*,*R*)-B



The title complex (*R*,*R*)-**B** (72.3 mg, 107.0 µmol, 99% yield) was obtained as a white solid according to general procedure **F**, using **80b** (48.0 mg, 108.2 µmol).

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.74 – 7.67 (m, 2H), 7.57 (td, *J* = 7.9, 2.2 Hz, 1H), 7.22 – 7.11 (m, 5H), 7.10 – 7.04 (m, 1H), 7.04 – 6.94 (m, 2H), 6.94 – 6.86 (m, 2H), 6.63 (ddd, *J* = 7.6, 5.0, 1.8 Hz, 1H), 4.94 (dd, *J* = 8.5, 1.4 Hz, 1H), 4.88 (t, *J* = 8.4 Hz, 1H), 3.53 – 3.43 (m, 1H), 2.73 (tdd, *J* = 12.5, 9.1, 5.1 Hz, 1H), 2.67 – 2.55 (m, 1H), 2.19 (dddd, *J* = 13.2, 9.9, 5.2, 1.5 Hz, 1H), 1.59 (d, *J* = 15.5 Hz, 9H), 1.02 (d, *J* = 15.7 Hz, 9H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 152.5 (d, *J* = 6.8 Hz), 141.5, 141.2, 135.1 (d, *J* = 2.3 Hz), 130.8 (d, *J* = 1.9 Hz), 130.6, 128.9, 128.7 (d, *J* = 5.5 Hz), 128.3, 128.1, 127.7, 127.4, 125.2 (d, *J* = 46.1 Hz), 123.9 (d, *J* = 7.3 Hz), 72.3, 64.4, 38.5 (d, *J* = 26.5 Hz), 38.3 (d, *J* = 26.3 Hz), 33.6, 32.0 (d, *J* = 6.7 Hz), 30.9 (d, *J* = 6.8 Hz), 29.5. **^{31}P{^{1}H} NMR** (202 MHz, CD_2Cl_2) δ 57.3. **HRMS** (ESI+) calculated for $[C_{30}H_{39}AuClNP]^+$ 676.2169 *m/z*; found $[M + H]^+$ 676.2155 *m/z*. **M.p.**= >215 ºC (decomposition). **α_D^{589}**= +90.9 deg·cm^2·g^{-1} (CH_2Cl_2, c 0.1, 303 K).

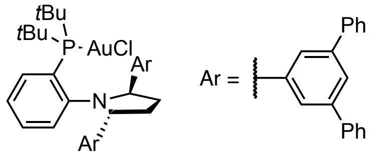
Complex (*R*,*R*)-C



The title complex (*R*,*R*)-**C** (88.1 mg, 97.9 µmol, 92% yield) was obtained as a white solid according to general procedure **F**, using **80c** (71.0 mg, 106.3 µmol).

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.82 (dd, *J* = 7.6, 2.2 Hz, 1H), 7.76 – 7.69 (m, 2H), 7.26 (dd, *J* = 8.6, 2.1 Hz, 1H), 7.24 – 7.13 (m, 5H), 7.12 – 7.05 (m, 1H), 6.95 – 6.85 (m, 2H), 6.82 (dd, *J* = 8.6, 4.4 Hz, 1H), 5.03 (dd, *J* = 8.4, 1.6 Hz, 1H), 4.92 (t, *J* = 8.4 Hz, 1H), 3.56 – 3.44 (m, 1H), 2.78 (dddd, *J* = 14.0, 12.4, 8.8, 5.2 Hz, 1H), 2.65 (dddd, *J* = 13.3, 9.7, 7.9, 5.7 Hz, 1H), 2.46 – 2.37 (m, 3H), 2.36 – 2.27 (m, 3H), 2.20 (dddd, *J* = 13.2, 9.9, 5.3, 1.6 Hz, 1H), 2.15 – 2.09 (m, 3H), 1.81 – 1.69 (m, 12H), 1.67 – 1.59 (m, 3H), 1.59 – 1.55 (m, 2H), 1.56 – 1.46 (m, 4H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 157.0 (d, *J* = 5.9 Hz), 141.3, 140.8, 133.0 – 132.8 (m), 130.5, 129.3 (d, *J* = 5.1 Hz), 128.6, 128.4, 128.3, 127.9, 127.6, 127.2 (m), 125.0 (d, *J* = 7.1 Hz), 124.8 (d, *J* = 6.9 Hz), 124.2 (q, *J* = 272.5 Hz), 124.1 (d, *J* = 41.9 Hz), 72.8, 64.8, 43.9 (d, *J* = 22.1 Hz), 43.4 (d, *J* = 2.7 Hz), 43.4 (d, *J* = 23.3 Hz), 42.1 (d, *J* = 2.7 Hz), 36.6 (d, *J* = 29.3 Hz), 36.5 (d, *J* = 29.4 Hz), 33.6, 30.1, 29.2 (d, *J* = 10.0 Hz). **^{31}P{^{1}H} NMR** (202 MHz, CD_2Cl_2) δ 61.3. **^{19}F{^{1}H} NMR** (471 MHz, CD_2Cl_2) δ –62.8. **HRMS** (ESI+) calculated for $[C_{43}H_{49}AuClNNaP]^+$ 922.2801 *m/z*; found $[M + Na]^+$ 922.2801 *m/z*. **M.p.** = >291 ºC (decomposition). **α_D^{589}**= +61.8 deg·cm^2·g^{-1} (CH_2Cl_2, c 0.1, 303 K).

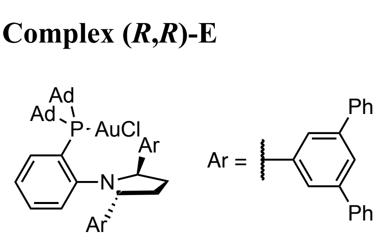
Complex (*R*,*R*)-D



The title complex (*R*,*R*)-**D** (50.0 mg, 51.0 μmol, 97% yield) was obtained as a white solid according to general procedure **F**, using **80d** (48.0 mg, 52.6 μmol).

^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.05 (d, *J* = 1.8 Hz, 2H), 7.72 – 7.62 (m, 6H), 7.61 (t, *J* = 1.7 Hz, 1H), 7.51 – 7.47 (m, 4H), 7.47 – 7.39 (m, 8H), 7.39 – 7.34 (m, 2H), 7.34 – 7.30 (m, 2H), 7.17 – 7.08 (m, 3H), 7.08 – 7.02 (m, 1H), 6.84 (ddd, *J* = 8.4, 4.9, 1.4 Hz, 1H), 5.14 (d, *J* = 7.5 Hz, 1H), 5.09 (t, *J* = 8.5 Hz, 1H), 3.63 (tdd, *J* = 13.3, 8.4, 5.7 Hz, 1H), 3.00 (tdd, *J* = 12.9, 8.9, 5.0 Hz, 1H), 2.79 (ddt, *J* = 15.3, 7.9, 5.5 Hz, 1H), 2.42 (ddd, *J* = 14.5, 10.5, 5.1 Hz, 1H), 1.61 (d, *J* = 15.4 Hz, 9H), 0.82 (d, *J* = 15.8 Hz, 9H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 152.5 (d, *J* = 6.9 Hz), 142.4, 142.1, 141.6, 141.6, 141.5, 141.1, 135.3 (d, *J* = 2.1 Hz), 131.1 (d, *J* = 2.0 Hz), 129.2, 129.1, 128.2, 127.9, 127.7, 127.6, 127.5, 126.7, 125.6 (d, *J* = 46.0 Hz), 125.2, 125.0, 124.3 (d, *J* = 7.2 Hz), 72.3, 64.7, 38.4 (d, *J* = 9.5 Hz), 38.2 (d, *J* = 9.5 Hz), 33.7, 31.9 (d, *J* = 6.6 Hz), 30.6 (d, *J* = 6.7 Hz), 29.3. **^{31}P{^{1}H} NMR** (202 MHz, CD_2Cl_2) δ 57.2. **HRMS** (ESI+) calculated for $[C_{54}H_{55}AuClNP]^+$ 980.3421 *m/z*; found $[M + H]^+$ 980.3383 *m/z*. **M.p.** = >183 ºC (decomposition). **α_D^{589}**= +135.1 deg·cm^2·g^{-1} (CH_2Cl_2, c 0.1, 303 K).

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

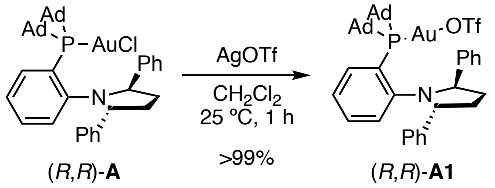


The title complex (*R*,*R*)-**E** (74.0 mg, 65.1 μmol, 98% yield) was obtained as a white solid according to general procedure **F**, using **80e** (60.0 mg, 66.4 μmol).

^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.03 (d, *J* = 1.7 Hz, 2H), 7.76 – 7.70 (m, 4H), 7.70 – 7.61 (m, 3H), 7.55 – 7.47 (m, 4H), 7.50 – 7.33 (m, 10H), 7.37 – 7.27 (m, 2H), 7.17 (d, *J* = 1.7 Hz, 2H), 7.10 (t, *J* = 7,4 Hz, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 6.90 (ddd, *J* = 8.2, 4.9, 1.4 Hz, 1H), 5.13 (dt, *J* = 8.6, 4.4 Hz, 2H), 3.64 (tdd, *J* = 13.2, 8.3, 5.8 Hz, 1H), 3.03 (tdd, *J* = 12.9, 8.6, 4.8 Hz, 1H), 2.78 (ddd, *J* = 13.6, 8.4, 4.9 Hz, 1H), 2.53 – 2.32 (m, 7H), 2.07 (d, *J* = 4.6 Hz, 3H), 1.81 – 1.69 (m, 9H), 1.62 – 1.52 (m, 2H), 1.52 –

1.45 (m, 4H), 1.36 – 1.22 (m, 6H). **^{13}C NMR** (101 MHz, CD$_2$Cl$_2$) δ 152.9 (d, *J* = 6.5 Hz), 142.6, 142.4, 141.6, 141.4, 141.2, 140.9, 136.2 (d, *J* = 1.8 Hz), 130.9, 129.3 (d, *J* = 5.6 Hz), 129.2, 129.1, 128.0, 127.9, 127.8, 127.5, 127.4, 126.8, 124.9, 123.8 (d, *J* = 7.0 Hz), 123.4 (d, *J* = 44.2 Hz), 72.5, 64.8, 43.7 (d, *J* = 2.5 Hz), 43.5 (d, *J* = 23.7 Hz), 43.1 (d, *J* = 24.1 Hz), 41.8 (d, *J* = 2.5 Hz), 36.7, 36.3, 33.4, 30.1, 29.3 (d, *J* = 9.7 Hz), 29.1 (d, *J* = 10.0 Hz). **^{31}P{^{1}H} NMR** (202 MHz, CD$_2$Cl$_2$) δ 59.7. **HRMS** (ESI+) calculated for [C$_{66}$H$_{66}$AuClNNaP]$^+$ 1158.4179 *m/z*; found [M + Na]$^+$ 1158.4205 *m/z*. **M.p.** = >193 ºC (decomposition). **α_D^{589}**= +202.8 deg·cm^2·g^{-1} (CH$_2$Cl$_2$, c 0.1, 303 K).

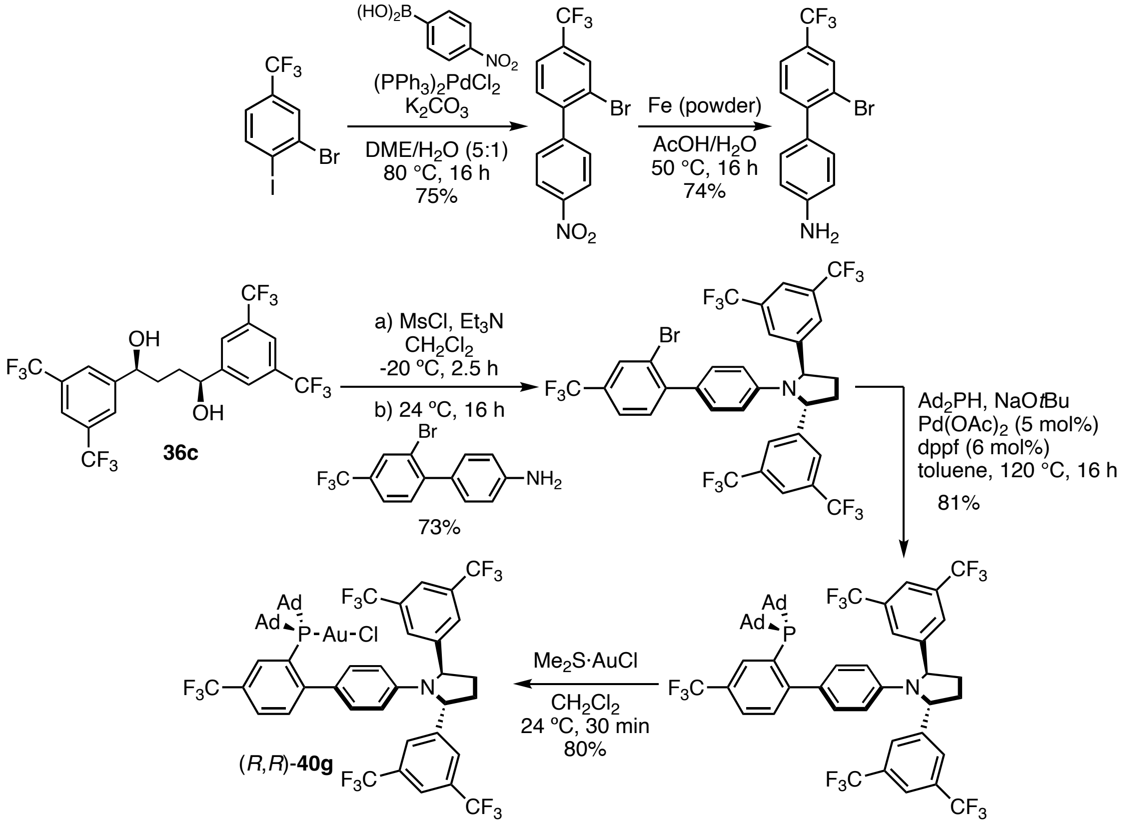
Chiral complex (*R*,*R*)-A1



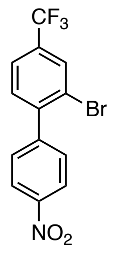
Under argon atmosphere, the chiral complex (*R*,*R*)-**A** (50.0 mg, 60.1 µmol, 1 equiv) was introduced into the glovebox, silver(I) trifluoromethanesulfonate (16.2 mg, 63.1 µmol, 1.05 equiv) and dichloromethane (1.2 mL, 0.1 M) were added and the reaction was taken out of the glovebox and stirred at 25 ºC for 1 h in the dark. Then, it was filtered through Celite®, affording (*R*,*R*)-**A1** (56.6 mg, 59.8 µmol, >99% yield) as a yellowish solid.

^{1}H NMR (400 MHz, CD$_2$Cl$_2$) δ 7.60 – 7.53 (m, 3H), 7.20 (dd, *J* = 5.0, 1.9 Hz, 3H), 7.20 – 7.11 (m, 2H), 7.11 – 7.04 (m, 3H), 6.92 – 6.86 (m, 2H), 6.73 – 6.65 (m, 1H), 4.96 (t, *J* = 8.3 Hz, 1H), 4.76 (d, *J* = 8.0 Hz, 1H), 3.20 – 3.05 (m, 1H), 2.71 (q, *J* = 8.3 Hz, 2H), 2.46 – 2.34 (m, 3H), 2.31 (dd, *J* = 14.3, 6.5 Hz, 1H), 2.27 – 2.20 (m, 3H), 2.11 (d, *J* = 2.5 Hz, 3H), 1.82 – 1.71 (m, 9H), 1.70 – 1.61 (m, 3H), 1.61 – 1.43 (m, 9H). **^{13}C{^{1}H} NMR** (126 MHz, CD$_2$Cl$_2$) δ 152.0 (d, *J* = 5.5 Hz), 140.9 (d, *J* = 38.1 Hz), 135.0 (d, *J* = 3.2 Hz), 131.1, 130.4, 130.1 (d, *J* = 5.0 Hz), 129.0, 128.4, 128.3, 127.9, 127.7, 124.2 (d, *J* = 7.7 Hz), 121.7, 121.3, 120.9 (q, *J* = 319.0 Hz), 72.6, 64.5, 43.6 (d, *J* = 25.4 Hz), 43.4, 43.0 (d, *J* = 26.3 Hz), 42.0, 36.6 (d, *J* = 1.8 Hz), 36.3 (d, *J* = 1.4 Hz), 32.4, 30.0, 29.2 (d, *J* = 10.0 Hz), 29.1 (d, *J* = 10.0 Hz). **^{31}P{^{1}H} NMR** (162 MHz, CD$_2$Cl$_2$) δ 56.4. **^{19}F{^{1}H} NMR** (471 MHz, CD$_2$Cl$_2$) δ –77.3. **HRMS** (ESI+) calculated for [C$_{42}$H$_{50}$AuNP]$^+$ 796.3341 *m/z*; found [M – OTf]$^+$ 796.3332 *m/z*. **M.p.** = >170 ºC (decomposition). **α_D^{589}** = +97.9 deg·cm^2·g^{-1} (CH$_2$Cl$_2$, c 0.1, 303 K).

Synthesis of chiral complex (*R*,*R*)-40g



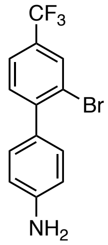
2-Bromo-4'-nitro-4-(trifluoromethyl)-1,1'-biphenyl



$(PPh_3)_2PdCl_2$ (51 mg, 730 µmol, 15 mol%), (4-nitrophenyl)boronic acid (890 mg, 5.33 mmol, 1.11 equiv), 2-bromo-1-iodo-4-(trifluoromethyl)benzene (1.7 g, 4.8 mmol, 1 equiv) and K_2CO_3 (1.674 g, 12.1 mmol, 2.5 equiv) were dissolved in water (2.5 mL) and DME (14.8 mL). The reaction mixture was degassed for 5 min with argon and then stirred at 80 ºC for 16 h. The reaction mixture was allowed to cool to 25 ºC and DME and EtOAc were added. The layers were separated and the aqueous phase was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The crude was purified by flash column chromatography on silica gel (cyclohexane/EtOAc 30:1) to yield the title compound 2-bromo-4'-nitro-4-(trifluoromethyl)-1,1'-biphenyl (1.25 g, 3.61 mmol, 75% yield) as a white solid.

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

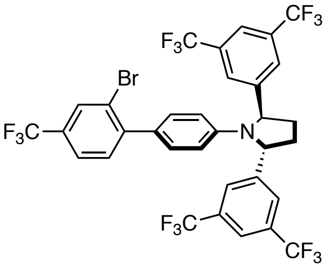
2'-Bromo-4'-(trifluoromethyl)-[1,1'-biphenyl]-4-amine



Iron powder (504 mg, 9.03 mmol, 2.5 equiv) was added to a solution of 2-bromo-4'-nitro-4-(trifluoromethyl)-1,1'-biphenyl (1.25 g, 3.61 mmol) in AcOH (12.3 mL)/water (0.61 mL) (20:1). The mixture was stirred at 50 ºC for 16 h, then allowed to cool to 25 ºC and filtered over Celite®. The filtrate was rinsed with AcOH and extracted with EtOAc (3x). The combined organic layers were washed with water, basified with Na_2CO_3, and then washed with $NaHCO_3$ and brine. The organic phase was dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (cyclohexane/EtOAc 10:1) to yield the title compound 2'-bromo-4'-(trifluoromethyl)-[1,1'-biphenyl]-4-amine (853 mg, 2.70 mmol, 74% yield) as a brown gum.

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

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

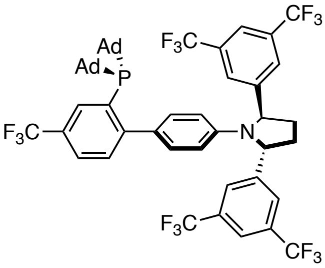


The title compound was synthesized adopting a previously reported procedure by our group.**¡Error! Marcador no definido.** To a solution of (1*S*,4*S*)-1,4-bis(3,5-bis(trifluoromethyl)phenyl)butane-1,4-diol **36c**23 (290 g, 0.56 mmol, 1.0 equiv) in CH_2Cl_2 (5.6 mL) at -20 ºC were added Et_3N (0.24 mL, 1.7 mmol, 3.0 equiv) and methanesulfonyl chloride (0.11 mL, 1.5 mmol, 2.6 equiv) under an atmosphere of argon. The mixture was stirred for 2.5 h at -20 ºC. Then, a solution of aniline 2'-bromo-4'-(trifluoromethyl)-[1,1'-biphenyl]-4-amine (873 mg, 2.7 mmol, 4.9 equiv) in CH_2Cl_2 (1.0 mL) was added and the resulting mixture was stirred at 25 ºC overnight. The volatile products were removed under reduced pressure and the organic materials were extracted with EtOAc. The combined organic phases were washed with brine and sat. $NaHCO_3$, dried over Na_2SO_4 and concentrated. The crude residue was purified by flash column chromatography on silica gel (cyclohexane/EtOAc 30:1) to yield title compound (2*R*,5*R*)-2,5-bis(3,5-bis(trifluoromethyl)phenyl)-1-(2'-bromo-4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)pyrrolidine (325 mg, 0.41 mmol, 73% yield) as a white solid.

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.87 (s, 1H), 7.84 (s, 2H), 7.73 (s, 4H), 7.54 (ddd, *J* = 8.0, 1.9, 0.8 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.18 – 7.10 (m, 2H), 6.43 – 6.36 (m, 2H), 5.48 (d, *J* = 6.9 Hz, 2H), 2.71 – 2.53 (m, 2H), 2.02 – 1.87 (m, 2H). **^{13}C{^{1}H} NMR** (101 MHz, CD_2Cl_2) δ 146.6, 146.4, 143.9, 132.3 (q, *J* = 32.9 Hz), 132.0, 130.6, 130.2, 130.5 – 130.3 (m), 129.3, 126.9 (d, *J* = 4.0 Hz), 124.6 (q, *J* = 3.7

Hz), 123.8 (q, J = 271.7 Hz), 123.3, 121.8 (p, J = 3.9 Hz), 114.1, 63.2, 32.5. **^{19}F{^{1}H} NMR** (376 MHz, CD$_2$Cl$_2$) δ –63.0, –63.3. **HRMS** (ESI+) the exact mass calculated for [C$_{33}$H$_{20}$BrF$_{15}$]$^+$ is 794.0534 *m/z*; found [M + H]$^+$ 794.0541 *m/z*. **M.p.** = 160–162 ºC. **α_D^{589}** = +29.5 deg·cm^2·g^{-1} (CHCl$_3$, c 1.0, 300 K).

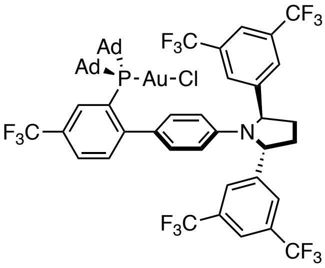
(2*R*,5*R*)-2,5-Bis(3,5-bis(trifluoromethyl)phenyl)-1-(2'-(di(adamantan-1-yl)phosphaneyl)-4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)pyrrolidine



The title compound was synthesized adopting a previously reported procedure by our group.23 A flame-dried 10 mL Schlenk flask was charged with aryl bromide **S3** (220 mg, 0.25 mmol, 1.0 equiv), Pd(OAc)$_2$ (2.83 mg, 13.0 µmol, 5 mol%), dppf (8.40 mg, 15.0 µmol, 6 mol%), NaO*t*Bu (29.0 mg, 0.30 mmol, 1.2 equiv) and toluene (1.3 mL) and the resulting suspension was stirred for 15 min at 25 ºC. Di(1-adamantyl)phosphine (84.0 mg, 0.28 mmol, 1.1 equiv) was added and the reaction mixture was stirred at 120 ºC for 16 h. Then, the reaction was allowed to cool to 25 ºC and the crude was purified by flash column chromatography on silica gel (cyclohexane/CH$_2$Cl$_2$ 40:1 then 4:1) to yield ligand (2*R*,5*R*)-2,5-bis(3,5-bis(trifluoromethyl)phenyl)-1-(2'-(di(adamantan-1-yl)phosphaneyl)-4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)pyrrolidine (208 mg, 0.20 mmol, 81% yield) as a white solid.

^{1}H NMR (400 MHz, CD$_2$Cl$_2$) δ 8.09 (s, 1H), 7.83 (s, 2H), 7.74 (s, 4H), 7.54 (d, J = 8.1 Hz, 1H), 7.30 (dd, J = 8.2, 3.9 Hz, 1H), 7.01 (d, J = 8.4 Hz, 2H), 6.35 – 6.26 (m, 2H), 5.49 (d, J = 6.4 Hz, 2H), 2.69 – 2.52 (m, 2H), 1.99 – 1.81 (m, 11H), 1.78 (s, 3H), 1.74 – 1.64 (m, 12H), 1.64 – 1.49 (m, 6H). **^{13}C{^{1}H} NMR** (126 MHz, CD$_2$Cl$_2$) δ 154.8 (d, J = 31.1 Hz), 146.4, 142.3, 134.8, 134.5, 133.3 – 133.0 (m), 131.8 (q, J = 33.2 Hz), 131.7 (d, J = 5.1 Hz), 131.5 (d, J = 6.4 Hz), 131.1 (d, J = 5.3 Hz), 126.5 (t, J = 3.9 Hz), 124.62 (q, J = 3.7 Hz), 124.58 (q, J = 273.8 Hz), 122.9 (q, J = 272.3 Hz), 121.2 (p, J = 4.0 Hz), 112.8, 62.6, 42.0 (d, J = 13.3 Hz), 41.4 (d, J = 13.1 Hz), 37.5 (d, J = 26.5 Hz), 37.2 (d, J = 27.1 Hz), 36.8, 36.69, 32.0, 29.0 (d, J = 8.6 Hz), 28.8 (d, J = 8.6 Hz). **^{31}P{^{1}H} NMR** (162 MHz, CD$_2$Cl$_2$) δ 23.7. **^{19}F{^{1}H} NMR** (376 MHz, CD$_2$Cl$_2$) δ –62.8 (d, J = 2.2 Hz), –63.2. **HRMS** (ESI+) the exact mass calculated for [C$_{53}$H$_{50}$F$_{15}$NP]$^+$ is 1016.3436 *m/z*; found [M + H]$^+$ 1016.3475 *m/z*. **M.p.** = >160 ºC (decomposition). **α_D^{589}** = –1.4 deg·cm^2·g^{-1} (CHCl$_3$, c 1.0, 300 K).

Complex (*R*,*R*)-40g



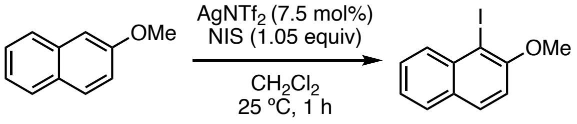
The title compound was synthesized adopting a modified procedure previously reported by our group.23 Me$_2$S·AuCl (18.7 mg, 64.0 µmol, 1.0 equiv) and ligand (2*R*,5*R*)-2,5-bis(3,5-bis(trifluoromethyl)phenyl)-1-(2'-(di(adamantan-1-yl)phosphaneyl)-4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)pyrrolidine (64.6 mg, 64.0 µmol, 1.0 equiv) were dissolved in CH$_2$Cl$_2$ (1.4 mL) under an atmosphere of argon. The reaction mixture was stirred at 24 ºC for 30 min. The mixture was filtered through a syringe filter and concentrated. The crude was purified by flash column chromatography on silica gel (cyclohexane/Et_2O 40:1) to yield complex (*R,R*)-**40g** (63.4 mg, 51.0 μmol, 80% yield) as a white solid.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.08 (d, *J* = 6.9 Hz, 1H), 7.91 (s, 4H), 7.82 (s, 2H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.41 (dd, *J* = 8.1, 3.9 Hz, 1H), 6.91 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.74 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.31 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.25 (dd, *J* = 8.5, 2.7 Hz, 1H), 5.50 (d, *J* = 6.9 Hz, 2H), 2.66 – 2.55 (m, 2H), 2.27 – 2.14 (m, 6H), 2.01 (s, 3H), 1.98 – 1.88 (m, 9H), 1.88 – 1.81 (m, 2H), 1.71 (s, 6H), 1.60 (q, *J* = 12.3 Hz, 6H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 154.7 (d, *J* = 11.9 Hz), 146.9, 144.3, 134.6 (d, *J* = 6.5 Hz), 132.1 (q, *J* = 33.1 Hz), 131.6 (q, *J* = 3.4 Hz), 130.0, 129.71, 129.6 (d, *J* = 6.1 Hz), 127.3 (d, *J* = 3.9 Hz), 126.0, 125.6, 123.90 (q, *J* = 272.6 Hz), 123.93 (q, *J* = 272.3 Hz), 121.5 (p, *J* = 4.0 Hz), 116.2, 114.0, 63.6, 43.5 (d, *J* = 22.5 Hz), 43.1 (d, *J* = 2.7 Hz), 42.7 (d, *J* = 22.3 Hz), 41.9 (d, *J* = 2.6 Hz), 36.6, 36.5, 29.3 (d, *J* = 9.8 Hz), 29.0 (d, *J* = 9.9 Hz). **^{31}P{^{1}H} NMR** (202 MHz, CD_2Cl_2) δ 65.4. **^{19}F{^{1}H} NMR** (471 MHz, CD_2Cl_2) δ –62.8, –63.1. **HRMS** (ESI+) the exact mass calculated for $[C_{53}H_{49}AuClF_{15}NNaP]^+$ is 1270.2610 *m/z*; found $[M + Na]^+$ 1270.2591 *m/z*. **M.p.** = >250 ºC (decomposition). **α_D^{589}** = +35.2 deg·cm^2·g^{-1} ($CHCl_3$, c 1.0, 300 K).

Atroposelective cyclization of sulfonamides

Synthesis of starting materials 85a-u[122]

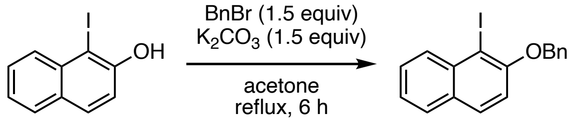
1-Iodo-2-methoxynaphthalene



To a solution of 2-methoxynaphthalene (2.00 g, 12.6 mmol, 1.0 equiv) in CH_2Cl_2 (50.0 mL, 0.25 M) at 25 ºC, were added 1-iodopyrrolidine-2,5-dione (2.99 g, 13.3 mmol, 1.05 equiv) and (bis((trifluoromethyl)sulfonyl) silver (368 mg, 948 µmol, 0.075 equiv). Upon completion of the reaction (TLC, 1 h), the reaction was diluted with CH_2Cl_2, washed with sat. Na_2CO_3, sat. Na_2SO_3, brine, dried over sodium sulfate and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (cyclohexane/EtOAc 10:1) to yield the title compound 1-iodo-2-methoxynaphthalene (3.31 g, 11.7 mmol, 92% yield) as a white solid. The spectral data are consistent with the literature.[123]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (dd, *J* = 8.6, 0.9 Hz, 1H), 7.83 (d, *J* = 8.6 Hz, 1H), 7.78 – 7.71 (m, 1H), 7.54 (ddd, *J* = 8.4, 6.8, 1.3 Hz, 1H), 7.38 (ddd, *J* = 8.0, 6.8, 1.1 Hz, 1H), 7.21 (d, *J* = 8.9 Hz, 1H), 4.03 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 156.8, 135.8, 131.4, 130.5, 130.1, 128.3, 128.2, 124.5, 113.1, 87.9, 57.4.

2-(Benzyloxy)-1-iodonaphthalene



To a suspension of 1-iodonaphthalene-2-ol (200 mg, 741 µmol, 1.0 equiv) and K_2CO_3 (154 mg, 1.11 mmol, 1.5 equiv) in acetone (25 mL, 0.03 M) was added benzyl bromide (128 µL, 1.11 mmol, 1.5 equiv). The resulting mixture was stirred at reflux for 6 h. After the consumption of the starting material, monitored by TLC (cyclohexane/Et_2O 5:1), the reaction was filtered and concentrated. The crude was purified by flash column chromatography on silica gel (cyclohexane/Et_2O 50:1) to yield the title compound 2-(benzyloxy)-1-iodonaphthalene (258 mg, 716 µmol, 97% yield) as a yellow solid. The spectral data are consistent with the literature.[124]

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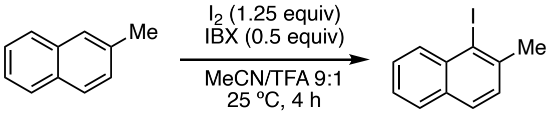
[122] The synthesis and characterization of the sulfonamides used as starting materials were mainly performed by Dr. Leonardo Nannini, Dr. Giuseppe Zuccarello and Matthias Peeters.

[123] Racys, D. T.; Sharif, S. A. I.; Pimlott, S. L.; Sutherland, A. *J. Org. Chem.* **2016**, *81*, 772–780.

[124] Hapke, M.; Kral, K.; Fischer, C.; Spannenberg, A.; Gutnov, A.; Redkin, D.; Heller, B. *J. Org. Chem.* **2010**, *75*, 3993–4003.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 7.6 Hz, 1H), 7.78 (d, *J* = 8.9 Hz, 1H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.60 – 7.51 (m, 3H), 7.45 – 7.37 (m, 3H), 7.36 – 7.31 (m, 1H), 7.22 (d, *J* = 8.9 Hz, 1H), 5.32 (s, 2H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 156.0, 136.8, 135.9, 131.5, 130.4, 130.3, 128.7, 128.3, 128.2, 128.1, 127.4, 124.7, 114.9, 89.2, 72.1.

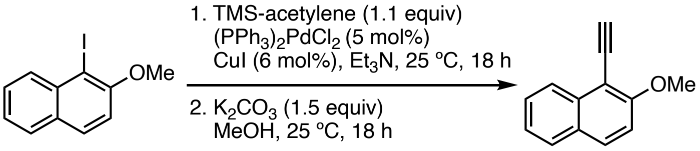
1-Iodo-2-methylnaphthalene



Following literature procedure:[125] IBX (547 mg, 45% Wt, 879 µmol, 0.50 equiv) was suspended in MeCN (9 mL)/TFA (1 mL) at 25 ºC. Iodine (558 mg, 2.20 mmol, 1.25 equiv) was added and the reaction was stirred at 25 ºC for 30 min then 2-methylnaphthalene (0.250 g, 1.76 mmol, 1.00 equiv) was added. The reaction was stirred for 4 h, then it was quenched with sat. aq. solution of sodium bisulfide and extracted with Et_2O (2x). The combined organic phases were washed with $NaHCO_3$ aq. sat. solution, brine, dried over sodium sulfate and concentrate under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (100% pentane) to yield the title compound 1-iodo-2-methylnaphthalene (0.324 g, 1.21 mmol, 69% yield). The spectral data are consistent with the literature.[126]

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (dd, *J* = 8.6, 1.0 Hz, 1H), 7.78 – 7.73 (m, 1H), 7.72 (d, *J* = 8.3 Hz, 1H), 7.55 (ddd, *J* = 8.5, 6.8, 1.3 Hz, 1H), 7.46 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1H), 7.37 (d, *J* = 8.3 Hz, 1H), 2.71 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 140.9, 135.3, 132.5, 132.4, 128.5, 128.3, 128.1, 127.8, 125.8, 105.7, 30.4.

1-Ethynyl-2-methoxynaphthalene



The title compound was prepared following a modified literature procedure:[127] 1-iodo-2-methoxynaphthalene (3.31 g, 11.7 mmol, 1.00 equiv), CuI (133 mg, 699 µmol, 6 mol%) and $PdCl_2(PPh_3)_2$ (409 mg, 583 µmol, 5 mol%) was dissolved in Et_3N (100 mL, 0.12 M). The solution was stirred for 5 min, then TMS-acetylene (1.26 g, 1.78 mL, 12.8 mmol, 1.10 equiv) was added at once. After stirring for 18 h, the reaction was filtered through a pad of celite, washing with Et_2O. The resulting solution was washed with sat. aq. NH_4Cl (2x), brine, dried over sodium sulfate and concentrated under

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[125] Moorthy, J. N.; Senapati, K.; Kumar, S. *J. Org. Chem.* **2009**, *74*, 6287–6290.

[126] Peez, T.; Scmalz, V.; Harms, K.; Koert, U. *Adv. Synth. Catal.* **2004**, *346*, 77–82.

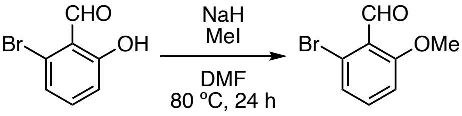
[127] Zheng, S. C.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2019**, *58*, 1494–1498.

reduced pressure. The crude residue was purified by flash column chromatography on silica gel (cyclohexane/Et_2O 10:1) to yield intermediate ((2-methoxynaphthalen-1-yl)ethynyl)trimethylsilane. The intermediate alkyne silane was dissolved in methanol (75 mL, 0.16 M) and then potassium carbonate (2.09 g, 15.2 mmol, 1.30 equiv) was added. After stirring the reaction for 18 h, TLC shows complete consumption of the starting material. The reaction was diluted in Et_2O, washed with sat. aq. NH_4Cl, brine, dried over sodium sulfate and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (cyclohexane/Et_2O 10:1) to yield the title compound 1-ethynyl-2-methoxynaphthalene (1.73 g, 9.51 mmol, 81% yield).

The spectral data are consistent with the literature.[128]

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.85 (d, *J* = 9.0 Hz, 1H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.55 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H), 7.39 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.26 (d, *J* = 9.1 Hz, 1H), 4.05 (s, 3H), 3.75 (s, 1H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 160.0, 135.0, 130.8, 128.6, 128.2, 127.7, 125.3, 124.4, 112.6, 105.2, 86.6, 78.4, 56.8.

2-Bromo-6-methoxybenzaldehyde



The title compound was synthesized according to a modified literature procedure.[129] A dried reaction flask was charged with 2-bromo-6-hydroxybenzaldehyde (300 mg, 1.49 mmol, 1.0 equiv) and dissolved in dry DMF (6 mL, 0.25 M). The reaction mixture was cooled to 0 ºC and NaH (60% in mineral oil, 65.7 mg, 1.64 mmol, 1.1 equiv) was added in small portions. After 5 min methyl iodide (121 mL, 1.94 mmol, 1.3 equiv) was added and the mixture was allowed to warm up first to 25 ºC and then was heated up to 80 ºC. The reaction was monitored by UHPLC-MS till full consumption of the starting material was observed. After 24 h, the mixture was diluted with water, extracted with EtOAc (3x), dried over sodium sulfate and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (cyclohexane/EtOAc 15:1 to 5:1) affording the 2-bromo-6-methoxybenzaldehyde (265 mg, 1.00 mmol, 83% yield) as a yellow solid.

The spectral data are consistent with the reported literature.[130]

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.42 (s, 1H), 7.33 (t, *J* = 8.2 Hz, 1H), 7.24 (d, *J* = 1.0 Hz, 1H), 6.95 (dd, *J* = 8.3, 1.0 Hz, 1H), 3.92 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 190.6, 162.1, 134.9, 126.6, 125.0, 123.6, 111.2, 56.4.

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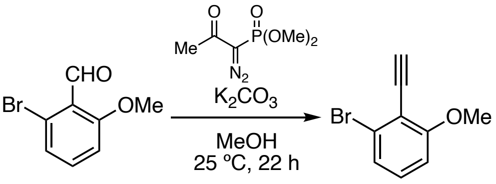
[128] Kadoya, N.; Murai, M.; Ishiguro, M.; Uenishi, J.; Uemura, M. *Tetrahedron Letters* **2013**, *54*, 512–514.

[129] Jyothish, K.; Wang, Q.; Zhang, W. *Adv. Synth. Catal.* **2012**, *354*, 2073–2078.

[130] Dubost, E.; Fossey, C.; Cailly, T.; Rault, S.; Fabis, F. *J. Org. Chem.* **2011**, *76*, 6414–6420.

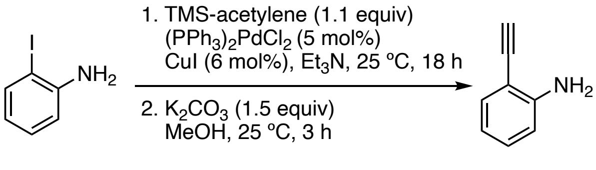
1-Bromo-2-ethynyl-3-methoxybenzene



A reaction flask was charged with bromo-6-methoxybenzaldehyde (1.79 g, 8.32 mmol, 1.0 equiv) and K_2CO_3 (2.29 g, 16.6 mmol, 2.0 equiv) in dry MeOH (80 mL, 0.1 M) under argon atmosphere. To this suspension, dimethyl 1-diazo-2-oxopropylphosphonate (Ohira-Bestmann reagent) (1.92 g, 10.0 mmol, 1.2 equiv) was added and the reaction mixture was stirred at 25 ºC for 22 h (monitored by TLC). The reaction mixture was quenched with sat. NH_4Cl and extracted with EtOAc (3x). The organic phase was dried over sodium sulfate and concentrated under reduced pressure. The crude compound was purified by flash column chromatography on silica gel (pentane/Et_2O 20:1 to 15:1) affording the title compound 1-bromo-2-ethynyl-3-methoxybenzene (1.09 g, 5.16 mmol, 62% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.17 (m, 1H), 7.15 (d, *J* = 8.1 Hz, 1H), 6.84 (dd, *J* = 8.0, 1.3 Hz, 1H), 3.90 (s, 3H), 3.62 (s, 1H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 162.0, 130.3, 127.1, 124.6, 113.8, 109.3, 86.0, 78.4, 56.3. **HRMS** (APCI+) the exact mass calculated for $[C_9H_8BrO]^+$ is 210.9750 *m/z*; found $[M + H]^+$ 210.9753 *m/z*. **M.p.** = 67–68 ºC.

2-Ethynylaniline



2-Ethynylaniline was prepared with a modification of a known procedure:[131] 2-Iodoaniline (2.09 g, 9.54 mmol, 1.0 equiv), CuI (109 mg, 573 µmol, 6 mol%) and $PdCl_2(PPh_3)_2$ (335 mg, 477 µmol, 5 mol%) were dissolved in NEt_3 (70 mL, 0.14 M). The solution was stirred for 5 min, then TMS-acetylene (1.46 mL, 10.5 mmol, 1.1 equiv) was added at once. The reaction was stirred for 18 h, then it was filtered through a pad of celite, washing with Et_2O. The resulting solution was washed with sat. aq. NH_4Cl. (2x), brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was used in the next step without further purification.

The crude product was dissolved in MeOH (100 mL, 0.1 M), then K_2CO_3 (1.98 g, 14.3 mmol, 1.50 equiv) was added. The reaction was stirred at 25 ºC for 3 h. The reaction was diluted with Et_2O then washed with sat. aq. NH_4Cl, brine, dried over Na_2SO_4 and concentrated under reduced pressure. The

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[131] Coelho, F. L., Gil, E. S., Gonçalves, P. F. B., Campo, L. F., & Schneider, P. H. *Chemistry - A European Journal* **2019**, *25*, 8157–8162.

crude residue was purified by flash column chromatography on silica gel (cyclohexane/EtOAc 10:1) to yield the title compound 2-ethynylaniline (910 mg, 7.77 mmol, 81% yield over 2 steps).

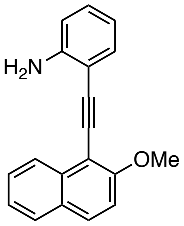
The spectral data are consistent with literature.131

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.15 (ddd, *J* = 8.2, 7.4, 1.6 Hz, 1H), 6.72 – 6.65 (m, 2H), 4.24 (br s, 2H), 3.39 (s, 1H). **$^{13}C\{^1H\}$ NMR** (126 MHz, $CDCl_3$) δ 148.7, 132.8, 130.3, 117.9, 114.4, 106.8, 82.6, 80.8.

General Procedure G: Sonogashira coupling

$PdCl_2(PPh_3)_2$ (2 mol%) and CuI (4 mol%) were added to a solution of the iodoarene (1.0 equiv) in dry NEt_3 (0.1 M) and the reaction mixture was stirred at 25 ºC for 5–10 min. The terminal alkyne (1.1 equiv) was then added, the reaction was stirred for the given time at the same temperature and monitored by GC-MS. After full conversion of the iodoarene, the reaction was diluted with EtOAc, filtered over Celite® and concentrated. The crude was purified by flash column chromatography.

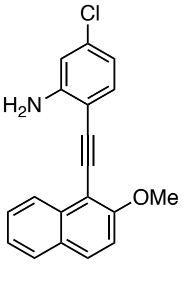
2-((2-Methoxynaphthalen-1-yl)ethynyl)aniline



The title compound 2-((2-methoxynaphthalen-1-yl)ethynyl)aniline (white solid, 310 mg, 1.11 mmol, 83% yield) was synthesized according to general procedure **G** using 2-iodoaniline (300 mg, 1.14 mmol) and 1-ethynyl-2-methoxynaphthalene (262 mg, 1.40 mmol). The reaction was stirred for 3 h and the crude was purified by flash column chromatography on silica gel (cyclohexane/EtOAc 5:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (d, *J* = 8.2 Hz, 1H), 7.94 (d, *J* = 9.1 Hz, 1H), 7.92 (d, *J* = 8.2 Hz, 1H), 7.72 – 7.63 (m, 1H), 7.61 (dt, *J* = 7.5, 2.0 Hz, 1H), 7.52 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.40 (d, *J* = 9.1 Hz, 1H), 7.31 – 7.24 (m, 1H), 6.95 – 6.81 (m, 2H), 4.71 (br s, 2H), 4.17 (s, 3H). **$^{13}C\{^1H\}$ NMR** (126 MHz, $CDCl_3$) δ 158.7, 148.2, 134.0, 131.6, 130.0, 129.7, 128.7, 128.2, 127.5, 125.5, 124.4, 117.9, 114.3, 112.6, 108.8, 107.0, 96.1, 89.7, 56.7. **HRMS** (ESI+) the exact mass calculated for $[C_{19}H_{16}NO]^+$ is 274.1226 *m/z*; found $[M + H]^+$ 274.1237 *m/z*. **M.p.** = 90–92 ºC.

5-Chloro-2-((2-methoxynaphthalen-1-yl)ethynyl)aniline

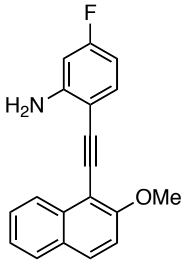


The title compound 5-chloro-2-((2-methoxynaphthalen-1-yl)ethynyl)aniline (white solid, 118 mg, 0.38 mmol, 65% yield) was synthesized according to general procedure **G** using 2-iodo-5-chloroaniline (150 mg, 0.59 mmol) and 1-ethynyl-2-methoxynaphthalene (113 mg, 0.62 mmol). The reaction was stirred for 3 h and the crude was purified by flash column chromatography on silica gel (cyclohexane/EtOAc 5:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 9.0 Hz, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.62 – 7.57 (m, 1H), 7.44 – 7.37 (m, 2H), 7.29 (d, *J* = 9.1 Hz, 1H), 6.83 (d, *J* = 2.0 Hz, 1H), 6.76

(dd, *J* = 8.2, 2.0 Hz, 1H), 4.07 (d, *J* = 2.7 Hz, 3H). **^{13}C{^{1}H} NMR** (126 MHz, CDCl$_3$) δ 158.8, 148.3, 135.3, 133.9, 132.4, 130.3, 128.7, 128.3, 127.6, 125.4, 124.5, 118.6, 114.5, 112.5, 107.8, 106.5, 95.0, 90.8, 56.7. **HRMS** (ESI+) the exact mass calculated for $[C_{19}H_{15}ClNO]^+$ is 308.0837 *m/z*; found $[M + H]^+$ 308.0837 *m/z*. **M.p.** = 150–155 ºC.

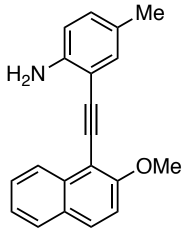
5-Fluoro-2-((2-methoxynaphthalen-1-yl)ethynyl)aniline



The title compound 5-fluoro-2-((2-methoxynaphthalen-1-yl)ethynyl)aniline (white solid, 111 mg, 0.38 mmol, 73% yield) was synthesized according to general procedure **G** using 5-fluoro-2-iodoaniline (124 mg, 0.52 mmol) and 1-ethynyl-2-methoxynaphthalene (100 mg, 0.55 mmol). The reaction was stirred for 1 h and the crude was purified by flash column chromatography on silica gel (cyclohexane/Et$_2$O 3:1 and then, cyclohexane/CH$_2$Cl$_2$).

^{1}H NMR (500 MHz, CDCl$_3$) δ 8.33 (dq, *J* = 8.4, 0.9 Hz, 1H), 7.83 (d, *J* = 8.8 Hz, 1H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.57 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H), 7.46 – 7.38 (m, 2H), 7.28 (d, *J* = 9.1 Hz, 1H), 6.50 – 6.39 (m, 2H), 4.73 (br s, 2H), 4.05 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, CDCl$_3$) δ 164.0 (d, *J* = 246.7 Hz), 158.6, 149.9 (d, *J* = 11.7 Hz), 133.9, 133.0 (d, *J* = 10.4 Hz), 130.0, 128.7, 128.3, 127.5, 125.4, 124.5, 112.5, 106.8, 105.1 (d, *J* = 22.7 Hz), 104.9 (d, *J* = 2.6 Hz), 101.0 (d, *J* = 25.5 Hz), 95.2, 89.4 (d, *J* = 1.5 Hz), 56.7. **^{19}F{^{1}H} NMR** (471 MHz, CDCl$_3$) δ –110.3. **HRMS** (ESI+) the exact mass calculated for $[C_{19}H_{15}FNO]^+$ is 292.1132 *m/z*; found $[M + H]^+$ 292.1124 *m/z*. **M.p.** = 154–156 ºC.

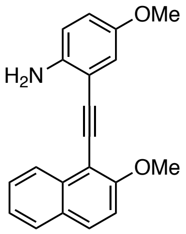
2-((2-Methoxynaphthalen-1-yl)ethynyl)-4-methylaniline



Title compound 2-((2-methoxynaphthalen-1-yl)ethynyl)-4-methylaniline (yellow solid, 133 mg, 0.46 mmol, 90% yield) was synthesized according to general procedure **G** using 2-iodo-4-methylaniline (120 mg, 0.52 mmol) and 1-ethynyl-2-methoxynaphthalene (103 mg, 0.57 mmol). The reaction was stirred for 3 h and the crude was purified by flash column chromatography on silica gel (cyclohexane/Et$_2$O 5:1, then 3:1).

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.36 (dq, *J* = 8.5, 0.9 Hz, 1H), 7.83 (d, *J* = 9.0 Hz, 1H), 7.80 (d, *J* = 7.7 Hz, 1H), 7.57 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H), 7.40 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.33 – 7.31 (m, 1H), 7.29 (d, *J* = 9.1 Hz, 1H), 6.98 (ddd, *J* = 8.1, 2.1, 0.7 Hz, 1H), 6.70 (d, *J* = 8.2 Hz, 1H), 4.45 (br s, 2H), 4.06 (s, 3H), 2.27 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, CDCl$_3$) δ 158.6, 145.9, 134.0, 131.7, 130.6, 129.9, 128.7, 128.2, 127.5, 127.1, 125.5, 124.4, 114.5, 112.6, 108.8, 96.3, 89.4, 56.7, 20.5. **HRMS** (ESI+) the exact mass calculated for $[C_{20}H_{18}NO]^+$ is 288.1383 *m/z*; found $[M + H]^+$ 288.1370 *m/z*. **M.p.** = 124–126 ºC.

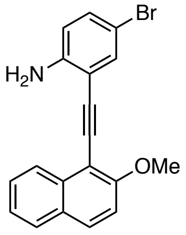
4-Methoxy-2-((2-methoxynaphthalen-1-yl)ethynyl)aniline



The title compound 4-methoxy-2-((2-methoxynaphthalen-1-yl)ethynyl)aniline (yellow gum, 180 mg, 0.59 mmol, 74% yield) was synthesized according to general procedure **G** using 4-methoxy-2-iodoaniline (200 mg, 0.80 mmol) and 1-ethynyl-2-methoxynaphthalene (154 mg, 0.84 mmol). The reaction was stirred for 1 h and the crude was purified by flash column chromatography on silica gel (cyclohexane/Et_2O 4:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.84 (d, *J* = 8.9 Hz, 1H), 7.80 (dt, *J* = 8.2, 0.7 Hz, 1H), 7.58 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H), 7.40 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.28 (d, *J* = 9.1 Hz, 1H), 7.05 (d, *J* = 2.9 Hz, 1H), 6.81 (dd, *J* = 8.8, 2.9 Hz, 1H), 6.73 (d, *J* = 8.7 Hz, 1H), 4.28 (br s, 2H), 4.06 (s, 3H), 3.80 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 158.8, 152.0, 142.5, 134.0, 130.1, 128.7, 128.3, 127.5, 125.5, 124.4, 117.4, 115.9, 115.4, 112.5, 109.4, 106.7, 96.1, 89.7, 56.7, 56.1. **HRMS** (ESI+) the exact mass calculated for $[C_{20}H_{18}NO_2]^+$ is 304.1332 *m/z*; found $[M + H]^+$ 304.1319 *m/z*.

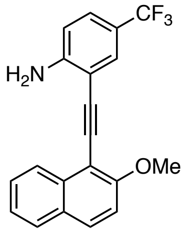
4-Bromo-2-((2-methoxynaphthalen-1-yl)ethynyl)aniline



The title compound 4-bromo-2-((2-methoxynaphthalen-1-yl)ethynyl)aniline (yellow solid, 165 mg, 0.47 mmol, 90% yield) was synthesized according to general procedure **G** using 4-bromo-2-iodoaniline (156 mg, 0.52 mmol) and 1-ethynyl-2-methoxynaphthalene (100 mg, 0.55 mmol). The reaction was stirred for 1 h and the crude was purified by flash column chromatography on silica gel (cyclohexane/Et_2O 4:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (dq, *J* = 8.4, 0.9 Hz, 1H), 7.84 (d, *J* = 9.5 Hz, 1H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.62 – 7.53 (m, 2H), 7.41 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.28 (d, *J* = 9.1 Hz, 1H), 7.23 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.65 (d, *J* = 8.6 Hz, 1H), 4.62 (br s, 2H), 4.05 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 158.9, 147.2, 133.9, 133.5, 132.4, 130.4, 128.7, 128.3, 127.7, 125.3, 124.5, 115.7, 112.4, 110.6, 108.9, 106.3, 94.7, 91.0, 56.6. **HRMS** (ESI+) the exact mass calculated for $[C_{19}H_{15}BrNO]^+$ is 352.0332 m/z; found $[M + H]^+$ 352.0332 *m/z*. **M.p.** = 157–159 ºC.

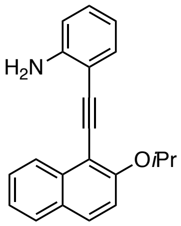
2-((2-Methoxynaphthalen-1-yl)ethynyl)-4-(trifluoromethyl)aniline



The title compound 2-((2-methoxynaphthalen-1-yl)ethynyl)-4-(trifluoromethyl)-aniline (white solid, 138 mg, 0.40 mmol, 77% yield) was synthesized according to general procedure **G** using 2-iodo-4-(trifluoromethyl)aniline (150 mg, 0.52 mmol) and 1-ethynyl-2-methoxynaphthalene (100 mg, 0.55 mmol). The reaction was stirred for 1 h and the crude was purified by flash column chromatography on silica gel (cyclohexane/Et_2O 3:1, then, cyclohexane/CH_2Cl_2 1:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (dq, *J* = 8.5, 0.9 Hz, 1H), 7.86 (d, *J* = 8.9 Hz, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.74 (d, *J* = 2.2 Hz, 1H), 7.60 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H), 7.42 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.37 (dd, *J* = 8.5, 1.4 Hz, 1H), 7.29 (d, *J* = 9.1 Hz, 1H), 6.78 (d, *J* = 8.5 Hz, 1H), 4.95 (br s, 2H), 4.06 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 158.9, 150.6, 133.9, 130.5, 128.71 (d, *J* = 3.9 Hz), 128.65, 128.3, 127.7, 126.5 (q, *J* = 3.7 Hz), 125.3, 124.7 (q, *J* = 271.7 Hz), 124.6, 119.7 (q, *J* = 32.9 Hz), 113.6, 112.3, 108.2, 106.2, 94.6, 91.0, 56.6. **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) δ –61.0. **HRMS** (ESI+) the exact mass calculated for $[C_{20}H_{15}F_3NO]^+$ is 342.1100 *m/z*; found $[M + H]^+$ 342.1103 *m/z*. **M.p.** = 174–176 ºC.

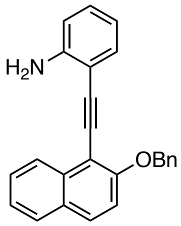
2-((2-Isopropoxynaphthalen-1-yl)ethynyl)aniline



The title compound 2-((2-isopropoxynaphthalen-1-yl)ethynyl)aniline (brown gum, 78.0 mg, 0.53 mmol, 46% yield) was synthesized according to general procedure **G** using 2-ethynylaniline (66.0 mg, 0.563 mmol, 1 equiv) and 1-iodo-2-isopropoxynaphthalene[132] (185 mg, 0.59 mmol, 1.05 equiv). The reaction was stirred for 1 h and the crude was purified by flash column chromatography on silica gel (cyclohexane/Et_2O 3:1) and then, further purified by a second flash column chromatography on silica gel (cyclohexane/CH_2Cl_2 1:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 8.5 Hz, 1H), 7.79 (dd, *J* = 8.8, 3.0 Hz, 2H), 7.62 – 7.55 (m, 1H), 7.50 (d, *J* = 7.7 Hz, 1H), 7.45 – 7.37 (m, 1H), 7.26 (d, *J* = 9.1 Hz, 1H), 7.22 – 7.13 (m, 1H), 6.82 – 6.73 (m, 2H), 4.83 (hept, *J* = 6.1 Hz, 1H), 4.61 (br s, 2H), 1.45 (d, *J* = 6.1 Hz, 6H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 157.3, 148.1, 134.1, 131.5, 129.6, 129.6, 128.8, 128.1, 127.3, 125.6, 124.5, 117.8, 115.9, 114.2, 108.9, 108.8, 95.7, 90.3, 72.3, 22.7. **HRMS** (ESI+) the exact mass calculated for $[C_{21}H_{20}NO]^+$ is 302.1539 *m/z*; found $[M + H]^+$ 302.1543 *m/z*.

2-((2-(Benzyloxy)naphthalen-1-yl)ethynyl)aniline



The title compound 2-((2-(benzyloxy)naphthalen-1-yl)ethynyl)aniline (yellow oil, 120 mg, 0.34 mmol, 88% yield) was synthesized according to general procedure **G** using 2-ethynylaniline (48.0 mg, 0.41 mmol) and 2-(benzyloxy)-1-iodonaphthalene (140 mg, 0.39 mmol). The reaction was stirred for 5 h and the crude was purified by flash column chromatography on silica gel (cyclohexane/EtOAc 5:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.87 – 7.78 (m, 2H), 7.62 – 7.53 (m, 3H), 7.48 – 7.36 (m, 5H), 7.34 (d, *J* = 9.1 Hz, 1H), 7.11 (ddd, *J* = 8.1, 7.3, 1.6 Hz, 1H), 6.71 (td, *J* = 7.5, 1.1 Hz, 1H), 6.64 (dd, *J* = 8.2, 1.1 Hz, 1H), 5.30 (s, 2H), 4.14 (br s, 2H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 157.9, 148.3, 136.7, 133.9, 131.5, 129.7, 129.6, 128.9, 128.8, 128.5, 128.2, 127.5, 125.6, 124.6, 117.6,

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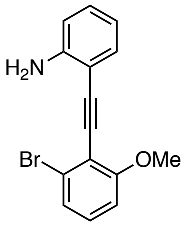
[132] Yang, Y.; Zhang, L.; Deng, G.-J.; Gong, H. *Sci Rep* **2017**, *7*, 40430.

114.0, 113.9, 108.5, 107.8, 96.5, 89.8, 71.6. **HRMS** (ESI+) the exact mass calculated for $[C_{25}H_{20}NO]^+$ is 350.1539 *m/z*; found $[M + H]^+$ 350.1532 *m/z*.

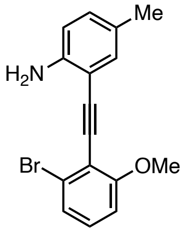
2-((2-Bromo-6-methoxyphenyl)ethynyl)aniline



The title compound 2-((2-bromo-6-methoxyphenyl)ethynyl)aniline (light-brown solid, 90.0 mg, 0.30 mmol, 85% yield) was synthesized according to general procedure **G** using 2-iodoaniline (77.0 mg, 0.35 mmol) and 1-bromo-2-ethynyl-3-methoxybenzene (82.0 mg, 0.39 mmol). The reaction was stirred for 4 h and the crude was purified by flash column chromatography on silica gel (cyclohexane/EtOAc 15:1 to 9:1).

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.37 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.24 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.20 – 7.12 (m, 2H), 6.91 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.74 (dd, *J* = 8.2, 1.1 Hz, 1H), 6.69 (td, *J* = 7.5, 1.1 Hz, 1H), 4.61 (br s, 2H), 3.93 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 161.2, 148.7, 132.3, 130.4, 129.8, 126.2, 125.0, 118.2, 115.9, 114.7, 109.7, 108.3, 95.9, 90.4, 56.7. **HRMS** (ESI+) the exact mass calculated for $[C_{15}H_{13}BrNO]^+$ is 302.0175 *m/z*; found $[M + H]^+$ 302.0179 *m/z*. **M.p.** = 102–104 ºC.

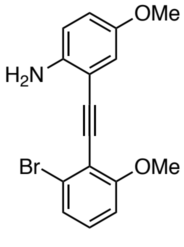
2-((2-Bromo-6-methoxyphenyl)ethynyl)-4-methylaniline



The title compound 2-((2-bromo-6-methoxyphenyl)ethynyl)-4-methylaniline (white solid, 400 mg, 1.27 mmol, 98% yield) was synthesized according to general procedure **G** using 2-iodo-4-methylaniline (300 mg, 1.29 mmol) and 1-bromo-2-ethynyl-3-methoxybenzene (299 mg, 1.42 mmol). The reaction mixture was stirred for 24 h and the crude compound was purified by flash column chromatography on silica gel (cyclohexane/EtOAc 20:1 to 10:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 – 7.18 (m, 2H), 7.12 (t, *J* = 8.2 Hz, 1H), 6.96 (ddd, *J* = 8.2, 2.1, 0.7 Hz, 1H), 6.85 (dd, *J* = 8.4, 1.0 Hz, 1H), 6.65 (d, *J* = 8.2 Hz, 1H), 4.42 (br s, 2H), 3.92 (s, 3H), 2.24 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 160.9, 146.3, 132.0, 131.0, 129.4, 127.0, 125.9, 124.6, 115.6, 114.5, 109.3, 107.9, 95.8, 89.8, 56.4, 20.4. **HRMS** (ESI+) the exact mass calculated for $[C_{16}H_{15}BrNO]^+$ is 316.0332 *m/z*; found $[M + H]^+$ 316.0325 *m/z*. **M.p.** = 122–124 ºC.

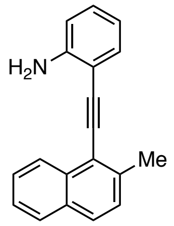
2-((2-Bromo-6-methoxyphenyl)ethynyl)-4-methoxyaniline



The title compound 2-((2-bromo-6-methoxyphenyl)ethynyl)-4-methoxyaniline (white solid, 70.0 mg, 0.21 mmol, 58% yield) was synthesized according to general procedure **G** using 2-iodo-4-methoxyaniline (90.0 mg, 0.36 mmol) and 1-bromo-2-ethynyl-3-methoxybenzene (84.0 mg, 0.40 mmol). The reaction mixture was stirred for 24 h and the crude compound was purified by flash column chromatography on silica gel (cyclohexane/EtOAc 5:1 to 1:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.14 (t, *J* = 8.2 Hz, 1H), 6.96 (d, *J* = 2.9 Hz, 1H), 6.86 (dd, *J* = 8.3, 1.0 Hz, 1H), 6.79 (dd, *J* = 8.8, 2.9 Hz, 1H), 6.69 (d, *J* = 8.8 Hz, 1H), 4.30 (br s, 2H), 3.92 (s, 3H), 3.77 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 160.6, 151.6, 142.6, 129.3, 125.7, 124.4, 117.8, 115.6, 115.1, 115.1, 109.0, 108.2, 95.3, 89.7, 56.1, 55.7. **HRMS** (ESI+) the exact mass calculated for $[C_{16}H_{15}BrNO_2]^+$ is 332.0281 *m/z*; found $[M + H]^+$ 332.0296 *m/z*. **M.p.** = 190–192 °C.

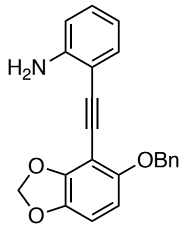
2-((2-Methylnaphthalen-1-yl)ethynyl)aniline



The title compound 2-((2-methylnaphthalen-1-yl)ethynyl)aniline (yellow gum, 240 mg, 0.93 mmol, 77% yield) was synthesized according to general procedure **G** using 2-ethynylaniline (170 mg, 1.45 mmol, 1.2 equiv) and 1-iodo-2-methylnaphthalene (324 mg, 1.21 mmol). The reaction was stirred for 2 h and the crude was purified by flash column chromatography on silica gel (cyclohexane/Et_2O 10:1).

^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.42 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.1 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.59 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H), 7.54 – 7.47 (m, 2H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.19 (ddd, *J* = 8.2, 7.3, 1.5 Hz, 1H), 6.91 – 6.71 (m, 2H), 4.43 (br s, 2H), 2.73 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 148.4, 139.2, 133.7, 132.5, 132.1, 130.3, 128.5, 128.5, 127.3, 126.1, 125.9, 119.8, 118.3, 114.8, 108.6, 100.4, 95.9, 91.9, 21.9. **HRMS** (ESI+) the exact mass calculated for $[C_{19}H_{16}N]^+$ is 258.1277 *m/z*; found $[M + H]^+$ 258.1272 *m/z*.

2-((5-(Benzyloxy)benzo[*d*][1,3]dioxol-4-yl)ethynyl)aniline



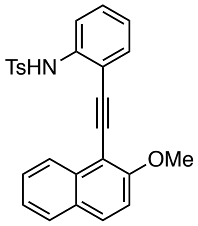
The title compound (brown solid, 196 mg, 0.57 mmol, 53% yield) was synthesized according to general procedure **G** using 2-ethynylaniline (126 mg, 1.07 mmol, 1.0 equiv) and 5-(benzyloxy)-4-iodobenzo[*d*][1,3]dioxole (400 mg, 1.13 mmol, 1.1 equiv). The reaction was stirred for 1 h and the crude was purified by flash column chromatography on silica gel (cyclohexane/Et_2O 5:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.43 (m, 2H), 7.46 – 7.37 (m, 3H), 7.36 – 7.30 (m, 1H), 7.14 – 7.04 (m, 1H), 6.69 (d, *J* = 8.5 Hz, 1H), 6.66 – 6.62 (m, 1H), 6.61 – 6.56 (m, 1H), 6.39 (d, *J* = 8.5 Hz, 1H), 6.04 (s, 2H), 5.06 (s, 2H), 4.07 (br s, 2H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 154.1, 148.7, 148.5 (d, *J* = 2.1 Hz), 142.0, 136.7 (d, *J* = 1.6 Hz), 131.4, 129.9 (d, *J* = 1.7 Hz), 128.7, 128.4, 128.4, 117.4, 113.9 (d, *J* = 1.7 Hz), 107.7, 107.3 (d, *J* = 1.6 Hz), 103.9, 102.0, 97.7, 94.9 (d, *J* = 1.8 Hz), 85.7, 71.7. **HRMS** (ESI+) the exact mass calculated for $[C_{22}H_{17}NNaO_3]^+$ is 366.1101 *m/z*; found $[M + Na]^+$ 366.1102 *m/z*. **M.p.** = 99–101 °C.

General Procedure H: Sulfonylation of anylines

The aniline (1.0 equiv) was placed in a MW vial and dissolved in dry pyridine (0.2 M), the corresponding sulfonyl chloride was added and the reaction was stirred for an indicated time at 25 ºC (if not specified otherwise). The reaction mixture was diluted with CH_2Cl_2 and washed with water (3x) and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated. The crude was purified by flash column chromatography to yield the corresponding product.

N-(2-((2-Methoxynaphthalen-1-yl)ethynyl)phenyl)-4-methylbenzenesulfonamide, 85a

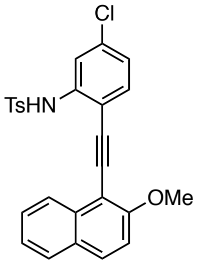


The title compound **85a** (white foam, 350 mg, 0.819 mmol, 83% yield) was synthesized according to general procedure **H** using 2-((2-methoxynaphthalen-1-yl)ethynyl)aniline (270 mg, 0.988 mmol) and tosyl chloride (282 mg, 1.48 mmol, 1.5 equiv). The reaction was stirred for 2 h and the crude was purified by flash column chromatography on silica gel (cyclohexane/EtOAc 10:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (s, 1H), 8.20 (dd, *J* = 8.4, 1.0 Hz, 1H), 7.90 (d, *J* = 9.1 Hz, 1H), 7.83 (dt, *J* = 8.2, 0.8 Hz, 1H), 7.76 – 7.68 (m, 3H), 7.57 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H), 7.47 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.42 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.37 (d, *J* = 9.1 Hz, 1H), 7.31 – 7.23 (m, 1H), 7.11 – 7.03 (m, 3H), 4.27 (s, 3H), 2.24 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 159.5, 143.8, 138.2, 136.4, 133.5, 130.9, 130.7, 129.6, 129.4, 128.5, 128.4, 127.7, 127.4, 125.1, 124.5, 124.2, 119.4, 114.8, 112.1, 105.4, 94.2, 92.1, 56.8, 21.6.

The spectral data are consistent with literature.[133]

N-(5-Chloro-2-((2-methoxynaphthalen-1-yl)ethynyl)phenyl)-4-methylbenzenesulfonamide, 85b



The title compound **85b** (white solid, 58.0 mg, 0.13 mmol, 77% yield) was synthesized according to general procedure **H** using 5-chloro-2-((2-methoxynaphthalen-1-yl)ethynyl)aniline (50.0 mg, 0.16 mmol) and TsCl (37.0 mg, 0.200 mmol, 1.2 equiv). The reaction was stirred for 2 h and the crude was purified by flash column chromatography on silica gel (cyclohexane/EtOAc 10:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (s, 1H), 8.17 (dd, *J* = 8.4, 1.0 Hz, 1H), 7.92 (d, *J* = 9.1 Hz, 1H), 7.86 – 7.81 (m, 1H), 7.76 (d, *J* = 2.0 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.57 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H), 7.42 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.39 (d, *J* = 3.8 Hz, 1H), 7.37 (d, *J* = 4.6 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 2H), 7.03 (dd, *J* = 8.3, 2.0 Hz, 1H), 4.27 (s, 3H), 2.28 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 159.6, 144.2, 139.2, 136.2, 135.2, 133.5, 131.4, 131.1, 129.8, 128.5, 128.4, 127.8, 127.4, 125.0, 124.6, 124.4, 119.3, 113.0, 112.1, 105.1, 93.3, 93.1, 56.9, 21.6. **HRMS** (ESI+) the exact mass

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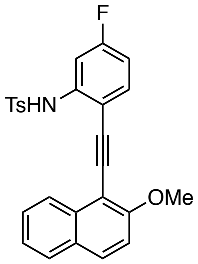
[133] He, Y.-P.; Wu, H.; Wang, Q.; Zhu J. *Angew. Chem. Int. Ed.* **2020**, 59, 2105–2109.

calculated for $[C_{26}H_{20}ClNNaO_3S]^+$ is 484.0745 *m/z*; found $[M + Na]^+$ 484.0729 *m/z*. **M.p.** = 153–155 ºC.

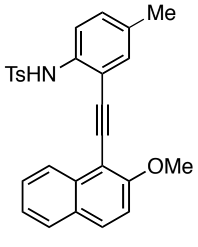
N-(5-Fluoro-2-((2-methoxynaphthalen-1-yl)ethynyl)phenyl)-4-methylbenzenesulfonamide, 85c



The title compound **85c** (white solid, 58.1 mg, 0.13 mmol, 54% yield) was synthesized according to general procedure **H** using 5-fluoro-2-((2-methoxynaphthalen-1-yl)ethynyl)aniline (84.5 mg, 0.24 mmol) and TsCl (110 mg, 0.58 mmol, 2.0 equiv). The reaction was stirred for 24 h and the crude was purified by flash column chromatography on silica gel (cyclohexane/Et_2O 4:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 8.18 (dq, *J* = 8.4, 0.9 Hz, 1H), 7.90 (d, *J* = 8.6 Hz, 1H), 7.83 (dt, *J* = 8.2, 0.7 Hz, 1H), 7.79 – 7.72 (m, 2H), 7.57 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H), 7.50 (dd, *J* = 10.6, 2.5 Hz, 1H), 7.46 – 7.39 (m, 2H), 7.36 (d, *J* = 9.1 Hz, 1H), 7.14 (dd, *J* = 8.6, 0.7 Hz, 2H), 6.76 (ddd, *J* = 8.6, 8.0, 2.5 Hz, 1H), 4.26 (s, 3H), 2.28 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 162.6 (d, *J* = 249.2 Hz), 159.3, 144.2, 139.8 (d, *J* = 11.5 Hz), 136.0, 133.3, 131.8 (d, *J* = 9.7 Hz), 130.7, 129.7, 128.4, 128.3, 127.6, 127.3, 124.9, 124.4, 112.0, 111.2 (d, *J* = 22.6 Hz), 110.3 (d, *J* = 3.3 Hz), 106.5 (d, *J* = 27.8 Hz), 105.1, 93.1 (d, *J* = 1.3 Hz), 91.8 (d, *J* = 1.7 Hz), 56.7, 21.5. **^{19}F{^{1}H} NMR** (471 MHz, $CDCl_3$) δ –107.5. **HRMS** (ESI+) the exact mass calculated for $[C_{26}H_{20}FNNaO_3S]^+$ is 468.1040 *m/z*; found $[M + Na]^+$ 468.1032 *m/z*. **M.p.** = 174–176 ºC.

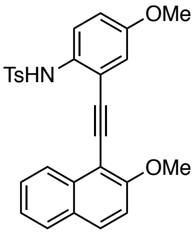
N-(2-((2-Methoxynaphthalen-1-yl)ethynyl)-4-methylphenyl)-4-methylbenzenesulfonamide, 85d



The title compound **85d** (yellow solid, 57.0 mg, 0.13 mmol, 74% yield) was synthesized according to general procedure **H** using 2-((2-methoxynaphthalen-1-yl)ethynyl)-4-methylaniline (50.0 mg, 0.17 mmol, 1.0 equiv) and TsCl (66.0 mg, 0.35 mmol, 2.0 equiv). The reaction was stirred for 2 h and the crude was purified by flash column chromatography on silica gel (cyclohexane/Et_2O 5:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (dq, *J* = 8.4, 0.9 Hz, 1H), 8.08 (s, 1H), 7.90 (d, *J* = 9.5 Hz, 1H), 7.83 (d, *J* = 8.2 Hz, 1H), 7.72 – 7.66 (m, 2H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.56 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H), 7.41 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.37 (d, *J* = 9.1 Hz, 1H), 7.30 – 7.27 (m, 1H), 7.08 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.05 (dd, *J* = 8.6, 0.7 Hz, 2H), 4.26 (s, 3H), 2.29 (s, 3H), 2.23 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 159.4, 143.7, 136.4, 135.8, 134.0, 133.6, 131.0, 130.7, 130.3, 129.6, 128.5, 128.4, 127.7, 127.4, 125.2, 124.5, 119.8, 114.9, 112.1, 105.6, 94.5, 91.6, 56.8, 21.6, 20.8. **HRMS** (ESI+) the exact mass calculated for $[C_{27}H_{23}NNaO_3S]^+$ is 464.1291 *m/z*; found $[M + Na]^+$ 464.1285 *m/z*. **M.p.** = 158–160 ºC.

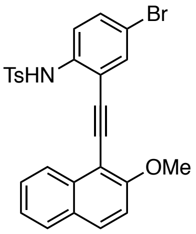
N-(4-Methoxy-2-((2-methoxynaphthalen-1-yl)ethynyl)phenyl)-4-methylbenzenesulfonamide, 85e



The title compound **85e** (white solid, 110 mg, 0.240 mmol, 81% yield) was synthesized according to general procedure **H** using 4-methoxy-2-((2-methoxynaphthalen-1-yl)ethynyl)aniline (90.0 mg, 0.30 mmol) and TsCl (113 mg, 0.59 mmol, 2.0 equiv). The reaction was stirred for 2 h and the crude was purified by flash column chromatography on silica gel (cyclohexane/Et_2O 2:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (dq, *J* = 8.4, 1.0 Hz, 1H), 7.95 – 7.88 (m, 2H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 9.0 Hz, 1H), 7.64 – 7.59 (m, 2H), 7.56 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H), 7.42 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.37 (d, *J* = 9.1 Hz, 1H), 6.99 (d, *J* = 7.8 Hz, 2H), 6.95 (d, *J* = 2.9 Hz, 1H), 6.86 (dd, *J* = 9.0, 2.9 Hz, 1H), 4.26 (s, 3H), 3.80 (s, 3H), 2.19 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 159.4, 156.5, 143.6, 136.2, 133.5, 131.5, 130.9, 129.4, 128.5, 128.4, 127.7, 127.4, 125.1, 124.5, 122.6, 116.8, 115.9, 114.9, 112.1, 105.3, 94.4, 91.7, 56.8, 55.7, 21.5. **HRMS** (ESI+) the exact mass calculated for $[C_{27}H_{23}NNaO_4S]^+$ is 480.1240 *m/z*; found $[M + Na]^+$ 480.1252 *m/z*. **M.p.** = 67–69 ºC.

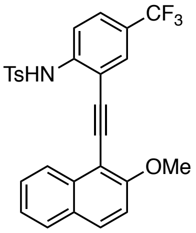
N-(4-Bromo-2-((2-methoxynaphthalen-1-yl)ethynyl)phenyl)-4-methylbenzenesulfonamide, 85f



The title compound **85f** (white solid, 98.0 mg, 0.19 mmol, 81% yield) was synthesized according to general procedure **H** using 4-bromo-2-((2-methoxynaphthalen-1-yl)ethynyl)aniline (84.5 mg, 0.24 mmol, 1.0 equiv) and TsCl (91.0 mg, 0.48 mmol, 2.0 equiv). The reaction was stirred for 24 h and the crude was purified by flash column chromatography on silica gel (cyclohexane/Et_2O 4:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 – 8.12 (m, 2H), 7.93 (d, *J* = 9.5 Hz, 1H), 7.83 (dt, *J* = 8.2, 0.7 Hz, 1H), 7.72 – 7.66 (m, 2H), 7.64 – 7.54 (m, 3H), 7.43 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.40 – 7.33 (m, 2H), 7.10 (dd, *J* = 8.3, 1.0 Hz, 2H), 4.27 (s, 3H), 2.27 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 159.7, 144.1, 137.3, 136.1, 133.5, 133.0, 132.2, 131.4, 129.8, 128.5, 128.4, 127.9, 127.4, 125.0, 124.7, 120.9, 116.9, 116.7, 112.1, 104.9, 93.4, 92.9, 56.8, 21.6. **HRMS** (ESI+) the exact mass calculated for $[C_{26}H_{20}BrNNaO_3S]^+$ is 528.0239 *m/z*; found $[M + Na]^+$ 528.0230 *m/z*. **M.p.** = 86–88 ºC.

N-(2-((2-Methoxynaphthalen-1-yl)ethynyl)-4-(trifluoromethyl)phenyl)-4-methylbenzenesulfonamide, 85g

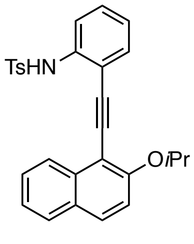


The title compound **85g** (white solid, 57.0 mg, 0.12 mmol, 65% yield) was synthesized according to general procedure **H** using 2-((2-methoxynaphthalen-1-yl)ethynyl)-4-(trifluoromethyl)aniline (60.0 mg, 0.18 mmol) and TsCl (94.0 mg, 0.50 mmol, 2.0 equiv). The reaction was stirred for 2 h and the crude was purified by flash column chromatography on silica gel (cyclohexane/Et_2O 5:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.20 (d, *J* = 8.5 Hz, 1H), 7.94 (dd, *J* = 9.1, 2.4 Hz, 1H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.80 (d, *J* = 8.7 Hz, 1H), 7.77 – 7.72 (m, 3H), 7.60 (t, *J* = 8.2 Hz, 1H), 7.49

(dd, *J* = 8.7, 2.1 Hz, 1H), 7.44 (t, *J* = 6.9 Hz, 1H), 7.39 (dd, *J* = 9.6, 2.6 Hz, 1H), 7.16 (d, *J* = 8.2 Hz, 2H), 4.28 (s, 3H), 2.30 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 159.9, 144.4, 141.0, 136.2, 133.5, 131.5, 129.9, 128.55, 128.46, 128.0, 127.8 (q, *J* = 3.9 Hz), 127.4, 126.1 (q, *J* = 3.7 Hz), 126.1 (q, *J* = 34.3 Hz), 125.0, 124.8, 123.7 (q, *J* = 271.9 Hz), 118.2, 114.5, 112.1, 104.8, 93.8, 92.8, 56.9, 21.6. **^{19}F{^{1}H} NMR** (471 MHz, $CDCl_3$) δ –62.5. **HRMS** (ESI+) the exact mass calculated for $[C_{27}H_{20}F_3NNaO_3S]^+$ is 518.1008 *m/z*; found $[M + Na]^+$ 518.1010 *m/z*. **M.p.** = 147–149 ºC.

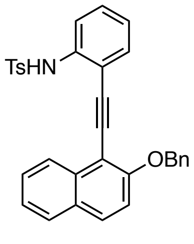
N-(2-((2-Isopropoxynaphthalen-1-yl)ethynyl)phenyl)-4-methylbenzenesulfonamide, 85h



The title compound **85h** (white solid, 67.0 mg, 0.150 mmol, 61% yield) was synthesized according to general procedure **H** using 2-((2-isopropoxynaphthalen-1-yl)ethynyl)aniline (72.3 mg, 0.240 mmol) and TsCl (91.5 mg, 0.480 mmol, 2.00 equiv). The reaction was stirred for 2 h and the crude residue was purified by flash column chromatography on silica gel(cyclohexane/EtOAc 10:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (dd, *J* = 8.4, 1.0 Hz, 1H), 7.86 (d, *J* = 9.1 Hz, 1H), 7.82 (d, *J* = 8.1 Hz, 1H), 7.78 (s, 1H), 7.71 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.66 – 7.58 (m, 2H), 7.55 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H), 7.47 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.41 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.35 – 7.28 (m, 2H), 7.10 (td, *J* = 7.6, 1.2 Hz, 1H), 6.96 (d, *J* = 7.9 Hz, 2H), 4.87 (dp, *J* = 12.0, 6.1 Hz, 1H), 2.17 (s, 3H), 1.58 (d, *J* = 6.1 Hz, 6H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 158.2, 143.8, 137.8, 136.2, 134.1, 131.3, 130.7, 129.5, 129.4, 128.5, 128.3, 127.6, 127.4, 125.1, 124.7, 124.5, 121.0, 115.8, 115.1, 106.9, 93.3, 91.9, 72.9, 22.5, 21.5. **HRMS** (ESI–) the exact mass calculated for $[C_{28}H_{24}NO_3S]^-$ is 454.1482 *m/z*; found $[M – H]^-$ 454.1489 *m/z*.

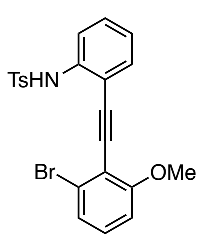
N-(2-((2-(Benzyloxy)naphthalen-1-yl)ethynyl)phenyl)-4-methylbenzenesulfonamide, 85i



The title compound **85i** (white solid, 88.0 mg, 0.130 mmol, 44% yield) was synthesized according to general procedure **H** using 2-((2-(benzyloxy)naphthalen-1-yl)ethynyl)aniline (100 mg, 0.290 mmol) and TsCl (65.0 mg, 0.340 mmol, 1.20 equiv). The reaction was stirred for 2 h and the crude was purified by flash column chromatography (cyclohexane/EtOAc 10:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (dd, *J* = 8.4, 1.0 Hz, 1H), 8.10 (s, 1H), 7.80 – 7.73 (m, 2H), 7.70 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.70 – 7.64 (m, 2H), 7.56 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H), 7.48 (td, *J* = 7.9, 1.3 Hz, 3H), 7.40 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.37 – 7.31 (m, 2H), 7.32 – 7.23 (m, 3H), 7.07 (td, *J* = 7.6, 1.1 Hz, 1H), 7.05 – 7.00 (m, 2H), 5.68 (s, 2H), 2.22 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 158.4, 143.8, 138.2, 137.2, 136.4, 133.7, 131.0, 130.6, 129.6, 129.5, 128.85, 128.6, 128.4, 128.0, 127.7, 127.4, 126.9, 125.1, 124.7, 124.2, 119.3, 114.7, 114.1, 106.3, 94.1, 92.0, 70.9, 21.6. **HRMS** (ESI+) the exact mass calculated for $[C_{32}H_{25}NNaO_3S]^+$ is 526.1447 *m/z*; found $[M + Na]^+$ 526.1447 *m/z*.

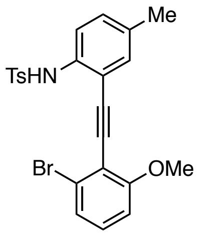
N-(2-((2-Bromo-6-methoxyphenyl)ethynyl)phenyl)-4-methylbenzenesulfonamide, 85j



Title compound **85j** (white solid, 70.0 mg, 0.700 mmol, 72% yield) was synthesized according to general procedure **H** using 2-((2-bromo-6-methoxyphenyl)ethynyl)aniline (71.3 mg, 0.240 mmol) and TsCl (90.0 mg, 0.470 mmol, 2.00 equiv). The reaction mixture was stirred for 20 h and the crude residue was purified by flash column chromatography on silica gel (cyclohexane/EtOAc 20:1 to 10:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.72 – 7.65 (m, 3H), 7.41 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.33 – 7.17 (m, 3H), 7.13 (d, *J* = 8.1 Hz, 2H), 7.02 (td, *J* = 7.6, 1.1 Hz, 1H), 6.94 (dd, *J* = 8.0, 1.3 Hz, 1H), 4.08 (s, 3H), 2.32 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 161.3, 144.0, 138.5, 136.2, 131.3, 130.4, 129.9, 129.7, 127.4, 125.6, 124.7, 124.0, 119.0, 114.4, 113.8, 109.3 93.2, 92.0, 56.7, 21.7. **HRMS** (ESI+) the exact mass calculated for $[C_{22}H_{18}BrNaNO_3S]^+$ is 478.0083 *m/z*; found $[M + Na]^+$ 478.0070 *m/z*. **M.p.** = > 60 ºC (decomposition).

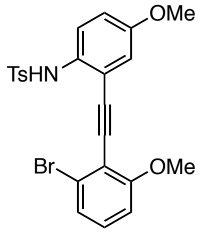
N-(2-((2-Bromo-6-methoxyphenyl)ethynyl)-4-methylphenyl)-4-methylbenzenesulfonamide, 85k



The title compound **85k** (white solid, 465 mg, 0.990 mmol, 90% yield) was synthesized according to general procedure **H** using 2-((2-bromo-6-methoxyphenyl)ethynyl)-4-methylaniline (347 mg, 1.10 mmol) and tosyl chloride (418 mg, 2.19 mmol, 2.00 equiv). The reaction mixture was stirred for 17 h and the crude residue was purified by flash column chromatography on silica gel (15:1 to 9:1 cyclohexane/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.70 – 7.62 (m, 2H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.28 – 7.16 (m, 3H), 7.15 – 7.04 (m, 3H), 6.93 (dd, *J* = 8.0, 1.3 Hz, 1H), 4.07 (s, 3H), 2.31 (s, 3H), 2.25 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 161.3, 143.8, 136.3, 136.1, 133.9, 131.5, 130.8, 130.3, 129.6, 127.4, 125.6, 124.7, 119.5, 114.5, 114.0, 109.3, 93.5, 91.5, 56.7, 21.6, 20.7. **HRMS** (ESI+) the exact mass calculated for $[C_{23}H_{20}BrNaNO_3S]^+$ is 492.0239 *m/z*; found $[M + Na]^+$ 492.0237 *m/z*. **M.p.** = 132–134 ºC.

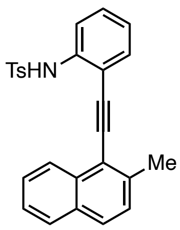
N-(2-((2-Bromo-6-methoxyphenyl)ethynyl)-4-methoxyphenyl)-4-methylbenzenesulfonamide, 85l



The title compound **85l** (brown solid, 36.0 mg, 74.0 μmol, 65% yield) was synthesized according to general procedure **H** using 2-((2-bromo-6-methoxyphenyl)ethynyl)-4-methoxyaniline (38.0 mg, 110 μmol) and TsCl (43.6 mg, 230 μmol, 2.00 equiv). The reaction mixture was stirred for 20 h and the crude residue was purified by flash column chromatography on silica gel (cyclohexane/EtOAc 10:1 to 5:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.63 (dd, *J* = 8.6, 0.9 Hz, 1H), 7.61 – 7.57 (m, 2H), 7.28 – 7.15 (m, 2H), 7.08 – 7.08 (m, 2H), 6.94 (dd, *J* = 7.8, 1.6 Hz, 1H), 6.90 – 6.82 (m, 2H), 4.08 (s, 3H), 3.76 (s, 3H), 2.30 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 161.0, 156.1, 143.5, 135.8, 131.6, 130.2, 129.2, 127.1, 125.3, 124.4, 122.0, 116.3, 115.6, 114.9, 114.0, 109.0, 93.1, 91.2, 56.4, 55.4, 21.3. **HRMS** (ESI+) the exact mass calculated for $[C_{23}H_{20}BrNNaSO_4]^+$ is 508.0189 *m/z*; found $[M + Na]^+$ 508.019 *m/z*. **M.p.** = > 80 ºC (decomposition).

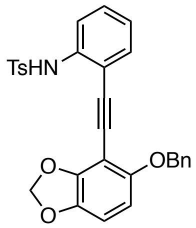
N-(2-((2-Bromo-6-methoxyphenyl)ethynyl)-4-methylphenyl)-4-methylbenzenesulfonamide, 85m



The title compound **85m** (white solid, 110 mg, 0.270 mmol, 86% yield) was synthesized according to general procedure **H** using 2-((2-methylnaphthalen-1-yl)ethynyl)aniline (80.0 mg, 0.310 mmol) and TsCl (90.0 mg, 0.470 mmol, 2.00 equiv). The reaction mixture was stirred for 17 h and the crude residue was purified by flash column chromatography on silica gel (9:1 cyclohexane/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (dd, *J* = 8.3, 1.0 Hz, 1H), 7.88–7.84 (m, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.72–7.65 (m, 3H), 7.60 (ddd, *J* = 8.3, 6.8, 1.4 Hz, 1H), 7.55–7.47 (m, 2H), 7.43–7.37 (m, 2H), 7.33 (td, *J* = 7.9, 1.6 Hz, 1H), 7.17–7.06 (m, 3H), 2.70 (s, 3H), 2.29 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 144.2, 139.6, 137.6, 133.4, 132.2, 131.7, 129.8, 129.8, 129.2, 128.5, 128.2, 127.4, 127.3, 125.9, 125.6, 124.5, 119.6, 118.4, 114.7, 93.6, 93.1, 21.9, 21.6. **HRMS** (ESI–) the exact mass calculated for $[C_{26}H_{20}NO_2S]^-$ is 410.1220 *m/z;* found $[M – H]^-$ 410.1225 *m/z*. **M.p.** = 132–135 ºC.

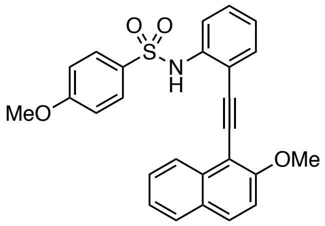
N-(2-((5-(Benzyloxy)benzo[*d*][1,3]dioxol-4-yl)ethynyl)phenyl)-4-methylbenzenesulfonamide, 85n



The title compound **85n** (white solid, 167 mg, 0.340 mmol, 72% yield) was synthesized according to general procedure **H** using 2-((5-(benzyloxy)benzo[*d*][1,3]dioxol-4-yl)ethynyl)aniline (160 mg, 0.470 mmol) and TsCl (160 mg, 0.470 mmol, 2.00 equiv). The reaction was stirred for 14 h and the crude was purified by flash column chromatography on silica gel (cyclohexane/CH_2Cl_2 1:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.71 – 7.65 (m, 3H), 7.47 – 7.42 (m, 2H), 7.39 – 7.34 (m, 3H), 7.32 – 7.28 (m, 1H), 7.27 – 7.23 (m, 1H), 7.14 – 7.09 (m, 2H), 7.01 (td, *J* = 7.6, 1.1 Hz, 1H), 6.68 (d, *J* = 8.5 Hz, 1H), 6.34 (d, *J* = 8.6 Hz, 1H), 6.09 (s, 2H), 5.31 (s, 2H), 2.30 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 153.6, 149.6, 143.9, 141.8, 138.3, 137.1, 136.3, 131.0, 129.7, 129.6, 128.7, 128.0, 127.5, 127.1, 124.0, 119.1, 113.9, 108.4, 104.9, 102.4, 96.6, 92.6, 88.0, 71.5, 21.6. **HRMS** (ESI–) the exact mass calculated for $[C_{29}H_{22}NO_5S]^-$ is 496.1224 *m/z;* found $[M – H]^-$ 496.1218 *m/z*. **M.p.** = 142–145 °C.

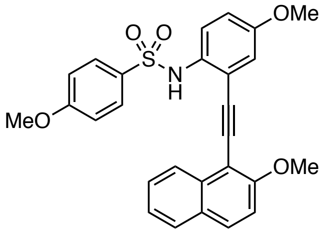
4-Methoxy-*N*-(2-((2-methoxynaphthalen-1-yl)ethynyl)phenyl)benzenesulfonamide, 85o



The title compound **85o** (white solid, 128 mg, 0.289 mmol, 99% yield) was synthesized according to general procedure **H** using 2-((2-methoxynaphthalen-1-yl)ethynyl)aniline (80.0 mg, 0.30 mmol) and 4-methoxybenzenesulfonyl chloride (67.0 mg, 0.320 mmol, 1.10 equiv). The reaction was stirred for 20 h and the crude was purified by flash column chromatography on silica gel (cyclohexane/EtOAc 5:1).

^{1}H NMR (500 MHz, CDCl$_3$) δ 8.19 (d, *J* = 8.4 Hz, 1H), 8.18 (s, 1H), 7.91 (d, *J* = 9.1 Hz, 1H), 7.83 (d, *J* = 8.2 Hz, 1H), 7.78 – 7.70 (m, 3H), 7.57 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H), 7.47 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.42 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.38 (d, *J* = 9.1 Hz, 1H), 7.31 – 7.24 (m, 1H), 7.07 (td, *J* = 7.6, 1.1 Hz, 1H), 6.77 – 6.70 (m, 2H), 4.27 (s, 3H), 3.68 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, CDCl$_3$) δ 163.2, 159.5, 138.3, 133.6, 131.0, 130.9, 130.7, 129.6, 129.4, 128.6, 128.4, 127.8, 125.2, 124.6, 124.2, 119.7, 114.9, 114.2, 112.2, 105.5, 94.3, 92.0, 56.8, 55.5. **HRMS** (ESI+) the exact mass calculated for [$C_{26}H_{21}NaO_4S$]$^+$ is 466.1083 *m/z*; found [M + Na]$^+$ 446.1076 *m/z*. **M.p.** = 135–137 ºC.

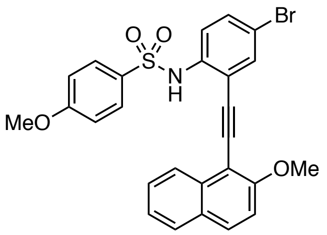
4-Methoxy-*N*-(4-methoxy-2-((2-methoxynaphthalen-1-yl)ethynyl)phenyl)benzenesulfonamide, 85p



The title compound **85p** (white solid, 45.0 mg, 0.0950 mmol, 72% yield) was synthesized according to general procedure **H** using 4-methoxy-2-((2-methoxynaphthalen-1-yl)ethynyl)aniline (40.0 mg, 0.130 mmol) and 4-methoxybenzenesulfonylchloride (30.0 mg, 0.150 mmol, 1.10 equiv). The reaction was stirred for 20 h and the crude was purified by flash column chromatography on silica gel (cyclohexane/EtOAc 5:1).

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.14 (dd, *J* = 8.4, 1.0 Hz, 1H), 7.91 (d, *J* = 9.1 Hz, 1H), 7.87 (s, 1H), 7.83 (d, *J* = 8.2 Hz, 1H), 7.70 – 7.61 (m, 3H), 7.57 (ddd, *J* = 8.4, 6.8, 1.3 Hz, 1H), 7.46 – 7.34 (m, 2H), 6.94 (d, *J* = 2.9 Hz, 1H), 6.87 (dd, *J* = 9.0, 2.9 Hz, 1H), 6.69 – 6.59 (m, 2H), 4.26 (s, 3H), 3.80 (s, 3H), 3.62 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, CDCl$_3$) δ 163.0, 159.5, 156.6, 133.5, 131.6, 130.9, 130.7, 129.6, 128.5, 128.4, 127.7, 125.1, 124.6, 122.8, 117.0, 115.9, 114.8, 114.0, 112.1, 105.4, 94.5, 91.6, 56.8, 55.7, 55.5. **HRMS** (ESI+) the exact mass calculated for [$C_{27}H_{23}NNaO_5S$]$^+$ is 496.1189 *m/z*; found [M + Na]$^+$ 496.1200 *m/z*. **M.p.** = 85–57 ºC.

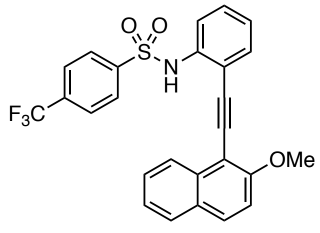
N-(4-Bromo-2-((2-methoxynaphthalen-1-yl)ethynyl)phenyl)-4-methoxybenzenesulfonamide, 85q



The title compound **85q** (white solid, 58.0 mg, 0.110 mmol, 98% yield) was synthesized according to general procedure **H** using 4-bromo-2-((2-methoxynaphthalen-1-yl)ethynyl)aniline (40.0 mg, 0.120 mmol) and 4-methoxybenzenesulfonylchloride (27.0 mg, 0.130 mmol, 1.10 equiv). The reaction was stirred for 20 h and the crude was purified by flash column chromatography on silica gel (cyclohexane/EtOAc 5:1).

^{1}H NMR (500 MHz, CDCl$_3$) δ 8.15 (dd, J = 8.3, 1.0 Hz, 1H), 8.13 (s, 1H), 7.93 (d, J = 9.1 Hz, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.76 – 7.70 (m, 2H), 7.64 – 7.54 (m, 3H), 7.43 (ddd, J = 8.1, 6.8, 1.2 Hz, 1H), 7.40 – 7.34 (m, 2H), 6.78 – 6.71 (m, 2H), 4.27 (s, 3H), 3.70 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, CDCl$_3$) δ 163.3, 159.8, 137.4, 133.5, 133.0, 132.3, 131.4, 130.6, 129.6, 128.5, 128.4, 128.0, 125.0, 124.7, 121.0, 116.9, 116.8, 114.3, 112.1, 104.9, 93.4, 92.9, 56.9, 55.6. **HRMS** (ESI+) the exact mass calculated for $[\mathrm{C_{26}H_{20}BrNNaO_4S}]^+$ is 544.0189 *m/z*; found $[\mathrm{M + Na}]^+$ 544.0192 *m/z*. **M.p.** = 85–87 ºC.

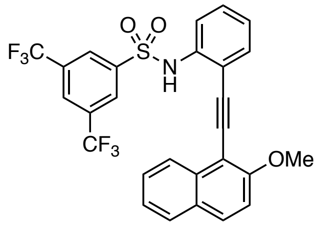
N-(2-((2-Methoxynaphthalen-1-yl)ethynyl)phenyl)-4-(trifluoromethyl)benzenesulfonamide, 85r



The title compound **85r** (white solid, 99.0 mg, 0.290 mmol, 70% yield) was synthesized according to general procedure **H** using 2-((2-methoxynaphthalen-1-yl)ethynyl)aniline (80.0 mg, 0.300 mmol) and 4-(trifluoromethyl)benzenesulfonyl chloride (67.0 mg, 0.320 mmol, 1.10 equiv). The reaction was stirred for 20 h and the crude was purified by flash column chromatography on silica gel (cyclohexane/EtOAc 5:1).

^{1}H NMR (500 MHz, CDCl$_3$) δ 8.28 (s, 1H), 8.16 (dd, J = 8.4, 1.0 Hz, 1H), 7.95 – 7.90 (m, 3H), 7.86 – 7.81 (m, 1H), 7.76 (dd, J = 8.3, 1.1 Hz, 1H), 7.58 (ddd, J = 8.3, 6.8, 1.3 Hz, 1H), 7.52 (d, J = 8.3 Hz, 2H), 7.48 (dd, J = 7.7, 1.5 Hz, 1H), 7.43 (ddd, J = 8.1, 6.8, 1.2 Hz, 1H), 7.38 (d, J = 9.1 Hz, 1H), 7.35 – 7.28 (m, 1H), 7.13 (td, J = 7.6, 1.1 Hz, 1H), 4.27 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, CDCl$_3$) δ 159.4, 142.8, 137.4, 134.6 (q, J = 33.0 Hz), 133.5, 131.1, 130.8, 129.6, 128.6, 128.4, 128.0, 127.9, 126.1 (q, J = 3.7 Hz), 123.2 (q, J = 273.1 Hz), 120.3, 115.5 112.0, 105.2, 94.0, 92.4, 56.8. **^{19}F{^{1}H} NMR** (471 MHz, CDCl$_3$) δ –63.4. **HRMS** (ESI+) the exact mass calculated for $[\mathrm{C_{26}H_{18}NNaO_3S}]^+$ is 504.0852 *m/z*; found $[\mathrm{M + Na}]^+$ 504.0842 *m/z*. **M.p.** = 160–162 ºC.

N-(2-((2-Methoxynaphthalen-1-yl)ethynyl)phenyl)-3,5-bis(trifluoromethyl)benzenesulfonamide, 85s

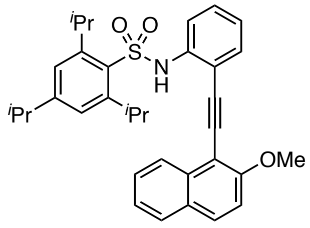


The title compound **85s** (white solid, 120 mg, 0.220 mmol, 75% yield) was synthesized according to general procedure **H** using 2-((2-methoxynaphthalen-1-yl)ethynyl)aniline (80.0 mg, 0.300 mmol) and 3,5-bis(trifluoromethyl)benzenesulfonyl chloride (100 mg, 0.320 mmol, 1.10

equiv). The reaction was stirred for 20 h and the crude was purified by flash column chromatography (cyclohexane/EtOAc 5:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (s, 2H), 8.10 (s, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.92 (d, *J* = 9.1 Hz, 1H), 7.85 – 7.76 (m, 3H), 7.55 (ddd, *J* = 8.3, 6.7, 1.3 Hz, 1H), 7.46 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.45 – 7.35 (m, 3H), 7.21 (td, *J* = 7.6, 1.2 Hz, 1H), 4.28 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 159.3, 141.6, 136.5, 133.4, 132.5 (q, *J* = 34.5 Hz), 131.4, 130.7, 129.7, 128.6, 128.4, 127.8, 127.8 (d, *J* = 3.8 Hz), 126.4 (m), 126.3, 124.7, 123.4, 122.0 (q, *J* = 192.4 Hz), 117.1, 111.8, 104.8, 93.6, 92.4, 56.7. **^{19}F{^{1}H} NMR** (471 MHz, $CDCl_3$) δ –63.6. **HRMS** (ESI+) the exact mass calculated for $[C_{27}H_{17}F_6NNaO_3S]^+$ is 572.0726 *m/z*; found $[M + Na]^+$ 572.0730 *m/z*. **M.p.** = 134–136 ºC.

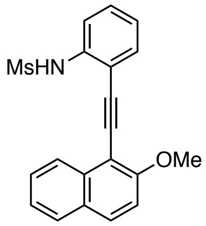
2,4,6-Triisopropyl-*N*-(2-((2-methoxynaphthalen-1-yl)ethynyl)phenyl)benzenesulfonamide, 85t



The title compound **85t** (white solid, 110 mg, 0.200 mmol, 56% yield) was synthesized according to general procedure **H** using 4-methoxy-2-((2-methoxynaphthalen-1-yl)ethynyl)aniline (100 mg, 0.370 mmol) and 2,4,6-triisopropylbenzenesulfonylchloride (166 mg, 0.550 mmol, 1.50 equiv). The reaction was stirred for 12 h at 60 ºC and the crude was purified by flash column chromatography on silica gel (cyclohexane/EtOAc 20:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (s, 1H), 8.28 (dd, *J* = 8.4, 1.0 Hz, 1H), 7.90 (d, *J* = 8.9 Hz, 1H), 7.83 (d, *J* = 8.2 Hz, 1H), 7.59 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H), 7.53 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.45 – 7.37 (m, 2H), 7.37 (d, *J* = 9.1 Hz, 1H), 7.17 (ddd, *J* = 8.5, 7.4, 1.6 Hz, 1H), 7.12 (s, 2H), 6.98 (td, *J* = 7.5, 1.1 Hz, 1H), 4.45 (p, *J* = 6.7 Hz, 2H), 4.23 (s, 3H), 2.84 (p, *J* = 6.9 Hz, 1H), 1.22 (d, *J* = 3.9 Hz, 6H), 1.21 (d, *J* = 3.9 Hz, 12H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 159.4, 153.2, 151.0, 138.9, 133.5, 132.3, 130.9, 130.8, 129.3, 128.5, 128.4, 127.7, 125.2, 124.5, 124.2, 122.5, 115.2, 112.3, 112.0, 105.6, 94.3, 92.5, 56.6, 34.2, 29.8, 25.0, 23.6. **HRMS** (ESI–) the exact mass calculated for $[C_{34}H_{36}NO_3S]^-$ is 538.2425 *m/z*; found $[M – H]^-$ 538.2421 *m/z*. **M.p.** = 111–113 ºC.

***N*-(2-((2-Methoxynaphthalen-1-yl)ethynyl)phenyl)methanesulfonamide, 85u**



The title compound **85u** (yellow solid, 102 mg, 0.29 mmol, 88% yield) was synthesized according to general procedure **H** using 2-((2-methoxynaphthalen-1-yl)ethynyl)aniline (90.0 mg, 0.33 mmol) and mesyl chloride (134 mg, 1.17 mmol, 2.00 equiv). The reaction mixture was stirred for 16 h and the crude compound was purified by flash column chromatography on silica gel (15:1 to 10:1 cyclohexane/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.5 Hz, 1H), 7.93 – 7.77 (m, 3H), 7.72 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.65 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.60 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H), 7.45 – 7.36 (m, 2H), 7.33 (d, *J* = 9.1 Hz, 1H), 7.21 (td, *J* = 7.6, 1.2 Hz, 1H), 4.17 (s, 3H), 3.04 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz,

$CDCl_3$) δ 159.84, 138.55, 133.84, 131.39, 131.32, 130.09, 128.83, 128.73, 128.18, 125.35, 125.23, 124.92, 120.75, 115.69, 112.36, 105.41, 94.46, 92.57, 57.00, 39.76. **HRMS** (ESI+) the exact mass calculated for $[C_{20}H_{17}NaNO_3S]^+$ is 374.0821 *m/z*; found $[M + Na]^+$ 374.0827 *m/z*. **M.p.** = 122–124 ºC.

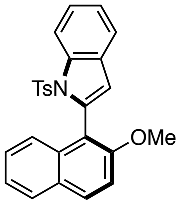
General procedure I: synthesis of axially-chiral indols

The Ts-protected anilines (1.0 equiv) and (*R*,*R*)-**40g** (5 mol%) were dissolved in 1,2-dichloroethane and the mixture was cooled to -4 ºC. A solution of $AgNTf_2$ (5 mol%) in 1,2-dichloroethane (total concentration 0.05 M) was added dropwise and the reaction was stirred at the same temperature for the given time. After full conversion of the starting material, the reaction was quenched by addition of 3 drops of NEt_3 and concentrated. The crude was purified by flash column chromatography or preparative TLC.

General procedure J: synthesis of axially-chiral indols

The Ts-protected aniline (1.0 equiv) was dissolved in α,α,α-trifluorotoluene (0.05 M) and the mixture was cooled to -20 ºC. (*R*,*R*)-**A1** (5 mol%) was added and the reaction was stirred at the same temperature for the giving time. After full conversion of the starting material, the reaction was quenched by addition of 3 drops of NEt_3 and concentrated. The crude was purified by flash column chromatography or preparative TLC.

2-(2-Methoxynaphthalen-1-yl)-1-tosyl-1*H*-indole, 86a



Catalysis with Complex (*R*,*R*)-**40g**

The title compound **86a** (white solid, 17.3 mg, 35.8 µmol, 84% yield, 91:9 *er*) was synthesized following general procedure **I** using *N*-(4-bromo-2-((2-methoxynaphthalen-1-yl)ethynyl)phenyl)-4-methylbenzenesulfonamide **85a** (20.7 mg, 48.4 µmol) whereby the reaction was stirred for 19 h. Purification was performed by flash column chromatography (cyclohexane/CH_2Cl_2 10:1).

α_D^{589} = +84.2 deg·cm^2·g^{-1} ($CHCl_3$, c 1.0, 297 K). **SFC** Chiralpak IC (100 × 3.0 mm, 3 µm) at 35 ºC, flow 1.2 mL/min, isocratic CO_2/EtOH 70:30, ABRP pressure 150 bar, 230 nm, t_R (major) 1.34; t_R (minor) 2.00.

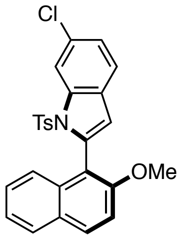
Catalysis with Complex (*R*,*R*)-**A1**

The title compound **86a** (white solid, 20.2 mg, 47.2 µmol, 97% yield, 6:94 *er*) was synthesized following general procedure **J** using *N*-(4-bromo-2-((2-methoxynaphthalen-1-yl)ethynyl)phenyl)-4-methylbenzenesulfonamide **85a** (20.7 mg, 48.5 µmol) whereby the reaction was stirred for 16 h. Purification was performed by flash column chromatography (SiO_2, cyclohexane/EtOAc from 10:0 to 8:2).

α_D^{589} = –73.3 deg·cm^2·g^{-1} ($CHCl_3$, c 0.1, 299 K). **SFC** Chiralpak IC (100 × 3.0 mm, 3 µm) at 35 ºC, flow 1.2 mL/min, isocratic CO_2/EtOH 70:30, ABRP pressure 150 bar, 230 nm, t_R (minor) 1.36; t_R (major) 1.97.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (dd, *J* = 8.4, 0.9 Hz, 1H), 7.98 (d, *J* = 9.0 Hz, 1H), 7.80 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.58 (d, *J* = 7.9 Hz, 1H), 7.38 (ddd, *J* = 8.5, 7.3, 1.4 Hz, 1H), 7.35 (d, *J* = 9.1 Hz, 1H), 7.33 – 7.26 (m, 2H), 7.25 – 7.20 (m, 3H), 7.14 (ddd, *J* = 8.3, 6.7, 1.3 Hz, 1H), 6.90 (d, *J* = 7.9 Hz, 2H), 6.64 (d, *J* = 0.8 Hz, 1H), 3.86 (s, 3H), 2.25 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 156.7, 144.3, 137.4, 136.3, 134.7, 134.6, 131.3, 130.0, 129.2, 128.6, 128.0, 127.1, 126.7, 124.9, 124.5, 123.4, 120.9, 115.3, 114.9, 112.9, 112.8, 56.4, 21.6. **HRMS** (ESI+) the exact mass calculated for $[C_{26}H_{21}NNaO_3S]^+$ is 450.1134 *m/z*; found $[M + Na]^+$ 450.1120 *m/z*. **M.p.** = 70–73 ºC.

6-Chloro-2-(2-methoxynaphthalen-1-yl)-1-tosyl-1*H*-indole, 86b



Catalysis with Complex (*R*,*R*)-**40g**

The title compound **86b** (white solid, 34.0 mg, 75.8 µmol, 97% yield, 92:8 *er*) was synthesized following general procedure **I** using *N*-(5-chloro-2-((2-methoxynaphthalen-1-yl)ethynyl)phenyl)-4-methylbenzenesulfonamide **85b** (35.0 mg, 75.8 µmol) whereby the reaction was stirred for 19 h. Purification was performed by flash column chromatography (cyclohexane/EtOAc 10:1).

α_D^{589} = +139.9 deg·cm^2·g^{-1} ($CHCl_3$, c 1.5, 296 K). **SFC** Chiralpak IC (100 × 3.0 mm, 3 µm) at 35 ºC, flow 1.2 mL/min, isocratic CO_2/EtOH 70:30, ABRP pressure 150 bar, 230 nm, t_R (major) 1.16; t_R (minor) 1.62.

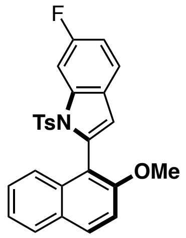
Catalysis with Complex (*R*,*R*)-**A1**

The title compound **86b** (white solid, 9.5 mg, 21.0 µmol, 77% yield, 7:93 *er*) was synthesized following general procedure **J** using *N*-(5-chloro-2-((2-methoxynaphthalen-1-yl)ethynyl)phenyl)-4-methylbenzenesulfonamide **85b** (12.4 mg, 26.8 µmol) whereby the reaction was stirred for 16 h. Purification was performed by preparative TLC (SiO_2, cyclohexane/EtOAc 8:2).

α_D^{589} = –118.6 deg·cm^2·g^{-1} ($CHCl_3$, c 0.1, 300 K). **SFC** Chiralpak IC (100 × 3.0 mm, 3 µm) at 35 ºC, flow 1.2 mL/min, isocratic CO_2/EtOH 70:30, ABRP pressure 150 bar, 230 nm, t_R (minor) 1.17; t_R (major) 1.64.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (dt, *J* = 1.9, 0.7 Hz, 1H), 7.98 (d, *J* = 9.1 Hz, 1H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.48 (dd, *J* = 8.3, 0.6 Hz, 1H), 7.34 (d, *J* = 9.1 Hz, 1H), 7.31 – 7.26 (m, 2H), 7.22 – 7.16 (m, 2H), 7.15 – 7.10 (m, 2H), 6.92 – 6.86 (m, 2H), 6.59 (d, *J* = 0.8 Hz, 1H), 3.85 (s, 3H), 2.26 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 156.8, 144.6, 137.7, 135.9, 135.4, 134.5, 131.6, 130.4, 129.3, 128.5, 128.4, 128.0, 127.2, 126.8, 124.7, 124.0, 123.4, 121.5, 115.4, 114.2, 112.8, 112.3, 56.3, 21.6. **HRMS** (ESI+) the exact mass calculated for $[C_{26}H_{20}ClNNaO_3S]^+$ is 484.0745 *m/z*; found $[M + Na]^+$ 484.0742 *m/z*. **M.p.** = 153–154 ºC.

6-Fluoro-2-(2-methoxynaphthalen-1-yl)-1-tosyl-1*H*-indole, 86c



Catalysis with Complex (*R*,*R*)-**40g**

The title compound **86c** (white solid, 27.6 mg, 62.0 µmol, 92% yield, 88:12 *er*) was synthesized following general procedure **I** using *N*-(5-fluoro-2-((2-methoxynaphthalen-1-yl)ethynyl)phenyl)-4-methylbenzenesulfonamide **85c** (30.0 mg, 67.0 µmol) whereby the reaction was stirred for 19 h. Purification was performed by flash column chromatography (cyclohexane/CH_2Cl_2 10:1).

α_D^{589} = +69.2 deg·cm^2·g^{-1} ($CHCl_3$, c 1.0, 296 K). **SFC** Chiralpak IC (100 × 3.0 mm, 3 µm) at 35 ºC, flow 1.2 mL/min, isocratic CO_2/MeOH 70:30, ABRP pressure 150 bar, 230 nm, t_R (major) 1.19; t_R (minor) 1.60.

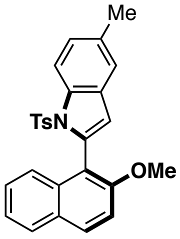
Catalysis with Complex (*R*,*R*)-**A1**

The title compound **86c** (white solid, 9.20 mg, 21.0 µmol, 76% yield, 6:94 *er*) was synthesized following general procedure **J** using *N*-(5-fluoro-2-((2-methoxynaphthalen-1-yl)ethynyl)phenyl)-4-methylbenzenesulfonamide **85c** (30.0 mg, 67.0 µmol) whereby the reaction was stirred for 16 h. Purification was performed by preparative TLC (SiO_2, cyclohexane/EtOAc 8:2).

α_D^{589} = –62.7 deg·cm^2·g^{-1} ($CHCl_3$, c 0.1, 300 K). **SFC** Chiralpak IC (100 × 3.0 mm, 3 µm) at 35 ºC, flow 1.2 mL/min, isocratic CO_2/MeOH 70:30, ABRP pressure 150 bar, 230 nm, t_R (minor) 1.19; t_R (major) 1.62.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (dd, *J* = 10.6, 2.0 Hz, 1H), 7.98 (d, *J* = 9.1 Hz, 1H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.49 (dd, *J* = 8.6, 5.5 Hz, 1H), 7.34 (d, *J* = 9.1 Hz, 1H), 7.31 – 7.26 (m, 1H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.18 – 7.10 (m, 2H), 7.06 (td, *J* = 8.9, 2.3 Hz, 1H), 6.90 (d, *J* = 8.2 Hz, 2H), 6.59 (s, 1H), 3.86 (s, 3H), 2.26 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 160.9 (d, *J* = 240.4 Hz), 156.8, 144.6, 137.5 (d, *J* = 12.6 Hz), 136.0, 135.0 (d, *J* = 4.2 Hz), 134.6, 131.5, 129.3, 128.5, 128.0, 127.1, 126.7, 126.2 (d, *J* = 1.5 Hz), 124.7, 123.4, 121.4 (d, *J* = 9.8 Hz), 114.4, 112.8, 112.3, 111.7 (d, *J* = 24.2 Hz), 102.7 (d, *J* = 29.0 Hz), 56.3, 21.6. **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) δ –116.6. **HRMS** (ESI+) the exact mass calculated for $[C_{26}H_{20}FNNaO_3S]^+$ is 468.1040 *m/z*; found $[M + Na]^+$ 468.1039 *m/z*. **M.p.** = 71–73 ºC.

2-(2-Methoxynaphthalen-1-yl)-5-methyl-1-tosyl-1*H*-indole, 86d



Catalysis with Complex (*R*,*R*)-**40g**

The title compound **86d** (white solid, 29.0 mg, 66.0 µmol, 97% yield, 95:5 *er*) was synthesized following general procedure **I** using *N*-(2-((2-methoxynaphthalen-1-yl)ethynyl)-4-methylphenyl)-4-methylbenzenesulfonamide **85d** (30.0 mg, 68.0 µmol) whereby the reaction was stirred for 19 h. Purification was performed by flash column chromatography (cyclohexane/CH_2Cl_2 10:1).

α_D^{589} = +83.1 deg·cm^2·g^{-1} ($CHCl_3$, c 1.0, 296 K). **SFC** Chiralpak IC (100 × 3.0 mm, 3 µm) at 35 ºC, flow 1.2 mL/min, isocratic CO_2/MeOH 70:30, ABRP pressure 150 bar, 230 nm, t_R (major) 1.79; t_R (minor) 2.53.

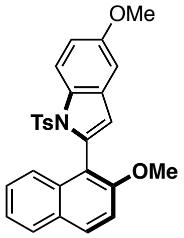
Catalysis with Complex (*R*,*R*)-**A1**

The title compound **86d** (white solid, 11.3 mg, 24.0 µmol, 98% yield, 9:91 *er*) was synthesized following general procedure **J** using *N*-(2-((2-methoxynaphthalen-1-yl)ethynyl)-4-methylphenyl)-4-methylbenzenesulfonamide **85d** (10.7 mg, 24.2 µmol) whereby the reaction was stirred for 16 h. Purification was performed by flash column chromatography (SiO_2, cyclohexane/EtOAc from 10:0 to 9:1).

α_D^{589} = –70.8 deg·cm^2·g^{-1} ($CHCl_3$, c 0.1, 300 K). **SFC** Chiralpak IC (100 × 3.0 mm, 3 µm) at 35 ºC, flow 1.2 mL/min, isocratic CO_2/MeOH 70:30, ABRP pressure 150 bar, 230 nm, t_R (minor) 1.81; t_R (major) 2.56.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.5 Hz, 1H), 7.97 (d, *J* = 9.1 Hz, 1H), 7.80 (d, *J* = 9.3 Hz, 1H), 7.38 – 7.32 (m, 2H), 7.30 – 7.26 (m, 1H), 7.25 – 7.18 (m, 4H), 7.16 – 7.10 (m, 1H), 6.93 – 6.86 (m, 2H), 6.57 – 6.55 (m, 1H), 3.85 (s, 3H), 2.47 (s, 3H), 2.25 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ156.6, 144.2, 136.3, 135.6, 134.7, 134.6, 133.0, 131.3, 130.2, 129.2, 128.5, 128.0, 127.1, 126.6, 125.8, 125.0, 123.4, 120.7, 115.0, 114.9, 112.8, 112.7, 56.3, 21.6, 21.4. **HRMS** (ESI+) calculated for $[C_{27}H_{23}NNaO_3S]^+$ 464.1291 *m/z*; found $[M + Na]^+$ 464.1285 *m/z*. **M.p.** = 85–87 ºC.

5-Methoxy-2-(2-methoxynaphthalen-1-yl)-1-tosyl-1*H*-indole, 86e



Catalysis with Complex (*R*,*R*)-**40g**

The title compound **86e** (white solid, 32.0 mg, 70.0 µmol, 97% yield, 93:7 *er*) was synthesized following general procedure **I** using *N*-(4-methoxy-2-((2-methoxynaphthalen-1-yl)ethynyl)phenyl)-4-methylbenzenesulfonamide **85e** (33.0 mg, 72.0 µmol) whereby the reaction was stirred for 19 h. Purification was performed by flash column chromatography (cyclohexane/CH_2Cl_2 10:1).

α_D^{589} = +63.7 deg·cm^2·g^{-1} ($CHCl_3$, c 1.0, 298 K). **SFC** Chiralpak IC (100 × 3.0 mm, 3 µm) at 35 ºC, flow 1.2 mL/min, isocratic CO_2/EtOH 70:30, ABRP pressure 150 bar, 230 nm, t_R (major) 1.58; t_R (minor) 2.30.

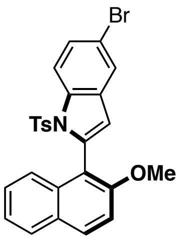
Catalysis with Complex (*R*,*R*)-**A1**

The title compound **86e** (white solid, 16.2 mg, 35.4 µmol, 71% yield, 8:92 *er*) was synthesized following general procedure **J** using *N*-(4-methoxy-2-((2-methoxynaphthalen-1-yl)ethynyl)phenyl)-4-methylbenzenesulfonamide **85e** (22.9 mg, 50.0 µmol) whereby the reaction was stirred for 16 h. Purification was performed by preparative TLC (SiO_2, cyclohexane/EtOAc 9:1).

α_D^{589} = –73.3 deg·cm^2·g^{-1} ($CHCl_3$, c 0.1, 300 K). **SFC** Chiralpak IC (100 × 3.0 mm, 3 µm) at 35 ºC, flow 1.2 mL/min, isocratic CO_2/EtOH 70:30, ABRP pressure 150 bar, 230 nm, t_R (minor) 1.60; t_R (major) 2.35.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 9.0 Hz, 1H), 7.97 (d, *J* = 9.1 Hz, 1H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.34 (d, *J* = 9.1 Hz, 1H), 7.31 – 7.26 (m, 1H), 7.24 – 7.19 (m, 3H), 7.14 (ddd, *J* = 8.4, 6.6, 1.3 Hz, 1H), 7.04 – 6.97 (m, 2H), 6.89 (d, *J* = 7.9 Hz, 2H), 6.57 (s, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 2.25 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 156.6, 156.5, 144.2, 136.2, 135.4, 134.6, 132.0, 131.3, 130.9, 129.2, 128.5, 128.0, 127.1, 126.7, 124.9, 123.4, 116.2, 114.9, 113.4, 112.9, 112.8, 103.2, 56.4, 55.9, 21.6. **HRMS** (ESI+) the exact mass calculated for $[C_{27}H_{23}NNaO_4S]^+$ is 480.1240 *m/z*; found $[M + Na]^+$ 480.1228 *m/z*. **M.p.** = 88–90 ºC.

5-Bromo-2-(2-methoxynaphthalen-1-yl)-1-tosyl-1*H*-indole, 86f



Catalysis with Complex (*R*,*R*)-**40g**

The title compound **86f** (white solid, 34.0 mg, 67.0 µmol, 93% yield, 88:12 *er*) was synthesized following general procedure **I** using *N*-(4-bromo-2-((2-methoxynaphthalen-1-yl)ethynyl)phenyl)-4-methylbenzenesulfonamide **85f** (36.0 mg, 72.0 µmol) whereby the reaction was stirred for 19 h. Purification was performed by flash column chromatography (cyclohexane/CH_2Cl_2 10:1).

$\boldsymbol{\alpha_D}^{589}$ = +62.6 deg·cm^2·g^{-1} ($CHCl_3$, c 1.0, 296 K). **SFC** Chiralpak IC (100 × 3.0 mm, 3 µm) at 35 ºC, flow 1.2 mL/min, isocratic CO_2/MeOH 70:30, ABRP pressure 150 bar, 230 nm, t_R (major) 1.90; t_R (minor) 2.66.

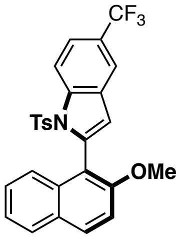
Catalysis with Complex (*R*,*R*)-**A1**

The title compound **86f** (white solid, 19.0 mg, 37.5 µmol, 75% yield, 12:88 *er*) was synthesized following general procedure **J** using *N*-(4-bromo-2-((2-methoxynaphthalen-1-yl)ethynyl)phenyl)-4-methylbenzenesulfonamide **85f** (25.3 mg, 50.0 µmol) whereby the reaction was stirred for 16 h. Purification was performed by preparative TLC (SiO_2, cyclohexane/EtOAc 9:1).

$\boldsymbol{\alpha_D}^{589}$ = –62.3 deg·cm^2·g^{-1} ($CHCl_3$, c 0.1, 300 K). **SFC** Chiralpak IC (100 × 3.0 mm, 3 µm) at 35 ºC, flow 1.2 mL/min, isocratic CO_2/MeOH 70:30, ABRP pressure 150 bar, 230 nm, t_R (minor) 1.91; t_R (major) 2.70.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.9 Hz, 1H), 7.99 (d, *J* = 9.1 Hz, 1H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.71 (d, *J* = 2.0 Hz, 1H), 7.47 (dd, *J* = 8.9, 2.0 Hz, 1H), 7.34 (d, *J* = 9.1 Hz, 1H), 7.31 – 7.27 (m, 1H), 7.22 – 7.16 (m, 2H), 7.13 (dd, *J* = 4.5, 1.0 Hz, 2H), 6.89 (d, *J* = 8.0 Hz, 2H), 6.57 (d, *J* = 0.6 Hz, 1H), 3.85 (s, 3H), 2.26 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 156.7, 144.6, 136.11, 136.08, 135.9, 134.5, 131.6, 129.3, 128.5, 128.0, 127.2, 127.1, 126.8, 124.6, 123.4, 116.8, 116.7, 114.1, 112.7, 111.9, 56.3, 21.6. **HRMS** (ESI+) the exact mass calculated for $[C_{26}H_{20}BrNNaO_3S]^+$ is 528.0239 *m/z*; found $[M + Na]^+$ 528.0226 *m/z*. **M.p.** = 80–82 ºC.

2-(2-Methoxynaphthalen-1-yl)-1-tosyl-5-(trifluoromethyl)-1*H*-indole, 86g



Catalysis with Complex (*R*,*R*)-**40g**

The title compound **86g** (colorless gum, 24.8 mg, 50.0 µmol, 89% yield, 87:13 *er*) was synthesized following general procedure **I** using *N*-(2-((2-methoxynaphthalen-1-yl)ethynyl)-4-(trifluoromethyl)phenyl)-4-methylbenzenesulfonamide **85g** (28.0 mg, 57.0 µmol) whereby the reaction was stirred for 72 h. Purification was performed by flash column chromatography (cyclohexane/CH_2Cl_2 10:1).

α_D^{589} = +64.4 deg·cm^2·g^{-1} ($CHCl_3$, c 1.0, 296 K). **SFC** Chiralpak IC (100 × 3.0 mm, 3 µm) at 35 ºC, flow 1.2 mL/min, isocratic CO_2/MeOH 85:15, ABRP pressure 150 bar, 230 nm, t_R (major) 1.35; t_R (minor) 2.06.

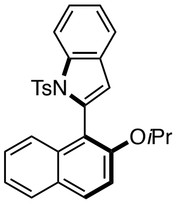
Catalysis with Complex (*R*,*R*)-**A1**

The title compound **86g** (colorless gum, 7.90 mg, 16.0 µmol, 87% yield, 7:93 *er*) was synthesized following general procedure **J** using *N*-(2-((2-methoxynaphthalen-1-yl)ethynyl)-4-(trifluoromethyl)phenyl)-4-methylbenzenesulfonamide **85g** (9.10 mg, 18.0 µmol) whereby the reaction was stirred for 16 h. Purification was performed by preparative TLC (SiO_2, cyclohexane/EtOAc 9:1).

α_D^{589} = –47.6 deg·cm^2·g^{-1} ($CHCl_3$, c 0.1, 300 K). **SFC** Chiralpak IC (100 × 3.0 mm, 3 µm) at 35 ºC, flow 1.2 mL/min, isocratic CO_2/MeOH 85:15, ABRP pressure 150 bar, 230 nm, t_R (minor) 1.35; t_R (major) 2.08.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 – 8.42 (m, 1H), 8.00 (d, *J* = 9.1 Hz, 1H), 7.90 – 7.86 (m, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.63 (dd, *J* = 9.0, 1.6 Hz, 1H), 7.35 (d, *J* = 9.1 Hz, 1H), 7.29 (ddd, *J* = 8.1, 5.6, 2.3 Hz, 1H), 7.22 – 7.17 (m, 2H), 7.16 – 7.08 (m, 2H), 6.92 – 6.87 (m, 2H), 6.70 (d, *J* = 0.7 Hz, 1H), 3.85 (s, 3H), 2.26 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 156.7, 144.8 (d, *J* = 1.7 Hz), 138.8, 136.7, 135.8, 134.5, 131.8, 129.5, 129.4, 128.5, 128.0, 127.2, 126.9, 125.8 (q, *J* = 31.9 Hz), 124.6, 123.5, 121.1 (q, *J* = 3.6 Hz), 118.3 (t, *J* = 4.2 Hz), 115.5, 113.9, 112.7, 112.5, 56.3, 21.6. **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) δ –60.9. **HRMS** (ESI+) calculated for $[C_{27}H_{20}F_3NNaO_3S]^+$ 518.1008 *m/z*; found $[M + Na]^+$ 518.1011 *m/z*.

2-(2-Isopropoxynaphthalen-1-yl)-1-tosyl-1*H*-indole, 86h



Catalysis with Complex (*R*,*R*)-**40g**

The title compound **86h** (white solid, 35.0 mg, 76.8 μmol, >99% yield, 92:8 *er*) was synthesized following general procedure **I** using *N*-(2-((2-isopropoxynaphthalen-1-yl)ethynyl)phenyl)-4-methylbenzenesulfonamide **85h** (35.0 mg, 76.8 μmol) whereby the reaction was stirred for 24 h. Purification was performed by flash column chromatography (cyclohexane/EtOAc 20:1).

α_D^{589} = +30.5 deg·cm^2·g^{-1} (CHCl$_3$, c 0.75, 296 K). **SFC** Chiralpak IC (100 × 3.0 mm, 3 μm) at 35 ºC, flow 1.2 mL/min, isocratic CO$_2$/EtOH 85:15, ABRP pressure 150 bar, 230 nm, t$_R$ (major) 2.59 min; t$_R$ (minor) 3.73 min.

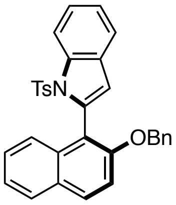
Catalysis with Complex (*R*,*R*)-**A1**

The title compound **86h** (white solid, 14.2 mg, 31.2 μmol, 62% yield, 9:91 *er*) was synthesized following general procedure **J** using *N*-(2-((2-isopropoxynaphthalen-1-yl)ethynyl)phenyl)-4-methylbenzenesulfonamide **85h** (22.8 mg, 50.0 μmol) whereby the reaction was stirred for 16 h. Purification was performed by preparative TLC (SiO$_2$, cyclohexane/EtOAc 9:1).

α_D^{589} = –25.3 deg·cm^2·g^{-1} (CHCl$_3$, c 0.1, 300 K). **SFC** Chiralpak IC (100 × 3.0 mm, 3 μm) at 35 ºC, flow 1.2 mL/min, isocratic CO$_2$/EtOH 85:15, ABRP pressure 150 bar, 230 nm, t$_R$ (minor) 2.59 min; t$_R$ (major) 3.69 min.

^{1}H NMR (500 MHz, CDCl$_3$) δ 8.25 (dd, *J* = 8.4, 0.9 Hz, 1H), 7.94 (d, *J* = 9.1 Hz, 1H), 7.81 (d, *J* = 7.4 Hz, 1H), 7.58 (d, *J* = 7.7 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.39 – 7.28 (m, 2H), 7.31 – 7.26 (m, 3H), 7.22 – 7.15 (m, 1H), 6.95 (d, *J* = 7.8 Hz, 2H), 6.61 (d, *J* = 0.8 Hz, 1H), 4.70 (hept, *J* = 6.1 Hz, 1H), 2.27 (s, 3H), 1.33 (d, *J* = 6.0 Hz, 3H), 1.24 (d, *J* = 6.0 Hz, 3H). **^{13}C{^{1}H} NMR** (126 MHz, CDCl$_3$) δ 155.2, 144.2, 137.0, 136.3, 135.5, 134.9, 130.9, 130.1, 129.2, 128.6, 127.9, 127.4, 126.6, 125.1, 124.2, 123.5, 123.3, 120.8, 116.6, 115.6, 115.1, 112.6, 71.7, 22.6, 22.5, 21.6. **HRMS** (ESI+) the exact mass calculated for [$C_{28}H_{25}NNaO_3S$]$^+$ is 478.1447 *m/z*; found [M + Na]$^+$ 478.1424 *m/z*. **M.p.** = 181–183 ºC.

2-(2-(Benzyloxy)naphthalen-1-yl)-1-tosyl-1*H*-indole, 86i



Catalysis with Complex (*R*,*R*)-**40g**

The title compound **86i** (white solid, 30.0 mg, 60.0 µmol, 92% yield, 93:7 *er*) was synthesized following general procedure **I** using *N*-(2-((2-(benzyloxy)naphthalen-1-yl)ethynyl)phenyl)-4-methylbenzenesulfonamide **85i** (21.3 mg, 42.3 µmol) whereby the reaction was stirred for 16 h. Purification was performed by preparative TLC (cyclohexane/EtOAc 9:1).

α_D^{589} = +19.5 deg·cm^2·g^{-1} (CHCl$_3$, c 1.0, 296 K). **SFC** Chiralpak IC-3 (100 × 3.0 mm, 3 µm) at 35 ºC, flow 1.2 mL/min, isocratic CO$_2$/EtOH 70:30, ABRP pressure 150 bar, 230 nm, t$_R$ (major) 1.64 min; t$_R$ (minor) 2.29 min.

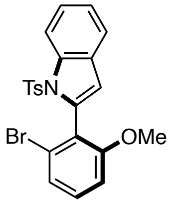
Catalysis with Complex (*R*,*R*)-**A1**

The title compound **86i** (white solid, 16.6 mg, 33.0 µmol, 78% yield, 22:78 *er*) was synthesized following general procedure **J** using *N*-(2-((2-(benzyloxy)naphthalen-1-yl)ethynyl)phenyl)-4-methylbenzenesulfonamide **85i** (21.3 mg, 42.3 µmol) whereby the reaction was stirred for 16 h. Purification was performed by preparative TLC (SiO$_2$, cyclohexane/EtOAc 9:1).

α_D^{589} = –17.7 deg·cm^2·g^{-1} (CHCl$_3$, c 0.1, 299 K). **SFC** Chiralpak IC-3 (100 × 3.0 mm, 3 µm) at 35 ºC, flow 1.2 mL/min, isocratic CO$_2$/EtOH 70:30, ABRP pressure 150 bar, 230 nm, t$_R$ (minor) 1.62 min; t$_R$ (major) 2.25 min.

^{1}H NMR (500 MHz, CDCl$_3$) δ 8.32 (dd, *J* = 8.4, 0.9 Hz, 1H), 7.94 (d, *J* = 9.0 Hz, 1H), 7.81 (t, *J* = 1.1 Hz, 1H), 7.58 (dt, *J* = 7.7, 1.1 Hz, 1H), 7.41 – 7.35 (m, 2H), 7.33 – 7.22 (m, 10H), 7.18 (ddd, *J* = 8.1, 6.8, 1.3 Hz, 1H), 6.85 – 6.73 (m, 2H), 6.64 (d, *J* = 0.8 Hz, 1H), 5.21 (d, *J* = 12.4 Hz, 1H), 5.17 (d, *J* = 12.3 Hz, 1H), 2.19 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, CDCl$_3$) δ 155.7, 144.3, 137.4, 136.2, 134.8, 134.7, 131.3, 130.1, 129.2, 128.8, 128.5, 128.0, 127.7, 127.2, 127.0, 126.7, 125.2, 124.4, 123.7, 123.4, 120.9, 116.0, 115.3, 114.5, 113.1, 71.2, 21.5. **HRMS** (ESI+) the exact mass calculated for [$C_{32}H_{25}NNaO_3S$]$^+$ is 526.1443 *m/z*; found [M + Na]$^+$ 526.1447 *m/z*. **M.p.** = 165–167 ºC.

2-(2-Bromo-6-methoxyphenyl)-1-tosyl-1*H*-indole, 86j



Catalysis with Complex (*R*,*R*)-**40g**

The title compound **86j** (white solid, 34.0 mg, 55.4 μmol, 77% yield, 88:12 *er*) was synthesized following general procedure I using *N*-(2-((2-bromo-6-methoxyphenyl)ethynyl)phenyl)-4-methylbenzenesulfonamide **85j** (44.0 mg, 72.0 μmol) whereby the reaction was stirred for 72 h. Purification was performed by flash column chromatography (cyclohexane/EtOAc 9:1).

α_D^{589} = +39.6 deg·cm^2·g^{-1} (CHCl$_3$, c 1.3, 298K) **SFC** Chiralpak IC (100 x 3 mm, 3 μm) at 35ºC, flow 1.2 mL/min, isocratic CO$_2$/EtOH 90:10, ABRP pressure 150 bar, 210 nm, t$_R$ (major) 4.63 min; t$_R$ (minor) 5.13 min.

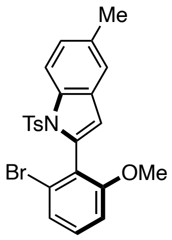
Catalysis with Complex (*R*,*R*)-**A1**

The title compound **86j** (white solid, 22.7 mg, 49.7 μmol, >99% yield, 9:91 *er*) was synthesized following general procedure J using *N*-(2-((2-bromo-6-methoxyphenyl)ethynyl)phenyl)-4-methylbenzenesulfonamide **85j** (22.8 mg, 50.0 μmol) whereby the reaction was stirred for 16 h. Purification was performed by preparative TLC (SiO$_2$, cyclohexane/EtOAc 9:1).

α_D^{589} = –45.6 deg·cm^2·g^{-1} (CHCl$_3$, c 0.1, 300 K). **SFC** Chiralpak IC (100 x 3 mm, 3 μm) at 35ºC, flow 1.2 mL/min, isocratic CO$_2$/EtOH 90:10, ABRP pressure 150 bar, 210 nm, t$_R$ (minor) 4.66 min; t$_R$ (major) 5.16 min.

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.17 (dq, *J* = 8.4, 0.9 Hz, 1H), 7.64 – 7.56 (m, 2H), 7.55 (ddd, *J* = 7.7, 1.4, 0.7 Hz, 1H), 7.38 – 7.29 (m, 1H), 7.30 – 7.23 (m, 3H), 7.15 (dd, *J* = 8.6, 0.7 Hz, 2H), 6.91 (dd, *J* = 6.4, 2.9 Hz, 1H), 6.60 (d, *J* = 0.8 Hz, 1H), 3.71 (s, 3H), 2.33 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, CDCl$_3$) δ 160.1, 144.6, 136.6, 136.4, 135.3, 131.2, 129.6, 129.5, 127.4, 126.5, 124.6, 123.3, 123.2, 121.2, 114.9, 112.4, 109.6, 56.0, 21.7. **HRMS** (ESI+) exact mass calculated for [C$_{22}$H$_{18}$BrNaNO$_3$S]$^+$ 478.0083 *m/z*; found [M + Na]$^+$ 478.0072 *m/z*. **M.p.** = 129–131 ºC.

2-(2-Bromo-6-methoxyphenyl)-5-methyl-1-tosyl-1*H*-indole, 86k



Catalysis with Complex (*R*,*R*)-**40g**

The title compound **86k** (white solid, 48.0 mg, 100 µmol, 96% yield, 97:3 *er*) was synthesized following general procedure **I** using *N*-(2-((2-bromo-6-methoxyphenyl)ethynyl)-4-methylphenyl)-4-methylbenzenesulfonamide **85k** (50.0 mg, 110 µmol) whereby the reaction was stirred for 45 h. Purification was performed by flash column chromatography (6:1 to 1:1 cyclohexane/CH_2Cl_2).

α_D^{589} = +70.1 deg·cm^2·g^{-1} ($CHCl_3$, c 1.925, 298K) **SFC** Chiralpak IC (100 x 3.0 mm, 3 µm) at 35ºC, flow 1.2 mL/min, isocratic CO_2/EtOH 85:15, ABRP pressure 150 bar, 230 nm, t_R (major) 3.16; t_R (minor) 3.52.

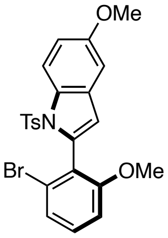
Catalysis with Complex (*R*,*R*)-**A1**

The title compound **86k** (white solid, 8.70 mg, 18.0 µmol, 64% yield, 12:88 *er*) was synthesized following general procedure J using *N*-(2-((2-bromo-6-methoxyphenyl)ethynyl)-4-methylphenyl)-4-methylbenzenesulfonamide **85k** (13.7 mg, 29.1 µmol) whereby the reaction was stirred for 16 h. Purification was performed by preparative TLC (SiO_2, cyclohexane/EtOAc 9:1).

α_D^{589} = –34.0 deg·cm^2·g^{-1} ($CHCl_3$, c 0,095, 300K). **SFC** Chiralpak IC (100 x 3.0 mm, 3 µm) at 35ºC, flow 1.2 mL/min, isocratic CO_2/EtOH 85:15, ABRP pressure 150 bar, 230 nm, t_R (minor) 3.07; t_R (major) 3.42.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.6 Hz, 1H), 7.61 – 7.55 (m, 2H), 7.34 (dt, *J* = 1.7, 0.8 Hz, 1H), 7.27 (dd, *J* = 6.9, 4.2 Hz, 2H), 7.15 (ddt, *J* = 7.9, 6.0, 0.7 Hz, 3H), 6.90 (dd, *J* = 6.6, 2.7 Hz, 1H), 6.52 (d, *J* = 0.8 Hz, 1H), 3.71 (s, 3H), 2.43 (s, 3H), 2.32 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 160.1, 144.4, 136.4, 135.3, 134.8, 132.9, 131.2, 129.9, 129.5, 127.3, 126.5, 126.0, 124.6, 123.3, 121.0, 114.5, 112.3, 109.6, 56.0, 21.7, 21.4. **HRMS** (ESI+) the exact mass calculated for $[C_{23}H_{21}BrNO_3S]^+$ is 470.0420 *m/z*; found $[M + H]^+$ 470.0419 *m/z*. **M.p.**= 154–156 ºC.

2-(2-Bromo-6-methoxyphenyl)-5-methoxy-1-tosyl-1*H*-indole, 86l

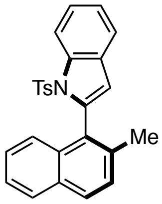


Catalysis with Complex (*R*,*R*)-**40g**

The title compound **86l** (white solid, 38.0 mg, 78.0 µmol, 95% yield, 94:6 *er*) was synthesized following general procedure **I** using *N*-(2-((2-bromo-6-methoxyphenyl)ethynyl)-4-methoxyphenyl)-4-methylbenzenesulfonamide **85l** (40.0 mg, 82.0 µmol) whereby the reaction was stirred for 16 h. Purification was performed by flash column chromatography (cyclohexane/EtOAc 9:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 9.1 Hz, 1H), 7.58 – 7.52 (m, 2H), 7.35 – 7.22 (m, 2H), 7.13 (d, *J* = 8.1 Hz, 2H), 6.99 (d, *J* = 2.6 Hz, 1H), 6.94 (dd, *J* = 9.1, 2.6 Hz, 1H), 6.90 (dd, *J* = 6.5, 2.8 Hz, 1H), 6.52 (d, *J* = 0.8 Hz, 1H), 3.83 (s, 3H), 3.71 (s, 3H), 2.32 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 160.1, 156.4, 144.5, 136.3, 135.9, 131.3, 131.2, 130.5,z 129.5, 127.3, 126.4, 124.6, 123.1, 115.8, 113.8, 112.5, 109.6, 103.4, 56.0, 55.8, 21.7. **HRMS** (ESI+) the exact mass calculated for $[C_{23}H_{20}BrNaSNO_4]^+$ is 508.0189 *m/z*; found $[M + Na]^+$ 508.0182 *m/z*. **M.p.** = 159–160 °C. **α_D^{589}** = +49.0 deg·cm^2·g^{-1} ($CHCl_3$, c 0.7, 298K). **SFC** Chiralpak IC (100 x 3.0 mm, 3 µm) at 35ºC, flow 1.2 mL/min, isocratic CO_2/EtOH 75:25, ABRP pressure 150 bar, 230 nm, t_R (major) 1.76 min; t_R (minor) 2.07 min.

2-(2-Methylnaphthalen-1-yl)-1-tosyl-1*H*-indole, 86m



Catalysis with Complex (*R*,*R*)-**40g**

The title compound **86m** (white solid, 27.0 mg, 66.0 µmol, 54% yield, 59:41 *er*) was synthesized following general procedure **I** using 4-methyl-*N*-(2-((2-methylnaphthalen-1-yl)ethynyl)phenyl)benzenesulfonamide **85m** (50.0 mg, 122 µmol) whereby the reaction was stirred for 96 h. Purification was performed by flash column chromatography (cyclohexane/EtOAc 20:1).

SFC Chiralpak IC (100 × 3.0 mm, 3 µm) at 35 ºC, flow 1.2 mL/min, isocratic CO_2/EtOH 70:30, ABRP pressure 150 bar, 230 nm, t_R (major) 1.07; t_R (minor) 1.19.

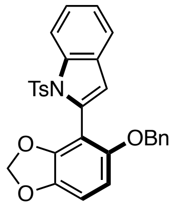
Catalysis with Complex (*R*,*R*)-**A1**

The title compound **86m** (white solid, 19.5 mg, 47.4 µmol, 95% yield, 49:51 *er*) was synthesized following general procedure **J** using 4-methyl-*N*-(2-((2-methylnaphthalen-1-yl)ethynyl)phenyl)benzenesulfonamide **85m** (20.6 mg, 50.0 µmol) whereby the reaction was stirred for 48 h. Purification was performed by preparative TLC (SiO_2, cyclohexane/EtOAc 9:1).

SFC Chiralpak IC (100 × 3.0 mm, 3 µm) at 35 ºC, flow 1.2 mL/min, isocratic CO_2/EtOH 70:30, ABRP pressure 150 bar, 230 nm, t_R (minor) 1.07; t_R (major) 1.20.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (dd, *J* = 8.4, 0.9 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.80 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.60 (dt, *J* = 7.7, 1.1 Hz, 1H), 7.47 – 7.40 (m, 2H), 7.38 – 7.29 (m, 2H), 7.17 – 7.11 (m, 2H), 7.08 – 6.98 (m, 2H), 6.87 – 6.80 (m, 2H), 6.58 (d, *J* = 0.8 Hz, 1H), 2.28 (s, 3H), 2.25 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 144.6, 138.2, 137.3, 137.1, 136.1, 134.0, 131.6, 129.7, 129.3, 129.3, 128.3, 127.8, 127.7, 127.3, 125.9, 125.9, 124.7, 124.6, 123.6, 120.9, 115.4, 112.3, 21.6, 21.3. **HRMS** (ESI+) the exact mass calculated for $[C_{26}H_{21}NNaO_2S]^+$ is 434.1185 *m/z*; was found $[M + Na]^+$ 434.1188 *m/z*. **M.p.** = 168–170 ºC.

2-(5-(Benzyloxy)benzo[*d*][1,3]dioxol-4-yl)-1-tosyl-1*H*-indole, 86n

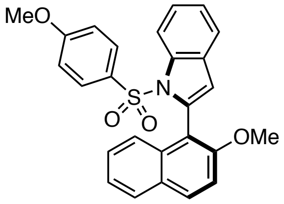


Catalysis with Complex (*R*,*R*)-**40g**

The title compound **86n** (white solid, 20.0 mg, 40.0 μmol, 61% yield, 51:49 *er*) was synthesized following general procedure **I** using *N*-(2-((5-(benzyloxy)benzo[*d*][1,3]dioxol-4-yl)ethynyl)phenyl)-4-methylbenzenesulfonamide (33.0 mg, 66.0 μmol) whereby the reaction was stirred for 96 h. Purification was performed by flash column chromatography (cyclohexane/EtOAc 20:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.3 Hz, 1H), 7.49 (d, *J* = 7.7 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.32 (ddd, *J* = 8.5, 7.3, 1.3 Hz, 1H), 7.24 (d, *J* = 5.9 Hz, 6H), 6.94 (d, *J* = 8.1 Hz, 2H), 6.81 (d, *J* = 8.5 Hz, 1H), 6.70 (d, *J* = 0.8 Hz, 1H), 6.44 (d, *J* = 8.5 Hz, 1H), 5.94 (d, *J* = 1.5 Hz, 1H), 5.89 (d, *J* = 1.5 Hz, 1H), 5.01 (q, *J* = 9.0 Hz, 2H), 2.19 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 152.9, 147.8, 144.4, 141.7, 137.6, 137.3, 135.7, 131.3, 130.3, 129.3, 128.5, 127.6, 126.9, 126.8, 124.7, 123.7, 121.0, 115.7, 114.0, 108.3, 106.2, 103.9, 101.8, 71.1, 21.6. **HRMS (ESI+)** the exact mass calculated for $[C_{29}H_{23}NNaO_5S]^+$ is 520.1189 *m/z*; was found $[M + Na]^+$ 520.1178 *m/z*. **M.p.** = 170–172 ºC. **SFC** Chiralpak IC (100 × 3.0 mm, 3 μm) at 35 ºC, flow 1.2 mL/min, isocratic CO_2/EtOH 75:25, ABRP pressure 150 bar, 230 nm, t_R (major) 1.84; t_R (minor) 3.10.

2-(2-Methoxynaphthalen-1-yl)-1-((4-methoxyphenyl)sulfonyl)-1*H*-indole, 86o



Catalysis with Complex (*R*,*R*)-**40g**

The title compound **86o** (white solid, 34.0 mg, 76.7 μmol, >99% yield, 94:6 *er*) was synthesized following general procedure **I** using 4-methoxy-*N*-(2-((2-methoxynaphthalen-1-yl)ethynyl)phenyl)benzenesulfonamide **85o** (34.0 mg, 76.7 μmol) whereby the reaction was stirred for 19 h. Purification was performed by flash column chromatography (cyclohexane/EtOAc 5:1).

α_D^{589} = +114.1 deg·cm^2·g^{-1} ($CHCl_3$, c 1.0, 296 K). **SFC** Chiralpak IC (100 × 3.0 mm, 3 μm) at 35 ºC, flow 1.2 mL/min, isocratic CO_2/EtOH 70:30, ABRP pressure 150 bar, 230 nm, t_R (major) 1.43; t_R (minor) 2.23.

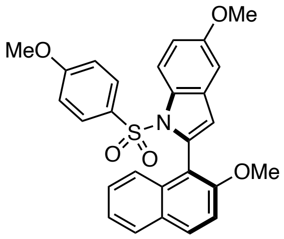
Catalysis with Complex (*R*,*R*)-**A1**

The title compound **86o** (white solid, 22.1 mg, 46.0 μmol, >99% yield, 6:94 *er*) was synthesized following general procedure **J** using 4-methoxy-*N*-(2-((2-methoxynaphthalen-1-yl)ethynyl)phenyl)benzenesulfonamide **85o** (22.2 mg, 50.0 μmol) whereby the reaction was stirred for 16 h. Purification was performed by flash column chromatography (SiO_2, cyclohexane/EtOAc from 10:0 to 9:1).

α_D^{589} = –109.3 deg·cm^2·g^{-1} ($CHCl_3$, c 0.1, 301 K). **SFC** Chiralpak IC (100 × 3.0 mm, 3 μm) at 35 ºC, flow 1.2 mL/min, isocratic CO_2/EtOH 70:30, ABRP pressure 150 bar, 230 nm, t_R (minor) 1.41; t_R (major) 2.21

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (dd, *J* = 8.4, 0.9 Hz, 1H), 7.97 (d, *J* = 9.0 Hz, 1H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.57 (d, *J* = 7.9 Hz, 1H), 7.37 (ddd, *J* = 8.5, 7.3, 1.4 Hz, 1H), 7.34 (d, *J* = 9.1 Hz, 1H), 7.31 – 7.23 (m, 4H), 7.19 (dd, *J* = 8.2, 0.8 Hz, 1H), 7.12 (ddd, *J* = 8.4, 6.6, 1.3 Hz, 1H), 6.62 (d, *J* = 0.8 Hz, 1H), 6.55 – 6.50 (m, 2H), 3.86 (s, 3H), 3.71 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 163.5, 156.8, 137.4, 134.7, 134.7, 131.3, 131.0, 129.3, 128.6, 128.0, 126.7, 125.0, 124.4, 123.4, 123.3, 120.9, 115.3, 115.0, 113.8, 113.0, 112.7, 56.4, 55.6. **HRMS** (ESI+) the exact mass calculated for $[C_{26}H_{21}NNaO_4S]^+$ is 466.1083 *m/z*; was found $[M + Na]^+$ 466.1065 *m/z*. **M.p.** = 161–163 ºC.

5-Methoxy-2-(2-methoxynaphthalen-1-yl)-1-((4-methoxyphenyl)sulfonyl)-1*H*-indole, 86p



Catalysis with Complex (*R*,*R*)-**40g**

The title compound **86p** (white solid, 30.0 mg, 63 µmol, >99% yield, 94:6 *er*) synthesized following general procedure **I** using *N*-(4-bromo-2-((2-methoxynaphthalen-1-yl)ethynyl)phenyl)-4-methoxybenzenesulfonamide **85p** (30 mg, 63 µmol) whereby the reaction was stirred for 20h at -20 ºC. Purification was performed by flash column chromatography (cyclohexane/EtOAc 5:1).

α_D^{589} = +101.7 deg·cm^2·g^{-1} (CHCl$_3$, c 1.0, 296 K). **SFC** Chiralpak IC (100 × 3.0 mm, 3 µm) at 35 ºC, flow 1.2 mL/min, isocratic CO$_2$/EtOH 70:30, ABRP pressure 150 bar, 230 nm, t$_R$ (major) 1.73; t$_R$ (minor) 2.70.

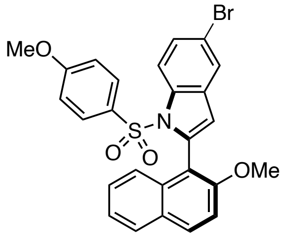
Catalysis with Complex (*R*,*R*)-**A1**

The title compound **86p** (white solid, 7.90 mg, 17.0 µmol, 95% yield, 9:91 *er*) synthesized following general procedure **J** using *N*-(4-bromo-2-((2-methoxynaphthalen-1-yl)ethynyl)phenyl)-4-methoxybenzenesulfonamide **85p** (8.30 mg, 18.0 µmol) whereby the reaction was stirred for 16 h. Purification was performed by flash column chromatography (SiO$_2$, cyclohexane/EtOAc from 10:0 to 9:1).

α_D^{589} = –84.9 deg·cm^2·g^{-1} (CHCl$_3$, c 0.1, 301 K). **SFC** Chiralpak IC (100 × 3.0 mm, 3 µm) at 35 ºC, flow 1.2 mL/min, isocratic CO$_2$/EtOH 70:30, ABRP pressure 150 bar, 230 nm, t$_R$ (minor) 1.71; t$_R$ (major) 2.74.

^{1}H NMR (500 MHz, CDCl$_3$) δ 8.24 (dt, *J* = 9.1, 0.7 Hz, 1H), 7.97 (d, *J* = 8.8 Hz, 1H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.35 (d, *J* = 9.1 Hz, 1H), 7.30 – 7.26 (m, 1H), 7.25 – 7.20 (m, 3H), 7.14 (ddd, *J* = 8.4, 6.7, 1.3 Hz, 1H), 7.03 (d, *J* = 2.5 Hz, 1H), 7.00 (dd, *J* = 9.1, 2.6 Hz, 1H), 6.57 (d, *J* = 0.8 Hz, 1H), 6.55 – 6.51 (m, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 3.72 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, CDCl$_3$) δ 163.4, 156.7, 156.5, 135.4, 134.6, 132.1, 131.3, 130.9, 130.8, 129.3, 128.6, 128.0, 126.7, 125.0, 123.4, 116.2, 115.0, 113.8, 113.4, 113.0, 112.8, 103.2, 56.4, 55.9, 55.6. **HRMS** (ESI+) the exact mass calculated for [$C_{27}H_{24}NO_5S$]$^+$ is 474.1370 *m/z*; was found [M + H]$^+$ 474.1374 *m/z*. **M.p.** = 154–156 ºC.

5-Bromo-2-(2-methoxynaphthalen-1-yl)-1-((4-methoxyphenyl)sulfonyl)-1*H*-indole, 86q



Catalysis with Complex (*R*,*R*)-**40g**

The title compound **86q** (white solid, 30.0 mg, 57.0 μmol, 97% yield, 89:11 *er*) synthesized following general procedure **I** using *N*-(4-bromo-2-((2-methoxynaphthalen-1-yl)ethynyl)phenyl)-4-methoxybenzenesulfonamide **85q** (31.0 mg, 59.0 μmol) whereby the reaction was stirred for 20 h at -12 ºC. Purification was performed by flash column chromatography (cyclohexane/EtOAc 5:1).

α_D^{589} = +89.4 deg·cm^2·g^{-1} (CHCl$_3$, c 0.8, 296 K). **SFC** Chiralpak IC (100 × 3.0 mm, 3 μm) at 35 ºC, flow 1.2 mL/min, isocratic CO$_2$/EtOH 70:30, ABRP pressure 150 bar, 230 nm, t$_R$ (major) 1.50; t$_R$ (minor) 2.40.

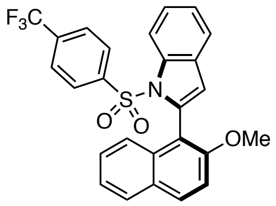
Catalysis with Complex (*R*,*R*)-**A1**

The title compound **86q** (white solid, 9.00 mg, 17.0 μmol, 77% yield, 12:88 *er*) synthesized following general procedure **J** using *N*-(4-bromo-2-((2-methoxynaphthalen-1-yl)ethynyl)phenyl)-4-methoxybenzenesulfonamide **85q** (11.7 mg, 22.4 μmol) whereby the reaction was stirred for 16h. Purification was performed by preparative TLC (SiO$_2$, cyclohexane/EtOAc 9:1).

α_D^{589} = –84.8 deg·cm^2·g^{-1} (CHCl$_3$, c 0.1, 301 K). **SFC** Chiralpak IC (100 × 3.0 mm, 3 μm) at 35 ºC, flow 1.2 mL/min, isocratic CO$_2$/EtOH 70:30, ABRP pressure 150 bar, 230 nm, t$_R$ (minor) 1.50; t$_R$ (major) 2.46.

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.23 (dt, *J* = 8.9, 0.7 Hz, 1H), 7.99 (d, *J* = 9.1 Hz, 1H), 7.80 (dt, *J* = 8.3, 1.1 Hz, 1H), 7.71 (dd, *J* = 2.0, 0.5 Hz, 1H), 7.47 (dd, *J* = 8.9, 2.0 Hz, 1H), 7.35 (d, *J* = 9.1 Hz, 1H), 7.30 – 7.24 (m, 1H), 7.23 – 7.17 (m, 2H), 7.16 – 7.08 (m, 2H), 6.56 (d, *J* = 0.8 Hz, 1H), 6.55 – 6.48 (m, 2H), 3.87 (s, 3H), 3.73 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, CDCl$_3$) δ 163.5, 156.6, 135.9, 135.8, 131.5, 130.3, 129.2, 128.3, 127.9, 127.1, 126.7, 124.5, 123.3, 123.3, 116.6, 116.5, 114.1, 113.7, 112.7, 111.6, 56.3, 55.5. **HRMS** (ESI+) the exact mass calculated for [C$_{26}$H$_{21}$BrNO$_4$S]$^+$ is 522.0369 *m/z*; was found [M + H]$^+$ 522.0371 *m/z*. **M.p.** = 154–156 ºC.

2-(2-Methoxynaphthalen-1-yl)-1-((4-(trifluoromethyl)phenyl)sulfonyl)-1*H*-indole, 86r



Catalysis with Complex (*R*,*R*)-**40g**

The title compound **86r** (white solid, 32.0 mg, 66.0 µmol, 91% yield, 89:11 *er*) synthesized following general procedure **I** using 4-trifluoromethyl-*N*-(2-((2-methoxynaphthalen-1-yl)ethynyl)phenyl)benzenesulfonamide **85r** (35.0 mg, 72.7 µmol) whereby the reaction was stirred for 48 h. Purification was performed by flash column chromatography (cyclohexane/EtOAc 10:1).

α_D^{589} = +108.4 deg·cm^2·g^{-1} ($CHCl_3$, c 1.0, 296 K). **SFC** Chiralpak OJ-3 (100 × 3.0 mm, 3 µm) at 35 ºC, flow 1.2 mL/min, isocratic CO_2/EtOH 70:30, ABRP pressure 150 bar, 230 nm, t_R (major) 0.89; t_R (minor) 1.31.

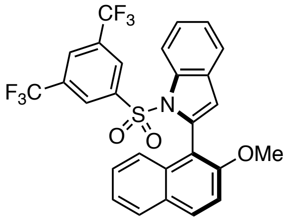
Catalysis with Complex (*R*,*R*)-**A1**

The title compound **86r** (white solid, 8.70 mg, 618 µmol, 78% yield, 8:92 *er*) synthesized following general procedure **J** using 4-trifluoromethyl-*N*-(2-((2-methoxynaphthalen-1-yl)ethynyl)phenyl)benzenesulfonamide **85r** (11.2 mg, 23.3 µmol) whereby the reaction was stirred for 16 h. Purification was performed by preparative TLC (SiO_2, cyclohexane/EtOAc 9:1).

α_D^{589} = –98.3 deg·cm^2·g^{-1} ($CHCl_3$, c 0.1, 301 K). **SFC** Chiralpak OJ-3 (100 × 3.0 mm, 3 µm) at 35 ºC, flow 1.2 mL/min, isocratic CO_2/EtOH 70:30, ABRP pressure 150 bar, 230 nm,; t_R (minor) 1.17; t_R (major) 1.60.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (dd, *J* = 8.4, 0.9 Hz, 1H), 8.00 (d, *J* = 9.1 Hz, 1H), 7.81 (d, *J* = 8.3 Hz, 1H), 7.62 (ddd, *J* = 7.7, 1.4, 0.7 Hz, 1H), 7.43 (ddd, *J* = 8.5, 7.3, 1.4 Hz, 1H), 7.41 – 7.31 (m, 6H), 7.28 (ddd, *J* = 8.1, 5.5, 2.4 Hz, 1H), 7.13 – 7.04 (m, 2H), 6.68 (d, *J* = 0.8 Hz, 1H), 3.85 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 156.9, 142.4, 137.5, 134.9 (q, *J* = 32.9 Hz), 134.5, 134.5, 131.7, 130.1, 128.5, 128.1, 127.5, 127.0, 125.7 (q, *J* = 3.7 Hz), 124.9, 123.1 (q, *J* = 273.1 Hz), 123.9, 123.6, 122.0, 121.2, 115.2, 114.1, 113.5, 112.8, 56.3. **^{19}F{^{1}H} NMR** (471 MHz, $CDCl_3$) δ –63.36. **HRMS** (ESI+) the exact mass calculated for $[C_{26}H_{18}F_3NNaO_3S]^+$ is 504.0852 *m/z*; was found $[M + Na]^+$ 504.0852 *m/z*. **M.p.** = 165–167 ºC.

1-((3,5-Bis(trifluoromethyl)phenyl)sulfonyl)-2-(2-methoxynaphthalen-1-yl)-1*H*-indole, 86s



Catalysis with Complex (*R*,*R*)-**40g**

The title compound **86s** (white solid, 34.0 mg, 61.9 µmol, 97% yield, 84:16 *er*) was synthesized following general procedure **I** using *N*-(2-((2-methoxynaphthalen-1-yl)ethynyl)phenyl)-3,5-bis(trifluoromethyl)benzenesulfonamide **85s** (35.0 mg, 63.7 µmol) whereby the reaction was stirred for 24 h at 25 ºC. Purification was performed by flash column chromatography (cyclohexane/EtOAc 10:1).

α_D^{589} = +14.5 deg·cm^2·g^{-1} ($CHCl_3$, c 1.0, 296 K). **SFC** Chiralpak OD-3 (100 × 3.0 mm, 3 µm) at 35 ºC, flow 1.2 mL/min, isocratic CO_2/EtOH 97:3, ABRP pressure 150 bar, 230 nm, t_R (major) 2.77; t_R (minor) 2.13.

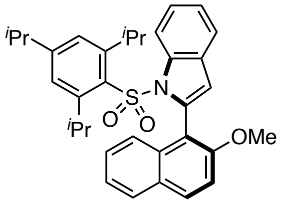
Catalysis with Complex (*R*,*R*)-**A1**

The title compound **86s** (white solid, 19.5 mg, 35.5 µmol, 97% yield, 6:94 *er*) was synthesized following general procedure **J** using *N*-(2-((2-methoxynaphthalen-1-yl)ethynyl)phenyl)-3,5-bis(trifluoromethyl)benzenesulfonamide **85s** (22.2 mg, 36.8 µmol) whereby the reaction was stirred for 48 h. Purification was performed by preparative TLC (SiO_2, cyclohexane/EtOAc 9:1).

α_D^{589} = –11.5 deg·cm^2·g^{-1} ($CHCl_3$, c 0.1, 299 K). **SFC** Chiralpak OD-3 (100 × 3.0 mm, 3 µm) at 35 ºC, flow 1.2 mL/min, isocratic CO_2/EtOH 97:3, ABRP pressure 150 bar, 230 nm, t_R (major) 2.08; t_R (minor) 2.74.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (dd, *J* = 8.4, 0.9 Hz, 1H), 8.00 (d, *J* = 9.1 Hz, 1H), 7.85 (s, 2H), 7.83 (s, 1H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.63 (ddd, *J* = 7.7, 1.4, 0.7 Hz, 1H), 7.45 (ddd, *J* = 8.5, 7.3, 1.4 Hz, 1H), 7.37 (td, *J* = 7.5, 1.0 Hz, 1H), 7.34 (d, *J* = 9.1 Hz, 1H), 7.30 (ddd, *J* = 8.1, 5.0, 2.9 Hz, 1H), 7.21 – 7.18 (m, 2H), 6.71 (d, *J* = 0.8 Hz, 1H), 3.85 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 156.6, 141.5, 137.3, 134.5, 134.4, 132.5 (d, *J* = 34.6 Hz), 132.1, 130.2, 128.5, 128.3, 127.4 (d, *J* = 3.9 Hz), 127.4, 127.0 (q, *J* = 3.6 Hz), 125.2, 124.3, 124.1, 123.9, 122.2 (q, *J* = 273.6 Hz), 121.4, 115.0, 114.2, 113.9, 112.9, 56.5.**^{19}F{^{1}H} NMR** (471 MHz, $CDCl_3$) δ –63.08. **HRMS** (ESI+) the exact mass calculated for $[C_{27}H_{17}F_6NNaO_3S]^+$ is 572.0726 *m/z*; was found $[M + H]^+$ 572.0712 *m/z*. **M.p.** = 181–183 ºC.

2-(2-Methoxynaphthalen-1-yl)-1-((2,4,6-triisopropylphenyl)sulfonyl)-1*H*-indole, 86t



Catalysis with Complex (*R*,*R*)-**40g**

The title compound **86t** (white solid, 35.0 mg, 64.8 µmol, 95% yield, 82:18 *er*) was synthesized following general procedure **I** using 2,4,6-triisopropyl-*N*-(2-((2-methoxynaphthalen-1-yl)ethynyl)phenyl)benzenesulfonamide **85t** (37.0 mg, 69.0 µmol) whereby the reaction was stirred for 19 h. Purification was performed by flash column chromatography (cyclohexane/EtOAc 20:1).

α_D^{589} = –34.3 deg·cm^2·g^{-1} ($CHCl_3$, c 1.0, 296 K). **SFC** Chiralpak IG-3 (100 × 3.0 mm, 3 µm) at 35 ºC, flow 1.2 mL/min, isocratic CO_2/MeOH 85:15, ABRP pressure 150 bar, 230 nm, t_R (major) 2.52; t_R (minor) 3.74.

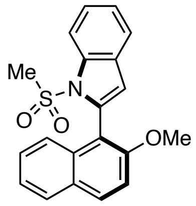
Catalysis with Complex (*R*,*R*)-**A1**

The title compound **86t** (white solid, 26.6 mg, 49.3 µmol, 99% yield, 9:91 *er*) was synthesized following general procedure **J** using 2,4,6-triisopropyl-*N*-(2-((2-methoxynaphthalen-1-yl)ethynyl)phenyl)benzenesulfonamide **85t** (27.0 mg, 50.0 µmol) whereby the reaction was stirred for 16 h. Purification was performed by flash column chromatography (SiO_2, cyclohexane/EtOAc from 10:0 to 9:1).

α_D^{589} = +56.4 deg·cm^2·g^{-1} ($CHCl_3$, c 1.0, 296 K). **SFC** Chiralpak IG-3 (100 × 3.0 mm, 3 µm) at 35 ºC, flow 1.2 mL/min, isocratic CO_2/MeOH 85:15, ABRP pressure 150 bar, 230 nm, t_R (minor) 2.47; t_R (major) 3.64.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (dd, *J* = 8.4, 0.9 Hz, 1H), 7.89 (d, *J* = 8.9 Hz, 1H), 7.74 (d, *J* = 7.1 Hz, 1H), 7.61 (ddd, *J* = 7.6, 1.5, 0.7 Hz, 1H), 7.43 – 7.32 (m, 2H), 7.31 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.30 – 7.18 (m, 2H), 7.08 (d, *J* = 9.1 Hz, 1H), 6.89 (s, 2H), 6.54 (d, *J* = 0.8 Hz, 1H), 3.52 (s, 3H), 3.45 (p, *J* = 6.6 Hz, 2H), 2.81 (p, *J* = 6.9 Hz, 1H), 1.23 (d, *J* = 3.6 Hz, 3H), 1.21 (d, *J* = 3.6 Hz, 3H), 0.85 (d, *J* = 6.7 Hz, 6H), 0.79 (d, *J* = 6.7 Hz, 6H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 156.4, 153.4, 151.4, 137.6, 135.0, 134.6, 133.7, 131.7, 129.1, 128.3, 127.4, 126.7, 125.6, 124.0, 123.6, 123.2, 122.5, 120.7, 114.7, 114.0, 112.1, 111.3, 55.8, 34.2, 28.9, 24.6, 24.2, 23.7, 23.7. **HRMS** (ESI+) the exact mass calculated for $[C_{34}H_{37}NNaO_3S]^+$ is 562.2386 *m/z*; found $[M + Na]^+$ 562.2379 *m/z*. **M.p.** = 124–126 ºC.

2-(2-Methoxynaphthalen-1-yl)-1-(methylsulfonyl)-1*H*-indole, 86u



Catalysis with Complex (*R*,*R*)-**40g**

The title compound **86u** (white foam, 29.5 mg, 83.9 μmol, 96% yield, 93:7 *er*) was synthesized following general procedure **I** using *N*-(2-((2-methoxynaphthalen-1-yl)ethynyl)phenyl)methanesulfonamide **85u** (30.8 mg, 87.6 μmol) whereby the reaction was stirred for 24 h. Purification was performed by flash column chromatography (20:1 to 9:1 cyclohexane/EtOAc).

α_D^{589} = –89.0 deg·cm^2·g^{-1} (CHCl$_3$, c 1.35, 298K). **SFC** Chiralpak IC (100 x 3.0 mm, 3 μm) at 35ºC, flow 1.2 mL/min, isocratic CO$_2$/EtOH 70:30, ABRP pressure 150 bar, 230 nm,; t$_R$ (minor) 0.97; t$_R$ (major) 1.26.

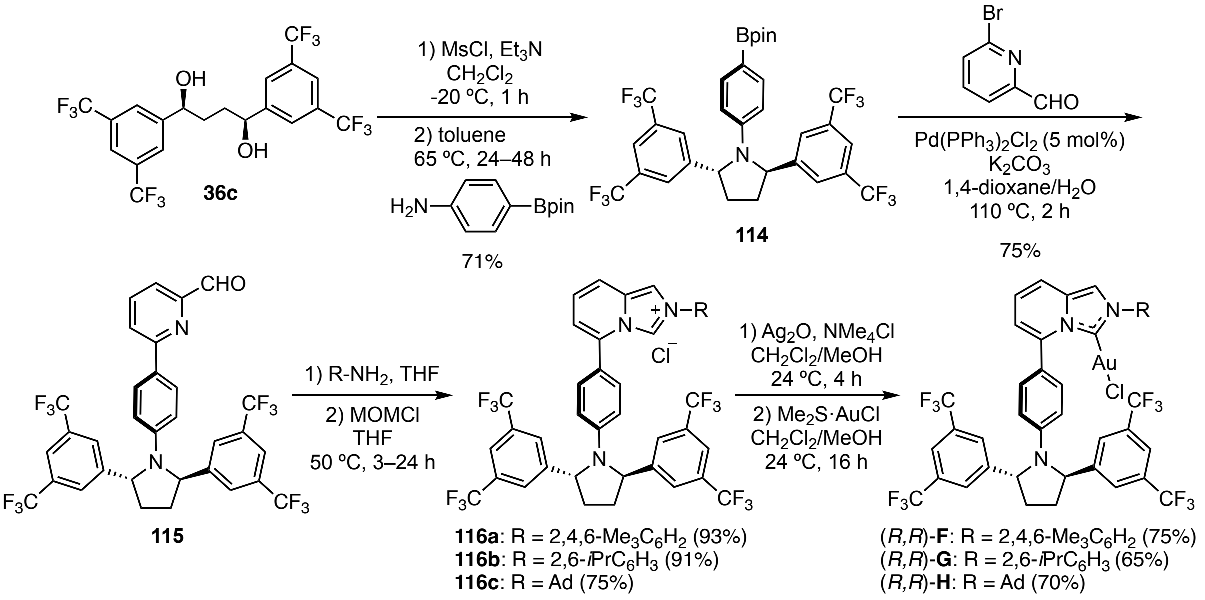
Catalysis with Complex (*R*,*R*)-**A1**

The title compound **86u** (white foam, 15.5 mg, 44.1 μmol, 88% yield, 7:93 *er*) was synthesized following general procedure **J** using *N*-(2-((2-methoxynaphthalen-1-yl)ethynyl)phenyl)methanesulfonamide **85u** (17.6 mg, 50.0 μmol) whereby the reaction was stirred for 16 h. Purification was performed by preparative TLC (cyclohexane/EtOAc 8:2).

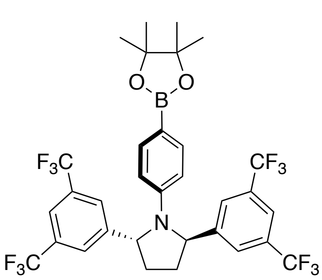
α_D^{589} = +101.4 deg·cm^2·g^{-1} (CHCl$_3$, c 0.1, 300 K). **SFC** Chiralpak IC (100 x 3.0 mm, 3 μm) at 35ºC, flow 1.2 mL/min, isocratic CO$_2$/EtOH 70:30, ABRP pressure 150 bar, 230 nm, t$_R$ (major) 0.96; t$_R$ (minor) 1.25.

^{1}H NMR (500 MHz, CDCl$_3$) δ 8.14 (dq, *J* = 8.3, 0.9 Hz, 1H), 7.98 (dd, *J* = 9.2, 0.8 Hz, 1H), 7.86 – 7.81 (m, 1H), 7.67 (ddd, *J* = 7.6, 1.5, 0.8 Hz, 1H), 7.56 – 7.51 (m, 1H), 7.44 – 7.32 (m, 5H), 6.71 (d, *J* = 0.8 Hz, 1H), 3.92 (s, 3H), 3.04 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, CDCl$_3$) δ 155.9, 136.9, 134.9, 134.8, 131.4, 130.1, 128.8, 128.2, 127.3, 124.8, 124.7, 124.0, 123.7, 121.1, 115.4, 114.5, 112.9, 112.5, 56.6, 40.4. **HRMS** (ESI+) exact mass was calculated for [C$_{20}$H$_{18}$NO$_3$S]$^+$ 352.1002 *m/z*; was found [M + H]$^+$ 352.0998 *m/z*. **M.p.**= 134–136 ºC.

Synthesis of the chiral complexes (*R*,*R*)-F, (*R*,*R*)-G and (*R*,*R*)-H



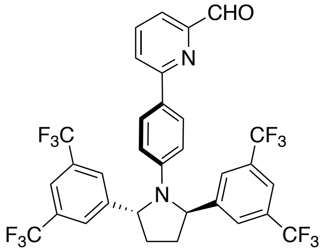
(2*R*,5*R*)-2,5-Bis(3,5-bis(trifluoromethyl)phenyl)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidine, 114



Under nitrogen atmosphere, a two-necked round bottom flask was charged with the diol (1*S*,4*S*)-1,4-bis(3,5-bis(trifluoromethyl)phenyl)butane-1,4-diol **36c**23 (280.0 mg, 544.7 µmol, 1.000 equiv) in dichloromethane (2.7 mL, 0.2 M) and triethylamine (0.23 mL, 1.63 mmol, 3.00 equiv), the solution was stirred for 10 min at -20 ºC (brine-ice bath). Methanesulfonyl chloride (0.110 mL, 1.42 mmol, 2.60 equiv) was added and it was stirred for 1 h at the same temperature. Then, the reaction was quenched with water and extracted with CH_2Cl_2 (3x). The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The dimesylated product was checked by ^{1}H NMR and it was used in the next step without further purification. Under nitrogen atmosphere, a solution of the dimesylated product and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (298.0 mg, 1.36 mmol, 2.50 equiv) in toluene (2.7 mL, 0.2 M) was stirred at 65 ºC for 24–48 h, controlled by ^{1}H NMR. Solvents were removed under reduced pressure and the crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc from 10:0 to 9:1) affording **114** (270.0 mg, 387.3 µmol, 71% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 2.0 Hz, 2H), 7.62 (d, *J* = 1.6 Hz, 4H), 7.52 – 7.47 (m, 2H), 6.31 – 6.25 (m, 2H), 5.44 (d, *J* = 7.2 Hz, 2H), 2.58 (td, *J* = 7.9, 1.8 Hz, 2H), 1.98 – 1.84 (m, 2H), 1.27 (d, *J* = 5.3 Hz, 12H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 146.1, 145.7, 136.4, 132.3 (q, *J* = 33.3 Hz), 126.3 (d, *J* = 2.9 Hz), 123.3 (q, *J* = 272.8 Hz), 121.7 – 121.3 (m), 113.6, 83.5, 62.5, 32.1, 25.1, 24.9. **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) δ –62.9. **HRMS** (ESI+) calculated for $[C_{32}H_{29}F_{12}NO_2{}^{10}B]^+$ 697.2131 *m/z*; found $[M + H]^+$ 697.2125 *m/z*. **M.p.** = 152–156 ºC. **α_D^{589}** = +22.4 deg·cm^2·g^{-1} (CHCl$_3$, c 0.1, 301 K).

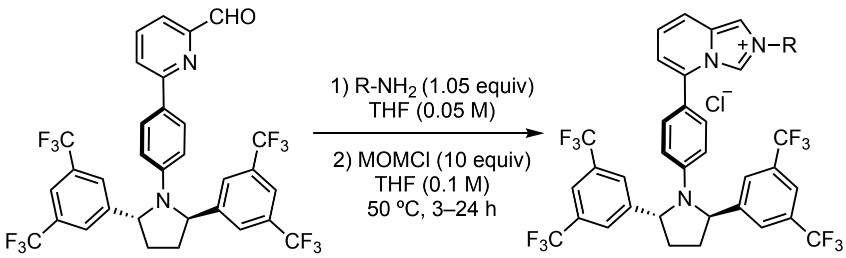
6-(4-((2*R*,5*R*)-2,5-Bis(3,5-bis(trifluoromethyl)phenyl)pyrrolidin-1-yl)phenyl)picolinaldehyde, 115



Under nitrogen atmosphere, dioxane (2.6 mL, 0.1 M) and water (0.52 mL, 0.5 M) were added into a microwave vial containing **114** (189 mg, 271 µmol, 1.05 equiv), 6-bromopicolinaldehyde (48.0 mg, 258 µmol, 1.00 equiv), PdCl$_2$(PPh$_3$)$_2$ (9.1 mg, 12.9 µmol, 5 mol%) and K$_2$CO$_3$ (89.2 mg, 645 µmol, 2.50 equiv), and it was stirred in a microwave reactor at 110 ºC for 2 h. Then, the reaction was quenched with water and extracted with Et$_2$O (3x). The combined organic phases were washed with brine, dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude was purified by flash column chromatography (SiO$_2$, cyclohexane/EtOAc from 10:0 to 9:1) affording **115** (130.1 mg, 192.3 µmol, 75% yield) as a yellowish solid.

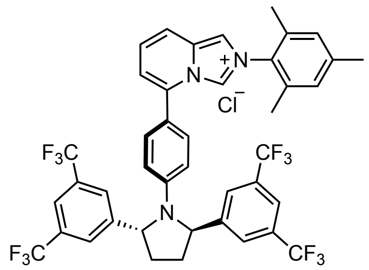
^{1}H NMR (400 MHz, CDCl$_3$) δ 10.06 (d, *J* = 0.7 Hz, 1H), 7.88 – 7.83 (m, 2H), 7.83 – 7.78 (m, 3H), 7.78 – 7.73 (m, 2H), 7.67 (s, 4H), 6.50 – 6.38 (m, 2H), 5.50 (d, *J* = 7.1 Hz, 2H), 2.71 – 2.54 (m, 2H), 2.06 – 1.86 (m, 2H). **^{13}C{^{1}H} NMR** (101 MHz, CDCl$_3$) δ 194.2, 157.7, 152.7, 146.0, 144.6, 137.6, 132.4 (q, *J* = 33.4 Hz), 128.3, 127.7, 126.2 (d, *J* = 3.3 Hz), 123.4, 123.3 (q, *J* = 272.9 Hz), 121.8 – 121.6 (m), 118.8, 114.5, 62.8, 32.2. **^{19}F{^{1}H} NMR** (376 MHz, CDCl$_3$) δ –62.9. **HRMS** (ESI+) calculated for $[C_{32}H_{20}F_{12}N_2NaO]^+$ 699.1276 *m/z*; found $[M + Na]^+$ 699.1282 *m/z*. **M.p.** = 195–199 ºC. **α_D^{589}** = +37.1 deg·cm^2·g^{-1} (CHCl$_3$, c 0.1, 301 K).

General procedure K: Synthesis of the N-heterocyclic salt precursors



In a flask, **115** (1.0 equiv) was dissolved in THF (0.05 M) and the corresponding aniline (1.05 equiv) was added. The mixture was concentrated under vacuum. Then, under nitrogen atmosphere, the product formed was dissolved in THF (0.1 M) and chloromethyl methyl ether (10.0 equiv) was added and the reaction was stirred at 50 ºC. The reaction was quenched with water and extracted with CH$_2$Cl$_2$ (3x). The combined organic phases were washed with brine, dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude was purified by SiO$_2$ flash column chromatography affording the corresponding N-heterocyclic salt precursor.

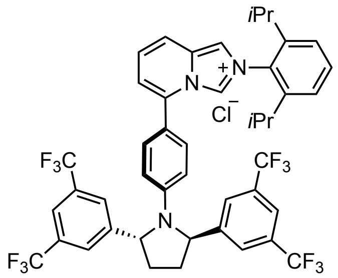
5-(4-((2*R*,5*R*)-2,5-Bis(3,5-bis(trifluoromethyl)phenyl)pyrrolidin-1-yl)phenyl)-2-mesitylimidazo[1,5-*a*]pyridin-2-ium chloride, 116a



The title compound **116a** (169.9 mg, 201.7 µmol, 93% yield) was obtained as an orange solid according to general procedure **K** at 50 ºC for 3 h, using **115** (147.0 mg, 217.3 µmol) and 2,4,6-trimethylaniline (32.0 µL, 228.2 µmol). It was purified by flash column chromatography (SiO_2, CH_2Cl_2/MeOH from 10:0 to 9:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (d, *J* = 1.6 Hz, 1H), 8.60 (d, *J* = 1.7 Hz, 1H), 8.25 (d, *J* = 9.3 Hz, 1H), 7.80 (s, 2H), 7.65 (d, *J* = 1.5 Hz, 4H), 7.47 (d, *J* = 8.8 Hz, 2H), 7.33 (dd, *J* = 9.3, 7.0 Hz, 1H), 7.01 (d, *J* = 2.9 Hz, 2H), 6.99 (d, *J* = 7.2, 1H), 6.49 (d, *J* = 8.9 Hz, 2H), 5.50 (d, *J* = 7.0 Hz, 2H), 2.61 (dt, *J* = 7.6, 3.9 Hz, 2H), 2.34 (s, 3H), 2.03 (s, 3H), 1.99 (s, 3H), 1.96 (d, *J* = 6.8 Hz, 2H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 145.8, 145.2, 141.7, 135.7, 134.2, 132.5, 132.4 (q, *J* = 33.3 Hz), 131.3, 130.0, 129.9, 126.3 (d, *J* = 3.2 Hz), 126.1, 123.2 (q, *J* = 272.8 Hz), 122.8, 122.0 – 121.7 (m), 119.6, 118.5, 118.4, 117.4, 115.2, 62.9, 32.2, 21.2, 17.7. **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) δ –62.9. **HRMS** (ESI+) calculated for $[C_{42}H_{32}F_{12}N_3]^+$ 806.2399 *m/z*; found $[M - Cl]^+$ 806.2411 *m/z*. **M.p.** = >135 ºC (decomposition). **α_D^{589}** = +45.8 deg·cm^2·g^{-1} ($CHCl_3$, c 0.1, 301 K).

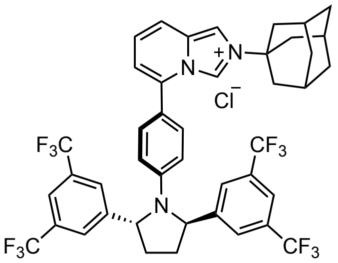
5-(4-((2*R*,5*R*)-2,5-Bis(3,5-bis(trifluoromethyl)phenyl)pyrrolidin-1-yl)phenyl)-2-(2,6-diisopropylphenyl)imidazo[1,5-a]pyridin-2-ium chloride, 116b



The title compound **116b** (119.0 mg, 134.6 µmol, 91% yield) was obtained as an orange solid according to general procedure **K** at 50 ºC for 3 h, using **115** (100.0 mg, 147.8 µmol) and 2,6-diisopropylaniline (27.5 mg, 155.2 µmol). It was purified by flash column chromatography (SiO_2, CH_2Cl_2/MeOH from 10:0 to 9:1).

^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.69 (d, *J* = 1.7 Hz, 1H), 8.63 (d, *J* = 1.8 Hz, 1H), 8.29 (d, *J* = 9.3 Hz, 1H), 7.82 (s, 2H), 7.69 (d, *J* = 1.5 Hz, 4H), 7.61 (t, *J* = 7.8 Hz, 1H), 7.47 (dd, *J* = 9.3, 7.1 Hz, 1H), 7.40 – 7.33 (m, 4H), 7.10 (dd, *J* = 7.1, 0.9 Hz, 1H), 6.57 – 6.45 (m, 2H), 5.51 (d, *J* = 7.0 Hz, 2H), 2.62 (td, *J* = 8.0, 1.8 Hz, 2H), 2.11 (dh, *J* = 17.8, 6.8 Hz, 2H), 2.02 – 1.86 (m, 2H), 1.19 (dd, *J* = 6.8, 4.4 Hz, 6H), 1.12 (d, *J* = 6.9 Hz, 3H), 1.03 (d, *J* = 6.8 Hz, 3H). **^{13}C{^{1}H} NMR** (101 MHz, CD_2Cl_2) δ 146.4, 145.8, 145.7, 145.6, 136.1, 133.0, 132.8, 132.6 (q, *J* = 33.3 Hz), 131.1, 129.9, 127.3, 126.9 (d, *J* = 3.3 Hz), 125.3 (d, *J* = 2.3 Hz), 123.8 (q, *J* = 272.9 Hz), 123.2, 122.3 – 122.0 (m), 119.6, 119.3, 118.6, 115.7, 63.4, 32.5, 29.3, 29.2, 24.7, 24.6, 24.6, 24.5. **^{19}F{^{1}H} NMR** (376 MHz, CD_2Cl_2) δ –63.3. **HRMS** (ESI+) calculated for $[C_{45}H_{38}F_{12}N_3]^+$ 848.2869 *m/z*; found $[M - Cl]^+$ 848.2859 *m/z*. **M.p.** = >150 ºC (decomposition). **α_D^{589}** = +34.0 deg·cm^2·g^{-1} ($CHCl_3$, c 0.1, 302 K).

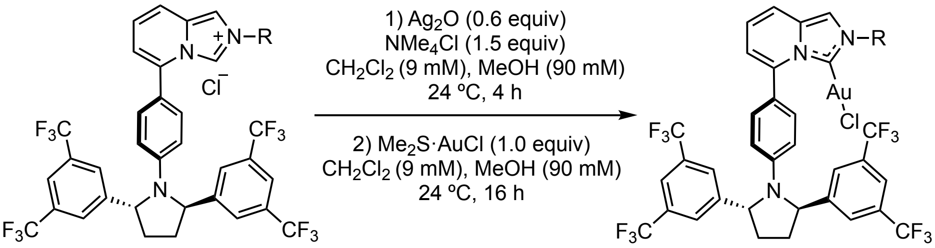
2-(Adamantan-1-yl)-5-(4-((2*R*,5*R*)-2,5-bis(3,5-bis(trifluoromethyl)phenyl)pyrrolidin-1-yl)phenyl)imidazo[1,5-*a*]pyridin-2-ium chloride, 116c



The title compound **116c** (81.2 mg, 94.6 µmol, 75% yield) was obtained as an orange solid according to general procedure **K** at 50 ºC for 24 h, using **115** (85.3 mg, 126.1 µmol) and 1-adamantylamine (20.0 mg, 132.4 µmol). It was purified by flash column chromatography (SiO_2, CH_2Cl_2/MeOH from 10:0 to 9:1).

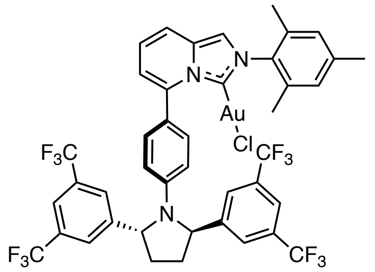
^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.83 (d, *J* = 1.9 Hz, 1H), 8.52 (d, *J* = 1.6 Hz, 1H), 7.93 (d, *J* = 9.3 Hz, 1H), 7.86 (s, 2H), 7.73 (s, 4H), 7.43 – 7.34 (m, 2H), 7.24 (dd, *J* = 9.3, 6.9 Hz, 1H), 6.87 (dd, *J* = 6.9, 0.9 Hz, 1H), 6.58 – 6.49 (m, 2H), 5.54 (d, *J* = 7.1 Hz, 2H), 2.64 (td, *J* = 7.9, 1.8 Hz, 2H), 2.33 – 2.27 (m, 3H), 2.25 (d, *J* = 2.9 Hz, 6H), 1.99 (dd, *J* = 6.1, 3.2 Hz, 2H), 1.81 (d, *J* = 3.0 Hz, 6H). **^{13}C{^{1}H} NMR** (101 MHz, CD_2Cl_2) δ 146.0, 145.8, 136.0, 132.4 (q, *J* = 33.3 Hz), 132.3, 130.0, 126.8 (d, *J* = 3.2 Hz), 125.8, 123.8 (q, *J* = 272.7 Hz), 122.1 – 121.9 (m), 119.9, 119.5, 117.9 (d, *J* = 1.7 Hz), 115.5, 113.3, 63.2, 62.5, 43.2, 35.6, 32.5, 30.1. **^{19}F{^{1}H} NMR** (376 MHz, CD_2Cl_2) δ –63.2. **HRMS** (ESI+) calculated for $[C_{43}H_{36}F_{12}N_3]^+$ 822.2712 *m/z*; found $[M - Cl]^+$ 822.2729 *m/z*. **M.p.** = >105 ºC (decomposition). **α_D^{589}** = +24.0 deg·cm^2·g^{-1} ($CHCl_3$, c 0.1, 301 K).

General procedure L: Synthesis of the N-heterocyclic carbene Au(I) chiral complexes



Under argon atmosphere, a mixture of the corresponding N-heterocyclic salt precursor **116a-c** (1.0 equiv), Ag_2O (0.6 equiv) and NMe_4Cl (1.5 equiv) in CH_2Cl_2 (9 mM) and MeOH (90 mM) was stirred at 24ºC for 4 h. Then, the reaction was filtered through Celite® with dichloromethane into a flask and solvents were removed. Dimethylsulfide gold(I) chloride (1.0 equiv) was added into the flask containing the silver complex and, under argon in CH_2Cl_2 (9.0 mM) and MeOH (90.0 mM), they were stirred at 24 ºC for 16 h. Then, it was filtered through a PPTS filter with CH_2Cl_2 and the crude was purified by SiO_2 flash column chromatography affording the corresponding gold(I) complex.

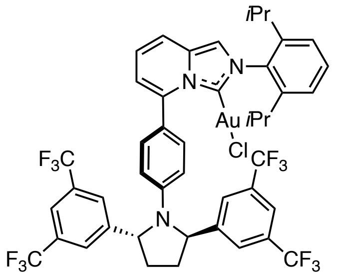
Chiral complex (*R*,*R*)-F



The title compound (*R*,*R*)-**F** (106.5 mg, 102.6 μmol, 75% yield) was obtained as a yellowish solid according to general procedure **L** using **116a** (115.0 mg, 136.6 μmol). It was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc from 10:0 to 7:3).

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.82 (s, 2H), 7.80 (s, 4H), 7.38 (dd, *J* = 9.3, 1.2 Hz, 1H), 7.36 (br s, 1H), 7.27 (s, 1H), 7.20 (br s, 1H), 7.01 (s, 1H), 7.00 (s, 1H), 6.96 (dd, *J* = 9.2, 6.7 Hz, 1H), 6.50 (dd, *J* = 6.7, 1.2 Hz, 1H), 6.40 (br s, 2H), 5.46 (d, *J* = 7.3 Hz, 2H), 2.69 – 2.54 (m, 2H), 2.35 (s, 3H), 1.97 (s, 3H), 1.87 (s, 3H), 1.88 – 1.80 (m, 2H). **^{13}C{^{1}H} NMR** (101 MHz, CD_2Cl_2) δ 165.1, 146.7, 145.3, 140.3, 140.1, 136.9, 134.9, 134.8, 132.6, 132.3 (q, *J* = 33.1 Hz), 131.6, 130.6, 129.6, 129.5, 126.9 (d, *J* = 4.8 Hz), 123.9 (q, *J* = 272.6 Hz), 123.7, 123.4, 121.9 – 121.7 (m), 116.9, 116.4, 115.4, 114.0, 112.8, 63.6, 32.4, 21.3, 17.9, 17.8. **^{19}F{^{1}H} NMR** (376 MHz, CD_2Cl_2) δ –62.9. **HRMS** (ESI+) calculated for $[C_{42}H_{32}AuClF_{12}N_3]^+$ 1038.1753 *m/z*; found $[M + H]^+$ 1038.1774 *m/z*. **M.p.** = >153 ºC (decomposition). **α_D^{589}** = +72.4 deg·cm^2·g^{-1} (CH_2Cl_2, c 0.1, 303 K).

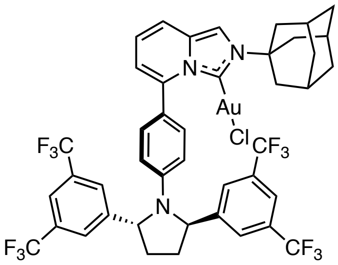
Chiral complex (*R*,*R*)-G



The title compound (*R*,*R*)-**G** (78.9 mg, 73.0 μmol, 65% yield) was obtained as a brown solid according to general procedure **L** using **116b** (100.0 mg, 113.1 μmol). It was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc from 10:0 to 7:3).

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.81 (s, 6H), 7.52 (t, *J* = 7.8 Hz, 1H), 7.39 (dd, *J* = 9.3, 1.2 Hz, 1H), 7.37 (br s, 1H), 7.32 (s, 1H), 7.28 (td, *J* = 7.8, 1.4 Hz, 2H), 7.19 (br s, 1H), 6.99 (dd, *J* = 9.2, 6.8 Hz, 1H), 6.54 (dd, *J* = 6.7, 1.2 Hz, 1H), 6.40 (br s, 2H), 5.47 (d, *J* = 7.0 Hz, 2H), 2.67 – 2.54 (m, 2H), 2.21 (hept, *J* = 6.5 Hz, 1H), 2.13 (p, *J* = 6.9 Hz, 1H), 1.90 – 1.77 (m, 2H), 1.25 (d, *J* = 6.9 Hz, 3H), 1.13 (d, *J* = 6.9 Hz, 3H), 1.11 (d, *J* = 6.9 Hz, 3H), 1.06 (d, *J* = 6.9 Hz, 3H). **^{13}C{^{1}H} NMR** (101 MHz, CD_2Cl_2) δ 166.1, 146.7, 145.7, 145.6, 145.3, 140.4, 136.4, 132.3, 132.2 (q, *J* = 33.1 Hz), 130.8, 127.0 (d, *J* = 2.6 Hz), 124.5, 124.4, 123.9, 123.8 (q, *J* = 272.8 Hz), 123.3, 122.0 – 121.6 (m), 116.9, 116.5, 115.4, 114.1, 63.5, 32.4, 28.8, 28.7, 24.7, 24.5, 24.4, 24.0. **^{19}F{^{1}H} NMR** (376 MHz, CD_2Cl_2) δ –62.9. **HRMS** (ESI+) calculated for $[C_{45}H_{38}AuClF_{12}N_3]^+$ 1080.2223 *m/z*; found $[M + H]^+$ 1080.2259 *m/z*. **M.p.** = >80 ºC (decomposition). **α_D^{589}** = +80.7 deg·cm^2·g^{-1} (CH_2Cl_2, c 0.1, 304 K).

Chiral complex (*R*,*R*)-H

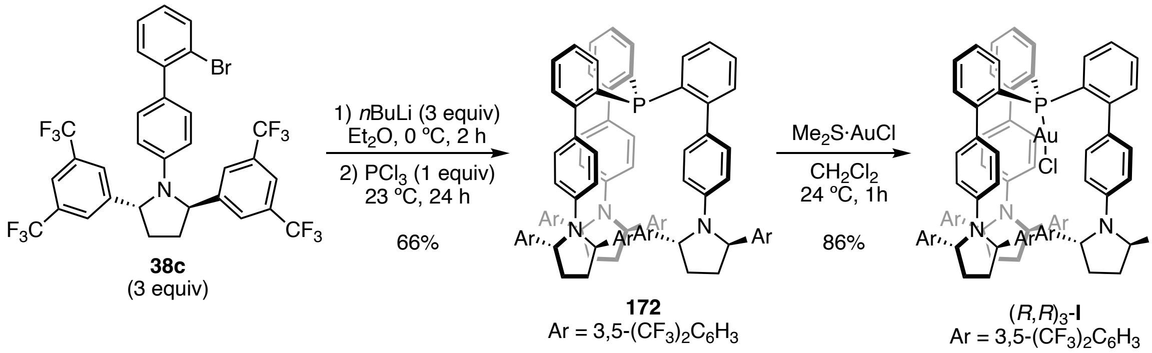


The title compound (*R*,*R*)-**H** (69.4 mg, 65.8 μmol, 70% yield) was obtained as a yellowish solid according to general procedure **L** using **116c** (81.2 mg, 94.6 μmol). It was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc from 10:0 to 7:3).

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.83 (s, 6H), 7.52 (s, 1H), 7.31 (dd, *J* = 9.2, 1.3 Hz, 1H), 7.20 (d, *J* = 8.3 Hz, 1H), 7.09 (d, *J* = 8.4 Hz, 1H), 6.84 (dd, *J* = 9.2, 6.7 Hz, 1H), 6.44 (d, *J* = 8.1 Hz, 1H), 6.39 (dd, *J* = 6.6, 1.3 Hz, 1H), 6.36 (d, *J* = 7.9 Hz, 1H), 5.48 (d, *J* = 7.1 Hz, 2H), 2.64 (td, *J* = 7.8, 1.5 Hz, 2H), 2.60 (d, *J* = 3.0 Hz, 6H), 2.29 – 2.22 (m, 3H), 1.85 (dd, *J* = 12.8, 9.8 Hz, 2H), 1.79 – 1.70 (m, 6H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 161.9, 146.9, 145.3, 139.9, 132.2 (q, *J* = 33.3 Hz), 131.3, 130.7, 130.5, 126.9 (d, *J* = 3.7 Hz), 124.2, 123.9 (q, *J* = 272.8 Hz), 122.6, 122.0 – 121.6 (m), 117.1, 116.6, 115.3, 113.9, 109.0, 63.6, 61.0, 44.3, 36.2, 32.4, 30.6. **^{19}F{^{1}H} NMR** (471 MHz, CD_2Cl_2) δ –62.8. **HRMS** (ESI+) calculated for $[C_{43}H_{36}AuClF_{12}N_3]^+$ 1054.2066 *m/z*; found $[M + H]^+$ 1054.2071 *m/z*. **M.p.** = >146 ºC (decomposition). **α_D^{589}** = +78.2 deg·cm^2·g^{-1} (CH_2Cl_2, c 0.1, 304 K).

Synthesis of the chiral sterically hindered complexes (*R*,*R*)$_3$-I, (*R*,*R*)$_2$-K and (*R*,*R*)-K

Synthesis of the chiral gold(I) complex (*R*,*R*)$_3$-I



Ligand 172

Under argon atmosphere, a solution of **38c** (200 mg, 275 μmol, 3.00 equiv) in diethyl ether (834 μL, 0.11 M) was charged in a Schlenk and cool down at 0 ºC. Then, *n*BuLi (2.46 M in hexane) (112 μL, 275 μmol, 3.00 equiv) was added dropwise and the mixture was stirred at the same temperature for 2 h. Phosphorus trichloride (8.0 μL, 92 μmol, 1.0 equiv) was slowly added and the reaction was warm up to 24 ºC and stirred for 24 h. The reaction was checked by UHPLC-MS, quenched with water and extracted with dichloromethane (3x). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by flash column chromatography

(SiO_2, cyclohexane/CH_2Cl_2 from 10:0 to 8:2) affording the ligand **172** (119 mg, 60 µmol, 66% yield) as a yellowish solid.

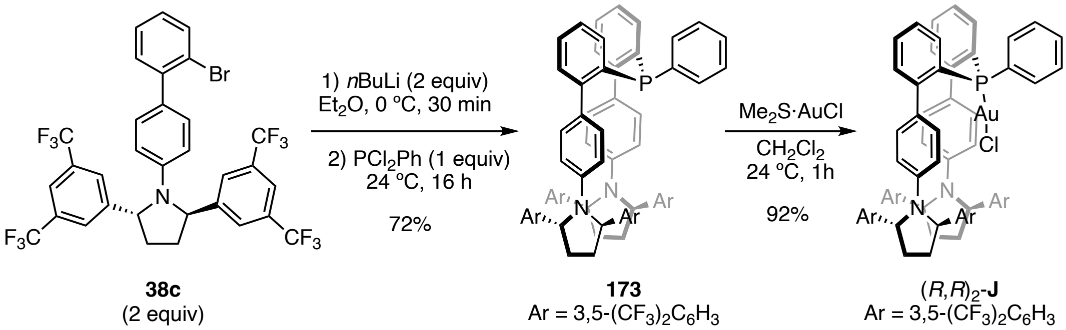
^{1}H NMR (400 MHz, TCE-d_2) **Mixture of rotamers** (significant signals specified) δ 7.72 (major rotamer, s, 5H), 7.69 (minor rotamer, s, 1H), 7.59 (minor rotamer, s, 1.9H), 7.57 (major rotamer, s, 10.1H), 7.09 (major rotamer, td, *J* = 7.5, 1.4 Hz, 2.6H), 7.00 (minor rotamer, t, *J* = 7.4 Hz, 0.4H), 6.91 – 6.77 (m, 6H), 6.65 (minor rotamer, d, *J* = 7.7 Hz, 0.4H), 6.57 (minor rotamer, d, *J* = 8.2 Hz, 1.2H), 6.40 (major rotamer, d, *J* = 8.1 Hz, 4.8H), 6.28 – 6.20 (major rotamer, m, 2.6H), 5.72 (d, *J* = 8.2 Hz, 6H), 5.30 (d, *J* = 6.5 Hz, 6H), 2.51 (s, 6H), 1.96 – 1.75 (m, 6H). **^{13}C{^{1}H} NMR** (101 MHz, TCE-d_2) **Major rotamer** δ 146.8, 146.5 (d, *J* = 25.6 Hz), 141.0, 133.4 (d, *J* = 19.3 Hz), 132.9, 131.6 (q, *J* = 33.1 Hz), 130.6 (d, *J* = 4.8 Hz), 130.4 – 130.1 (m), 129.4 – 129.1 (m), 127.6, 126.1 – 125.7 (m), 123.1 (q, *J* = 272.9 Hz), 121.1 – 120.5 (m), 111.9, 61.6, 31.5. **^{31}P{^{1}H} NMR** (162 MHz, TCE-d_2) δ –18.1 (minor rotamer), –19.8 (major rotamer). **^{19}F{^{1}H} NMR** (376 MHz, TCE-d_2) δ –63.2 (major rotamer), –63.3 (minor rotamer). **HRMS** (ESI+) calculated for $[C_{96}H_{60}F_{36}N_3NaP]^+$ 1992.3842 *m/z*; found $[M + Na]^+$ 1992.3814 *m/z*. **M.p.** = >147 ºC (decomposition; CH_2Cl_2). **α_D^{589}** = +80.9 deg·cm^2·g^{-1} ($CHCl_3$, c 0.1, 302 K).

Complex (*R*,*R*)$_3$-I

Under argon atmosphere, a mixture of the ligand **172** (100 mg, 50.7 µmol, 1.00 equiv) and $Me_2S\cdot AuCl$ (14.9 mg, 50.7 µmol, 1.00 equiv) in dichloromethane (0.73 mL, 0.07 M) was stirred at 24 ºC for 1 h. The crude was filtered over neutral alumina, the volatiles were evaporated under vacuum, and further purify by flash column chromatography (SiO_2, cyclohexane/EtOAc from 10:0 to 8:2) affording the gold(I) complex (*R*,*R*)$_3$-**I** (96 mg, 44 µmol, 86% yield) as a white solid.

^{1}H NMR (400 MHz, CD_2Cl_2) **Mixture of rotamers** δ 7.81 (br s, 2H), 7.69 (s, 4H), 7.66 (s, 12H), 7.30 – 7.07 (m, 4H), 6.95 (t, *J* = 9.6 Hz, 3H), 6.79 (br s, 4H), 6.52 (br s, 1H), 6.29 (br s, 2H), 6.16 (d, *J* = 8.0 Hz, 4H), 5.93 (d, *J* = 8.2 Hz, 6H), 5.30 (d, *J* = 6.7 Hz, 6H), 2.64 – 2.40 (m, 6H), 1.88 – 1.73 (m, 6H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 148.3 (d, *J* = 15.5 Hz), 147.2, 143.4, 135.5 – 134.8 (m), 132.8 – 132.6 (m), 132.6 – 131.5 (m), 130.5, 130.2 – 129.3 (m), 127.0 – 126.4 (m), 123.8 (q, *J* = 272.7 Hz), 121.8 – 121.3 (m), 114.2 – 113.2 (m), 63.3, 32.4. **^{31}P{^{1}H} NMR** (162 MHz, CD_2Cl_2) δ 33.2 (minor rotamer), 11.5 (major rotamer). **^{19}F{^{1}H} NMR** (376 MHz, CD_2Cl_2) δ –63.2. **HRMS** (ESI+) calculated for $[C_{96}H_{60}AuClF_{36}N_3NaP]^+$ 2224.3196 *m/z*; found $[M + Na]^+$ 2224.3151 *m/z*. **M.p.** = >154 ºC (decomposition; CH_2Cl_2). **α_D^{589}** = –23.5 deg·cm^2·g^{-1} (CH_2Cl_2, c 0.1, 304 K).

Synthesis of the chiral gold(I) complex (*R*,*R*)₂-J



Ligand 173

Under argon atmosphere, a solution of **38c** (244 mg, 335 µmol, 2.00 equiv) in diethyl ether (1.7 mL, 0.10 M) was charged in a Schlenk and cool down at 0 ºC. Then, *n*BuLi (2.46 M in hexane) (136 µL, 335 µmol, 2.00 equiv) was added dropwise and the mixture was stirred at the same temperature for 30 min. Phosphorus trichloride (22.7 µL, 168 µmol, 1.00 equiv) was slowly added and the reaction was warm up to 24 ºC and stirred for 16 h. The reaction was checked by UHPLC-MS, quenched with water and extracted with dichloromethane (3x). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by flash column chromatography (SiO_2, cyclohexane/CH_2Cl_2 from 10:0 to 8:2) affording the ligand **173** (169 mg, 120 µmol, 72% yield) as a white solid.

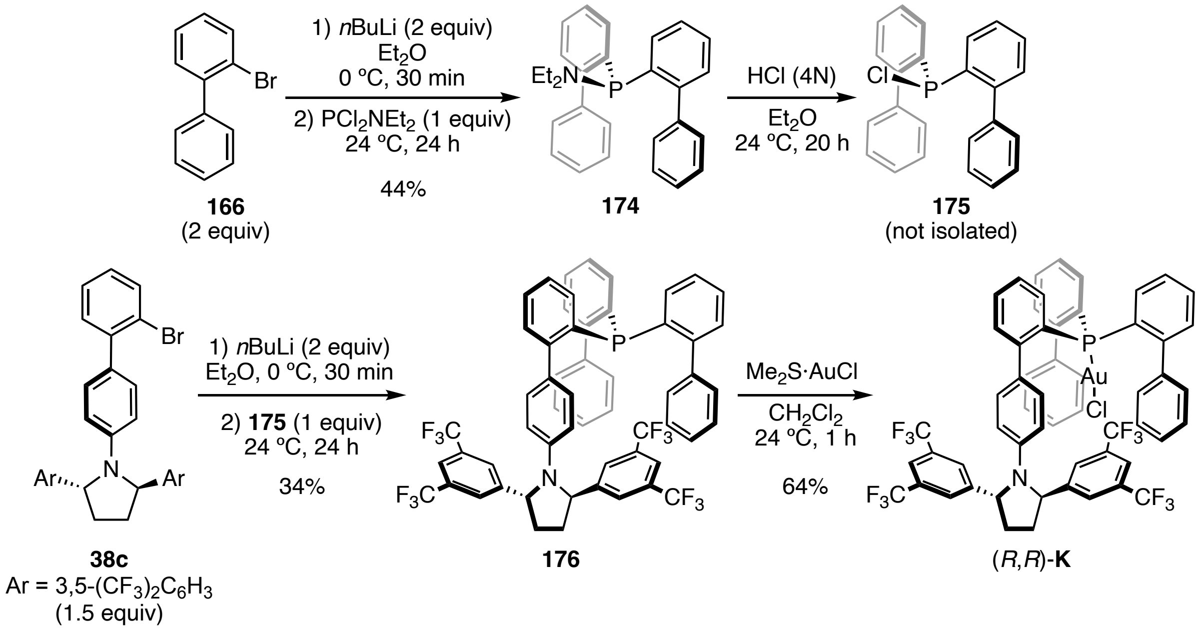
^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.81 (s, 2H), 7.79 (s, 2H), 7.67 (s, 4H), 7.63 (s, 4H), 7.25 – 7.12 (m, 3H), 7.10 – 6.94 (m, 6H), 6.87 – 6.81 (m, 2H), 6.81 – 6.75 (m, 3H), 6.73 – 6.68 (m, 1H), 6.62 (d, *J* = 8.2 Hz, 2H), 6.19 – 6.13 (m, 2H), 6.03 – 5.97 (m, 2H), 5.39 (d, *J* = 6.8 Hz, 2H), 5.31 (d, *J* = 6.4 Hz, 2H), 2.64 – 2.43 (m, 4H), 1.92 – 1.79 (m, 4H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 147.4 (d, *J* = 26.2 Hz), 147.4 (d, *J* = 25.8 Hz), 147.2, 147.0, 142.7, 142.5, 137.4 (d, *J* = 14.3 Hz), 136.7 (d, *J* = 15.0 Hz), 136.6 (d, *J* = 16.2 Hz), 135.1, 134.9, 134.2, 133.8, 132.3 (q, *J* = 33.2 Hz), 132.2 (q, *J* = 33.1 Hz), 131.6 (d, *J* = 4.8 Hz), 131.4 (d, *J* = 5.1 Hz), 130.8 (d, *J* = 4.7 Hz), 130.7 – 130.5 (m), 128.7, 128.6, 128.5, 128.3, 128.2, 127.0, 126.8, 126.7 (d, *J* = 3.8 Hz), 123.9 (q, *J* = 272.7 Hz), 123.8 (q, *J* = 272.7 Hz), 121.8 – 121.6 (m), 113.5, 113.2, 62.9, 62.8, 32.3. **^{31}P{^{1}H} NMR** (162 MHz, CD_2Cl_2) δ –13.7. **^{19}F{^{1}H} NMR** (376 MHz, CD_2Cl_2) δ –63.2, –63.3. **HRMS** (ESI+) calculated for $[C_{70}H_{46}F_{24}N_2P]^+$ 1401.3010 *m/z*; found $[M + H]^+$ 1401.2998 *m/z*. **M.p.** = 133–145 ºC. **α_D^{589}** = +27.6 deg·cm^2·g^{-1} ($CHCl_3$, c 0.1, 302 K).

Complex (*R*,*R*)₂-J

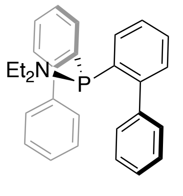
Under argon atmosphere, a mixture of the ligand **173** (30.8 mg, 22.0 µmol, 1.00 equiv) and $Me_2S{\cdot}AuCl$ (6.50 mg, 22.0 µmol, 1.00 equiv) in dichloromethane (220 µL, 0.1 M) was stirred at 24 ºC for 1 h. The crude was filtered over neutral alumina, the volatiles were evaporated under vacuum, and further purify by flash column chromatography (SiO_2, cyclohexane/EtOAc from 10:0 to 8:2) affording the gold(I) complex (*R*,*R*)$_2$-**J** (33.0 mg, 20.2 µmol, 92% yield) as a white solid.

^{1}H NMR (400 MHz, CD$_2$Cl$_2$) δ 7.87 (s, 2H), 7.79 (d, *J* = 1.7 Hz, 4H), 7.72 (s, 2H), 7.65 (d, *J* = 1.7 Hz, 4H), 7.38 (tt, *J* = 7.6, 1.4 Hz, 1H), 7.35 – 7.24 (m, 4H), 7.24 – 7.16 (m, 2H), 7.11 (dtdd, *J* = 10.3, 7.6, 4.1, 1.4 Hz, 4H), 6.86 (ddd, *J* = 7.1, 5.0, 1.6 Hz, 1H), 6.79 (ddd, *J* = 11.6, 7.9, 1.3 Hz, 1H), 6.64 (d, *J* = 8.0 Hz, 2H), 6.16 – 6.08 (m, 2H), 5.98 (q, *J* = 8.3 Hz, 4H), 5.39 (d, *J* = 6.6 Hz, 2H), 5.35 (d, *J* = 7.1 Hz, 2H), 2.65 – 2.49 (m, 4H), 1.90 – 1.76 (m, 4H). **^{13}C{^{1}H} NMR** (126 MHz, CD$_2$Cl$_2$) δ 148.2 (d, *J* = 15.7 Hz), 147.5 (d, *J* = 14.7 Hz), 147.1, 143.6, 143.4, 135.7 (d, *J* = 15.1 Hz), 134.7 (d, *J* = 6.1 Hz), 133.6 (d, *J* = 7.3 Hz), 133.0 (d, *J* = 8.0 Hz), 132.2 (q, *J* = 33.2 Hz), 131.7 (d, *J* = 2.5 Hz), 131.4 (d, *J* = 8.1 Hz), 131.1, 130.9 (d, *J* = 60.7 Hz), 130.9 (d, *J* = 2.2 Hz), 130.9 (d, *J* = 2.3 Hz), 130.2, 130.0 (d, *J* = 64.8 Hz), 129.7 (d, *J* = 2.7 Hz), 129.6, 129.5 (d, *J* = 7.8 Hz), 129.2, 128.8, 128.7, 127.3 (d, *J* = 15.5 Hz), 127.2 (d, *J* = 15.9 Hz), 127.0 – 126.9 (m), 126.8 – 126.7 (m), 124.0 (q, *J* = 272.7 Hz), 123.7 (q, *J* = 272.7 Hz), 121.9 – 121.3 (m), 114.4, 113.7, 63.3, 63.2, 32.4, 32.3. **^{31}P{^{1}H} NMR** (162 MHz, CD$_2$Cl$_2$) δ 22.8. **^{19}F{^{1}H} NMR** (376 MHz, CD$_2$Cl$_2$) δ –62.9, –63.2. **HRMS** (ESI+) calculated for $[C_{70}H_{45}AuClF_{24}N_2NaP]^+$ 1655.2184 *m/z*; found $[M + Na]^+$ 1655.2144 *m/z*. **M.p.** = >148 ºC (decomposition; CH$_2$Cl$_2$). **α_D^{589}** = +23.5 deg·cm^2·g^{-1} (CH$_2$Cl$_2$, c 0.1, 304 K).

Synthesis of the chiral gold(I) complex (*R*,*R*)-K



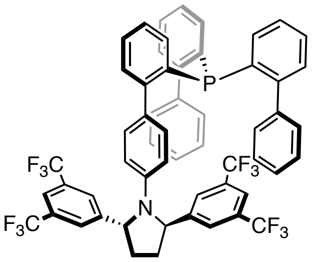
1,1-di([1,1'-biphenyl]-2-yl)-*N*,*N*-diethylphosphanamine, 174



Under argon atmosphere, a solution of 2-bromobiphenyl **166** (643 mg, 2.76 mmol, 4.00 equiv) in diethyl ether (6.9 mL, 0.4 M) was charged in a pressure tube and cooled down to 0 ºC. Then, *n*BuLi (2.2 M in hexane) (1.25 mL, 2.76 mmol, 4.00 equiv) was added dropwise and the mixture was stirred at the same temperature for 30 min. PCl$_2$NEt$_2$ (100 μL, 690 μmol, 1.00 equiv) was slowly added and the reaction was warmed up to 24 ºC and stirred for 24 h. After completion (checked by UHPLC-MS), the reaction was quenched with water and extracted with dichloromethane (3x). The combined organic phases were washed with brine, dried over Mg_2SO_4 and concentrated under reduced pressure. The crude was purified by flash column chromatography (SiO_2, cyclohexane/CH_2Cl_2 from 10:0 to 8:2) affording **174** (280 mg, 690 μmol, 99% yield) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.25 (m, 3H), 7.25 – 7.23 (m, 1H), 7.23 – 7.22 (m, 1H), 7.22 – 7.18 (m, 7H), 7.08 – 7.01 (m, 6H), 2.90 (dq, *J* = 8.8, 7.0 Hz, 4H), 0.72 (t, *J* = 7.0 Hz, 6H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 146.2 (d, *J* = 26.4 Hz), 142.2 (d, *J* = 4.5 Hz), 139.4 (d, *J* = 18.9 Hz), 131.9 (d, *J* = 2.4 Hz), 129.9 (d, *J* = 3.3 Hz), 129.6 (d, *J* = 4.5 Hz), 128.0, 127.5, 126.7 (d, *J* = 4.7 Hz), 44.6 (d, *J* = 17.8 Hz), 14.5 (d, *J* = 3.1 Hz). **^{31}P{^{1}H} NMR** (202 MHz, $CDCl_3$) δ 51.5. **HRMS** (ESI+) calculated for $[C_{28}H_{29}NP]^+$ 410.2032 *m/z*; found $[M + H]^+$ 410.2047 *m/z*.

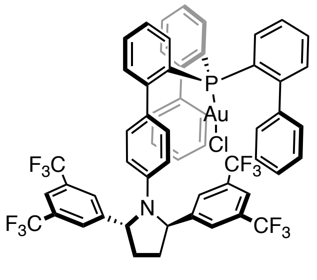
Ligand 176



Under argon atmosphere, a solution of **174** (117 mg, 286 μmol, 1.00 equiv) in diethyl ether (0.4 mL, 0.7 M) was charged in a Schlenk and cooled down to 0 ºC. HCl (143 μL, 4 N in dioxane) was then added to the mixture and the reaction was warmed up to 24 ºC and stirred at that temperature for 24 h yielding di([1,1'-biphenyl]-2-yl)chlorophosphane **175** quantitatively which was poured into a 2 mL microwave vial through filtration via cannula rinsing with anhydrous diethyl ether. In a separate 20 mL microwave vial, under argon atmosphere, a solution of **38c** (311 mg, 429 μmol, 1.50 equiv) in diethyl ether (0.5 mL, 0.6 M) was charged and cooled down to 0 ºC. Then, *n*BuLi (193 μL, 429 μmol, 1.50 equiv, 2.22 M) was added dropwise and the mixture was stirred at the same temperature for 30 min. A solution of di([1,1'-biphenyl]-2-yl)chlorophosphane in the minimum amount needed of diethyl ether was then slowly added to the mixture and the reaction was allowed to warm up to 24 ºC and stirred for 24 h. The reaction is checked by UHPLC-MS, quenched with water and extracted with dichloromethane (3x). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by flash column chromatography (SiO_2, cyclohexane/CH_2Cl_2 from 10:0 to 8:2) affording the ligand **176** (96 mg, 98 μmol, 34% yield) as a white solid.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.81 (s, 2H), 7.68 (s, 4H), 7.31 (td, *J* = 7.5, 1.4 Hz, 1H), 7.23 (dtd, *J* = 10.7, 7.5, 1.4 Hz, 2H), 7.17 (td, *J* = 7.5, 1.4 Hz, 1H), 7.15 – 7.09 (m, 4H), 7.08 – 6.97 (m, 5H), 6.97 – 6.91 (m, 3H), 6.89 (ddd, *J* = 7.7, 3.1, 1.4 Hz, 1H), 6.84 (ddd, *J* = 7.7, 2.9, 1.3 Hz, 1H), 6.81 (dt, *J* = 8.3, 1.3 Hz, 2H), 6.66 (ddd, *J* = 7.8, 3.9, 2.1 Hz, 4H), 6.18 – 6.12 (m, 2H), 5.41 (d, *J* = 7.1 Hz, 2H), 2.64 – 2.51 (m, 2H), 1.95 – 1.81 (m, 2H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 148.2 (d, *J* = 25.3 Hz), 148.0 (d, *J* = 29.0 Hz), 147.9 (d, *J* = 24.7 Hz), 147.2, 142.6, 142.1, 142.0, 136.8 (d, *J* = 19.2 Hz), 136.8 (d, *J* = 19.4 Hz), 136.0 (d, *J* = 19.0 Hz), 135.6, 134.9, 132.2 (q, *J* = 33.1 Hz), 131.4 (d, *J* = 5.6 Hz), 130.9 (d, *J* = 5.5 Hz), 130.4 (d, *J* = 4.6 Hz), 130.1 (d, *J* = 4.3 Hz), 129.9, 129.9, 129.9, 129.8 (d, *J* = 4.4 Hz), 128.7, 128.6, 128.5, 127.5, 127.5, 127.4, 127.3, 127.0, 126.9, 126.8 (d, *J* = 3.7 Hz), 126.8, 123.8 (q, *J* = 272.7 Hz), 121.9 – 121.4 (m), 113.3, 63.0, 32.4. **^{31}P{^{1}H} NMR** (202 MHz, CD_2Cl_2) δ –23.6. **^{19}F{^{1}H} NMR** (471 MHz, CD_2Cl_2) δ –63.1. **HRMS** (ESI+) calculated for $[C_{56}H_{39}F_{12}NP]^+$ 984.2623 *m/z*; found $[M + H]^+$ 984.2615 *m/z*. **M.p.** = 111–143 ºC. **α_D^{589}** = +23.3 deg·cm^2·g^{-1} (CH_2Cl_2, c 0.1, 299 K).

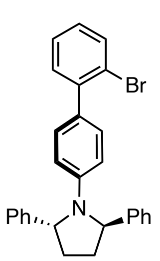
Complex (*R*,*R*)-K



Under argon atmosphere, a mixture of the ligand **176** (94 mg, 96 μmol, 1.0 equiv) and $Me_2S{\cdot}AuCl$ (28 mg, 96 μmol, 1.0 equiv) in dichloromethane (1.4 mL, 0.07 M) was stirred at 24 ºC for 1 h. The crude was filtered over neutral alumina, evaporated and further purified by flash column chromatography (SiO_2, cyclohexane/EtOAc from 10:0 to 8:2) affording the gold(I) complex (*R*,*R*)-**K** (70 mg, 58 μmol, 60% yield) as a white solid.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.81 (s, 2H), 7.70 (s, 4H), 7.57 – 7.46 (m, 3H), 7.41 – 7.31 (m, 4H), 7.30 – 7.22 (m, 4H), 7.21 – 7.17 (m, 2H), 7.15 – 7.09 (m, 1H), 7.05 (t, *J* = 7.7 Hz, 2H), 6.92 (t, *J* = 7.6 Hz, 2H), 6.62 (s, 2H), 6.52 (d, *J* = 8.1 Hz, 2H), 6.47 (d, *J* = 7.5 Hz, 2H), 6.07 (d, *J* = 9.0 Hz, 2H), 5.33 (d, *J* = 5.1 Hz, 2H, overlapped with CD_2Cl_2), 2.62 – 2.49 (m, 2H), 1.82 – 1.71 (m, 2H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 148.2 (d, *J* = 16.3 Hz), 147.9 (d, *J* = 16.2 Hz), 147.9 (d, *J* = 15.5 Hz), 147.1, 144.0, 140.8 (d, *J* = 7.1 Hz), 140.5 (d, *J* = 6.9 Hz), 136.0 (d, *J* = 5.8 Hz), 135.8 – 135.6 (m), 135.6 – 135.3 (m), 133.3 (d, *J* = 8.5 Hz), 132.7 (d, *J* = 8.2 Hz), 132.5 (d, *J* = 8.4 Hz), 132.1 (q, *J* = 33.2 Hz), 131.2 – 131.0 (m), 130.5 (d, *J* = 60.2 Hz), 130.4, 130.3 (d, *J* = 60.0 Hz), 130.0 (d, *J* = 7.4 Hz), 129.8, 129.7, 129.2 (d, *J* = 60.7 Hz), 128.4 – 128.1 (m), 128.1, 127.9, 127.7 (d, *J* = 7.7 Hz), 127.7 (d, *J* = 8.1 Hz), 127.4 (d, *J* = 8.3 Hz), 127.0 – 126.8 (m), 123.9 (q, *J* = 272.8 Hz), 121.9 – 121.5 (m), 114.0, 63.3, 32.4. **^{31}P{^{1}H} NMR** (202 MHz, CD_2Cl_2) δ 12.3. **^{19}F{^{1}H} NMR** (471 MHz, CD_2Cl_2) δ –62.8. **HRMS** (ESI+) calculated for $[C_{56}H_{38}AuClF_{12}NNaP]^+$ 1238.1797 *m/z*; found $[M + Na]^+$ 1238.1778 *m/z*. **M.p.** = >243 ºC (decomposition). **α_D^{589}** = +19.6 deg·cm^2·g^{-1} (CH_2Cl_2, c 0.1, 298 K).

(2*R*,5*R*)-1-(2'-Bromo-[1,1'-biphenyl]-4-yl)-2,5-diphenylpyrrolidine, 176



It was synthesized following the procedure reported and used for the synthesis of its enantiomer.23 Under argon atmosphere, to a solution of (1*S*,4*S*)-1,4-diphenylbutane-1,4-diol (*S,S*)**-75a** (1.00 g, 4.13 mmol, 1.00 equiv) in CH_2Cl_2 (41.3 mL, 0.1 M) at -20 ºC were added NEt_3 (1,73 mL, 12.4 mmol, 3.00 equiv) and methanesulfonyl chloride (0.830 mL, 10.7 mmol, 2.60 equiv). The mixture was stirred for 2.5 h at -20 ºC. Then, a solution of aniline **30** (5.12 g, 20.6 mmol, 5.00 equiv) in CH_2Cl_2 (8.3 mL, final concentration 0.08 M) was added and the resulting solution was stirred at 24 ºC for 40 h. The volatiles were removed under reduced pressure and the organic materials were dissolved in EtOAc. The organic phase was washed with brine and sat. solution of $NaHCO_3$, dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash column chromatography (SiO_2, cyclohexane/CH_2Cl_2 from 1:0 to 1:1) affording (*R*,*R*)-**176** (936 mg, 2.06 µmol, 50% yield) as a white solid.

The data were consistent with those previously reported.23 **^{1}H NMR** (400 MHz, CD_2Cl_2) δ7.58 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.38 – 7.33 (m, 4H), 7.30 – 7.20 (m, 8H), 7.11 – 7.04 (m, 3H), 6.43 – 6.37 (m, 2H), 5.27 (d, *J* = 7.3 Hz, 2H), 2.66 – 2.54 (m, 2H), 1.88 – 1.75 (m, 2H). **^{13}C NMR** (101 MHz, CD_2Cl_2) δ145.1, 144.6, 143.0, 133.6, 132.0, 130.3, 129.1, 128.7, 128.3, 127.9, 127.3, 126.7, 123.1, 113.7, 63.9, 32.8. **M.p.** = 120–130 ºC. **α_D^{589}** = +58.5 deg·cm^2·g^{-1} ($CHCl_3$, c 0.1, 298 K).

Crystallographic Data

Complex (*R*,*R*)-A

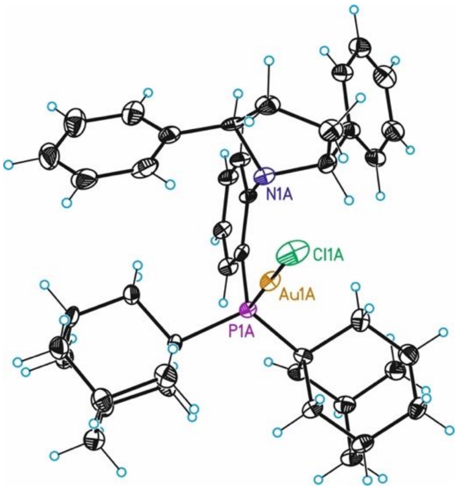


Table 1. Crystal data and structure refinement for Complex (*R*,*R*)-**A**.

Identification code	mo_NFA0143_0m	
Empirical formula	C84 H99.30 Au2 Cl2 N2 P2	
Formula weight	1663.72	
Temperature	100(2)K	
Wavelength	0.71073 Å	
Crystal system	monoclinic	
Space group	P 21	
Unit cell dimensions	a = 9.8797(4)Å	a= 90°.
	b = 17.2620(7)Å	b = 94.5075(13)°.
	c = 20.6821(9)Å	g = 90°.
Volume	3516.3(3) Å^3	
Z	2	
Density (calculated)	1.571 Mg/m^3	
Absorption coefficient	4.337 mm^{-1}	
F(000)	1679	
Crystal size	0.100 x 0.100 x 0.010 mm^3	
Theta range for data collection	0.988 to 31.741°.	
Index ranges	-13<=h<=14,-25<=k<=16,-29<=l<=30	
Reflections collected	47251	
Independent reflections	17726[R(int) = 0.0537]	
Completeness to theta =31.741°	99.0%	
Absorption correction	Multi-scan	
Max. and min. transmission	0.74 and 0.57	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	17726/ 421/ 1011	
Goodness-of-fit on F^2	1.058	
Final R indices [I>2sigma(I)]	R1 = 0.0436, wR2 = 0.0907	
R indices (all data)	R1 = 0.0544, wR2 = 0.0946	
Flack parameter	x =-0.004(6)	
Largest diff. peak and hole	2.415 and -1.706 e.Å^{-3}	

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

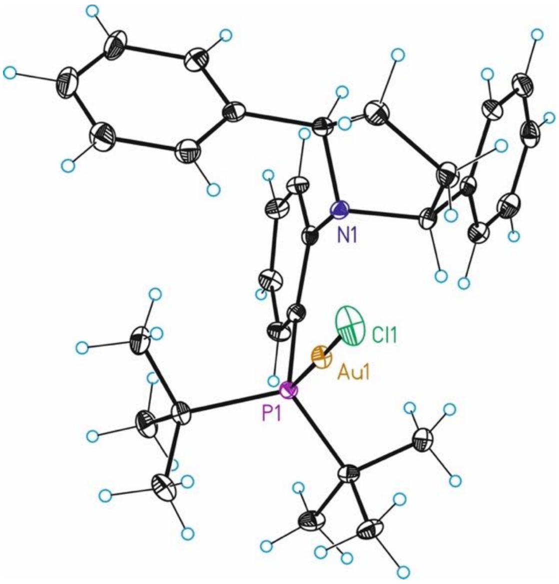


Table 1. Crystal data and structure refinement for Complex (*R*,*R*)-**B**.

Identification code	mo_NFA01060_0m	
Empirical formula	C30 H38 Au Cl N P	
Formula weight	676.00	
Temperature	100(2)K	
Wavelength	0.71073 Å	
Crystal system	monoclinic	
Space group	P 21	
Unit cell dimensions	a = 8.0803(3)Å	a= 90°.
	b = 17.6290(6)Å	b = 99.7971(8)°.
	c = 9.7608(3)Å	g = 90°.
Volume	1370.13(8) Å^3	
Z	2	
Density (calculated)	1.639 Mg/m^3	
Absorption coefficient	5.543 mm^{-1}	
F(000)	672	
Crystal size	0.300 x 0.100 x 0.050 mm^3	
Theta range for data collection	2.117 to 31.510°.	
Index ranges	-11<=h<=7,-24<=k<=24,-14<=l<=14	
Reflections collected	13880	
Independent reflections	8164[R(int) = 0.0195]	
Completeness to theta =31.510°	95.9%	
Absorption correction	Multi-scan	
Max. and min. transmission	0.74 and 0.56	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	8164/ 1/ 313	
Goodness-of-fit on F^2	1.033	
Final R indices [I>2sigma(I)]	R1 = 0.0157, wR2 = 0.0374	
R indices (all data)	R1 = 0.0162, wR2 = 0.0376	
Flack parameter	x =-0.009(3)	
Largest diff. peak and hole	0.775 and -0.572 e.Å^{-3}	

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

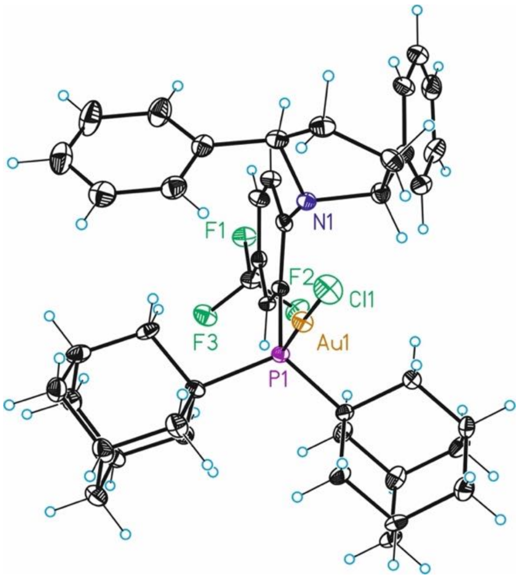


Table 1. Crystal data and structure refinement for Complex (*R*,*R*)-**C**.

Identification code	mo_NFA01059_0m	
Empirical formula	C44 H51 Au Cl3 F3 N P	
Formula weight	985.14	
Temperature	100(2)K	
Wavelength	0.71073 Å	
Crystal system	orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 10.1591(6)Å	a= 90°.
	b = 10.2418(6)Å	b = 90°.
	c = 37.962(2)Å	g = 90°.
Volume	3949.9(4) Å^3	
Z	4	
Density (calculated)	1.657 Mg/m^3	
Absorption coefficient	4.016 mm^{-1}	
F(000)	1976	
Crystal size	0.300 x 0.100 x 0.020 mm^3	
Theta range for data collection	1.609 to 30.660°.	
Index ranges	-14<=h<=14,-14<=k<=12,-44<=l<=47	
Reflections collected	76480	
Independent reflections	11339[R(int) = 0.0435]	
Completeness to theta =30.660°	94.2%	
Absorption correction	Multi-scan	
Max. and min. transmission	0.74 and 0.58	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	11339/ 0/ 479	
Goodness-of-fit on F^2	1.157	
Final R indices [I>2sigma(I)]	R1 = 0.0301, wR2 = 0.0672	
R indices (all data)	R1 = 0.0308, wR2 = 0.0675	
Flack parameter	x =0.0079(19)	
Largest diff. peak and hole	1.684 and -2.293 e.Å^{-3}	

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

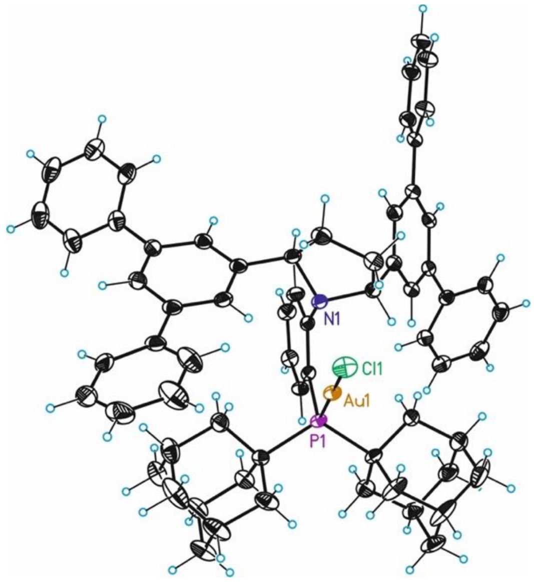


Table 1. Crystal data and structure refinement for Complex (*R*,*R*)-**E**.

Identification code	NFA01-091	
Empirical formula	C71.62 H78.32 Au Cl6.84 N P	
Formula weight	1423.53	
Temperature	100(2)K	
Wavelength	0.71073 Å	
Crystal system	orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 10.16445(12)Å	a= 90°.
	b = 20.9654(3)Å	b = 90°.
	c = 29.6364(4)Å	g = 90°.
Volume	6315.57(13) Å^3	
Z	4	
Density (calculated)	1.497 Mg/m^3	
Absorption coefficient	2.688 mm^{-1}	
F(000)	2901	
Crystal size	0.200 x 0.100 x 0.070 mm^3	
Theta range for data collection	3.403 to 31.128°.	
Index ranges	-14<=h<=14,-29<=k<=30,-42<=l<=42	
Reflections collected	134716	
Independent reflections	18960[R(int) = 0.0324]	
Completeness to theta =31.128°	95.4%	
Absorption correction	Multi-scan	
Max. and min. transmission	1.00 and 0.69	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	18960/ 282/ 815	
Goodness-of-fit on F^2	1.136	
Final R indices [I>2sigma(I)]	R1 = 0.0295, wR2 = 0.0699	
R indices (all data)	R1 = 0.0330, wR2 = 0.0712	
Flack parameter	x =0.0003(12)	
Largest diff. peak and hole	1.322 and -1.837 e.Å^{-3}	

Product 86a

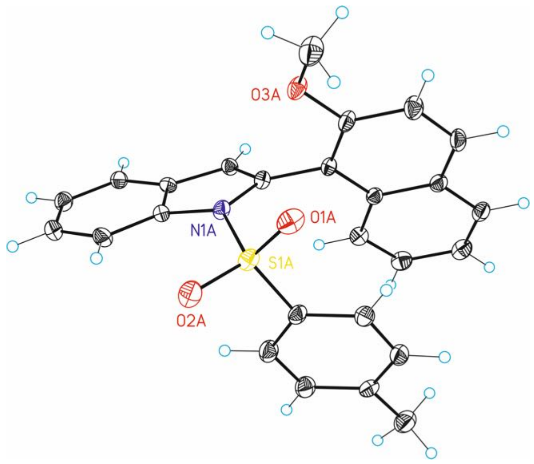


Table 1. Crystal data and structure refinement for Product **86a**.

Identification code	mo_LJN063-05	
Empirical formula	C26 H21 N O3 S	
Formula weight	427.50	
Temperature	100(2)K	
Wavelength	0.71073 Å	
Crystal system	monoclinic	
Space group	P 21	
Unit cell dimensions	a = 7.8486(5)Å	a= 90°.
	b = 13.8902(9)Å	b = 92.4847(19)°.
	c = 19.2063(12)Å	g = 90°.
Volume	2091.9(2) Å^3	
Z	4	
Density (calculated)	1.357 Mg/m^3	
Absorption coefficient	0.184 mm^{-1}	
F(000)	896	
Crystal size	? x ? x ? mm^3	
Theta range for data collection	1.061 to 31.543°.	
Index ranges	-11<=h<=11,-20<=k<=20,-28<=l<=28	
Reflections collected	13072	
Independent reflections	13072[R(int) = ?]	
Completeness to theta =31.543°	99.8%	
Absorption correction	Multi-scan	
Max. and min. transmission	0.74 and 0.54	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	13072/ 1/ 564	
Goodness-of-fit on F^2	1.036	
Final R indices [I>2sigma(I)]	R1 = 0.0544, wR2 = 0.1314	
R indices (all data)	R1 = 0.0592, wR2 = 0.1354	
Flack parameter	x =-0.04(5)	
Largest diff. peak and hole	0.312 and -0.632 e.Å^{-3}	

Product 86n

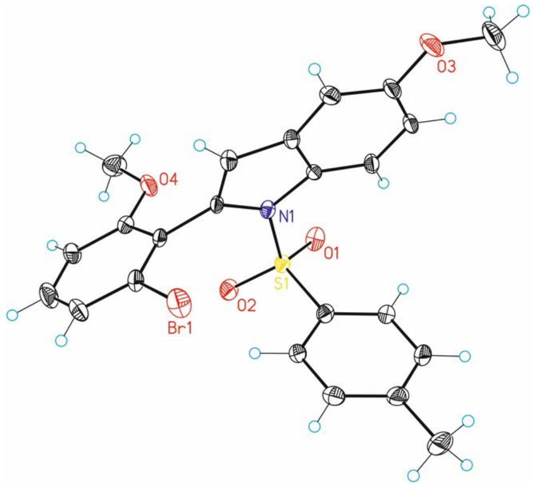


Table 1. Crystal data and structure refinement for Product **86n**.

Identification code	MP-1-040	
Empirical formula	C23 H20 Br N O4 S	
Formula weight	486.37	
Temperature	100(2)K	
Wavelength	0.71073 Å	
Crystal system	orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 7.85550(10)Å	a= 90°.
	b = 16.0243(3)Å	b = 90°.
	c = 16.5968(3)Å	g = 90°.
Volume	2089.19(6) Å^3	
Z	4	
Density (calculated)	1.546 Mg/m^3	
Absorption coefficient	2.098 mm^{-1}	
F(000)	992	
Crystal size	0.400 x 0.400 x 0.300 mm^3	
Theta range for data collection	2.542 to 29.615°.	
Index ranges	-10<=h<=10,-22<=k<=20,-22<=l<=22	
Reflections collected	30402	
Independent reflections	5417[R(int) = 0.0348]	
Completeness to theta =29.615°	94.7%	
Absorption correction	Multi-scan	
Max. and min. transmission	1.00 and 0.77	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5417/ 0/ 274	
Goodness-of-fit on F^2	1.016	
Final R indices [I>2sigma(I)]	R1 = 0.0370, wR2 = 0.1188	
R indices (all data)	R1 = 0.0407, wR2 = 0.1208	
Flack parameter	x =0.016(3)	
Largest diff. peak and hole	1.157 and -0.750 e.Å^{-3}	

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

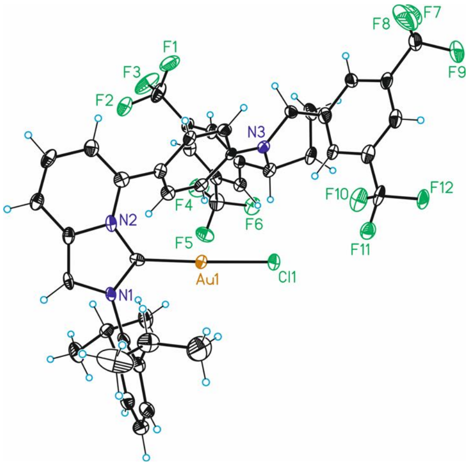


Table 1. Crystal data and structure refinement for Complex (*R*,*R*)-**G**.

Identification code	mo_LJNNHC403_0m_5	
Empirical formula	C45 H37 Au Cl F12 N3	
Formula weight	1080.19	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 11.624(2) Å	α= 64.349(4)°.
	b = 13.751(3) Å	β= 81.438(5)°.
	c = 15.771(3) Å	γ = 69.115(5)°.
Volume	2123.1(7) Å^3	
Z	2	
Density (calculated)	1.690 Mg/m^3	
Absorption coefficient	3.617 mm^{-1}	
F(000)	1064	
Crystal size	0.120 x 0.060 x 0.050 mm^3	
Theta range for data collection	1.739 to 27.851°.	
Index ranges	-14<=h<=14, -15<=k<=17, 0<=l<=20	
Reflections collected	8556	
Independent reflections	8556 [R(int) = 0.0907]	
Completeness to theta = 25.242°	98.3 %	
Absorption correction	Twinabs	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	8556 / 156 / 620	
Goodness-of-fit on F^2	1.040	
Final R indices [I>2sigma(I)]	R1 = 0.0541, wR2 = 0.1310	
R indices (all data)	R1 = 0.0705, wR2 = 0.1422	
Extinction coefficient	n/a	
Largest diff. peak and hole	4.125 and -2.017 e.Å^{-3}	

Complex (*R*,*R*)$_3$-I

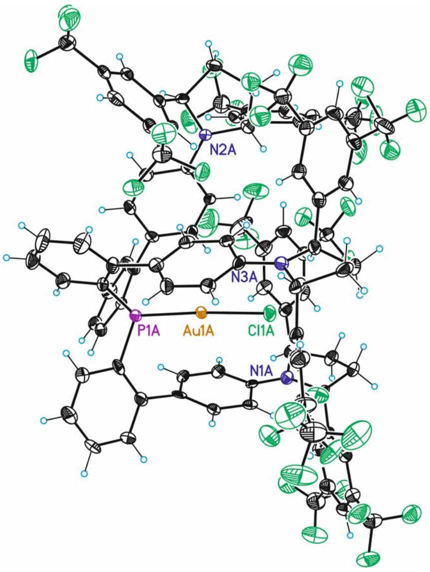


Table 1. Crystal data and structure refinement for Complex (*R*,*R*)$_3$-**I**.

Identification code	mo_AAB3158-b	
Empirical formula	C204.25 H147 Au2 Cl2 F72 N6 P2	
Formula weight	4580.04	
Temperature	100(2)K	
Wavelength	0.71073 Å	
Crystal system	monoclinic	
Space group	P 21	
Unit cell dimensions	a = 18.663(2)Å	a= 90º.
	b = 18.9561(19)Å	b = 98.831(3)º.
	c = 27.919(3)Å	g = 90º.
Volume	9760.0(18) Å^3	
Z	2	
Density (calculated)	1.558 Mg/m^3	
Absorption coefficient	1.669 mm^{-1}	
F(000)	4569	
Crystal size	0.200 x 0.200 x 0.010 mm^3	
Theta range for data collection	1.104 to 26.803º.	
Index ranges	-19<=h<=23,-24<=k<=21,-34<=l<=35	
Reflections collected	142758	
Independent reflections	40589[R(int) = 0.1252]	
Completeness to theta =26.803º	99.6%	
Absorption correction	Multi-scan	
Max. and min. transmission	0.74 and 0.60	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	40589/ 3240/ 3525	
Goodness-of-fit on F^2	0.982	
Final R indices [I>2sigma(I)]	R1 = 0.0480, wR2 = 0.1061	
R indices (all data)	R1 = 0.0678, wR2 = 0.1126	
Flack parameter	x =-0.022(4)	
Largest diff. peak and hole	1.687 and -1.586 e.Å^{-3}	

Complex (*R*,*R*)$_2$-J

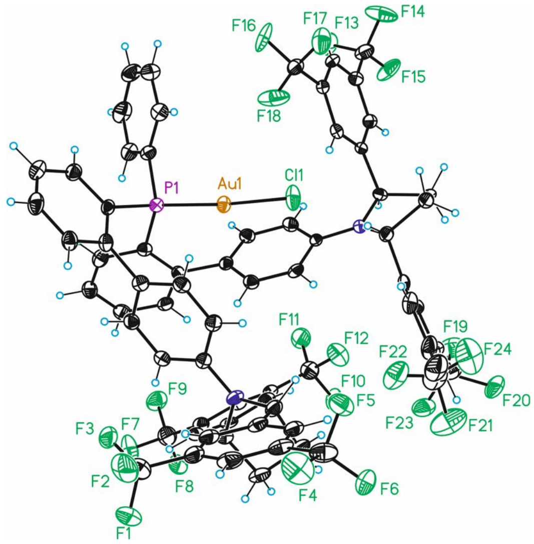


Table 1. Crystal data and structure refinement for Complex (*R*,*R*)$_2$-**J**.

Identification code	AAB-3-157-P21212	
Empirical formula	C80.50 H69 Au Cl F24 N2 P	
Formula weight	1783.76	
Temperature	100(2)K	
Wavelength	0.71073 Å	
Crystal system	orthorhombic	
Space group	P 21 21 2	
Unit cell dimensions	a = 16.4392(4)Å	a= 90º.
	b = 24.8406(5)Å	b = 90º.
	c = 18.8716(5)Å	g = 90º.
Volume	7706.4(3) Å^3	
Z	4	
Density (calculated)	1.537 Mg/m^3	
Absorption coefficient	2.067 mm^{-1}	
F(000)	3572	
Crystal size	0.500 x 0.060 x 0.020 mm^3	
Theta range for data collection	3.500 to 30.152º.	
Index ranges	-23<=h<=16,-32<=k<=34,-25<=l<=26	
Reflections collected	74556	
Independent reflections	20454[R(int) = 0.0670]	
Completeness to theta =30.152º	92.5%	
Absorption correction	Multi-scan	
Max. and min. transmission	1.00 and 0.80	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	20454/ 941/ 1264	
Goodness-of-fit on F^2	1.023	
Final R indices [I>2sigma(I)]	R1 = 0.0402, wR2 = 0.0645	
R indices (all data)	R1 = 0.0627, wR2 = 0.0692	
Flack parameter	x =-0.0173(19)	
Largest diff. peak and hole	1.678 and -1.719 e.Å^{-3}	

Complex (*R*,*R*)-K

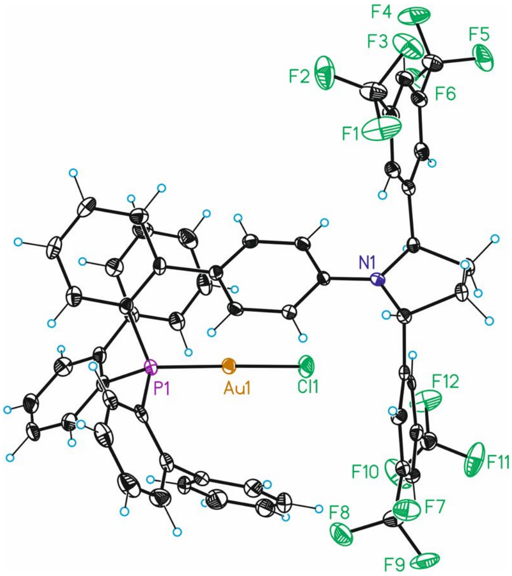


Table 1. Crystal data and structure refinement for Complex (*R*,*R*)-**K**.

Identification code	VG2020LT	
Empirical formula	C56 H38 Au Cl F12 N P	
Formula weight	1216.26	
Temperature	100(2)K	
Wavelength	0.71073 Å	
Crystal system	orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 8.10619(11)Å	a= 90°.
	b = 11.78923(17)Å	b = 90°.
	c = 50.2506(9)Å	g = 90°.
Volume	4802.23(13) Å^3	
Z	4	
Density (calculated)	1.682 Mg/m^3	
Absorption coefficient	3.240 mm^{-1}	
F(000)	2400	
Crystal size	0.500 x 0.500 x 0.500 mm^3	
Theta range for data collection	3.454 to 29.425°.	
Index ranges	-10<=h<=10,-14<=k<=15,-63<=l<=68	
Reflections collected	36678	
Independent reflections	11820[R(int) = 0.0254]	
Completeness to theta =29.425°	92.1%	
Absorption correction	Multi-scan	
Max. and min. transmission	1.00 and 0.77	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	11820/ 147/ 705	
Goodness-of-fit on F^2	1.177	
Final R indices [I>2sigma(I)]	R1 = 0.0275, wR2 = 0.0543	
R indices (all data)	R1 = 0.0305, wR2 = 0.0547	
Flack parameter	x =-0.0149(18)	
Largest diff. peak and hole	1.466 and -1.145 e.Å^{-3}	

Chapter II: “Amino Acid-Phos Gold(I) Complexes”

Introduction

Amino Acids[1]

Amino acids are organic compounds that contain amino and carboxylic acid functional groups and a side chain (R) in their structure (Figure 1).[2] Their absolute configuration is specified by the D/L system or the *R*/*S* system, the latter more commonly used in organic chemistry.

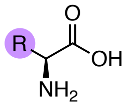
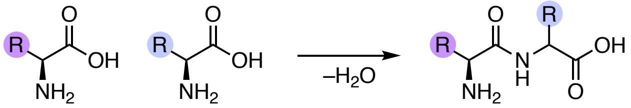


Figure 1. General structure amino acid.

Two amino acids can form a dipeptide through a peptide bond. It is synthesized by the condensation reaction when the carboxylic group of one amino acid reacts with the amino group of other amino acid, affording an amide bond and a molecule of water (Scheme 1). Short chains of amino acids can be linked by peptide bonds forming peptides and if the chains are long, they are called proteins. The formation of this bond needs an activation energy being necessary the chemical modification of the carboxylic bond.



Scheme 1. Dipeptide formation by a peptide bond.

There are hundreds of amino acids present in nature and only 20 α-amino acids are commonly found in proteins, being the L stereoisomer exclusively found. Other uncommon amino acids can be found in proteins created by modifications in common amino acids. They are usually named and showed as neutral structures to avoid nomenclatural problems. Amino acids can be classified according to their structures differing in their side chain (at pH 7) in five different groups (Figure 2): non-polar (aliphatic R groups), aromatic R groups, polar (uncharged R groups), positively or negatively charged R groups.[1]

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[1] Lehninger, A. L.; Nelson, D. L.; Cox, M. M. *Lehninger Principles of Biochemistry*, 4th ed.; W.H. Freeman: New York, **2005**.

[2] Nomenclature and Symbolism for Amino Acids and Peptides. Recommendations 1983. *Eur J Biochem* **1984**, *138*, 9–37.

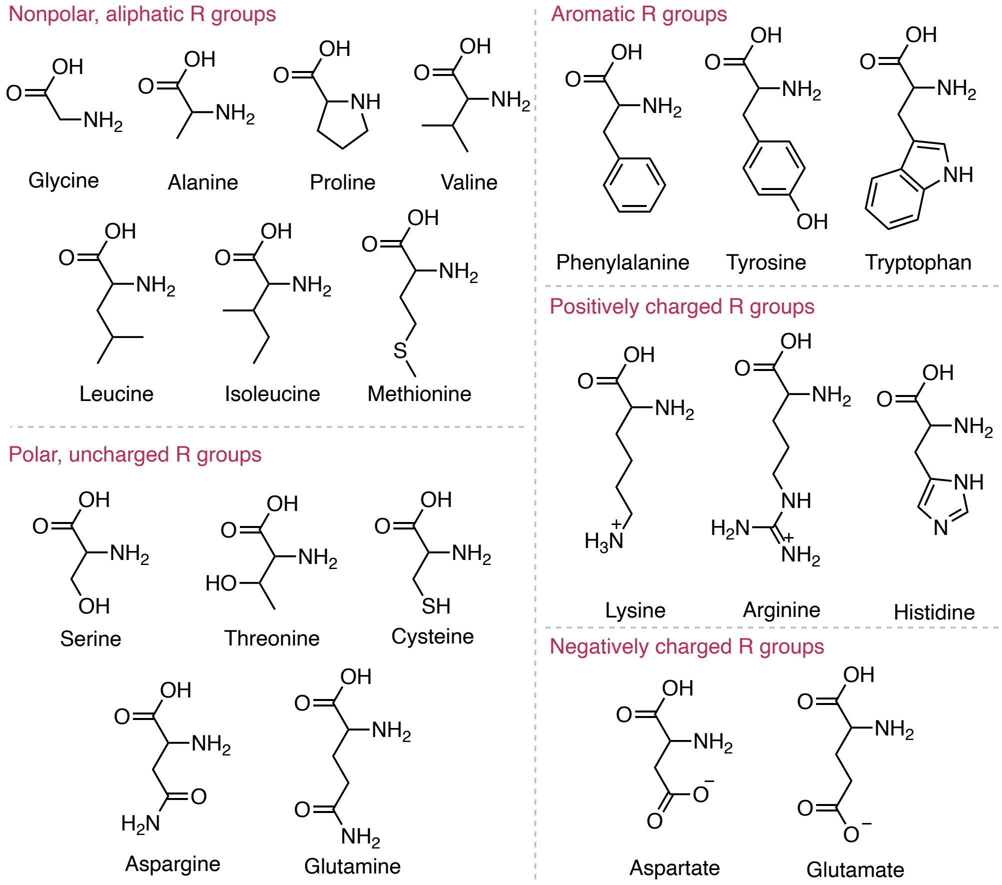

Figure 2. The 20 common amino acids of proteins.

Amino Acids as Catalysts in Asymmetric Organocatalysis

Amino acid can act as catalysts for some reactions. An example is the catalytic activity of histidine in many enzymatic reactions, in acid-base reactions or in the stabilization of intermediates. Other amino acids can also act as nucleophiles or electrophiles, such as cysteine, serine and threonine.[3]

Furthermore, amino acids and peptides are also used as catalysts providing a chiral environment for asymmetric catalyzed transformations,[4] such as in aldol reactions,[5] hydrocyanation,[6] epoxidations[7] and cycloadditions.[8] One of the most used amino acids used in this field is the L-proline. For example, in

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[3] Berg, J. M.; Tymoczko, J. L.; Gatto, G. J.; Stryer, L. *Biochemistry*, Ninth edition.; Macmillan International, Higher Eduction: New York, **2019**.

[4] Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481–2495

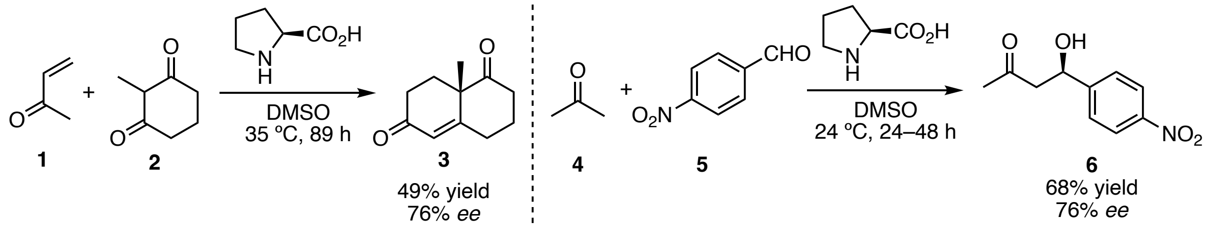
[5] (a) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 496–497. (b) List, B. J. *Am. Chem. Soc.* **2000**, *122*, 9336–9337. (c) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827–833.

[6] (a) Inoue, S.; Oku, J.-I. J. *Chem. Soc. Chem. Commun.* **1981**, 229–230. (b) Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. *J. Am. Chem. Soc.* **1996**, *118*, 4910–4911. (c) Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. *Amino Acids* **1996**, *11*, 259–268.

[7] (a) Juliá, S.; Masana, J.; Vega, J. C. *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 929–931. (b) Porter, M. J.; Skidmore, J. *Chem. Commun*. **2000**, 1215–1225.

[8] Riant, O.; Kagan, H. B. *Tetrahedron Lett.* **1989**, *52*, 7403–7406.

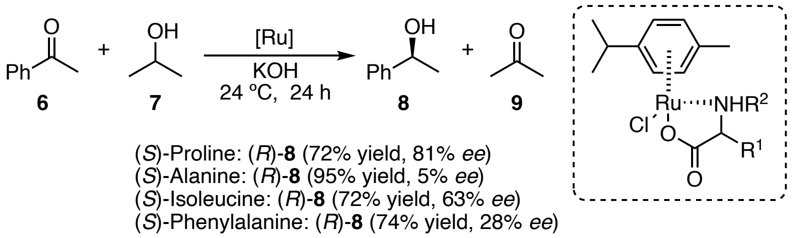
2000, Barbas III reported the synthesis of the Wieland-Miescher ketone **3**, through an L-proline-catalyzed asymmetric Robinson annulation reaction (Scheme 2, left).[9] Other example was reported in 2001 for the asymmetric aldol addition reaction of acetone to **5** (Scheme 2, right).[10]



Scheme 2. Proline-catalyzed asymmetric reactions.

Amino Acids in Asymmetric Metal Catalysis

Amino acids have been also used in asymmetric catalysis in combination with metals.[11] For example, amino acids have been used as ligands in the catalysis for the asymmetric transfer hydrogenation of ketones using $[RuCl_2(arene)]_2$.[12] It was studied the hydrogenation of the acetophenone **6** in 2-propanol **7** to afford **8** (Scheme 3). The results showed that the enantioinduction was highly dependent on the amino acid tested.



(*S*)-Proline: (*R*)-**8** (72% yield, 81% *ee*)
(*S*)-Alanine: (*R*)-**8** (95% yield, 5% *ee*)
(*S*)-Isoleucine: (*R*)-**8** (72% yield, 63% *ee*)
(*S*)-Phenylalanine: (*R*)-**8** (74% yield, 28% *ee*)

Scheme 3. Asymmetric catalysis of transfer hydrogenation of ketones.

Another example is the asymmetric imine alkynylation has been reported via hydrogen-bonding amino acid derivatives catalyzed by copper. This method was used to access to different propargylic amines **12** in good yields and excellent enantioselectivities (Scheme 4).[13]

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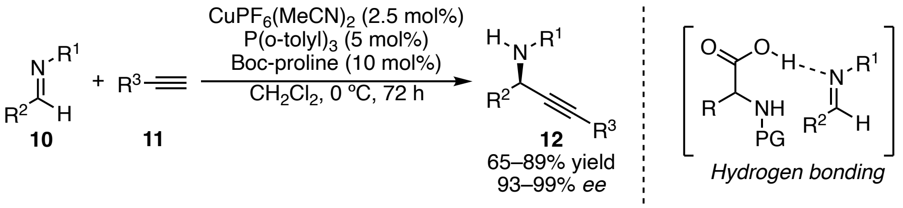
[9] Bui, T.; Barbas, C. F. *Tetrahedron Letters* **2000**, *41*, 6951–6954.

[10] Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F. *J. Am. Chem. Soc.* **2001**, *123*, 5260–5267.

[11] Paradowska, J.; Stodulski, M.; Mlynarski, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 4288–4297.

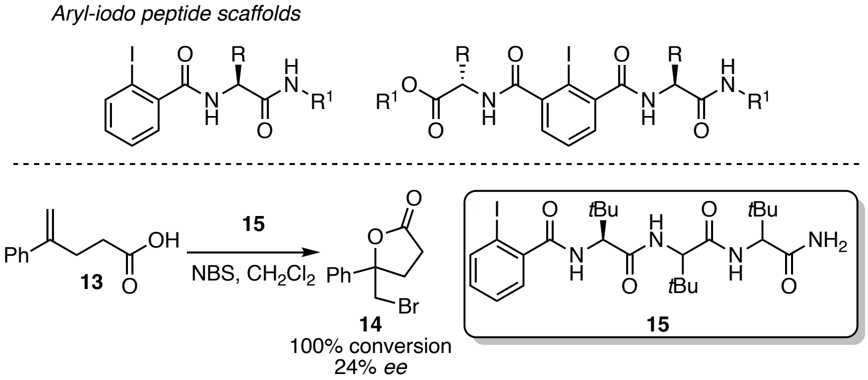
[12] Ohta, T.; Nakahara, S.; Shigemura, Y.; Hattori, K.; Furukawa, I. *Appl. Organometal. Chem.* **2001**, *15*, 699–709.

[13] Lu, Y.; Johnstone, T. C.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2009**, *131*, 11284–11285.



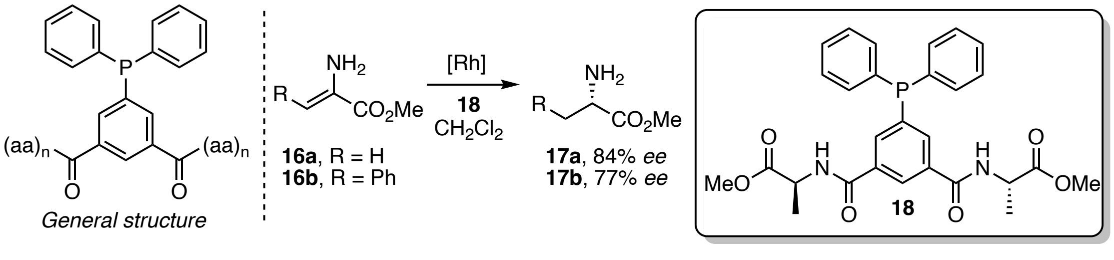
Scheme 4. Asymmetric imine alkynylation.

It has been also reported the synthesis of 37 aryl-iodo peptide catalysts with the structure shown in Scheme 5.[14] They studied their enantioinduction in the asymmetric bromolactonization of the 4-phenyl-4-pentenoic acid **13**, most of them did not show any enantioinduction and the best result was obtained using the tripeptide iodo-aryl amide **15** with 24% *ee*.



Scheme 5. Aryl-iodo peptide catalyzed for the bromolactonization of **13**.

Amino acids have been also used for the synthesis of 28 triphenylphosphine ligands and used in rhodium catalysis (Scheme 6).[15] They have been used to induce chirality in the asymmetric hydrogenation of 2-acetamidoacrylate **16a** and *Z*-α-acetamidocinnamate **16b**, obtaining the highest selectivity with the ligand with the smallest chain substituents **18**.



Scheme 6. Rhodium asymmetric hydrogenation reaction.

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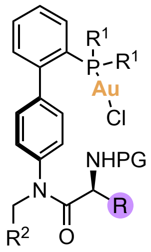
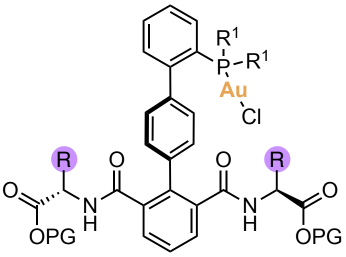
[14] Whitehead, D. C.; Fhaner, M.; Borhan, B. *Tetrahedron Letters* **2011**, *52*, 2288–2291.

[15] Kokan, Z.; Kirin, S. I. *Eur. J. Org. Chem.* **2013**, *2013*, 8154–8161.

Objectives

The main objective of this project was the design and synthesis of JohnPhos-type gold(I) complexes with one or more amino acids in their structures. The natural chirality of amino acids could induce enantioselectivity to the transformations.





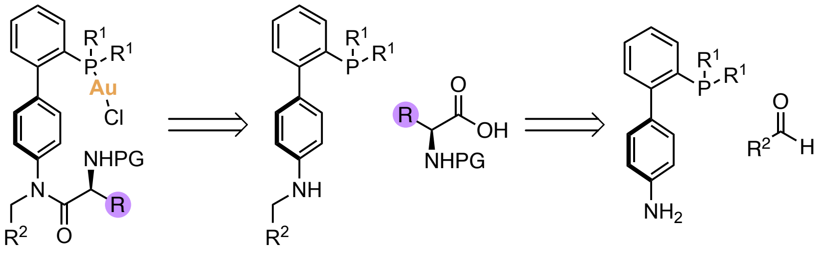
A plausible route for the synthesis of these complexes will be developed. They will be tested in different transformations in order to know their behavior in terms on reactivity and enantioinduction.

Results and Discussion

Aminoacid-Phos Gold(I) Complexes

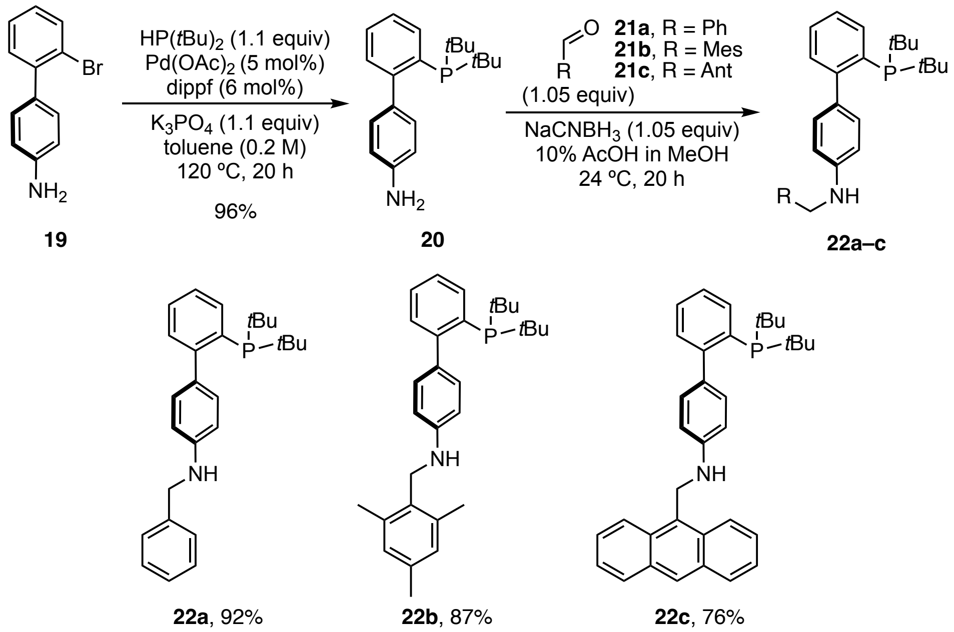
Synthesis

For the synthesis of gold(I) complexes containing one amino acid in their structure we followed the retrosynthetic analysis shown in Scheme 7. The formation of the amide was synthesized after a reductive amination.



Scheme 7. Retrosynthetic analysis for the synthesis of the mono-aminoacid-Phos gold(I) complexes. PG = protecting group.

The synthesis started with the introduction of a phosphine to the biaryl aniline **19**[16] using di-*tert*-butyl phosphine to obtain **20** in excellent yield (Scheme 8).[17] Then, the addition of the corresponding arylaldehyde **21a–c** to **20** afforded the imine followed by its reduction allowed the synthesis of **22a–c**.



Scheme 8. Synthesis of intermediates **22a–c**.

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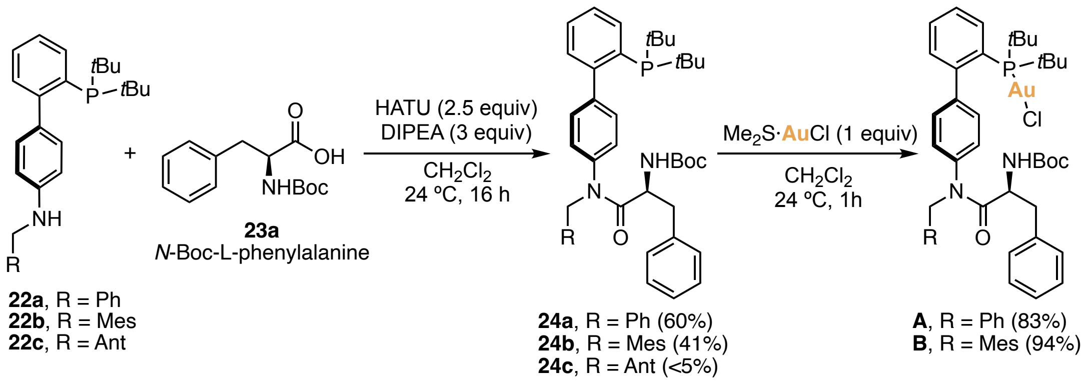
[16] Zuccarello, G.; Mayans, J. G.; Escofet, I.; Scharnagel, D.; Kirillova, M. S.; Pérez-Jimeno, A. H.; Calleja, P.; Boothe, J. R.; Echavarren, A. M. *J. Am. Chem. Soc.* **2019**, *141*, 11858–11863.

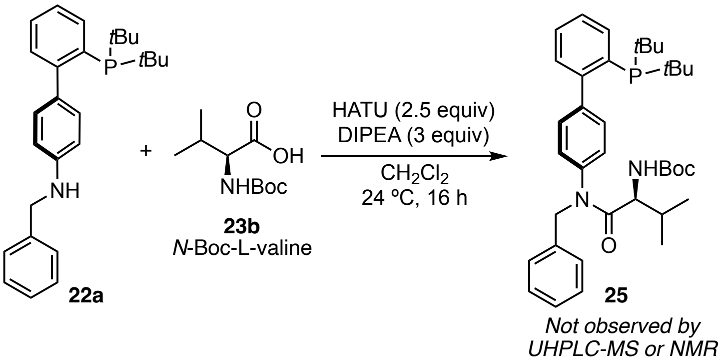
[17] Franchino, A.; Martí, À.; Echavarren A. M. *J. Am. Chem. Soc.* **2022**, *144*, 3497–3509.

We used the *N*-protected amino acid *N*-Boc-L-phenylalanine (**23a**) to form the amide bond using HATU as coupling agent (Scheme 9). With a phenyl group as a substituent (**22a**) the ligand **24a** was obtained in 60% yield. The formation of the amide whit a bulkier substituent, such as a mesityl group in **22b**, was also possible but in a lower yield affording **24b**. However, with an anthracene as a substituent (**22c**) almost no conversion to **24c** was observed. Finally, complexation of **24a** and **24b** using chloro(dimethylsulfide)gold(I) afforded the chiral complexes (*S*)-**A** and (*S*)-**B**.



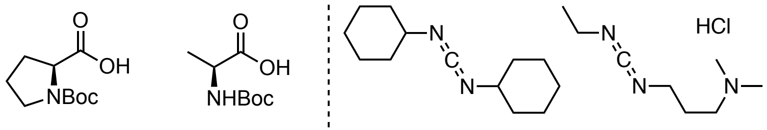
Scheme 9. Synthesis of the chiral complexes (*S*)-**A** and (*S*)-**B**.

The amide formation using other amino acid, *N*-Boc-L-valine (**23b**), and aniline **22a** did not lead to the formation of the corresponding ligand **25** (Scheme 10).



Scheme 10. First attempt in the formation of a ligand with *N*-Boc-L-valine **23b**.

This method for the condensation reaction did not work either between the aniline **22a** and other *N*-Boc-amino acids, such as proline **23c** and alanine **23d** (Figure 3). Instead of HATU in dichloromethane at 24 ºC, it was tested in *N*,*N*-dimethylformamide at 24 ºC and 90 ºC, but they led to the same outcome. Other coupling agents, such as *N*,*N*'-dicyclohexylcarbodiimide (DCC) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC·HCl), did not improve the results (Figure 3). And other conditions for the formation of the corresponding acid chlorides, using $SOCl_2$ and oxalyl chloride, did not work either.



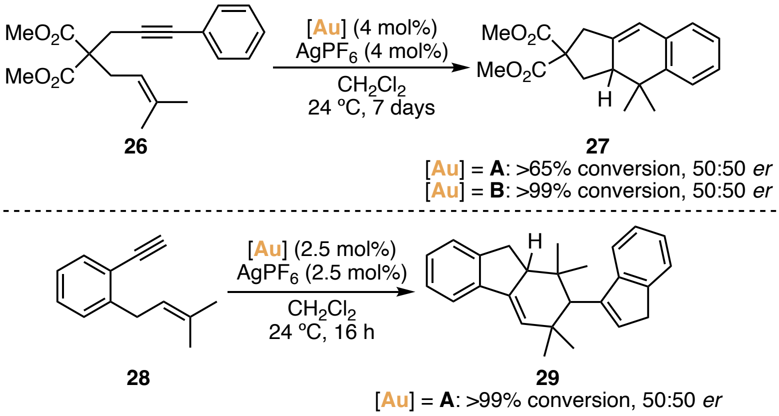
23c *N*-Boc-L-proline **23d** *N*-Boc-L-alanine DCC EDC·HCl

Figure 3. *N*-Boc-amino acids (left) and coupling agents (right).

Preliminary Studies

Whereas we were trying to solve the introduction of other amino acids, we carry out some experiments to study the reactivity of the complexes **A** and **B**.

The formal [4+2] cycloaddition of 1,6-arylenyne **26** was carried out obtaining a racemic mixture of **27** with both catalysts (Scheme 11).[18] The reaction of **28** with catalyst **A** gave the cycloadduct **29** with very low enantioselectivity.



Scheme 11. Gold(I)-catalyzed cycloaddition reactions.

Different alkoxycyclization reactions were studied using these complexes and the aryl-tethered 1,6-enynes **30**, **32** and **34** (Scheme 12). Unfortunately, both the catalysis led to the same outcome, low enantioinduction.

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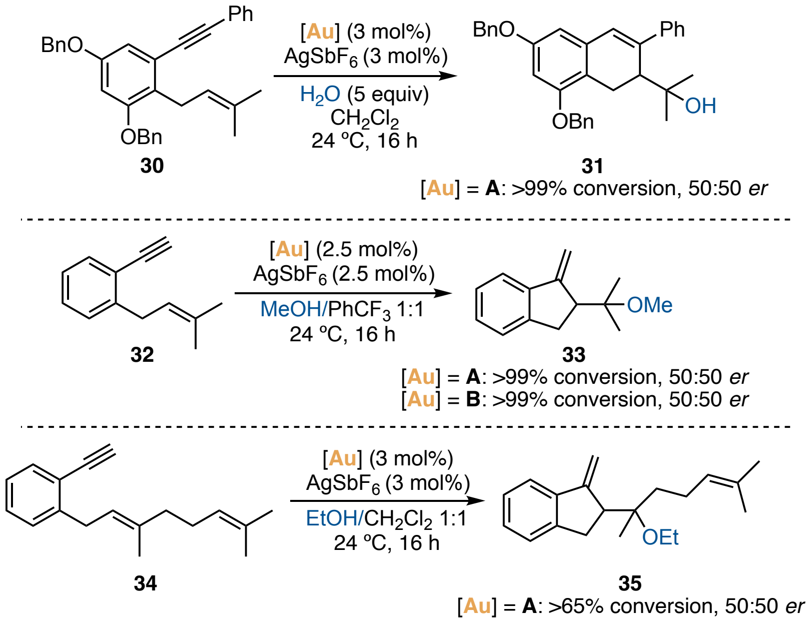
18 (a) Nieto-Oberhuber, C.; Pérez-Galán, P.; Herrero-Gómez, E.; Lauterbach, T.; Rodríguez, C.; López, S.; Bour, C.; Rosellón, A.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2008**, *130*, 269–279. (b) Zuccarello, G.; Mayans, J. G.; Escofet, I.; Scharnagel, D.; Kirillova, M. S.; Pérez-Jimeno, A. H.; Calleja, P.; Boothe, J. R.; Echavarren, A. M. *J. Am. Chem. Soc.* **2019**, *141*, 11858–11863.



Scheme 12. Gold(I)-catalyzed alkoxycyclization reactions.

Racemization issues

When a carboxylic acid is activated to carry out the condensation reaction, it exists the possibility of racemization of the α-amino acid due to the acidity of the α-hydrogen (Figure 4). That is something that could have happened in the formation of complexes **A** and **B**, so meanwhile we were trying to find an approach to synthesized complexes bearing other amino acid we also wanted to try to avoid this issue.

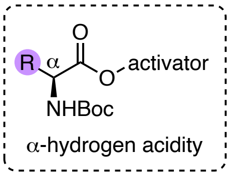


Figure 4. Acidity of the α-hydrogen.

We found in literature different methods to avoid this racemization issue, EDC·HCl with 10-camphorsulfonic acid (CSA),[19] propanephosphonic acid anhydride (T3P)[20] at different temperatures and with different bases, and DMTMM.[21] We used these conditions over a model substrate **36** and *N*-Boc-L-isoleucine (to check the racemization by NMR). These methods did not work, the product was not observed by UHPLC-MS or NMR.

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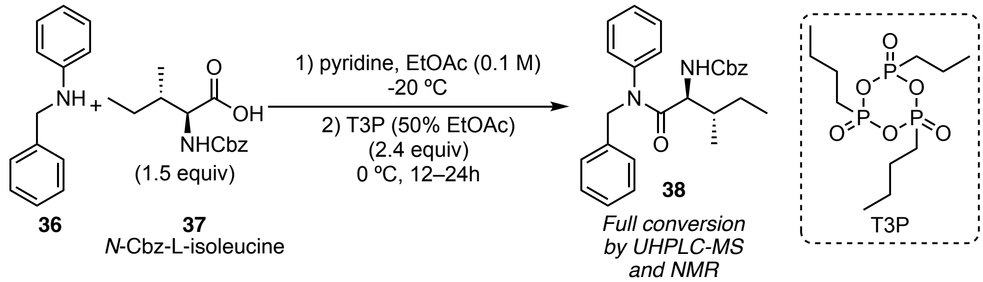
[19] de Castro, P. P.; Rimulo, I. M. R.; de Almeida, A. M.; Diniz, R.; Amarante, G. W. *ACS Omega* **2017**, *2*, 2967–2976.

[20] Dunetz, J. R.; Xiang, Y.; Baldwin, A.; Ringling, J. *Org. Lett.* **2011**, *13*, 5048–5051.

[21] Moore, M. J.; Qu, S.; Tan, C.; Cai, Y.; Mogi, Y.; Jamin Keith, D.; Boger, D. L. *J. Am. Chem. Soc.* **2020**, *142*, 16039–16050.

The use of T3P with isoleucine was reported with another protecting group in the amino functional group, carboxybenzyl (Cbz),[20] and when these conditions were tested to **37** the desired product **38** was successfully obtained, not observing the product coming from its racemization (Scheme 13).



Scheme 13. Amide formation using model substrate **36** and *N*-Cbz-L-isoleucine **37** with T3P.

In the preliminary studies using these complexes

Thanks to the crystals of both complexes, we also observed that the chiral part of the complexes was located on the opposite site of the reactive center because the phenyl and the mesityl groups were not enough sterically hindered to avoid this conformation. We had already unsuccessfully tried to introduce a bulkier group, an anthracene, in that position. For this reason, despite we had probably solved the racemization problem in the synthesis, we decided to focus on other complexes containing a C_2-symmetric moiety with two amino acids.The low enantioinduction could be explained because of the racemization of the stereocenter during the synthesis. Crystals of both complexes **A** and **B** were obtained and they were measured by X-ray-diffraction. We observed that the (*R*)-**A** enantiomer had crystalized (Figure 5).

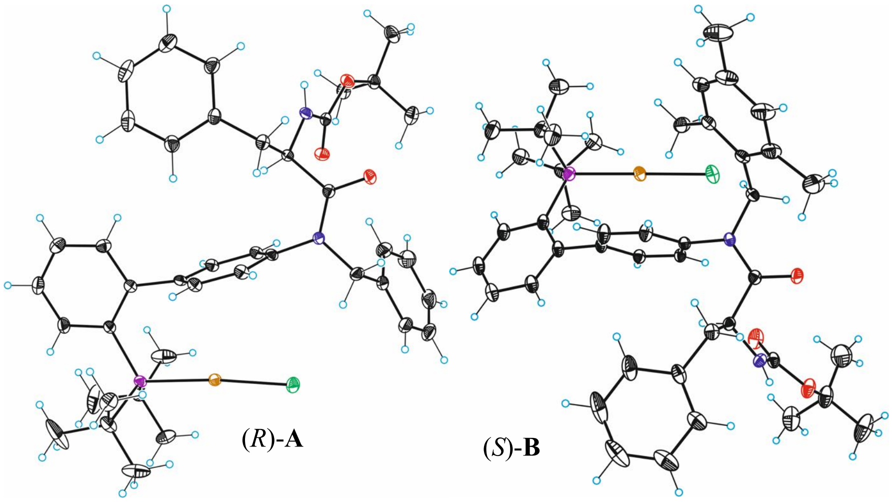
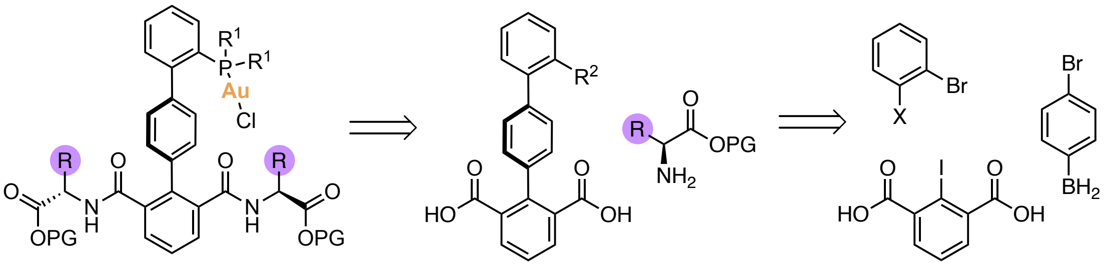


Figure 5. X-ray structures (*R*)-**A** and (*S*)-**B**.

(Aminoacid)$_2$-Phos Gold(I) Complex

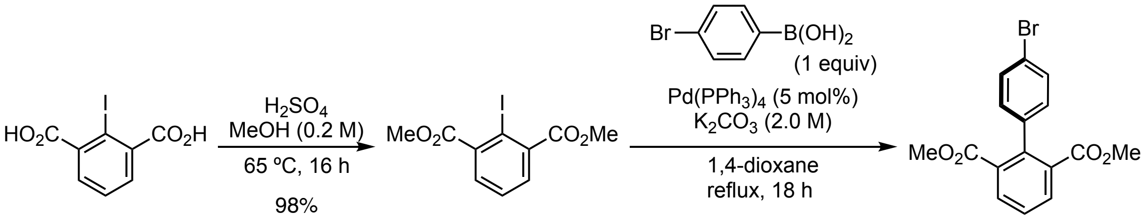
Synthesis

For the synthesis of gold(I) complexes containing an amino acid twice in their structure we followed the retrosynthetic analysis showed in Scheme 14. The amide formation will be prepared using a carboxylic acid-protected amino acid and a moiety prepared from commercially available starting materials.



Scheme 14. Retrosynthetic analysis for the synthesis of the bis-aminoacid-Phos gold(I) complexes. PG = protecting group.

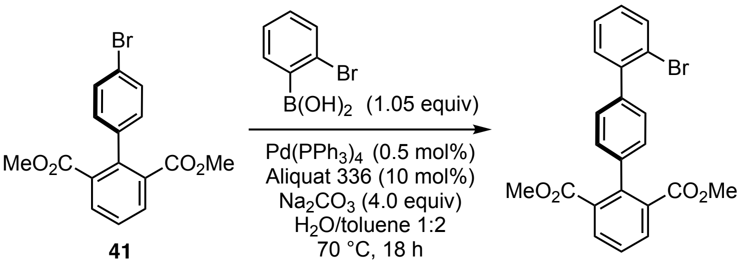
The formation of **40** was synthesized after the esterification of the dicarboxylic acid **39** in excellent yield (Scheme 15). Then, a second aryl group was introduced through a Suzuki-Miyaura cross-coupling reaction of **40** with the (4-bromophenyl)boronic acid to obtain **41**.



39 **40** **41**

Scheme 15. Synthesis of intermediate **41**.

The introduction of the third aryl moiety was first tried using (2-bromophenyl)boronic acid by a Suzuki-Miyaura cross-coupling reaction with **41** (Scheme 16), but the reaction lead to **42** but with a mixture of products, we could not separate them by column chromatography due to the similar polarity. Other palladium sources, bases, solvents and temperatures were also tested leading to the same outcome.

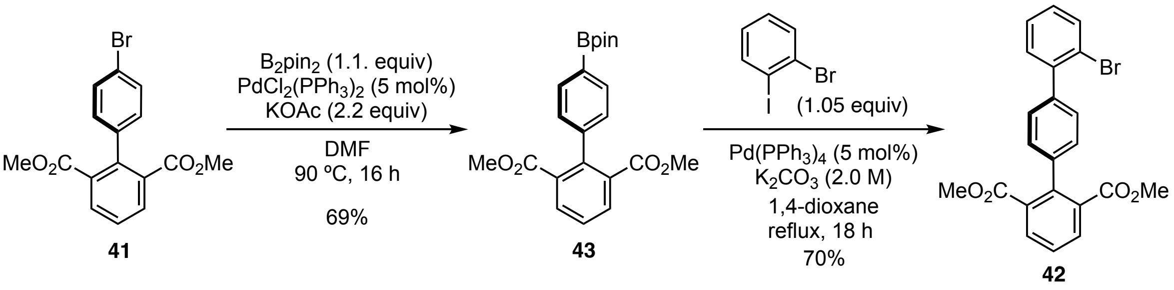


41 **42**

Not pure
Mixture of products

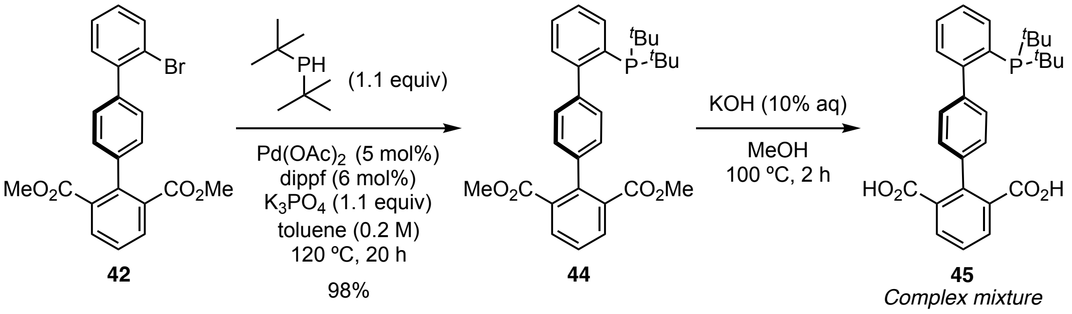
Scheme 16. First attempt in the synthesis of **42**.

Therefore, to introduce the third aryl group, it was necessary first the borylation of **41** using bis(pinacolato)diboron followed by the Suzuki-Miyaura cross coupling reaction of **43** with 1-bromo-2-iodobenzene, affording **42** (Scheme 17).



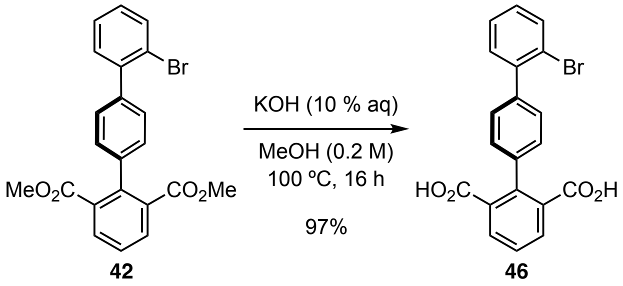
Scheme 17. Synthesis of intermediate **42**.

The introduction of the di-tert-butyl phosphine to **42** was achieved affording **44**, but the hydrolysis of the carboxylic esters using KOH in methanol afforded a complex mixture of products by NMR and UHPLC-MS (Scheme 18).



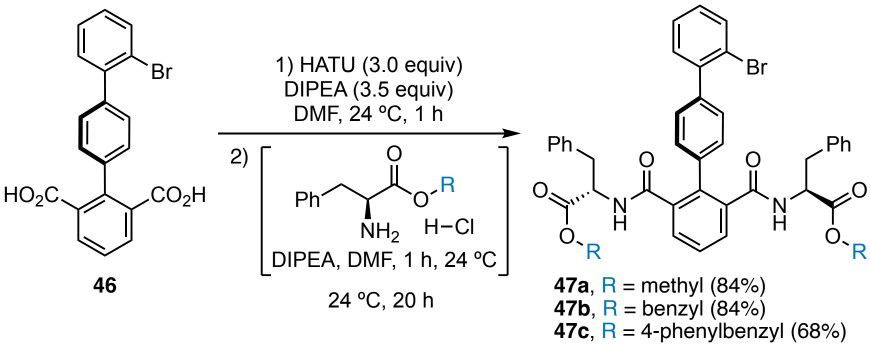
Scheme 18. Attempt in the synthesis of **45**.

Therefore, other approach was tested, the double hydrolysis of the carboxylic esters of **42** was performed first, yielded product **46** in excellent yield (Scheme 19).



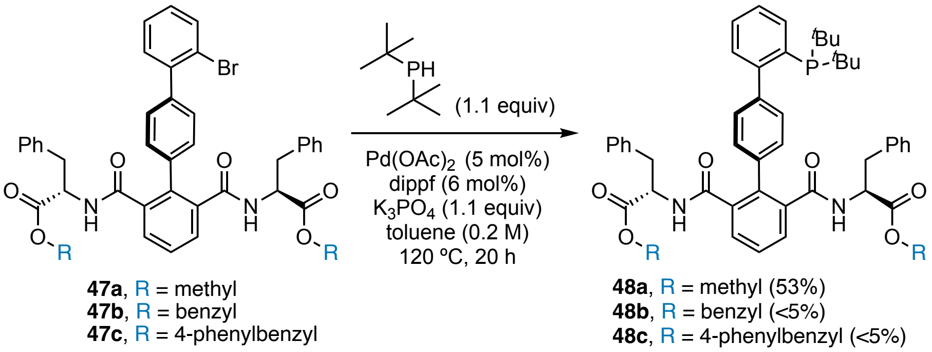
Scheme 19. Double hydrolysis of **42**.

The amide formation was carried out using **46** and L-phenylalanine with different protecting groups in the carboxylic acid (Scheme 20). With a methyl and a benzyl groups the corresponding products **47a** and **47c** were afforded in 84% yield, obtaining product **47c** with a bulkier substituent in lower yield.



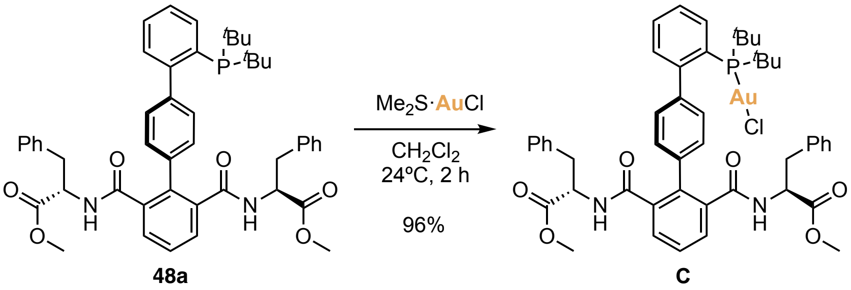
Scheme 20. Amide formation for the synthesis of **47a–c**.

The introduction of di-*tert*-butyl phosphine was only possible using **47a** affording **48a**. However, almost no conversion was observed with bulkier substituents (Scheme 21).



Scheme 21. Introduction of di-*tert*-butyl phosphine.

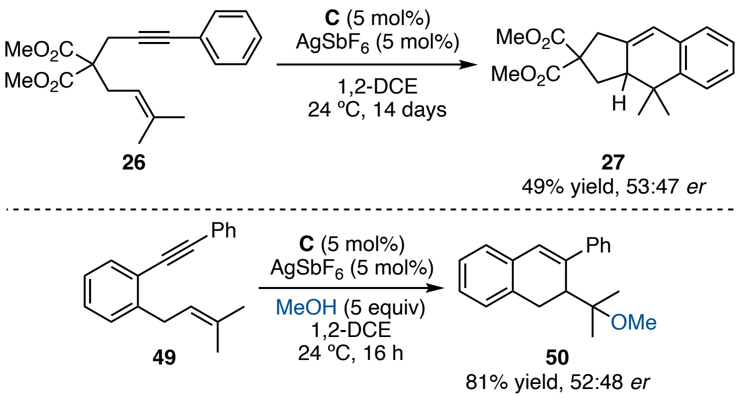
Finally, complexation of **48a** with using chloro(dimethylsulfide)gold(I) afforded the chiral complex (*S*,*S*)-**C** in excellent yield (Scheme 22).



Scheme 22. Synthesis of the chiral complex (*S*,*S*)-**C**.

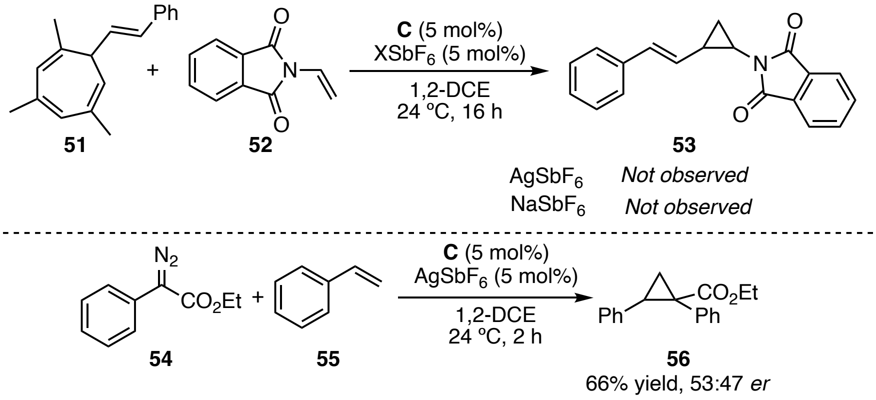
Preliminary Studies

The reactivity of catalyst (*S*,*S*)-**C** was studied in different transformations. The formal [4+2] cycloaddition of 1,6-arylenyne **26** was carried out obtaining a racemic mixture of **27** (Scheme 23, top). The alkoxycyclization reaction was studied using complex (*S*,*S*)-**C** and the aryl-tethered 1,6-enyne **49** (Scheme 23, bottom). Unfortunately, the catalysis led to low enantioinduction.



Scheme 23. Gold(I)-catalyzed cycloaddition and alkoxycyclization reactions.

The retro Buchner reaction using **51** and **52** did not afford the cyclopropane **53** (Scheme 24, top).[22] The cyclopropanation reaction using **54** and styrene **55** afforded the cyclopropane **56** in good yield but with low enantioselectivity (Scheme 24, bottom).[23]



Scheme 24. Gold(I)-catalyzed cyclopropanation reactions.

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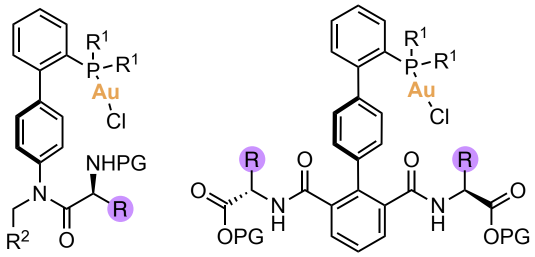
[22] (a) Herlé, B.; Holstein, P. M.; Echavarren, A. M. *ACS Catal.* 2017, *7*, 3668–3675. (b) Mato, M.; Herlé, B.; Echavarren, A. M. *Org. Lett.* 2018, *20*, 4341–4345. (c) Mato, M.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2019**, *58*, 2088–2092.

[23] Xu, Z.-H.; Zhu, S.-N.; Sun, X.-L.; Tang, Y.; Dai, L.-X. *Chem. Commun.* **2007**, *19*, 1960–1962.

Conclusions and Outlook

The synthesis of gold(I) catalyst bearing amino acids has been carried out.

- The synthesis of complexes with one amino acid in their structures presented synthetic problems, because the amide formation was dependent on the amino acid and their protecting group used. We also observed racemization issues due to the acidity of the *α*-hydrogen. This structure happened to not be the ideal for enantioselective transformations because of the asymmetry of the aniline substituents.
- On the other hand, chiral gold(I) complexes containing a C_2-symmetric moiety with two amino acids solved two problems mentioned before, the racemization of the stereocenters and the asymmetry of the substituents. Regardless, this gold(I) complex did not give enantioinduction in different transformations, probably due to the free rotation of the amino acid moieties.



Other gold(I)-complexes structure designs should be considered to take advantage of the natural chirality of amino acids to induce enantioselectivity to the transformations.

Experimental Section

General Information

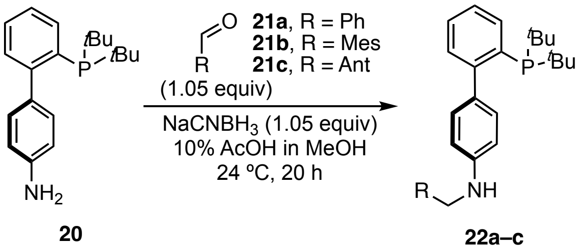
Unless otherwise stated, all the reactions reported herein were carried out under argon or nitrogen atmosphere. Reactions were carried out in solvents dried by passing through an activated alumina column on a PureSolv^{TM} Solvent Purification System (SPS, Innovative Technologies, Inc., MA), in commercially available anhydrous solvents purchased from ACROS Organics or in HPLC-grade solvents. Yields refer to chromatographically and spectroscopically pure (^{1}H NMR) homogeneous material, unless otherwise stated. Reactions were monitored by TLC (thin layer chromatography), UHPLC-MS, NMR analysis and/or GC-MS. Thin layer chromatography was carried out using TLC aluminum sheets coated with 0.2 mm of silica gel (Merck 60 F_{254}) using short-wave UV light as visualizing agent and acidic solution of vanillin in ethanol or a basic solution of KMnO4 in water as stain followed by heat as developing agents. UHPLC-MS was performed in Agilent Technologies 1290 Infinity II, LC-MS with single-squad detector InfinityLab (APCI ionization source). Chromatographic purifications were carried out using flash grade silica gel (SDS Chromatogel 60 ACC, 40-60 μm) as the stationary phase manually, or using a CombiFlash® R_f instrument with normal phase disposable columns of different sizes (Teledyne Isco). NMR spectra were recorded at 298 K on a Bruker Avance 300 Ultrashield, a Bruker Avance 400 Ultrashield (400 MHz for ^{1}H and 101 MHz for ^{13}C) or a Bruker Avance 500 Ultrashield (500 MHz for ^{1}H and 126 MHz for ^{13}C) spectrometers. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane, using as reference residual solvent (^{1}H NMR: $CDCl_3$ at 7.26 ppm, CD_2Cl_2 at 5.31 ppm, $(CD_3)_2SO$ at 2.50 ppm; for $^{13}C\{^1H\}$ NMR: $CDCl_3$ at 77.16 ppm, CD_2Cl_2 at 54.00 ppm, $(CD_3)_2SO$ at 39.52 ppm) or tetramethylsilane. Coupling constants (*J*) are reported in hertz (*Hz*). The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintuplet, m = multiplet, br s = broad singlet. Mass spectra were recorded on MicroTOF Focus or Maxis Impact spectrometers (both from Bruker Daltonics). Melting points were determined using a MP70 Melting Point System (Mettler Toledo). Single-crystal X-ray diffraction data were collected at 100 K on a Rigaku MicroMax-007HF, Mo *Kα* rotating anode, equipped with a Pilatus 200 K detector or on a Bruker APEX DUO, Mo *Kα* Microfocus source E025 IuS anode, equipped with an APEX DUO detector using omega scans. Chiral HPLC analyses were performed on an Agilent Technologies 1200 series. SFC analyses were performed on an Agilent Technologies 1260 Infinity II, a Waters ACQUITY UPC2 System with diode array detector and by Chiral Technologies Europe analytical service. 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 2 mL (100 mm pathlength) cells.

Reagents were obtained from commercial sources and used without further purification. The preparation of the following compounds has been previously described: **19**,[16] **20**.[17]

Synthetic Procedures and Analytical Data

Aminoacid-Phos Gold(I) Complexes

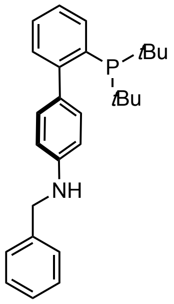
Synthesis of 22a-c



General procedure A:

Under nitrogen atmosphere, a mixture of 2'-(di-*tert*-butylphosphaneyl)-[1,1'-biphenyl]-4-amine **20**[17] (1.0 equiv), the corresponding arylaldehyde **21a-c** (1.05 equiv) and acetic acid 10% in MeOH (0.2 M) was stirred for 3 hours at 23 ºC. Then $NaCNBH_3$ (1.05 equiv) was added and it was stirred at 25 ºC for 16 h. The reaction was quenched with an aqueous saturated solution of $NaHCO_3$ and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The crude was purified by flash column chromatography.

N-Benzyl-2'-(di-*tert*-butylphosphaneyl)-[1,1'-biphenyl]-4-amine, 22a

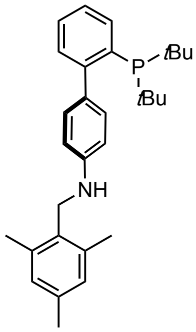


The title compound **22a** (1.21 g, 3.01 mmol, 92% yield) was obtained as a light orange solid according to general procedure **A**, using 2'-(di-*tert*-butylphosphaneyl)-[1,1'-biphenyl]-4-amine **20** (1.02 g, 3.27 mmol, 1.0 equiv) and benzaldehyde **21a** (0.35 mL, 3.43 mmol, 1.05 equiv). It was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc from 10:0 to 5:5).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (dt, *J* = 7.6, 1.6 Hz, 1H), 7.45 – 7.40 (m, 2H), 7.40 – 7.33 (m, 3H), 7.33 – 7.27 (m, 2H), 7.25 – 7.22 (m, 1H), 7.12 – 7.07 (m, 2H), 6.68 – 6.61 (m, 2H), 4.35 (s, 2H), 1.15 (d, *J* = 11.5 Hz, 18H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 151.5 (d, *J* = 31.7 Hz), 146.8, 139.7, 135.5 (d, *J* = 3.1 Hz), 131.6 (d, *J* = 4.1 Hz), 131.1 (d, *J* = 5.9 Hz), 130.3, 128.8, 128.5, 128.0, 127.4, 125.3, 111.8, 48.7, 32.9 (d, *J* = 25.3 Hz), 30.9 (d, *J* = 15.4 Hz). **^{31}P{^{1}H} NMR** (162 MHz, $CDCl_3$) δ 21.7. **HRMS** (ESI+) the exact mass calculated for $[C_{27}H_{35}NP]^+$ is 404.2502 *m/z*; found $[M + H]^+$ 404.2511 *m/z*. **M.p.** = 90–97 ºC.

2'-(Di-*tert*-butylphosphaneyl)-*N*-(2,4,6-trimethylbenzyl)-[1,1'-biphenyl]-4-amine, 22b

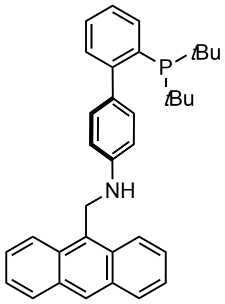
The title compound **22b** (271 mg, 0,608 mmol, 87% yield) was obtained as a white solid according to general procedure **A**, using 2'-(di-*tert*-butylphosphaneyl)-[1,1'-biphenyl]-4-amine **20** (220 mg, 0.702



mmol, 1.0 equiv) and 2,4,6-trimethylbenzaldehyde **21b** (0.109 mL, 0.737 mmol, 1.05 equiv). It was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc from 10:0 to 9.4:0.6).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (dt, *J* = 7.6, 1.6 Hz, 1H), 7.35 (tt, *J* = 7.3, 1.1 Hz, 1H), 7.30 – 7.24 (m, 2H), 7.15 – 7.10 (m, 2H), 6.91 (s, 2H), 6.67 – 6.62 (m, 2H), 4.23 (s, 2H), 3.44 (bs, 1H), 2.39 (s, 6H), 2.30 (s, 3H), 1.16 (d, *J* = 11.6 Hz, 18H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 151.6 (d, *J* = 31.8 Hz), 147.1, 137.8, 137.4, 135.9, 135.7, 135.6 (d, *J* = 3.3 Hz), 133.0 (d, *J* = 6.9 Hz), 132.5, 131.6 (d, *J* = 4.1 Hz), 131.2 (d, *J* = 5.8 Hz), 129.2, 128.5, 125.2, 111.6, 42.5, 32.9 (d, *J* = 25.0 Hz), 30.9 (d, *J* = 15.3 Hz), 21.1, 19.7. **^{31}P{^{1}H} NMR** (202 MHz, $CDCl_3$) δ 21.6. **HRMS** (ESI+) the exact mass calculated for $[C_{30}H_{41}NP]^+$ is 446.2971 *m/z*; found $[M + H]^+$ 446.2979 *m/z*. **M.p.** = 171–174 ºC.

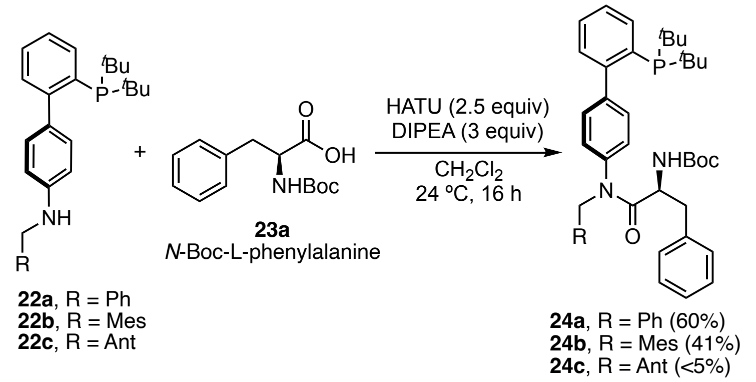
N-(Anthracen-9-ylmethyl)-2'-(di-*tert*-butylphosphaneyl)-[1,1'-biphenyl]-4-amine, 22c



The title compound **22c** (137.2 mg, 0,283 mmol, 76% yield) was obtained as a yellow solid according to general procedure **A**, using 2'-(di-*tert*-butylphosphaneyl)-[1,1'-biphenyl]-4-amine **20** (116.9 mg, 0.373 mmol, 1.0 equiv) and anthracene-9-carbaldehyde **21c** (81.0 mg, 0.392 mmol, 1.05 equiv). It was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc from 10:0 to 8.5:1.5).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.36 (dt, *J* = 8.8, 1.1 Hz, 2H), 8.10 – 8.02 (m, 2H), 7.92 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.60 – 7.48 (m, 5H), 7.44 – 7.37 (m, 1H), 7.36 – 7.29 (m, 2H), 7.25 – 7.18 (m, 2H), 6.85 – 6.78 (m, 2H), 5.20 (s, 2H), 3.88 (bs, 1H), 1.20 (d, *J* = 11.6 Hz, 18H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 151.6 (d, *J* = 31.8 Hz), 147.0, 136.0, 135.7, 135.6 (d, *J* = 3.3 Hz), 133.5 (d, *J* = 7.1 Hz), 131.7 (d, *J* = 4.2 Hz), 131.7, 131.2 (d, *J* = 5.8 Hz), 130.7, 129.7, 129.2, 128.5, 128.0, 126.6, 125.3, 124.5, 111.7, 41.0, 32.9 (d, *J* = 25.0 Hz), 31.0 (d, *J* = 15.4 Hz). **^{31}P{^{1}H} NMR** (162 MHz, $CDCl_3$) δ 21.8. **HRMS** (ESI+) the exact mass calculated for $[C_{35}H_{39}NP]^+$ is 504.2815 *m/z*; found $[M + H]^+$ 504.2830 *m/z*. **M.p.** = 215–222 ºC.

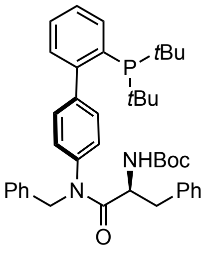
Synthesis of ligands 24a-c



General procedure B:

Under nitrogen atmosphere, a mixture of (*tert*-butoxycarbonyl)-*L*-phenylalanine **23a** (1.5 equiv), HATU (2.5 equiv) and DIPEA (3 equiv) in dichloromethane (0.31 M) was stirred at 24 ºC for 1 h. Then, the corresponding aniline **22a–c** (1 equiv) in dichloromethane (0.31 M) was added and the mixture was stirred at 24 ºC for 16 h. The reaction was quenched with water and extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The crude was purified by flash column chromatography.

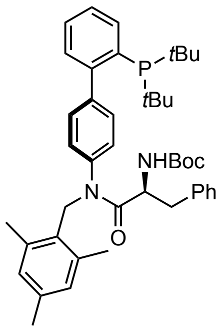
tert-Butyl (*S*)-(1-(benzyl(2'-(di-*tert*-butylphosphaneyl)-[1,1'-biphenyl]-4-yl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate, 24a



The title compound **24a** (193 mg, 0.298 mmol, 60% yield) was obtained as white solid according to general procedure **B**, using **22a** (200 mg, 0.496 mmol, 1.0 equiv) and (*tert*-butoxycarbonyl)-*L*-phenylalanine **23a** (197 mg, 0.743 mmol, 1.5 equiv). It was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc from 10:0 to 8:2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 7.5 Hz, 1H), 7.45 – 7.32 (m, 2H), 7.30 – 7.22 (m, 4H), 7.24 – 7.12 (m, 7H), 6.97 (bs, 2H), 6.69 (bs, 2H), 5.22 (bs, 1H), 4.95 (d, J = 14.2 Hz, 1H), 4.80 (d, J = 14.1 Hz, 1H), 4.62 (bs, 1H), 2.99 (dd, J = 13.3, 6.8 Hz, 1H), 2.76 (dd, J = 13.0, 7.0 Hz, 1H), 1.38 (s, 9H) 1.14 (d, J = 11.6 Hz, 9H), 1.13 (d, J = 11.7 Hz, 9H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 172.0, 155.0, 150.2 (d, J = 30.6 Hz), 139.1, 137.0, 136.8, 135.5, 132.1 (d, J = 4.7 Hz), 130.5 (d, J = 6.2 Hz), 129.7, 129.2, 128.7, 128.5, 128.4, 127.5, 127.2, 126.7, 126.3, 79.5, 53.6, 52.9, 39.6, 33.5 – 32.4 (m), 30.8 (dd, J = 15.4, 5.7 Hz), 28.4. **^{31}P{^{1}H} NMR** (162 MHz, $CDCl_3$) δ 21.1. **HRMS** (ESI+) the exact mass calculated for $[C_{41}H_{52}N_2O_3P]^+$ is 651.3710 *m/z*; found $[M + H]^+$ 651.3720 *m/z*. **M.p.** = 163–168 ºC. **α_D^{589}** = –1.7 deg·cm^2·g^{-1} ($CHCl_3$, c 0.1, 300 K).

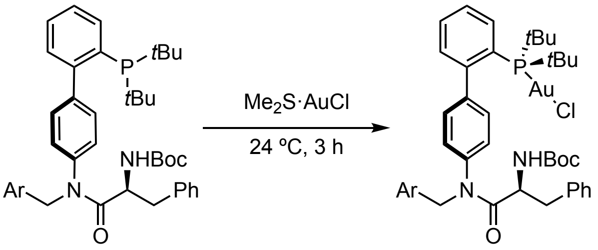
tert-Butyl (*S*)-(1-((2'-(di-*tert*-butylphosphaneyl)-[1,1'-biphenyl]-4-yl)(2,4,6-trimethylbenzyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate, 24b



The title compound **24b** (32.2 mg, 46.4 µmol, 41% yield) was obtained as white solid according to general procedure **B**, using **22b** (50.0 mg, 112 µmol, 1.0 equiv) and (*tert*-butoxycarbonyl)-*L*-phenylalanine **23a** (44.7 mg, 16.8 µmol, 1.5 equiv). It was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc from 10:0 to 7:3).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.5 Hz, 1H), 7.43 – 7.30 (m, 2H), 7.25 – 7.12 (m, 4H), 7.12 – 6.83 (m, 5H), 6.71 (s, 2H), 6.28 (bs, 1H), 5.15 (d, *J* = 9.1 Hz, 1H), 5.11 – 4.92 (m, 2H), 4.48 (bs, 1H), 3.01 (dd, *J* = 13.6, 5.9 Hz, 1H), 2.69 (dd, *J* = 13.6, 8.3 Hz, 1H), 2.18 (s, 3H), 2.05 (s, 6H), 1.37 (s, 9H), 1.10 (t, *J* = 11.2 Hz, 18H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 171.6, 155.2, 150.4 (d, *J* = 35.3 Hz), 138.6, 137.1, 135.4, 130.2, 129.5, 129.1, 128.5, 128.5, 126.7, 126.3, 79.5, 53.1, 45.7, 39.4, 32.9 (d, *J* = 29.3 Hz), 31.0 – 30.5 (m), 28.4, 21.0, 20.1 (d, *J* = 2.0 Hz). **^{31}P{^{1}H} NMR** (162 MHz, $CDCl_3$) δ 20.5. **HRMS** (ESI+) the exact mass calculated for $[C_{44}H_{58}N_2O_3P]^+$ is 693.4180 *m/z*; found $[M + H]^+$ 693.4181 *m/z*. **M.p.** = 183–193 ºC. α_D^{589} = –2.8 deg·cm^2·g^{-1} ($CHCl_3$, c 0.1, 300 K).

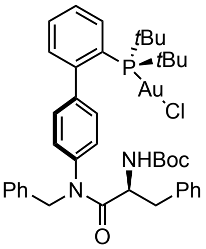
Synthesis of complexes A and B



General procedure C:

Under argon atmosphere, the corresponding phosphine **24a–b** (1 equiv) and dimethyl sulfide gold(I) chloride (1 equiv) in dichloromethane (0.1 M) was stirred at 24 ºC for 1 h. Then, it was filtered through a path of neutral Al_2O_3 and concentrated.

Complex A

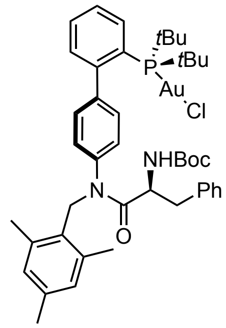


The title compound complex **A** (33.6 mg, 38.0 µmol, 83% yield) was obtained as white solid according to general procedure **C**, using **24a** (30 mg, 46 µmol, 1.0 equiv).

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.92 (t, *J* = 7.4 Hz, 1H), 7.66 – 7.51 (m, 2H), 7.46 (d, *J* = 7.4 Hz, 2H), 7.38 – 7.20 (m, 6H), 7.20 – 7.13 (m, 3H), 7.10 (d, *J* = 7.9 Hz, 1H), 6.87 (bs, 2H), 6.69 (d, *J* = 8.2 Hz, 1H), 5.32 (d, *J* = 14.8 Hz, 1H), 5.22 (d, *J* = 9.1 Hz, 1H), 5.05

(d, *J* = 14.7 Hz, 1H), 4.51 (d, *J* = 8.3 Hz, 1H), 2.95 (dd, *J* = 13.4, 5.9 Hz, 1H), 2.66 (dd, *J* = 13.5, 7.8 Hz, 1H), 1.41 (d, *J* = 15.6 Hz, 18H), 1.36 (s, 9H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 172.2, 155.4, 149.3 (d, *J* = 13.3 Hz), 143.2 – 142.7 (m), 139.0, 137.5, 134.3, 134.0 (d, *J* = 7.4 Hz), 132.3 (d, *J* = 9.8 Hz), 132.3 (d, *J* = 2.9 Hz), 131.1 (d, *J* = 2.3 Hz), 131.0, 130.8, 129.7, 129.3, 129.0, 128.9 (d, *J* = 11.9 Hz), 128.6, 128.5, 127.6 (d, *J* = 6.9 Hz), 127.2, 126.9, 125.9 (d, *J* = 45.2 Hz), 79.6, 53.1, 39.6, 38.2 (d, *J* = 25.9 Hz), 38.2 (d, *J* = 25.9 Hz), 31.1 (d, *J* = 6.5 Hz), 31.0 (d, *J* = 6.6 Hz), 30.1, 28.4. **^{31}P{^{1}H} NMR** (162 MHz, CD_2Cl_2) δ 63.3. **HRMS** (ESI+) the exact mass calculated for $[C_{41}H_{52}AuClN_2O_3P]^+$ is 883.3064 *m/z*; found $[M + H]^+$ 883.3063 *m/z*. **M.p.** = >192 ºC (decomposition). **α_D^{589}** = –4.5 deg·cm^2·g^{-1} (CH_2Cl_2, c 0.2, 299 K).

Complex B



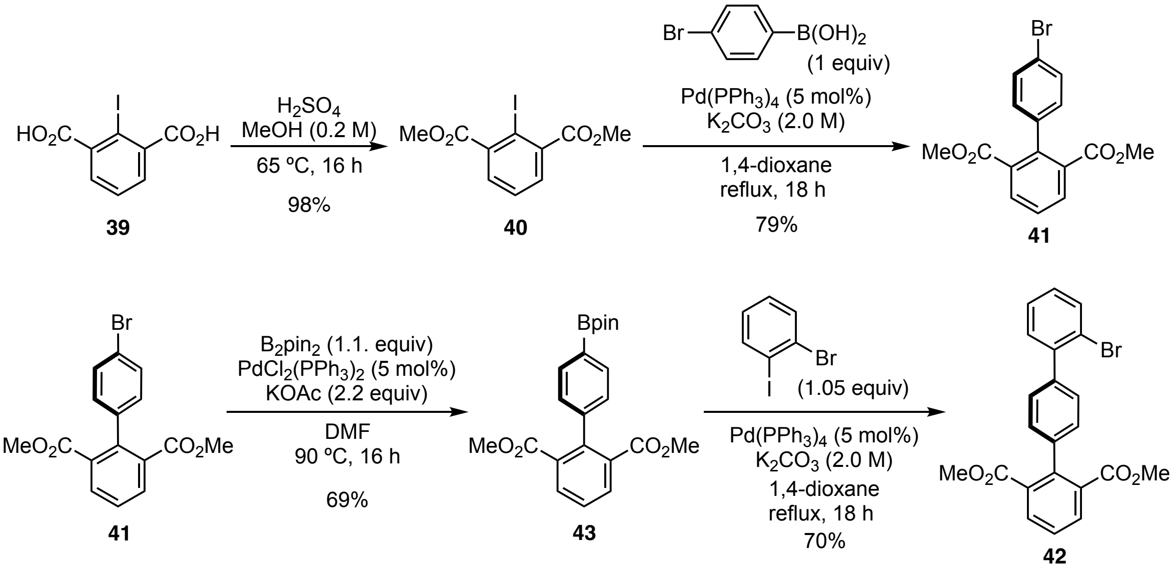
The title compound complex **B** (18.8 mg, 20.7 µmol, 94% yield) was obtained as white solid according to general procedure **C**, using **24b** (15.0 mg, 22.0 µmol, 1.0 equiv).

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.94 – 7.87 (m, 1H), 7.60 – 7.45 (m, 3H), 7.24 – 7.15 (m, 4H), 7.15 – 6.97 (m, 3H), 6.89 (d, *J* = 8.1 Hz, 1H), 6.75 (s, 3H), 5.13 – 4.96 (m, 2H), 4.89 (br s, 1H), 4.74 (br s, 1H), 3.06 – 2.91 (m, 1H), 2.75 (br s, 1H), 2.22 (s, 3H), 2.17 (br s, 6H), 1.44 (d, *J* = 15.6 Hz, 9H), 1.40 (d, *J* = 15.7 Hz, 9H), 1.36 (br s, 9H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 172.1, 155.2, 149.4 (d, *J* = 12.8 Hz), 142.4, 141.6, 138.6, 137.8, 137.0, 134.3, 132.3 (d, *J* = 9.7 Hz), 131.1 (d, *J* = 2.3 Hz), 130.9 (d, *J* = 15.1 Hz), 130.2, 129.6, 129.1, 129.0 – 128.7 (m), 128.5, 127.4 (d, *J* = 6.7 Hz), 126.8, 125.6 (d, *J* = 44.6 Hz), 79.3, 39.2, 38.3 (d, *J* = 25.9 Hz), 38.2 (d, *J* = 25.9 Hz), 31.2 (d, *J* = 6.7 Hz), 31.0 (d, *J* = 6.6 Hz), 28.4, 21.0. **^{31}P{^{1}H} NMR** (203 MHz, CD_2Cl_2) δ 63.1. **HRMS** (ESI+) the exact mass calculated for $[C_{44}H_{58}AuClN_2O_3P]^+$ is 925.3534 *m/z*; found $[M + H]^+$ 925.3524 *m/z*. **M.p.** = >148 ºC (decomposition).

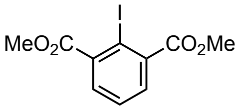
α_D^{589} = –1.9 deg·cm^2·g^{-1} (CH_2Cl_2, c 0.2, 299 K).

(Aminoacid)$_2$-Phos Gold(I) Complex

Synthesis of compound 42



Dimethyl 2-iodoisophthalate, 40



Procedure described in the literature:[24] a concentrated sulfuric acid (12.7 mL) was slowly added into a mixture of 2-iodoisophthalic acid (5.00 g, 17.1 mmol, 1 equiv) in MeOH (96.7 mL, 0.18 M). The reaction mixture was refluxed at 65 ºC for 16 h. Then the reaction was diluted with H_2O and extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc from 10:0 to 8:2) affording the title compound **40** (5.35 g, 16.7 mmol, 98% yield) as a white solid.

The spectral data are consistent with the literature.[25]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.7 Hz, 2H), 7.44 (dd, *J* = 8.1, 7.2 Hz, 1H), 3.95 (s, 6H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 168.2, 139.9, 131.5, 128.1, 91.9, 52.9. **HRMS** (ESI+) the exact mass calculated for $[C_{10}H_9INaO_4]^+$ is 342.9438 *m/z*; found $[M + Na]^+$ 342.9430 *m/z*. **M.p.** = 48–52 ºC.

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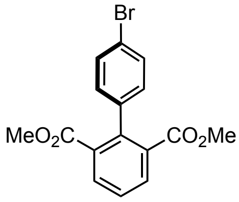
[24] Dilly, S.; Fotso Fotso, A.; Lejal, N.; Zedda, G.; Chebbo, M.; Rahman, F.; Companys, S.; Bertrand, H. C.; Vidic, J.; Noiray, M.; Alessi, M.-C.; Tarus, B.; Quideau, S.; Riteau, B.; Slama-Schwok, A. *J. Med. Chem.* **2018**, *61*, 7202–7217.

[25] Zhdankin, V. V.; Koposov, A. Y.; Litvinov, D. N.; Ferguson, M. J.; McDonald, R.; Luu, T.; Tykwinski, R. R. *J. Org. Chem.* **2005**, *70*, 6484–6491.

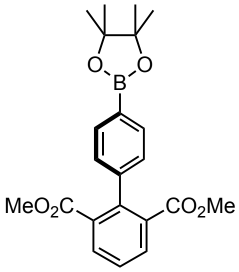
Dimethyl 4'-bromo-[1,1'-biphenyl]-2,6-dicarboxylate, 41



Procedure modified from literature:[24] under argon atmosphere, a mixture of **40** (5.35 g, 16.7 mmol, 1 equiv), (4-bromophenyl)boronic acid (3.36 g, 16.7 mmol, 1 equiv), $Pd(PPh_3)_4$ (579 mg, 0.501 mmol, 3 mol%) and a 2 M aqueous solution of K_2CO_3 (16.7 mL) in 1,4-dioxane (41.8 mL, 0.4 M) was stirred at 110 ºC for 16 h. The reaction was filtered through a pad of Celite® with dichloromethane. Both layers were separated and aqueous layer was extracted with CH_2Cl_2 (2x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc from 10:0 to 8:2) affording the title compound **41** (4.59 g, 13.1 mmol, 79% yield) as an orange-brown solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.8 Hz, 2H), 7.53 – 7.47 (m, 3H), 7.11 – 7.04 (m, 2H), 3.59 (s, 6H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 167.9, 140.6, 138.2, 132.9, 132.3, 130.8, 130.2, 127.8, 121.7, 52.3. **HRMS** (ESI+) the exact mass calculated for $[C_{16}H_{13}BrNaO_4]^+$ is 370.9889 *m/z*; found $[M + Na]^+$ 370.9883 *m/z*. **M.p.** = 61–68 ºC.

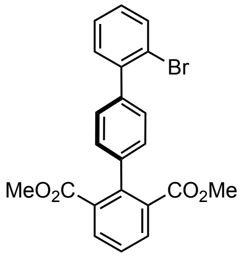
Dimethyl 4'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-2,6-dicarboxylate, 43



Under nitrogen atmosphere, a mixture of **41** (1.40 g, 4.01 mmol, 1.0 equiv), B_2pin_2 (1.12 g, 4.41 mmol, 1.1 equiv), $PdCl_2(PPh_3)_2$ (140.7 mg, 200.5 μmol, 5 mol%) and KOAc (881 mg, 8.98 mmol, 2.2 equiv) in DMF (40.1 mL, 0.1 M) was stirred at 90 ºC for 2 days. The reaction was quenched with water and extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc from 10:0 to 2:8) affording the title compound **43** (1.10 g, 2.77 mmol, 69% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.8 Hz, 2H), 7.83 – 7.77 (m, 2H), 7.47 (t, *J* = 7.8 Hz, 1H), 7.23 – 7.18 (m, 2H), 3.55 (s, 6H), 1.36 (s, 12H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 168.3, 142.1, 141.7, 134.2, 133.1, 132.0, 127.8, 127.5, 83.9, 52.3, 25.1. **HRMS** (ESI+) the exact mass calculated for $[C_{22}H_{25}NaO_6{}^{11}B]^+$ is 419.1636 *m/z*; found $[M + Na]^+$ 419.1628 *m/z*. **M.p.** = 93–96 ºC.

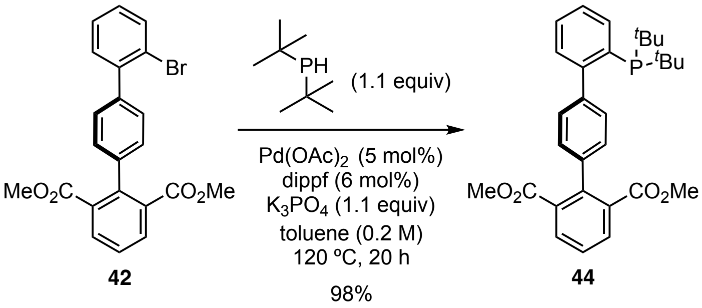
Dimethyl 2''-bromo-[1,1':4',1''-terphenyl]-2,6-dicarboxylate, 42



Procedure modified from literature:[24] Under argon atmosphere, a mixture of **43** (1.70 g, 4.29 mmol, 1 equiv), 1-bromo-2-iodobenzene (1.27 g, 4.50 mmol, 1.05 equiv), $Pd(PPh_3)_4$ (248 mg, 215 mmol, 5 mol%) and a 2 M aqueous solution of K_2CO_3 (4.3 mL) in 1,4-dioxane (10.7 mL, 0.4 M) was stirred at 110 ºC for 16 h. The reaction was quenched with H_2O and it was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc from 10:0 to 9:1) affording the title compound **42** (1.28 g, 3.01 mmol, 70% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.7 Hz, 2H), 7.68 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 1H), 7.43 – 7.34 (m, 4H), 7.28 – 7.26 (m, 1H), 7.26 – 7.24 (m, 1H), 7.22 (ddd, *J* = 8.0, 7.0, 2.1 Hz, 1H), 3.57 (s, 6H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 168.6, 142.5, 141.2, 140.2, 138.8, 133.3, 133.2, 132.0, 131.4, 128.9, 128.8, 128.0, 127.6, 127.5, 122.9, 52.3. **HRMS** (ESI+) the exact mass calculated for $[C_{22}H_{17}BrNaO_4]^+$ is 447.0202 *m/z*; found $[M + Na]^+$ 447.0196 *m/z*.

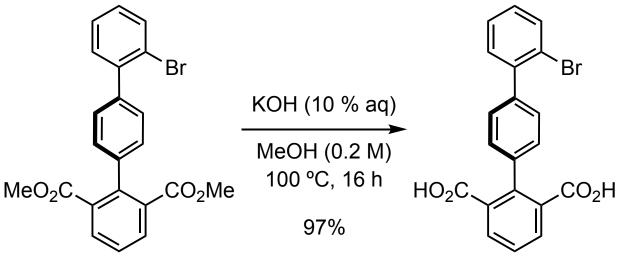
Synthesis of dimethyl 2''-(di-*tert*-butylphosphaneyl)-[1,1':4',1''-terphenyl]-2,6-dicarboxylate, 44



Procedure from literature:[17] under argon atmosphere, **42** (100 mg, 235 μmol, 1.0 equiv), $Pd(OAc)_2$ (2.6 mg, 11.8 μmol, 5 mol%), dippf (5.9 mg, 14.1 μmol, 6 mol%) and K_3PO_4 (54.9 mg, 259 μmol, 1.1 equiv) were introduced into the glovebox in a microwave vial. Inside, toluene (1.2 mL, 0.2 M) and di-*tert*-butylphosphane (48.9 μL, 259 μmol, 1.1 equiv) were added and the mixture was taken out of the glovebox. The reaction mixture was stirred at 120 ºC for 20 h. Then, solvent was removed under vacuum and the reaction was filtered through Celite® with CH_2Cl_2 and EtOAc. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc from 10:0 to 8:2) affording the title compound **44** (113.6 mg, 231.6 μmol, 98% yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 – 7.86 (m, 3H), 7.49 (t, *J* = 7.7 Hz, 1H), 7.42 – 7.29 (m, 3H), 7.24 (d, *J* = 7.9 Hz, 2H), 7.16 (d, *J* = 8.2 Hz, 2H), 3.61 (s, 6H), 1.13 (d, *J* = 11.6 Hz, 18H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 169.2, 151.1 (d, *J* = 33.1 Hz), 143.1 (d, *J* = 7.3 Hz), 141.2, 137.2, 136.1, 135.9, 135.4 (d, *J* = 3.2 Hz), 133.6, 131.8, 130.6 (d, *J* = 6.1 Hz), 130.2 (d, *J* = 4.1 Hz), 128.5, 127.3, 127.0, 126.0, 52.4 (d, *J* = 3.6 Hz), 32.9 (d, *J* = 25.7 Hz), 30.9 (d, *J* = 15.6 Hz). **^{31}P{^{1}H} NMR** (202 MHz, $CDCl_3$) δ 20.9. **HRMS** (ESI+) the exact mass calculated for $[C_{30}H_{36}O_4P]^+$ is 491.2346 *m/z*; found $[M + H]^+$ 491.2361 *m/z*. **M.p.** = 201–214 ºC.

Synthesis of 2''-bromo-[1,1':4',1''-terphenyl]-2,6-dicarboxylic acid, 46



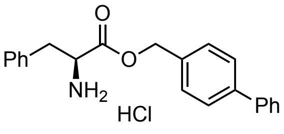
42 **46**

Procedure modified from literature:[26] a 2 M aqueous solution of KOH (11.9 mL) is added into a flask containing **42** (1.26 g, 2.96 mmol, 1 equiv) and MeOH (14.8 mL, 0.2 M). The reaction mixture was stirred at 100 ºC for 16 h. Solvents were removed, water was added and the reaction was washed with EtOAc (2x). The pH of the aqueous layer was adjusted with a solution of HCl 1M to pH 4.0, and it was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum, affording the title compound **46** (1.14 g, 2.87 mmol, 97% yield) as a white solid. It was used in the next step without further purification.

^{1}H NMR (400 MHz, DMSO) δ 12.90 (bs, 2H), 7.81 (d, *J* = 7.7 Hz, 2H), 7.76 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.56 (dd, *J* = 8.0, 7.4 Hz, 1H), 7.49 (td, *J* = 7.4, 1.3 Hz, 1H), 7.43 – 7.37 (m, 3H), 7.33 (ddd, *J* = 8.0, 7.3, 1.8 Hz, 1H), 7.30 – 7.25 (m, 2H). **^{13}C{^{1}H} NMR** (101 MHz, DMSO) δ 169.0, 141.6, 139.1, 138.4, 138.2, 134.7, 133.2, 131.4, 130.1, 129.3, 128.4, 128.3, 128.1, 127.5, 121.7.

HRMS (ESI–) the exact mass calculated for $[C_{20}H_{12}BrO_4]^-$ is 394.9924 *m/z*; found $[M - H]^-$ 394.9923 *m/z*. **M.p.** = 266–268 ºC.

Synthesis of [1,1'-biphenyl]-4-ylmethyl *L*-phenylalaninate hydrochloride



Under nitrogen atmosphere, a mixture of (*tert*-butoxycarbonyl)-*L*-phenylalanine (200.0 mg, 753.8 µmol, 1 equiv), [1,1'-biphenyl]-4-ylmethanol (166.7 mg, 904.6 µmol, 1.2 equiv) and pyridine (182 µL, 2.262 mmol, 3 equiv) in EtOAc (2.5 mL, 0.3 M) was cooled down to 0 ºC and T3P (50% in EtOAc) (1.07 mL, 1.809 mmol, 2.4 equiv) was slowly added and the reaction mixture was warmed up to 23 ºC and stirred 16 h. The reaction was cooled down to 0 ºC and an aqueous solution of HCl 1M was added. Then, at room temperature, both layers were separated and the organic phase was washed with the aqueous solution of HCl 1M (2x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. Then, dioxane (2.5 mL, 0.3 M) an aqueous solution of HCl 4M (0.57 mL) were added and the mixture was stirred at 23 ºC for 3 h. Solvents were removed,

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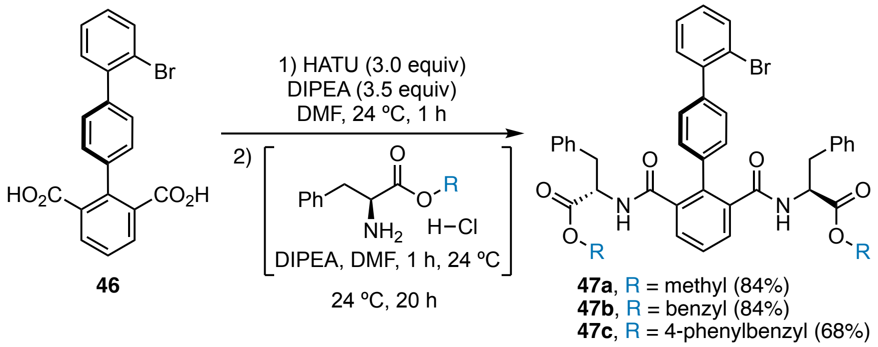
[26] af Gennäs, G. B.; Talman, V.; Aitio, O.; Ekokoski, E.; Finel, M.; Tuominen, R. K.; Yli-Kauhaluoma, J. *J. Med. Chem.* **2009**, *52*, 3969–3981.

Et_2O was added, the suspension was filtered, the solid was washed with Et_2O and dried, affording the title compound (210.3 mg, 571.7 µmol, 76% yield) as a white solid.

^{1}H NMR (500 MHz, DMSO) δ 8.75 (bs, 3H), 7.72 – 7.63 (m, 4H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.41 – 7.38 (m, 1H), 7.38 – 7.31 (m, 2H), 7.31 – 7.26 (m, 3H), 7.21 (dd, *J* = 7.3, 2.2 Hz, 2H), 5.26 – 5.11 (m, 2H), 4.33 (dd, *J* = 7.9, 5.6 Hz, 1H), 3.25 (dd, *J* = 14.0, 5.5 Hz, 1H), 3.19 – 3.05 (m, 1H). **^{13}C{^{1}H} NMR** (126 MHz, DMSO) δ 170.3, 168.9, 140.2, 139.6, 134.6, 134.0, 129.4, 129.0, 129.0, 128.6, 127.6, 127.2, 126.7, 126.7, 66.8, 53.2, 35.9. **HRMS** (ESI+) the exact mass calculated for $[C_{22}H_{22}NO_2]^+$ is 332.1645 *m/z*; found $[M - Cl]^+$ 332.1638 *m/z*. **M.p.** = 94–97 ºC. **α_D^{589}** = 3.1 deg·cm^2·g^{-1} (EtOH, c 0.1, 299 K).

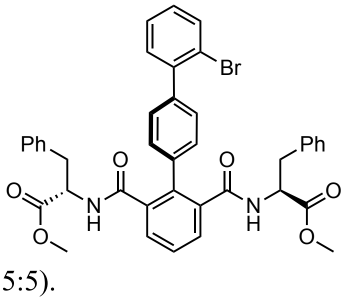
Synthesis of 47a-c



General procedure D:

Under nitrogen atmosphere, a mixture of **46** (1.0 equiv), HATU (3.0 equiv) and DIPEA (3.5 equiv) in DMF (0.25 M) was stirred at 24 ºC for 30 min. Meanwhile, DIPEA (4.9 equiv) was added into a mixture of the corresponding protected amino acid (2.4–2.8 equiv) in DMF (0.17 M) and it was stirred at 24 ºC for 30 min. This last mixture was added into the previous one and the reaction was stirred at 24 ºC for 16 h. The reaction was quenched with water and extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The crude was purified by flash column chromatography.

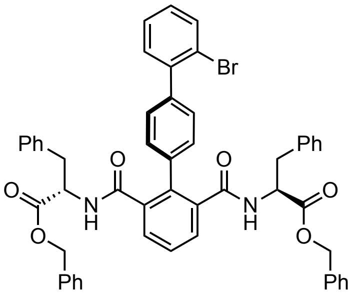
Dimethyl 2,2'-((2''-bromo-[1,1':4',1''-terphenyl]-2,6-dicarbonyl)bis(azanediyl))(2*S*,2'*S*)-bis(3-phenylpropanoate), 47a



The title compound **47a** (762.6 mg, 1.06 mmol, 84% yield) was obtained as white solid according to general procedure **D**, using **46** (500.0 mg, 1.259 mmol, 1.0 equiv) and methyl *L*-phenylalaninate hydrochloride (760.2 mg, 3.524 mmol, 2.8 equiv). It was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc from 10:0 to 5:5).

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.67 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.62 (d, *J* = 7.7 Hz, 2H), 7.51 – 7.44 (m, 3H), 7.44 – 7.40 (m, 2H), 7.36 (td, *J* = 7.4, 1.2 Hz, 1H), 7.30 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.27 – 7.19 (m, 7H), 6.98 – 6.94 (m, 4H), 5.98 (d, *J* = 7.6 Hz, 2H), 4.73 (dt, *J* = 7.6, 6.2 Hz, 2H), 3.61 (s, 6H), 2.94 (dd, *J* = 13.8, 5.8 Hz, 2H), 2.85 (dd, *J* = 13.8, 6.4 Hz, 2H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 171.7, 168.3, 142.1, 141.3, 137.6, 137.0, 136.7, 136.3, 133.6, 131.8, 130.0, 129.6, 129.5, 129.4, 128.9, 128.3, 127.9, 127.4, 122.6, 54.1, 52.5, 38.2. **HRMS** (ESI+) the exact mass calculated for $[C_{40}H_{36}BrN_2O_6]^+$ is 719.1751 *m/z*; found $[M + H]^+$ 719.1746 *m/z*. **M.p.** = 154–160 ºC. α_D^{589} = 55.5 deg·cm^2·g^{-1} ($CHCl_3$, c 0.1, 300 K).

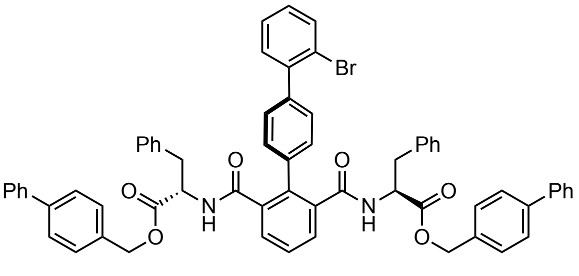
Dibenzyl 2,2'-((2''-bromo-[1,1':4',1''-terphenyl]-2,6-dicarbonyl)bis(azanediyl))(2*S*,2'*S*)-bis(3-phenylpropanoate), 47b



The title compound **47b** (184.1 mg, 211.2 µmol, 84% yield) was obtained as yellowish solid according to general procedure ***D***, using **46** (100.0 mg, 251.7 µmol, 1.0 equiv) and benzyl *L*-phenylalaninate hydrochloride (205.7 mg, 704.9 µmol, 2.8 equiv). It was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc from 10:0 to 5:5).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.62 (m, 3H), 7.48 – 7.39 (m, 5H), 7.35 – 7.28 (m, 7H), 7.25 – 7.11 (m, 12H), 6.85 – 6.79 (m, 4H), 5.82 (d, *J* = 7.7 Hz, 2H), 5.04 (d, *J* = 12.1 Hz, 2H), 4.99 (d, *J* = 12.2 Hz, 2H), 4.81 (td, *J* = 6.9, 5.2 Hz, 2H), 2.94 (dd, *J* = 13.8, 5.3 Hz, 2H), 2.76 (dd, *J* = 13.8, 6.8 Hz, 2H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 170.8, 168.2, 141.7, 141.3, 137.0, 136.4, 136.2, 135.5, 135.0, 133.4, 131.5, 130.1, 130.0, 129.3, 129.1, 129.1, 128.7, 128.6, 128.6, 128.6, 128.2, 127.6, 127.2, 122.5, 67.3, 53.8, 37.9. **HRMS** (ESI+) the exact mass calculated for $[C_{52}H_{43}BrN_2NaO_6]^+$ is 893.2197 *m/z*; found $[M + Na]^+$ 893.2177 *m/z*. **M.p.** = 112–119 ºC. α_D^{589} = 14.2 deg·cm^2·g^{-1} ($CHCl_3$, c 0.1, 299 K).

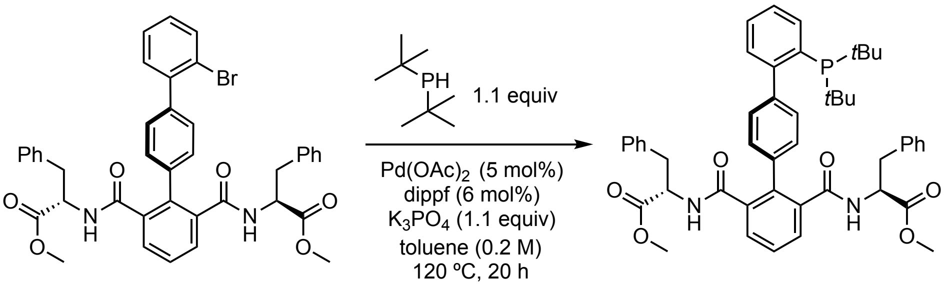
Bis([1,1'-biphenyl]-4-ylmethyl) 2,2'-((2''-bromo-[1,1':4',1''-terphenyl]-2,6-dicarbonyl)bis(azanediyl))(2*S*,2'*S*)-bis(3-phenylpropanoate), 47c



The title compound **47c** (79.0 mg, 77.0 µmol, 68% yield) was obtained as white solid according to general procedure ***D***, using **46** (45.0 mg, 113 µmol, 1.0 equiv) and [1,1'-biphenyl]-4-ylmethyl L-phenylalaninate hydrochloride (100 mg, 272 µmol, 2.4 equiv). It was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc from 10:0 to 5:5).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.7 Hz, 2H), 7.63 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.60 – 7.55 (m, 4H), 7.55 – 7.50 (m, 4H), 7.50 – 7.41 (m, 9H), 7.41 – 7.33 (m, 2H), 7.30 – 7.20 (m, 6H), 7.20 – 7.10 (m, 7H), 6.88 – 6.77 (m, 4H), 5.82 (d, *J* = 7.6 Hz, 2H), 5.08 (d, *J* = 12.2 Hz, 2H), 5.03 (d, *J* = 12.2 Hz, 2H), 4.82 (td, *J* = 7.1, 5.2 Hz, 2H), 2.96 (dd, *J* = 13.7, 5.2 Hz, 2H), 2.77 (dd, *J* = 13.7, 6.9 Hz, 2H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 170.9, 168.2, 141.8, 141.6, 141.4, 140.7, 137.0, 136.4, 136.2, 135.5, 134.0, 133.4, 131.5, 130.2, 130.0, 129.4, 129.2, 129.1, 129.1, 129.0, 128.7, 128.2, 127.7, 127.6, 127.4, 127.3, 127.2, 122.5, 67.0, 53.8, 38.0. **HRMS** (ESI+) the exact mass calculated for $[C_{64}H_{51}BrN_2NaO_6]^+$ is 1045.2823 *m/z*; found $[M + Na]^+$ 1045.2813 *m/z*. **M.p.** = 103–109 ºC. $\boldsymbol{\alpha_D}^{589}$ = 7.2 deg·cm^2·g^{-1} (CHCl$_3$, c 0.1, 300 K).

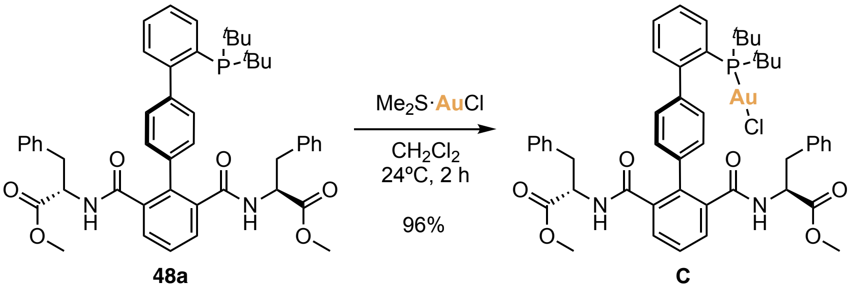
Synthesis of dimethyl 2,2'-((2''-(di-*tert*-butylphosphaneyl)-[1,1':4',1''-terphenyl]-2,6-dicarbonyl)bis(azanediyl))(2*S*,2'*S*)-bis(3-phenylpropanoate), 48a



Procedure from literature:[17] Under argon atmosphere, **47a** (590 mg, 820 µmol, 1.0 equiv), Pd(OAc)$_2$ (9.2 mg, 41 µmol, 5 mol%), dippf (20.6 mg, 49.2 µmol, 6 mol%) and K$_3$PO$_4$ (191.4 mg, 901.9 µmol, 1.1 equiv) were introduced into the glovebox in a microwave vial. Inside, toluene (4.1 mL, 0.2 M) and di-*tert*-butylphosphane (0.17 mL, 902 µmol, 1.1 equiv) were added and the mixture was taken out of the glovebox. The reaction mixture was stirred at 120 ºC for 20 h. Then, solvent was removed under vacuum and the reaction was filtered through Celite® with CH$_2$Cl$_2$ and EtOAc. The crude was purified by flash column chromatography (SiO$_2$, cyclohexane/EtOAc from 10:0 to 1:9) affording the title compound **48a** (328.8 mg, 418.9 µmol, 51% yield) as a white solid.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.89 (dt, *J* = 7.5, 1.8 Hz, 1H), 7.66 (d, *J* = 7.7 Hz, 2H), 7.50 – 7.38 (m, 5H), 7.31 (dtd, *J* = 8.6, 7.1, 1.6 Hz, 2H), 7.25 – 7.15 (m, 6H), 7.11 (ddd, *J* = 7.5, 4.0, 1.8 Hz, 1H), 6.94 – 6.87 (m, 4H), 5.76 (d, *J* = 7.7 Hz, 2H), 4.77 (dt, *J* = 7.8, 5.8 Hz, 2H), 3.64 (s, 6H), 2.99 (dd, *J* = 13.7, 5.5 Hz, 2H), 2.81 (dd, *J* = 13.7, 6.2 Hz, 2H), 1.09 (d, *J* = 11.6 Hz, 9H), 1.01 (d, *J* = 11.6 Hz, 9H). **^{13}C{^{1}H} NMR** (101 MHz, CDCl$_3$) δ 171.5, 168.5, 150.5 (d, *J* = 33.3 Hz), 144.9 (d, *J* = 7.0 Hz), 137.0, 136.3, 135.7, 135.6, 135.5, 135.4, 134.9, 131.1 (d, *J* = 4.0 Hz), 131.0 (d, *J* = 6.3 Hz), 130.3, 129.5, 128.7, 128.6, 128.0, 127.3, 126.2, 53.7, 52.3, 37.8 (d, *J* = 2.5 Hz), 33.1 (d, *J* = 25.2 Hz), 33.0 (d, *J* = 25.2 Hz), 30.8 (d, *J* = 15.2 Hz), 30.6 (d, *J* = 15.2 Hz). **^{31}P{^{1}H} NMR** (162 MHz, CDCl$_3$) δ 19.7. **HRMS** (ESI+) the exact mass calculated for $[C_{48}H_{54}N_2O_6P]^+$ is 785.3714 *m/z*; found $[M + H]^+$ 785.3725 *m/z*. **M.p.** = 150–158 ºC. $\boldsymbol{\alpha_D}^{589}$ = 63.3 deg·cm^2·g^{-1} (CHCl$_3$, c 0.1, 300 K).

Synthesis of chiral complex (*S*,*S*)-C



Under argon atmosphere, **48a** (50.0 mg, 63.7 μmol, 1.0 equiv) and dimethyl sulfide gold(I) chloride (18.8 mg, 63.7 μmol, 1.0 equiv) in dichloromethane (0.1 M) was stirred at 24 ºC for 1 h. Then, it was filtered through a path of neutral Al_2O_3 and concentrated affording complex (*S*,*S*)-**C** (64.4 mg, 63.73 μmol, 99% yield) as a white solid.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.91 – 7.85 (m, 1H), 7.59 (ddd, *J* = 14.6, 7.9, 2.1 Hz, 2H), 7.55 (d, *J* = 7.6 Hz, 2H), 7.51 – 7.47 (m, 2H), 7.43 (dd, *J* = 8.2, 7.1 Hz, 1H), 7.37 (dd, *J* = 7.9, 2.0 Hz, 1H), 7.32 – 7.27 (m, 1H), 7.27 – 7.16 (m, 7H), 7.04 (d, *J* = 7.4 Hz, 4H), 6.69 (s, 2H), 4.67 (q, *J* = 7.0 Hz, 2H), 3.58 (s, 6H), 3.02 (d, *J* = 6.7 Hz, 4H), 1.40 (d, *J* = 15.7 Hz, 9H), 1.31 (d, *J* = 15.7 Hz, 9H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 171.6, 169.5, 149.5 (d, *J* = 12.4 Hz), 142.4 (d, *J* = 6.0 Hz), 137.8, 135.7, 135.1, 134.3 (d, *J* = 2.8 Hz), 134.0 (d, *J* = 7.4 Hz), 131.8, 131.2 (d, *J* = 2.4 Hz), 130.9, 130.4, 129.9, 129.7, 128.7, 128.0, 127.4 (d, *J* = 6.9 Hz), 127.1, 125.6 (d, *J* = 45.0 Hz), 54.7, 52.2, 38.4 (d, *J* = 25.7 Hz), 38.1 (d, *J* = 25.7 Hz), 38.0, 31.2 (d, *J* = 6.6 Hz), 30.8 (d, *J* = 6.5 Hz). **^{31}P{^{1}H} NMR** (202 MHz, CD_2Cl_2) δ 63.2. **HRMS** (ESI+) the exact mass calculated for $[C_{48}H_{53}AuClN_2NaO_6P]^+$ is 1039.2888 *m/z*; found $[M + Na]^+$ 1039.2866 *m/z*. **M.p.** =>122 ºC (decomposition; CH_2Cl_2). **α_D^{589}** = 12.3 deg·cm^2·g^{-1} (CH_2Cl_2, c 0.1, 300 K).

Crystallographic Data

Complex (*R*)-A

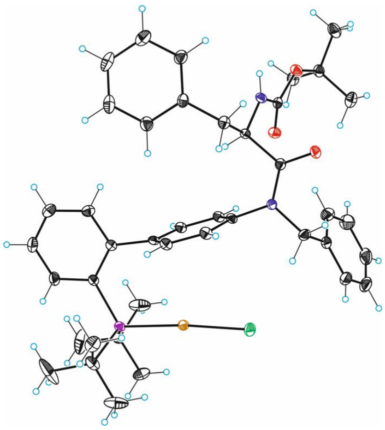


Table 1. Crystal data and structure refinement for **Complex (*R*)-A**.

Identification code	mo_AAB2023_0m	
Empirical formula	C43 H55 Au Cl3 N2 O3 P	
Formula weight	982.17	
Temperature	100(2)K	
Wavelength	0.71073 Å	
Crystal system	triclinic	
Space group	P -1	
Unit cell dimensions	a = 11.0615(6)Å	a= 72.1289(14)º.
	b = 14.0516(8)Å	b = 89.0892(15)º.
	c = 14.4583(8)Å	g = 86.7613(13)º.
Volume	2135.4(2) Å^3	
Z	2	
Density (calculated)	1.528 Mg/m^3	
Absorption coefficient	3.710 mm^{-1}	
F(000)	992	
Crystal size	0.100 x 0.050 x 0.020 mm^3	
Theta range for data collection	1.770 to 32.770º.	
Index ranges	-16<=h<=13,-21<=k<=20,-21<=l<=20	
Reflections collected	31216	
Independent reflections	15058[R(int) = 0.0213]	
Completeness to theta =32.770º	95.3%	
Absorption correction	Multi-scan	
Max. and min. transmission	0.74 and 0.66	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	15058/ 0/ 487	
Goodness-of-fit on F^2	1.005	
Final R indices [I>2sigma(I)]	R1 = 0.0227, wR2 = 0.0526	
R indices (all data)	R1 = 0.0272, wR2 = 0.0542	
Largest diff. peak and hole	0.974 and -0.921 e.Å^{-3}	

Complex (*S*)-B

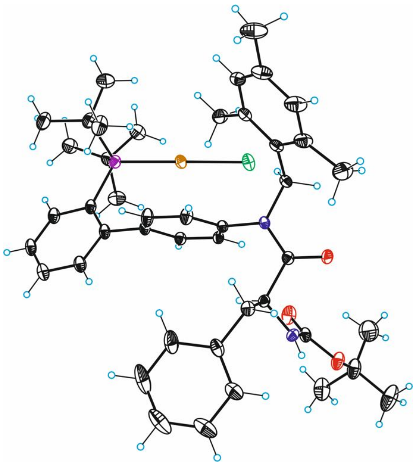


Table 1. Crystal data and structure refinement for **Complex (*S*)-B**.

Identification code	mo_AAB2054P-05	
Empirical formula	C96 H130 Au2 Cl10 N4 O6 P2	
Formula weight	2246.41	
Temperature	100(2)K	
Wavelength	0.71073 Å	
Crystal system	triclinic	
Space group	P -1	
Unit cell dimensions	a = 11.6302(6)Å	a= 67.3338(10)º.
	b = 13.8761(7)Å	b = 79.0460(11)º.
	c = 17.1092(8)Å	g = 81.8100(10)º.
Volume	2494.1(2) Å^{3}	
Z	1	
Density (calculated)	1.496 Mg/m^{3}	
Absorption coefficient	3.290 mm^{-1}	
F(000)	1140	
Crystal size	0.500 x 0.400 x 0.200 mm^{3}	
Theta range for data collection	1.647 to 30.675º.	
Index ranges	-16<=h<=16,-18<=k<=19,0<=l<=24	
Reflections collected	14916	
Independent reflections	14916[R(int) = ?]	
Completeness to theta =30.675º	96.6%	
Absorption correction	Multi-scan	
Max. and min. transmission	0.74 and 0.32	
Refinement method	Full-matrix least-squares on F^{2}	
Data / restraints / parameters	14916/ 290/ 628	
Goodness-of-fit on F^{2}	1.018	
Final R indices [I>2sigma(I)]	R1 = 0.0324, wR2 = 0.0834	
R indices (all data)	R1 = 0.0361, wR2 = 0.0860	
Largest diff. peak and hole	2.232 and -1.818 e.Å^{-3}	

Chapter III: “Design of Gold(I) Catalysts for Targeting Senescent Cells”

*The work described in this chapter was carried out in collaboration with **Dr. Anna Sadurní** and **Dr. Marc Montesinos-Magraner***

Introduction

Senescent cells

A cell is a basic structural unit that can function independently and compose all living beings. There are different types of cells with different composition, properties and activities. Cells are composed by different macromolecules, such as proteins, polysaccharides and nucleic acids, and they are delimited by a membrane that allows the exchange of matter. Specialized cells are organized together forming tissues and organs in multicellular organisms.[1]

Cell cycle is the events that take place in a cell until it is divided. These events include their preparation and division in two daughters, genetically identical than the original one. In eukaryotic cells (contain a nucleus), the cell cycle is formed by two major phases: interphase and M phase.1

- Interphase is divided in three phases: G1, S and G2. G1 and G2 are preparative phases in which the cell grows, makes proteins and organelles. In the S phase (from synthesis), a copy of the DNA is generated in the nucleus.
- Phase M has two processes: mitosis (nuclear division, generating two nuclei) and cytokinesis (cell division, forming two daughter cells).

When a cell cycle is arrested, it has stopped to replicate itself, getting outside of the common cycle processes of the cells. This can happen in any phase of the cell cycle. There are different reasons why a cell becomes arrested. The most common reasons are because it has reached the end of its life or because it has been damaged. Arrested cells can evolve in three different ways: apoptosis (death of the cells through a natural way of getting rid of them); go back into the cycle; or become senescent by being permanently arrested.[2] Senescence was first noticed in 1961 by Hayflick and co-workers, in their studies of the serial cultivation of human diploid cells.[3]

Senescent cells have different morphology[4] and properties than other cells (Figure 1), they are usually larger, flatter and have an irregular shape. They also exhibit other secretory phenotype known as senescence-associated secretory phenotype (SASP). Senescent cells are necessary because they can affect the behavior of other cells having different functions, for example in remodeling and reparation

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[1] Alberts, B.; Johnson, A.; Lewis, J.; Raff, M.; Roberts, K.; Walter, P. *Biología Molecular de la Célula*, 5th ed.; Omega, 2010.

[2] Lozano-Torres, B.; Estepa-Fernández, A.; Rovira, M.; Orzáez, M.; Serrano, M.; Martínez-Máñez, R.; Sancenón, F. *Nat Rev Chem* **2019**, *3*, 426–441.

[3] Hayflick, L.; Moorhead, P. S. *Exp. Cell Res.* **1961***, 25*, 585–621.

[4] Muñoz-Espín, D.; Serrano, M. *Nat. Rev. Mol. Cell. Biol.* **2014**, *15*, 482–496.

of tissues, or in embryonic development, thanks to the SASP factors.[5] Nevertheless, an accumulation of these cells in tissues can cause negative effects, leading to inflammation and producing age-related diseases.[6] They are associated to many degenerative pathologies, such as brain disorders,[7] liver fibrosis[8] or cancer.[9]

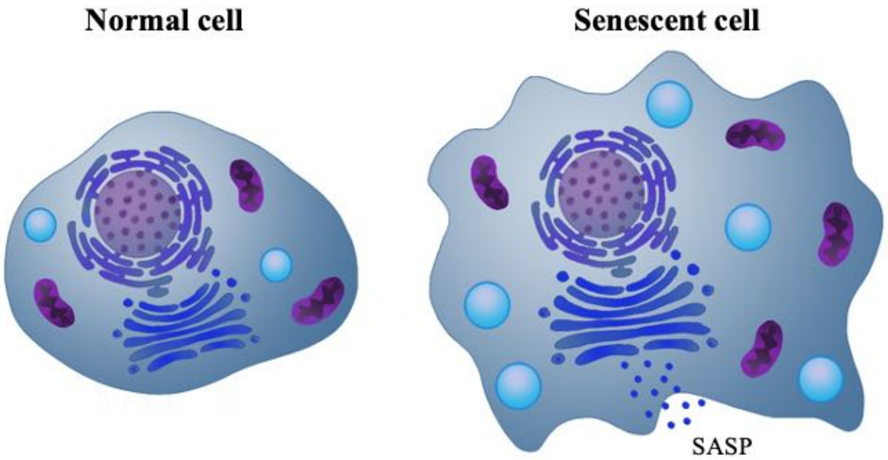

Figure 1. Morphology comparation between a normal cell (left) and a senescent cell (right).

Due to the important role that these cells perform, detecting and eliminating them is important for the cure of these diseases. Senolytic drugs target specific vulnerabilities in senescent cells, so they are able to kill them over non-senescent cells.[10] However, there is not a drug able to remove all senescent cells and senolytics have associated toxicities that need to be diminished. Senescent cells have different markers[11] and it is commonly necessary the detection of multiple markers for confirming the presence of these cells. Among all these markers, we could highlight the senescence-associated β-galactosidase (SA-β-Gal) activity.[12] Lysosomes overexpress β-galactosidase (enzyme that hydrolyzes the glycosidic bond of terminal β-galactoses), so the level of β-galactosidase is higher in senescent cells than in non-

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[5] For some examples see: (a) Kong, X.; Feng, D.; Wang, H.; Hong, F.; Bertola, A.; Wang, F.-S.; Gao, B. *Hepatology* **2012**, *56*, 1150–1159. (b) Mosteiro, L.; Pantoja, C.; de Martino, A.; Serrano, M. *Aging Cell* **2018**, *17*, 12711–12722. (c) Li, C.; Chai, Y.; Wang, L.; Gao, B.; Chen, H.; Gao, P.; Zhou, F.-Q.; Luo, X.; Crane, J. L.; Yu, B.; Cao, X.; Wan, M. *Nat. Commun.* **2017**, *8*, 1312. (d) Storer, M.; Storer, M.; Mas, A.; Robert-Moreno, A.; Pecoraro, M.; Ortells, M. C.; Di Giacomo, V.; Yosef, R.; Pilpel, N.; Krizhanovsky, V.; Sharpe, J.; Keyes, W. M. *Cell* **2013**, *155*, 1119–1130.

[6] Kirkland, J. L.; Tchkonia, T.; Zhu, Y.; Niedernhofer, L. J.; Robbins, P. D. *J. Am. Geriatr. Soc.* **2017**, *65*, 2297–2301.

[7] Baker, D. J.; Petersen, R. C. *J. Clin. Invest.* **2018**, *128*, 1208–1216.

[8] Wandrer, F.; Han, B.; Liebig, S.; Schlue, J.; Manns, M. P.; Schulze-Osthoff, K.; Bantel, H. *Aliment. Pharmacol. Ther.* **2018**, *48*, 270–280.

[9] For some examples see: (a) Sutherland, R. L. & Musgrove, E. A. *Breast Cancer Res.* **2009**, *11*, 112–113. (b) Schosserer, M.; Grillari, J.; Breitenbach, M. *Front. Oncol.* **2017**, *7*, 2781–2793.

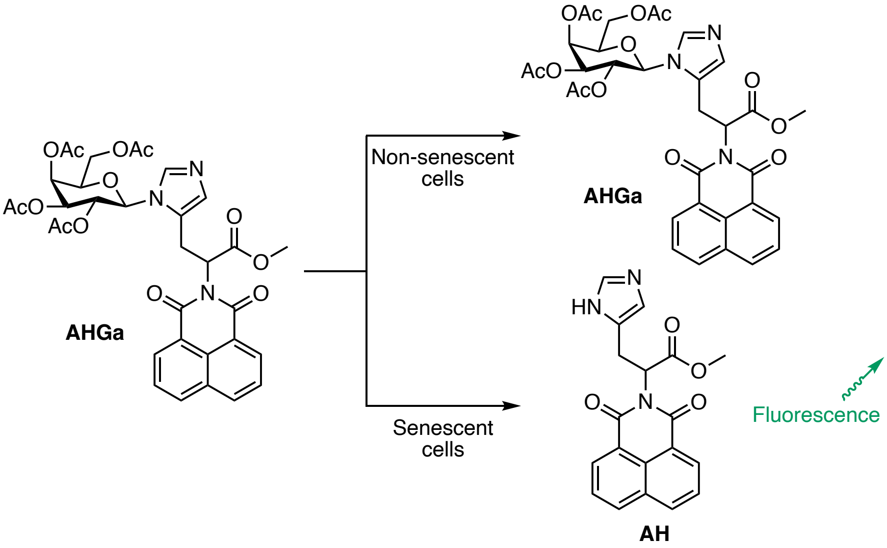
[10] Zhu, Y. et al. *Aging Cell* **2015**, *14*, 644–658.

[11] Sikora, E.; Mosieniak, G.; Sliwinska, M. A. *Curr. Drug Targets* **2016**, *17*, 377–387.

[12] Dimri, G. P.; Lee, X.; Basile, G.; Acosta, M.; Scott, G.; Roskelley, C.; Medranos, E. E.; Linskens, M.; Rubelj, I.; Pereira-Smith, O.; Peacocke, M.; Campisi, J. *Proc. Natl Acad. Sci. USA* **1995**, *92*, 9363–9367.

senescent cells. The high levels of SA-*β*-Gal in senescent cells have been recently used as target for the detection and elimination of these cells.

In 2017, Sancenón and coworkers described the use of a naphthalimide core containing a L-histidine methyl ester linked to a tetraacetylated galactose (AHGa) for the detection of senescent cells. Compound AHGa generates the fluorescent probe AH upon hydrolysis of the glycosidic bond, causing an increase in fluorescent emission intensity, which can be associated to the augmented SA-*β*-Gal activity of senescent cells (Scheme 1). It was also studied *in vivo*, also showing a fluorescence signal in senescent tumors in mice due to the presence of AH, and not in other organs.[13]



Scheme 1. Representation of the activation of AHGa in senescent cells, generating fluorescence emission.

Another example of advance in the detection of this cells was described by the same groups in 2021,[14] with the synthesis of a fluorescent naphthalimide core linked to a styrene (Heck) that through a glycosylation reaction is introduced an acetylated galactose in the phenolic substituent (HeckGal, non-fluorescent). Again, when HeckGal is in a senescent cell, it is hydrolyzed by SA-*β*-Gal producing a fluorescence emission. HeckGal has also been tested *in vivo* allowing the detection of senescence in tissues and tumors.

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[13] Lozano-Torres, B.; Galiana, I.; Rovira, M.; Garrido, E.; Chaib, S.; Bernardos, A.; Muñóz-Espín, D.; Serrano, M.; Martínez-Máñez, R.; Sancenón, F. *J. Am. Chem. Soc.* **2017**, *139*, 8808–8811.

[14] Lozano-Torres, B.; Blandez, J. F.; Galiana, I.; Lopez-Dominguez, J. A.; Rovira, M.; Paez-Ribes, M.; González-Gualda, E.; Muñóz-Espín, D.; Serrano, M.; Sancenón, F.; Martínez-Máñez, R. *Anal. Chem.* **2021**, *93*, 3052–3060.

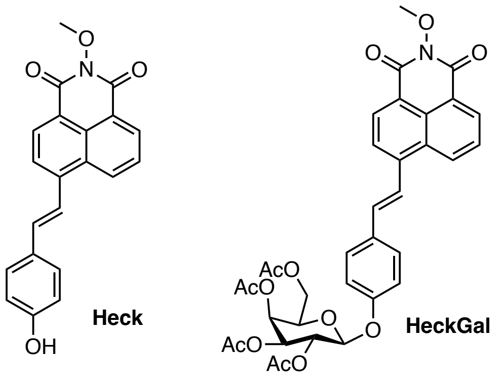

Figure 2. Structures of Heck and its acetylated-galactose derivative HeckGal.

The same working principle can be applied to the delivery of senolytic drugs to senescent cells selectively by the administration of galactose-substituted prodrugs. For example, Navitoclax,[15] a senolytic drug, linked to a galactose is a potent senolytic prodrug (Nav-Gal), whose structures are shown in Figure 3. In 2020, it was demonstrated that Nav-Gal kills selectively senescent cells *in vitro*, by hydrolysis of the glycosidic bond, and that the combination of galacto-senolytics could reduce toxicities.[16]

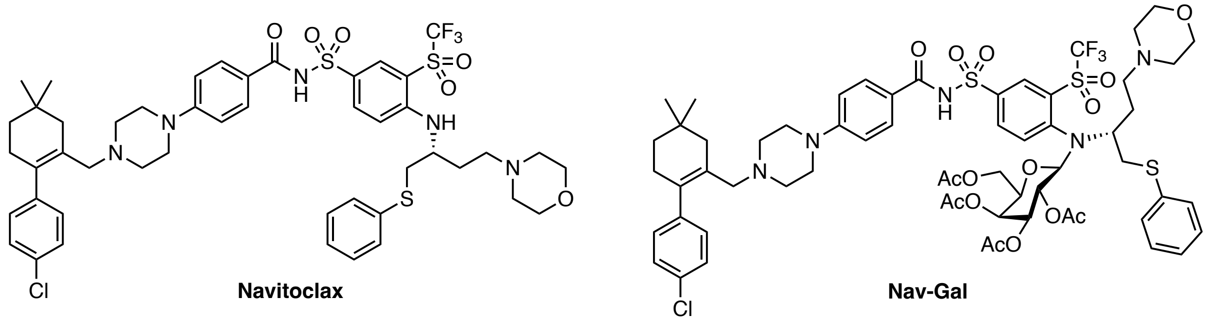

Figure 3. Structures of Navitoclax and Nav-Gal.

Another example of galactose-modified prodrug was described as a new source of senlotytic agent the same year.[17] In this case the prodrug is derived from the natural antibiotic duocarmycin,[18] which is a cytostatic compound. They demonstrated that this prodrug is able to eliminate different types of senescent cells *in vitro* and preliminary studies were successfully carried out *in vivo*.

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[15] (a) Zhu, Y.; Tchkonia, T.; Fuhrmann-Stroissnigg, H.; Dai, H.M.; Ling, Y.Y.; Stout, M.B.; Pirtskhalava, T.; Giorgadze, N.; Johnson, K.O.; Giles, C.B.; Wren, J.D.; Niedernhofer, L.J.; Robbins, P.D.; Kirkland, J.L. *Aging Cell* **2016**, *15*, 428–435. (b) Cang, S.; Iragavarapu, C.; Savooji, J.; Song, Y.; Liu, D. *J Hematol Oncol* **2015**, *8*, 129.

[16] González-Gualda, E.; Pàez-Ribes, M.; Lozano-Torres, B.; Macias, D.; Wilson III, J. R.; González-López, C.; Ou, H.-L.; Mirón-Borroso, S.; Zhang, Z.; Lérida-Viso, A.; Blandez, J. F.; Bernardos, A.; Sancenón, F.; Rovira, M.; Fruk, L.; Martins, C. P.; Serrano, M.; Doherty, G. J.; Martínez-Máñez, R.; Muñoz-Espín, D. *Aging Cell*. **2020**;19:e13142.

[17] Guerrero, A.; Guiho, R.; Herranz, N.; Uren, A.; Withers, D. J.; Martínez-Barbera, J. P.; Tietze, L. F.; Gil, J. *Aging Cell* **2020**;19:e13133.

[18] Boger, D. L.; Johnson, D. S. *Proc. Natl. Acad. Sci. USA* **1995**, *92*, 3642–3649.

Another prodrug design with the same characteristic is SSK1.[19] It is activated by *β*-galactosidase generating cytotoxic gemcitabine that eliminates senescent cells (Figure 4). The proposed mechanism for this transformation is the hydrolysis of the glycosidic bond by the *β*-galactosidase generating a phenoxide, followed by a self-immolation to release gemcitabine.[20]

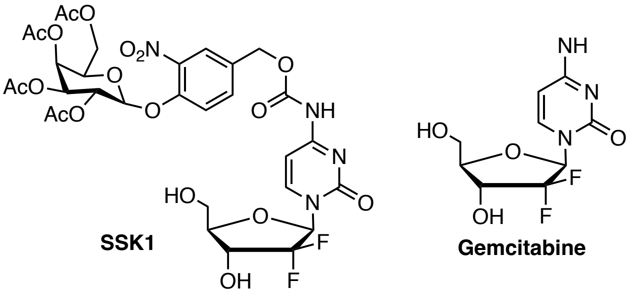

Figure 4. SSK1 and gemcitabine structures.

N-heterocyclic carbenes gold(I) complexes in cells

Since the last years, the field of metal-catalyzed reactions in biological media is receiving increasing attention.[21] In this field, the most common catalysts used are based on palladium, copper or ruthenium, but also there are some examples based on gold, iridium or iron.

The important role of gold(I) in catalysis for the activation of alkynes has been already described in the *General Introduction*. Taking into account that alkynes are exogenous (not naturally produced nor present in the organisms) and bioorthogonal (do not react with endogenous biomolecules, not interfering in biological processes),[22] they can be a perfect target for gold(I) catalysts in biological environments.[23,24]

An example of gold(I) catalyzed reaction in biological media was reported by the group of Mascareñas in 2018.[25] The intramolecular hydroarylation reaction of **1** (Scheme 2) gives the fluorescent coumarin

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[19] Cai, Y.; Zhou, H.; Zhu, Y.; Sun, Q.; Ji, Y.; Xue, A.; Wang, Y.; Chen, W.; Yu, X.; Wang, L.; Chen, H.; Li, C.; Luo, T.; Deng, H. *Cell Res* **2020**, *30*, 574–589.

[20] Xiong, J.; Chu, J. C. H.; Fong, W.-P.; Wong, C. T. T.; Ng, D. K. P. *J. Am. Chem. Soc.* **2022**, *144*, 10647–10658.

[21] (a) Yang, M.; Chen, R. P. *Chem. Soc. Rev.* **2014**, *43*, 6511–6526. (b) Vinogradova, E. V. *Pure. Appl. Chem.* **2017**, *89*, 1619–1641. (c) Rebelein, J. G.; Ward, T. R. *Curr. Opin. Biotechnol.* **2018**, *53*, 106–114. (d) Martínez-Calvo, M.; Mascareñas, J. L. *Coord. Chem. Rev.* **2018**, *359*, 57–79. (e) Liu, Y.; Bai, Y. *ACS Appl. Bio Mater.* **2020**, *3* 4717–4746.

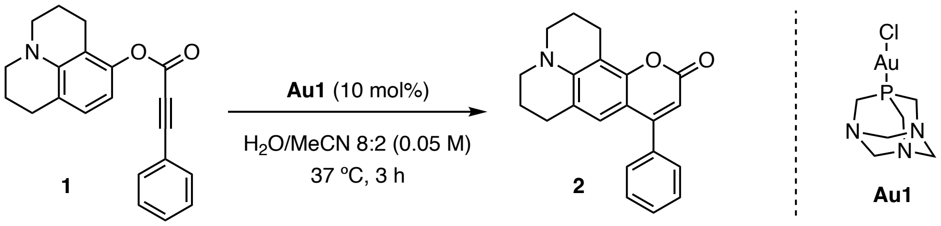
[22] Sletten, E. M.; Bertozzi, C. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 6974–6998.

[23] Tsubokura, K.; Vong, K. K. H.; Pradipta, A. R.; Ogura, A.; Urano, S.; Tahara, T.; Nozaki, S.; Onoe, H.; Nakao, Y.; Regina Sibgatullina, R.; Kurbangalieva, A.; Watanabe, Y.; Tanaka, K. *Angew. Chem. Int. Ed.* **2017**, *56*, 3579–3584.

[24] Pérez-López, A. M.; Rubio-Ruiz, B.; Sebastián, V.; Hamilton, L.; Adam, C.; Bray, T. L.; Irusta, S.; Brennan, P. M.; Lloyd-Jones, G. C.; Sieger, D.; Santamaría, J.; Unciti-Broceta A. *Angew. Chem. Int. Ed.* **2017**, *56*, 12548–12552.

[25] Vidal, C.; Tomás-Gamasa, M.; Destito, P.; López, F.; Mascareñas, J. L. *Nat. Commun.* **2018**, *9*, 1913.

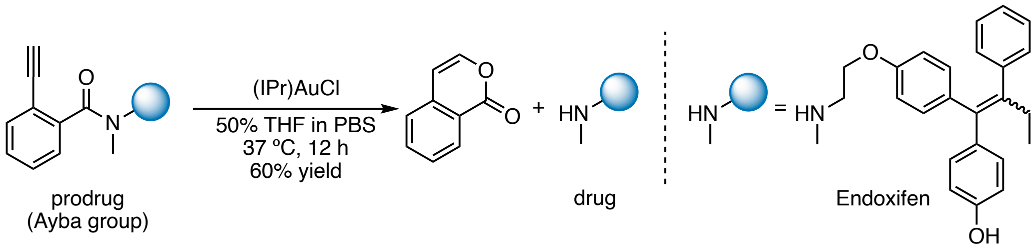
2 as product and it can be carried out not only in biological media, but also in the interior of living cells. The presence of a chloride scavenger is not necessary to promote these transformations since it has been observed that water is able to activate gold(I) catalysts.[26]



Scheme 2. Hydroarylation reaction catalyzed in biological media.

Among all the ligands that are established for Au(I), N-heterocyclic carbenes are one of the most stable and robust. Properties like their solubility, permeability, biocompatibility and toxicity can be modulated, being suitable as complexes used in aqueous media26[b,c,d] and even in biological media.

In this context, the group of Tanaka has recently reported the use of N-heterocyclic carbene gold(I) complexes for the synthesis of bioactive compounds.[27] Anticancer drugs (endoxifen and doxorubicin) containing a secondary amine are released by a gold(I) triggered cyclization reaction (Scheme 3), showing an effect *in vitro* in biological media.



Scheme 3. Gold(I)-triggered release of endoxifen.

Carbohydrates

For a better understanding of the synthesis processes carried out in this chapter, a brief introduction in carbohydrates and their main concepts are presented.

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[26] For some examples see: (a) Feng, E.; Zhou, Y.; Zhao, F.; Chen, X.; Zhang, L.; Jiang, H. Liu, H. *Green Chem.* **2012**, *14*, 1888–1895. (b) Tomás-Mendivil, E.; Toullec, P. Y.; Borge, J.; Conejero, S.; Michelet, V.; Cadierno, V. *ACS Catal.* **2013**, *3*, 3086–3098. (c) Ibrahim, H.; de Frémont, P.; Braunstein, P.; Théry, V.; Nauton, L.; Cisnetti, F.; Gautier, A. *Adv. Synth. Catal.* **2015**, *357*, 3893–3900. (d) Belger, K.; Krause, N. *Org. Biomol. Chem.* **2015**, *13*, 8556–8560. (e) Rodríguez-Álvarez, M. J.; Vidal, C.; Schumacher, S.; Borge, J.; García- Álvarez, J. *Chem. Eur. J.* **2017**, *23*, 3425–3431.

[27] Vong, K.; Yamamoto, T.; Changa, T.-C.; Tanaka, K. *Chem. Sci.* **2020**, *11*, 10928–10938.

Carbohydrates are structures highly present in nature and they usually have an important participation in biological processes. At the end of the last century, vaccines or antibiotics have been developed with carbohydrates in their structures.[28]

Among all the different types of carbohydrates that can be identified depending on their structures, this chapter will be focused on galactose, a monosaccharide whose structure is shown in Figure 5.

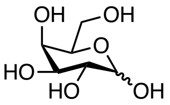


Figure 5. Galactose.

Depending on the conformation of the anomeric carbon, carbohydrates are classified as *α* or *β* products. In a Fischer projection (Figure 6), this classification is based on the substituents of two carbons: the exocyclic oxygen of the anomeric carbon (C1) and the oxygen (usually the endocyclic oxygen) of the chiral carbon named with the highest number (usually C5). *α*-anomer is defined when these two substituents are on the same side and *β*-anomer when they are in the opposite side (definition by IUPAC).[29]

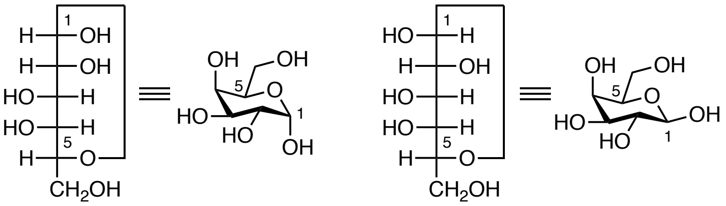
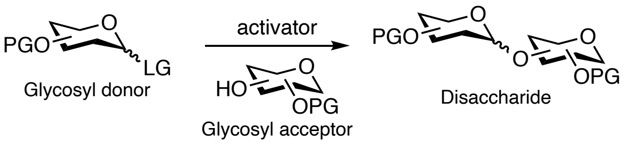


Figure 6. *α* (left) and *β* (right) anomers of galactose.

Every monosaccharide can be linked with another monosaccharide or other molecule via a glycosidic bond (Scheme 4). The mechanism of this reaction can involve a S_N1, S_N1-type, S_N2 or S_N2-type mechanisms. For the synthesis of a disaccharide, the formation of the new bond occurs between the anomeric carbon of a glycosyl donor and a glycosyl acceptor, electrophile and nucleophile respectively.



Scheme 4. Glycosylation reaction between two monosaccharides

There are different factors involved in the outcome of glycosylation reactions: leaving groups, activators, protecting groups, solvents or temperature. In the last couple of centuries there have been many advances in the study of these conditions. Since the end of the 19th century, different leaving

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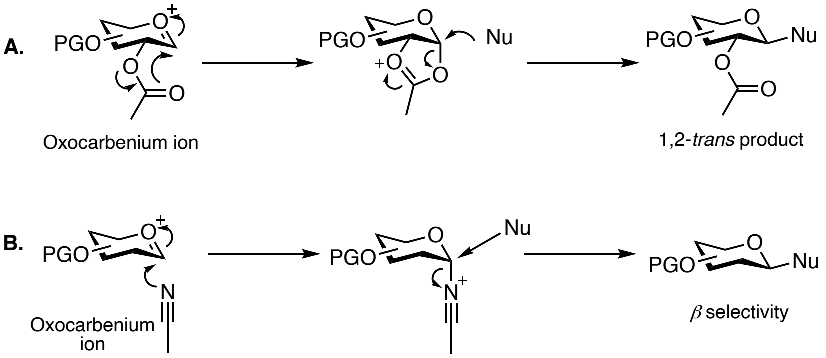
[28] Sears, P.; Wong, C.-H. *Angew. Chem. Int. Ed.* **1999**, *38*, 2301–2324.

[29] McNaught, A.D. Nomenclature of carbohydrates (recommendations 1996). *Adv. Carbohydr. Chem. Biochem.* **1997**, *52*, 43–177.

groups on the anomeric carbon have been studied and also their activators. Some of the leaving groups used and/or still in use are Cl and Br,[30] OC(=NH)CCl_3 (TCA),[31] and fluorine.[32] And some of their activators are for example silver or mercury salts, Bu_4NBr,[33] $SnCl_2$-AgOTf or TMSOTf.[34] Moreover, protecting groups are a big area of study in this field, since it is necessary the use of different protected groups in order to be able to react specific hydroxy groups as nucleophiles.

However, predicting the glycosylation stereoselectivity is challenging and it represents a big topic of study nowadays. The chemical synthesis of glycosidic bonds requires stereo and regiochemical control. There are different factors that influence this control:[35] permanent factors (referred to the coupling partners) and environmental (conditions chosen). Permanent factors would be for example: leaving groups on the anomeric position of the donor, protecting groups, neighboring group effect (fluorine[36] and acetate effects) and type of acceptor. And environmental factors would be for example: activators, concentration, thermodynamic anomeric effect, kinetic anomeric effect and solvent participation (e.g., acetonitrile). Between these factors, there are some to be highlighted:

- Neighboring group effect: acetates are commonly used as protecting groups and they can have an effect in the formation of 1,2-*trans* carbohydrates (Scheme 5, A).
- Solvents: Solvents can coordinate to the oxocarbenium ion from one face or the other, forcing the nucleophile to attack for the opposite side. A general formation of α-selectivity has been observed with the use of ethereal solvents, while β-selectivity is favored in acetonitrile (Scheme 5, B).



Scheme 5. Examples of factors that affect selectivity. **A**. Influence of the selectivity due to neighboring group effect. **B**. Solvent influence in the glycosylation reaction, using acetonitrile as example.

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[30] Koenigs, W.; Knorr, E. *Ber. Dtsch. Chem. Ges*. **1901**, *34*, 957–981.

[31] Schmidt, R. R.; Michel, J. *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 731–732.

[32] Mukaiyama, T.; Murai, Y.; Shoda, S. *Chem. Lett.* **1981**, 431–432.

[33] Lemieux, R. U.; Hendriks, K. B.; Stick, R. V.; James, K. *J. Am. Chem. Soc.* **1975**, *97,* 4056–4062.

[34] Haehimoto, S.; Hayashi, M.; Noyori, R. *Tetrahedron Lett.* **1984**, *25*, 1379–1382.

[35] Chatterjee, S.; Moon, S.; Hentschel, F.; Gilmore, K.; Seeberger, P. H. *J. Am. Chem. Soc.* **2018**, *140*, 11942–11953.

[36] (a) Bucher, C.; Gilmour, R. *Angew. Chem.* **2010**, *122*, 8906–8910; *Angew. Chem. Int. Ed*. **2010**, *49*, 8724–8728. (b) Bucher, C.; Gilmour, R. *Synlett* **2011**, 1043–1046.

- Thermodynamic and kinetic anomeric effect: depending on the temperature the stereoselectivity control can change. Thermodynamic control, or higher temperatures, favors the *α*-configuration because of the anomeric effect (Figure 7). And kinetic control, or lower temperatures, favors the *β*-configuration because of the stability of the lowest energy transition state.

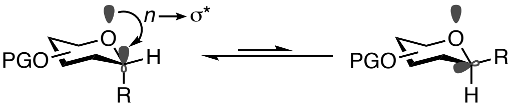

Figure 7. Anomeric effect: electronic donation of the lone pair of the endocyclic oxygen to the *σ** orbital of the C–O bond at the anomeric position (C1), favoring the axial conformation.

Objectives

The main goal of this project is to find a gold(I) complex active in senescent cells. The senescence-associated *β*-galactosidase (SA-*β*-Gal) is present in these cells and this enzyme could cleavage *β*-galactoses of the gold(I) complex. The complex, with *β*-galactoses in it, would be inactive against of a prodrug or fluorophore under biological conditions. However, this system in presence of *β*-galactosidases will be active due to the cleavage of the galactoses releasing the active gold(I) complex, allowing the reaction with the prodrug or fluorophore. This system would be able to identify or eliminate senescent cells *in vitro* and *in vivo* in biological media, due to the presence of senescence-associated *β*-galactosidase (SA-*β*-Gal) activity in senescent cells, but not in the normal ones (Figure 8).

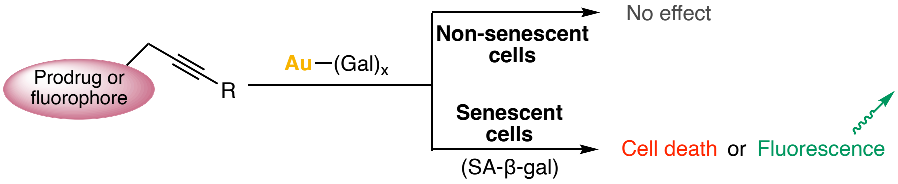

Figure 8. General concept of the objectives of this project.

The short-term main objectives will be:

- Design and synthesis of N-heterocyclic carbene gold(I) complexes without (**Au1**) and with galactose-derivatives (**Au2**) (Figure 9).

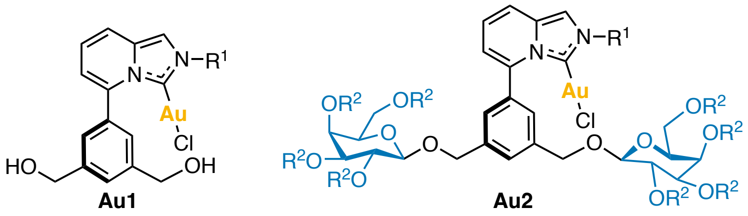

Figure 9. Schematic design of NHC-Au(I) complexes.

- The preliminary studies of the catalytic activity of these complexes will be tested in the synthesis of a fluorescent coumarin under aqueous conditions.25

The ideal scenario will be to find a difference in reactivity when using the catalyst with the galactoses (**Au2**) or the one without them (**Au1**). With catalyst **Au2** there should be no reactivity or it should be less reactive than **Au1**. Then, catalyst **Au2** together with a beta-galactosidase should recover the reactivity of **Au1** (Figure 10).

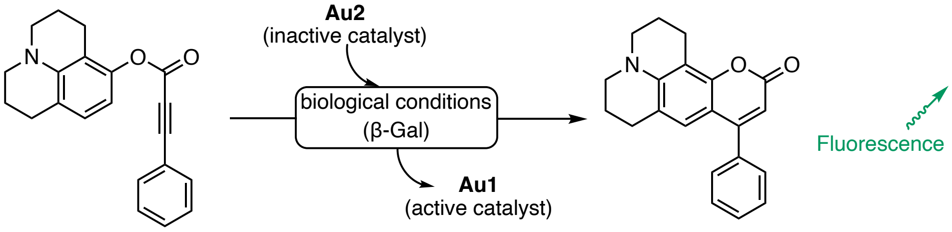

Figure 10. Preliminary study of the project.

Results and discussion

Design and synthesis of gold(I) complexes

As it was mentioned above, N-heterocyclic carbenes (NHC) are good ligands for gold(I), due to their stability and robustness. NHC-Au(I) complexes are easily prepared from simple reagents and their structure can be modified, tunning their properties. The schematic and possible designs of the gold(I) complexes are showed in Figure 11. In the schematic design (Figure 11, left), the nitrogen-substituent (R^1) of the imidazo[1,5-*a*]pyridinelydene could be changed to modulate the steric and electronic properties; the linkers to attach the galactoses (X) could be hydroxy or amino groups, commonly used in glycosylation reactions; and the protected galactoses (R^2) would block the active site of the catalyst. In the proposed design **B** (Figure 11, right), a mesityl group would be the R^1 group, benzylic hydroxy groups would act as linkers (X) and galactoses would be protected with acetates (R^2). The presence of acetyl moieties as protecting groups of galactoses is known to favor the permeability through the lysosomal membrane, facilitating their disponibility.[37] We have designed a modular approach in which easy modifications can be carry out (Figure 11, bottom). The synthesis include the coupling between both main moieties, prepared from easily accessible starting materials.

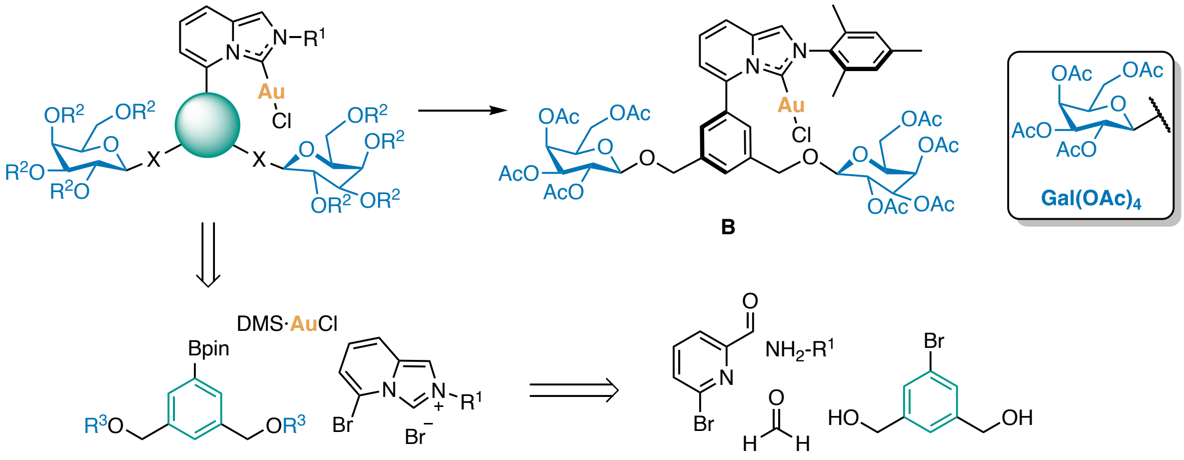

Figure 11. Schematic (left) and preliminary (right) designs. General retrosynthetic analysis.

For the synthesis of the gold(I) complexes, we started with the preparation of compound **5** (Scheme 6) from 5-bromoisophtalic acid **3** following a reported procedure[38] that involves the reduction to the diol, followed by its protection as THP afforded **4**. Then, boron pinacolate was introduced through a Miyaura borylation reaction to obtain **5**.

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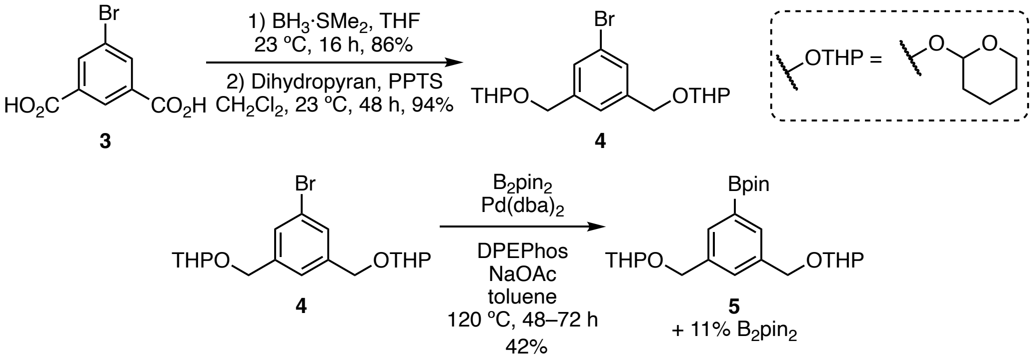
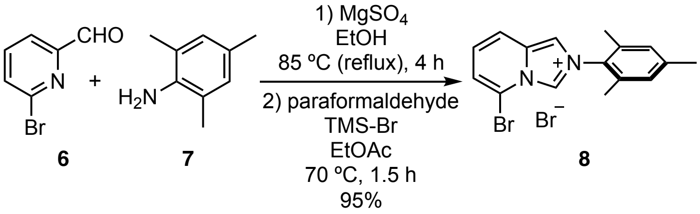
[37] Lee, S.-U.; Li, C. F.; Mortales, C.-L.; Pawling, J.; Dennis, J. W.; Grigorian, A.; Demetriou, M. *PLoS ONE* **2019**, *14*: e0214253.

[38] Richelle, G. J. J.; Ori, S.; Hiemstra, H.; van Maarseveen, J. H.; Timmerman, P. *Angew. Chem. Int. Ed.* **2018**, *57*, 501–505.



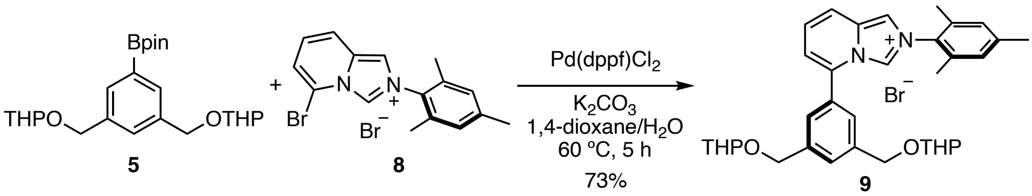
Scheme 6. Synthesis of intermediate **5**.

The imidazo[1,5-*a*]pyridinium bromide salt moiety **8** was prepared in excellent yield from 6-bromopicolinaldehyde **6** and mesitylamine **7**, preforming the imine following by the addition of paraformaldehyde and bromotrimethylsilane (Scheme 7).[39]



Scheme 7. Synthesis of intermediate **8**.

N-heterocyclic carbene (NHC) salt precursor **9**[40] (Scheme 8) was formed with **5** and the imidazo[1,5-*a*]pyridinium bromide salt **8**, through a Pd-catalyzed Suzuki-Miyaura coupling.



Scheme 8. Synthesis of intermediate **9**.

Then, by introducing silver to **9** to form the metallic carbene and followed by a transmetalation reaction with dimethyl sulfide gold(I) chloride, complex **10** was obtained in 88% yield (Scheme 7). Finally, the deprotection of both hydroxy groups was achieved with PPTS affording the desired gold(I) complex **A**. However, the deprotection using HCl in 1,4-dioxane was also tested, giving also complex **A** in excellent

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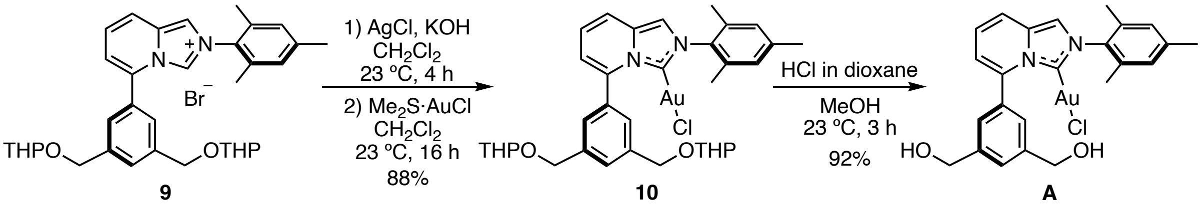
[39] Azouzi, K.; Duhayon, C.; Benaissa, I.; Lugan, N.; Canac, Y.; Bastin, S.; César, V. *Organometallics* **2018**, *37*, 4726–4735.

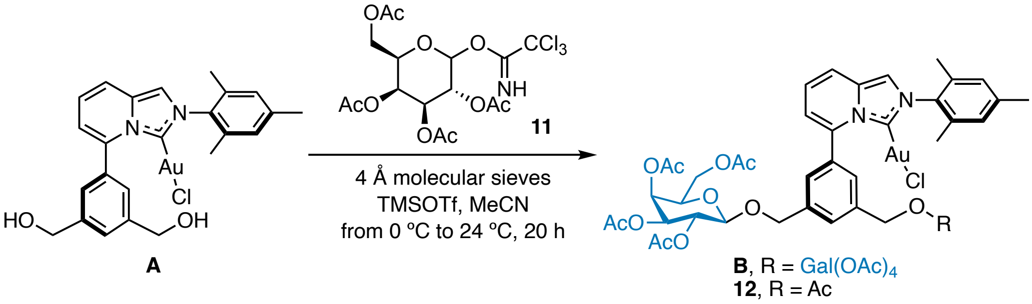
[40] **9** decomposed over cold storage and upon purification over silica gel or neutral alumina. Attempts of purification lead to decomposition. So, it was extracted and used in the next step without further purification (see the Experimental Section). Also, different quantities of B2pin2 were still obtained in the different attempts.

yield and more pure than with PPTS, for practical reasons these last conditions were used for the following attempts (Scheme 9).



Scheme 9. Synthesis of gold(I) complex **A**.

Once we had in hand complex **A**, we tried to perform the double glycosylation reaction using trichloroacetimidate-galactose (TCA-galactose) donor protected with acetates **11** (Scheme 10). As mentioned before, the use of acetates as protecting groups and acetonitrile as a solvent would favor *β* selectivity in the glycosylation reaction. In our first attempts, we tried different solvents and temperatures (such as dichloromethane at -78 ºC; acetonitrile at -30 ºC and 0 ºC; PPTS instead of TMSOTf) but at lower temperatures the reaction was slower and we always observed, by UHPLC-MS and ^{1}H NMR, mainly the formation of the *β*,*β*-di-glycosylated product **B** and the *β*-mono-glycosylated side-product **12**. Trying to separate them was unsuccessful by different techniques, such as flash column chromatography, preparative TLC or HPLC.



Scheme 10. Glycosylation reaction between complex **A** and TCA-donor **11**.

In order to explain the formation of compound **12**, we can take a look into the following mechanism (Scheme 11)[41,42] The acyl transfer competes with the glycosylation reaction. If the reaction leads an S_N1 reaction, intermediate **Int-1** is generated which can react with the nucleophile through **Int-2** giving *β*-glycosidic product or through **Int-3** giving the *α*-glycosidic product. But intermediate **Int-1** can also lead to intermediate **Int-4** by isomerization, which would be favored. The intermediate **Int-4** favors the formation of the *β*-glycosidic product but conveys in a regioselective issue, because it can react with the nucleophile in two different sites, through **Int-5** or **Int-6**, but the most stable intermediate is **Int-5** that form the acyl transfer product ROAc and **Int-7**.

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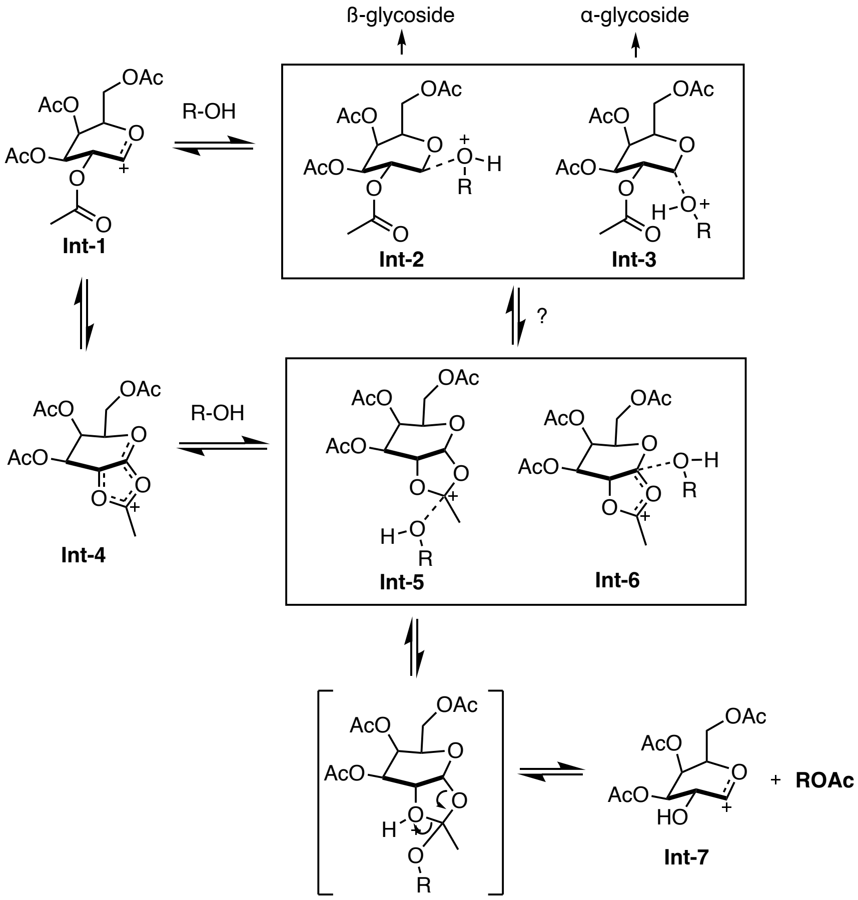
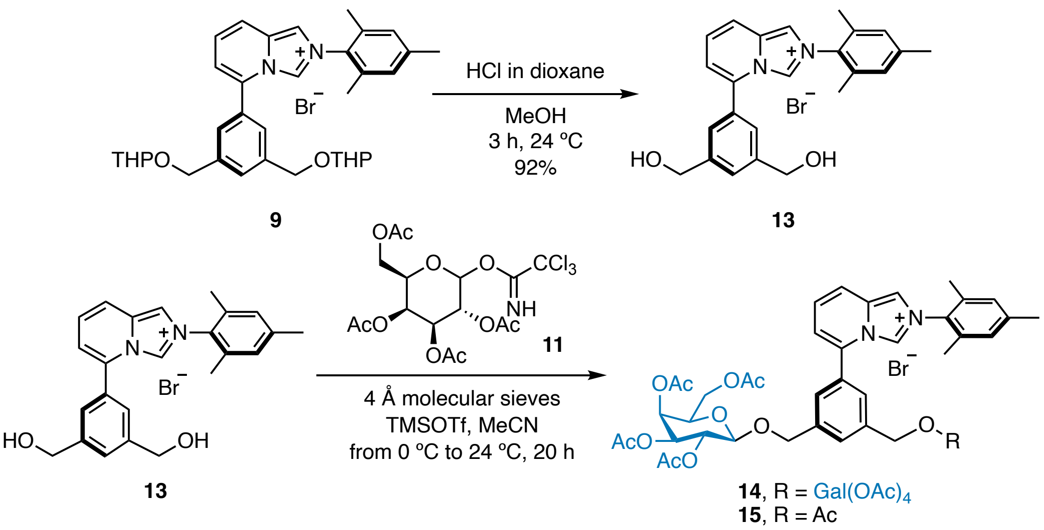
[41] Nukada, T.; Berces, A.; Zgierski, M. Z.; Whitfield, D. M. *J. Am. Chem. Soc.* **1998**, *120*, 13291–13295.

[42] Nukada, T.; Berces, A.; Whitfield, D. M. *J. Org. Chem.* **1999**, *64*, 9030–9045.



Scheme 11. Proposed mechanism for the formation of the acyl transfer product in a glycosylation reaction.

In order to avoid this undesired reactivity, two different approaches were planned. One of them was performing the glycosylation reaction directly on the NHC salt precursor **13**, synthesized by the deprotection of both hydroxy groups of **7**, and then introducing the Au(I). The rational behind this approach was to reduce steric hindrance around the hydroxyl groups, so the glycosylation reaction could be favored over the acyl transfer reaction. Unfortunately, both products, **14** and **15**, were observed by UHPLC-MS and selectivity could not be improved further (Scheme 12).



Scheme 12. First approach to avoid acyl transfer or, at least, to manage its elimination after purification.

For the second approach, we decided to switch the protecting groups of the galactose, using pivaloyl groups instead of acetates. In this case, our hypothesis was that increasing the steric hinderance of the acyl substituents would minimize their transfer to the nucleophile. In a computational study of 2004, different acyl substituents were compared in a glycosylation reaction, observing that such transfer of benzoyl and pivaloyl groups was not happening.[43] In this context there are several groups that have used pivaloyl esters at the C2 to avoid the acyl transfer.[44] In order to carry out this approach, we started preparing the corresponding *O*-glycosyl trichloroacetimidate donor or TCA donor **17**. This compound can be easily synthesized from the anomeric hydroxy group of the carbohydrate and trichloroacetonitrile with catalytic amounts of DBU. We started with the peracetylated galactose **16**, removing all the acetate groups and introducing the pivaloyl groups obtaining **17** with some Piv_2O (Scheme 13). Then, the OPiv group of the anomeric position was exchanged by a bromide leading to **18** in only 19% yield. The bromide was then substituted by a hydroxy group, affording **19**, followed by the introduction of the trichloroacetonitrile to give TCA donor **20**. We should point out that this synthetic route delivered the desired compound, albeit with some practical flaws regarding purity of intermediates and final compound **20**.

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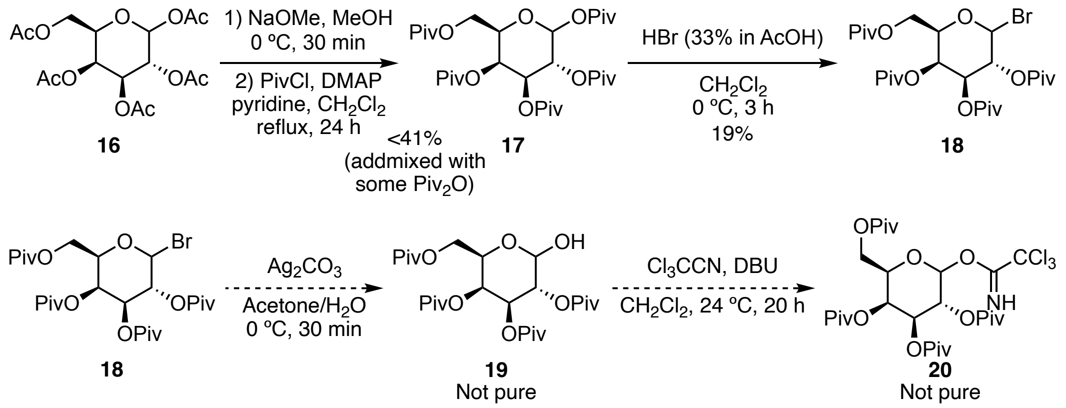
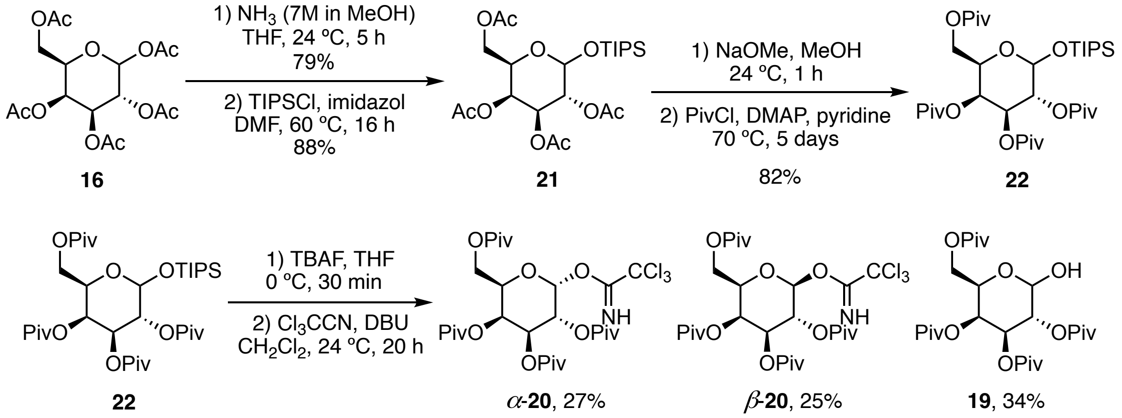
[43] Berces, A.; Whitfield, D. M.; Nukada, T.; do Santos Z., I.; Obuchowska, A.; Krepinsky, J. J. *Can. J. Chem.* **2004**, *82*, 1157–1171.

[44] For some examples see: (a) Sato, S.; Nunomura, T.; Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1988**, *29*, 4097–4100. (b) Thompson, M. J.; Hutchinson, E. J.; Stratford, T. H.; Bowler, W. B.; Blackburn, G. M. *Tetrahedron Lett.* **2004**, *45*, 1207–1210.



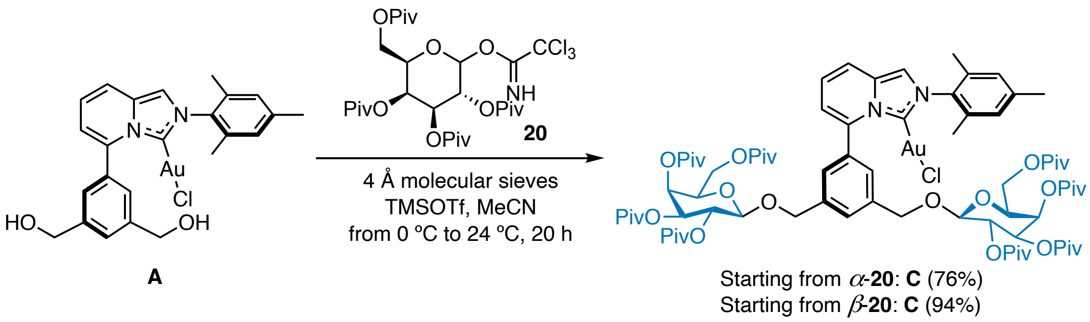
Scheme 13. First attempt for the synthesis of the TCA donor **20**.

So, we developed a different strategy to successfully prepare the TCA donor **20** (Scheme 14). Starting from the pentaacetate protected galactose **16**, only the anomeric hydroxy group was deprotected and then protected again using TIPSCl, in 79% and 88% yield respectively. The remaining acetate groups of the galactose **21** were removed and pivaloyl groups were introduced. In order to achieve full conversion to **22**, several addition of PivCl were needed in combination with the use of pyridine and DMAP at 70 ºC, affording **22** in good yield. Then, the anomeric hydroxy group was deprotected using TBAF delivering **20**, which was treated with DBU and trichloroacetonitrile to obtain the corresponding TCA donors. Both anomers, *α*-**20** and *β*-**20** TCA donors, were prepared in 27% and 25% yield respectively, together with 34% of compound **19**. Interestingly, the product mixture can be efficiently purified by column chromatography, isolating the different species with high purity.



Scheme 14. Second attempt for the synthesis of the TCA donor **20**.

Both TCA donors, *α*-**20** and *β*-**20**, were independently tested in the glycosylation reaction (Scheme 15), obtaining *β,β*-digalactoses selectively in both cases. NHC gold(I) complex **C** was obtained in 76% and 94% yield, respectively, without noticing transfer of the pivaloyl group.



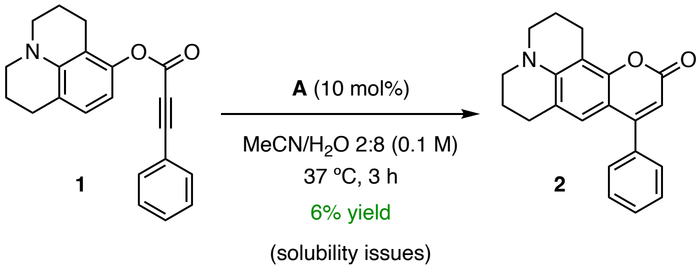
Starting from α-**20**: **C** (76%)
Starting from β-**20**: **C** (94%)

Scheme 15. Last step for the synthesis of complex **C**.

Study of the reactivity of the catalysts

As previously discussed in the objectives section, the aqueous-media hydroarylation reaction, showed in Scheme 2,25 was chosen for the preliminary studies of the gold(I) complexes synthesized in this project.

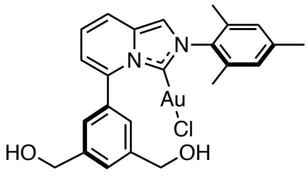
Complex **A** was first tested in the hydroarylation reaction of **1** (Scheme 16) giving fluorescent coumarin **2** in 6% yield by ^{1}H NMR (using diphenylmethane as internal standard). This low yield could be due to solubility issues with the starting material, nevertheless this reaction has been already studied for intracellular reactivity and it should not be a problem for *in vivo* studies, since it is used in a very low concentration. The presence of **2** is easily noticed because of its fluorescence.



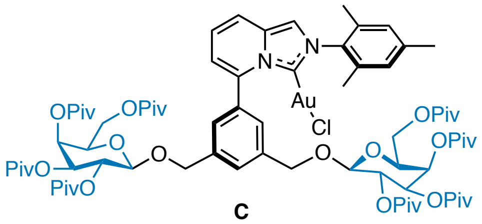
Scheme 16. Hydroarylation reaction of **1** using complex **A**.

One of the main issues in gold(I)-catalyzed reactions in aqueous media is the solubility of the catalysts. We tested the solubility of the different catalysts in a mixture of 2:8 acetonitrile/water (Table 1) in order to determine the highest molarity in which the catalysts **A** and **C** were soluble. We started measuring the solubility of complexes **A** and **C** only in acetonitrile. From the tested values, We observed that **A** was soluble in acetonitrile only when at 2.5 mM (Table 1, entry 1) and **C** was soluble in acetonitrile at 5 mM and 2.5 mM (Table 1, entry 2). However, both gold(I) complexes **A** and **C** precipitated with the first drops of water in these three experiments.

Table 1. Solubility tests of the catalysts in MeCN/H_2O 2:8 at different concentrations.



A



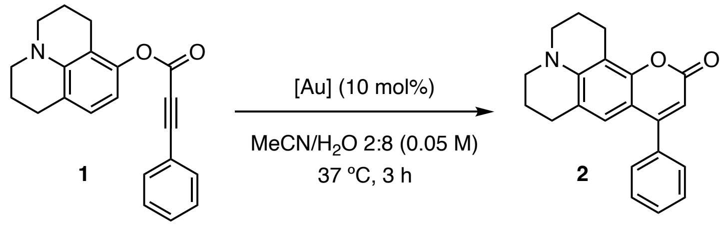
C

Entry	[Au]	10 mM[b]	5 mM[b]	2.5 mM[b]	+ H_2O
1	**A**	Not soluble	Cloudy	Soluble	Precipitated
2	**C**	Cloudy	Soluble	Soluble	Precipitated

[b] Final molarity of **A** and **C** with acetonitrile/water 2:8, only acetonitrile was added. [c] Precipitation observed after the addition of the first drops.

Next, we studied the cyclization reaction with the conditions shown in Table 2, with a concentration of 5 mM of the catalysts. We obtained the cyclized product **2** using $HAuCl_4$ (63% yield), only 1% yield when we used catalyst **A** and no product formation was observed with complex **C**.

Table 2. Preliminary results of the hydroarylation reaction.



Entry	[Au] (5 mM)	Yield (%)[a]
1	$HAuCl_4$	63
2	**A**	1
3	**C**	-

[a] Yield calculated by ^1H NMR using diphenylmethane as internal standard.

From the results shown above, it was clear that we should continue our studies using lower concentrations of catalyst, which will mimic better the final conditions in cells. We performed a new study of solubility of complexes **A** and **C** in acetonitrile/water 2:8 at different concentrations (Figure 12). We observed that catalyst **A** was not soluble at 0.625 mM, but it was soluble at lower concentrations. On the other hand, complex **C** was only soluble at 0.125 and 0.063 mM.

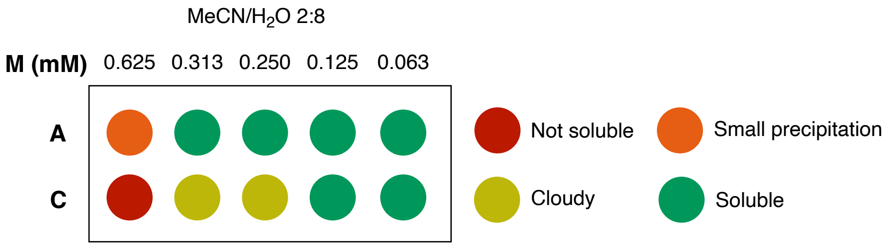
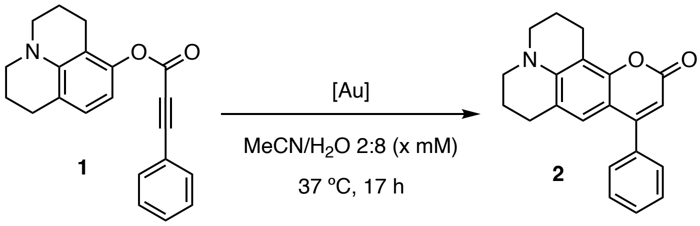


Figure 12. Solubilities of **A** and **C** in mixtures of acetonitrile/H_2O 2:8.

A study of the reaction in a mixture of acetonitrile and water (2:8) was performed (Table 3), using complexes **A** and **C** in different concentrations and catalyst loadings. No reaction, or virtually no reaction, was observed with both catalysts at 25 mM of substrate (Table 3, entries 1–6) and at 12.5 mM with lower catalyst loading (Table 3, entries 9–12). However, reactions using 12.5 mM of substrate and 2.5 mol% of catalysts **A** and **C**, equivalent to 0.313 mM of metal complex, delivered the desired coumarin **2** in 7% and 1% yield, respectively (Table 3, entries 7 and 8). This result is very interesting, as it is aligned with our initial hypothesis for the design of the catalyst, albeit the results are still preliminar.

Table 3. Study of the reaction in acetonitrile/H_2O 2:8.

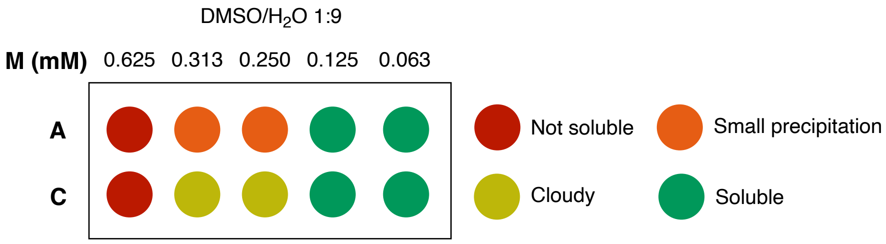


Entry	M of 1 (mM)	[Au]	mol% ([Au] mM)[a]	Conversion (%)[b]	Yield (%)[b]
1	25	**A**	2.5 (0.625)	16	1
2	25	**C**	2.5 (0.625)	8	-
3	25	**A**	1 (0.25)	13	-
4	25	**C**	1 (0.25)	18	-
5	25	**A**	0.5 (0.125)	16	-
6	25	**C**	0.5 (0.125)	22	-
7	12.5	**A**	2.5 (0.313)	25	7
8	12.5	**C**	2.5 (0.313)	24	1
9	12.5	**A**	1 (0.125)	18	-
10	12.5	**C**	1 (0.125)	19	-
11	12.5	**A**	0.5 (0.063)	22	-

12	12.5	**C**	0.5 (0.063)	25	-

[a] Catalyst loading [Au]. [b] Yield calculated by ^1H NMR using diphenylmethane as internal standard.

Since DMSO is highly used as solvent for *in vitro* and *in vivo* studies in low quantities, we also performed a solubility study in DMSO/water 1:9 (Figure 13), using the same concentrations of catalysts **A** and **C** than with acetonitrile. In general, we observed a lower solubility in this mixture of solvents than in acetonitrile and water.



DMSO/H_2O 1:9

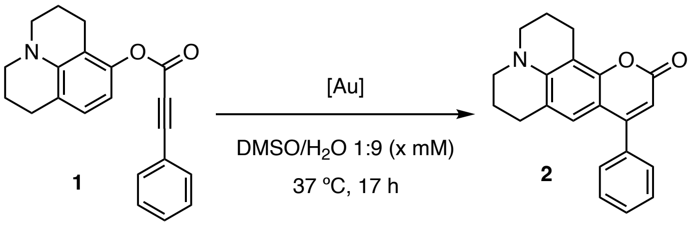
M (mM)	0.625	0.313	0.250	0.125	0.063
A	🔴	🟠	🟠	🟢	🟢
C	🔴	🟡	🟡	🟢	🟢

🔴 Not soluble
🟠 Small precipitation
🟡 Cloudy
🟢 Soluble

Figure 13. Solubilities of **A** and **C** in mixtures of DMSO/H_2O 1:9.

A study of the reaction in DMSO/water 1:9 was also performed (Table 4) with different concentrations and catalyst loading. The best promising results were obtained using 2.5 mol% of catalysts in a concentration of 25 mM (Table 4, entries 1 and 2), in which the concentration of the catalysts was 0.625 mM (Figure 13), and 12.5 mM (Table 4, entries 7 and 8), in which the concentration of the catalysts was 0.313 mM (Figure 13). Where we have also observed a difference in reactivity between both catalyst **A** and precatalyst **C**.

Table 4. Study of the reaction in DMSO/H_2O 1:9.

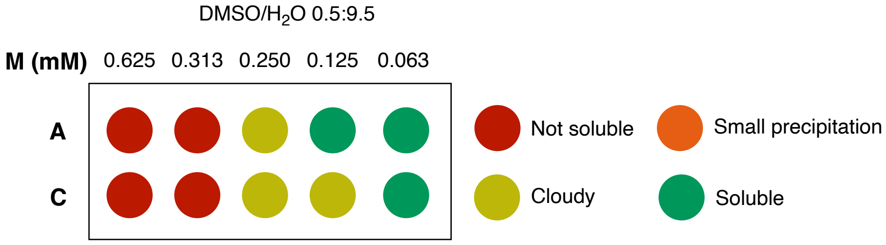


Entry	M of 1 (mM)	[Au]	mol%[a] ([Au] mM)	Conversion (%)[b]	Yield (%)[b]
1	25	**A**	2.5 (0.625)	22	4
2	25	**C**	2.5 (0.625)	25	1
3	25	**A**	1 (0.25)	21	1
4	25	**C**	1 (0.25)	24	-
5	25	**A**	0.5 (0.125)	25	1
6	25	**C**	0.5 (0.125)	19	-
7	12.5	**A**	2.5 (0.313)	5	4

8	12.5	**C**	2.5 (0.313)	3	1
9	12.5	**A**	1 (0.125)	26	1
10	12.5	**C**	1 (0.125)	28	-
11	12.5	**A**	0.5 (0.063)	4	-
12	12.5	**C**	0.5 (0.063)	16	-

[a] Catalyst loading [Au]. [b] Yield calculated by ^{1}H NMR using diphenylmethane as internal standard.

In order to decrease the amount of DMSO as much as possible, as we should use as little as possible for the cell studies, we performed a study of solubility in DMSO/H_2O 0.5:9.5 (Figure 14). As we expected, both gold complexes were less soluble.



DMSO/H_2O 0.5:9.5

M (mM)	0.625	0.313	0.250	0.125	0.063
A	🔴	🔴	🟡	🟢	🟢
C	🔴	🔴	🟡	🟡	🟢

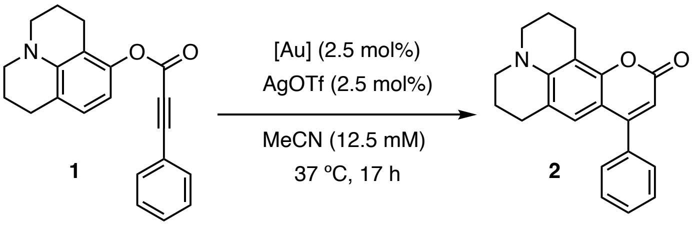
🔴 Not soluble
🟠 Small precipitation
🟡 Cloudy
🟢 Soluble

Figure 14. Solubilities of **A** and **C** in mixtures of DMSO/H_2O 0.5:9.5.

Control experiments

As a control experiment, we performed the reaction using AgOTf in acetonitrile at 37 ºC, obtaining in both cases the desired product (Table 5). Using both complexes, **A** and **C**, coumarin **2** was obtained in 92% and 77% yields, respectively. With these results, we could check that both catalysts were reactive in this reaction when they are properly activated. However, kinetic experiments have not been performed.

Table 5. Hydroarylation reaction using **A** and **C** and a chloride scavenger.

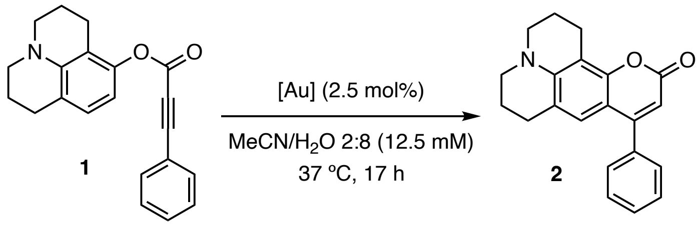


Entry	[Au]	% yield[a]
1	**A**	92
2	**C**	77

[a] Yield calculated by ^{1}H NMR using diphenylmethane as internal standard.

An additional set of control experiments was performed in order to check how the quenching of the reaction influences in its outcome. In previous experiments (Table 3, entries 7 and 8) we used a Genevac multievaporator to quench them. This time, we set up the reactions, in two of them we used the Genevac to check if it was reproducible (Table 6, entries 1 and 2) and with the other two we performed extractions with dichloromethane (Table 6, entries 3 and 4). Conversions and yields were checked by ^{1}H NMR and we obtained the same trend observed before between **A** and **C**.

Table 6. Hydroarylation reaction studies.



Entry	[Au]	Conversion (%)[b]	Yield (%)[b]
1[d]	**A**	17	8
2[d]	**C**	30	3
3[e]	**A**	25	10
4[e]	**C**	25	4

[a] Catalyst loading [Au]. [b] Yield calculated by ^{1}H NMR using diphenylmethane as internal standard. [d] Reactions were stopped evaporating solvents in the Genevac. [e] Reactions were stopped by extraction using dichloromethane.

UV-visible and fluorescence studies

As described above, the starting material and gold complexes show solubility issues under the reaction conditions of interest. Nevertheless, product formation can be detected easily taking advantage of its fluorescence, even at very low concentration. So, we decided quantify the formation of **1** using UV-Vis absorbance instead of ^{1}H NMR. The samples of the entries from 1 to 4 (Table 6) were analyzed by UV-Vis and fluorescence spectroscopies since we only needed small quantities of substrates to perform these measurements, obtaining the following results shown in the spectra below (Figure 15 and Figure 16). The starting material **1** and the product **2** absorb at different wavelength (λ_{abs} = 266 nm and λ_{abs} = 402 nm respectively) by UV-Vis absorption spectroscopy. In Figure 15 (bottom), there is a zoom of the area in which **2** absorbs, where it could be observed that the absorbance results followed the same trend than the yields observed by ^{1}H NMR.

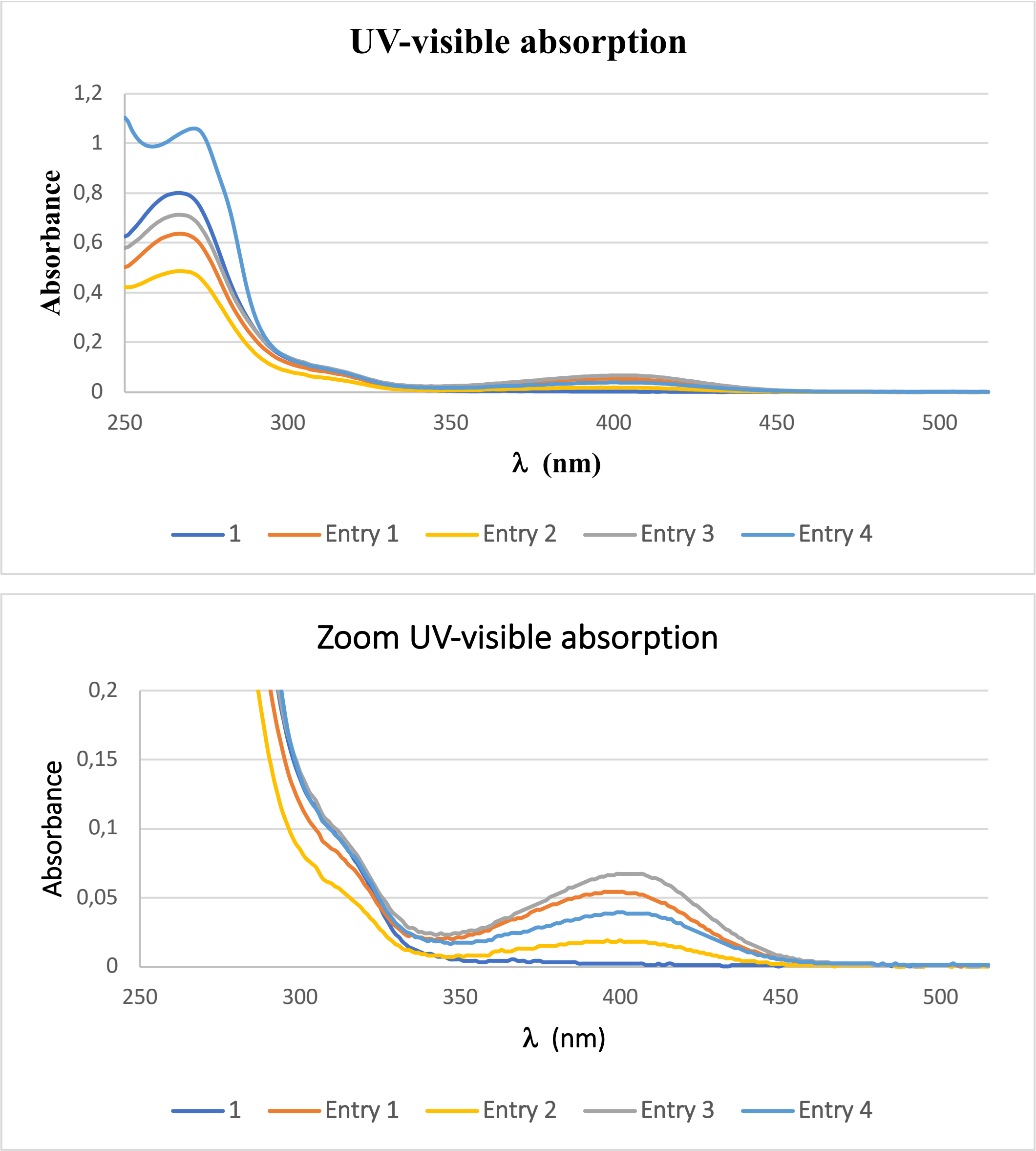


Figure 15. Comparison of UV/Vis absorption spectra of entries from 1 to 4 (Table 6) and starting material **1** (30 µM) in EtOH (2.0 mL).

By fluorescence spectroscopy, samples were excited at 402 nm and the same trend of the results obtained by UV-Vis spectroscopy and ^{1}H NMR were observed (Figure 16).

Fluorescence spectroscopy is a complementary technique, in which the fluorescence intensity is generally proportional to the concentration of the fluorophore. Therefore, the fluorimeter could be used as a technique for quantify the product **2**, when already having a calibration line.

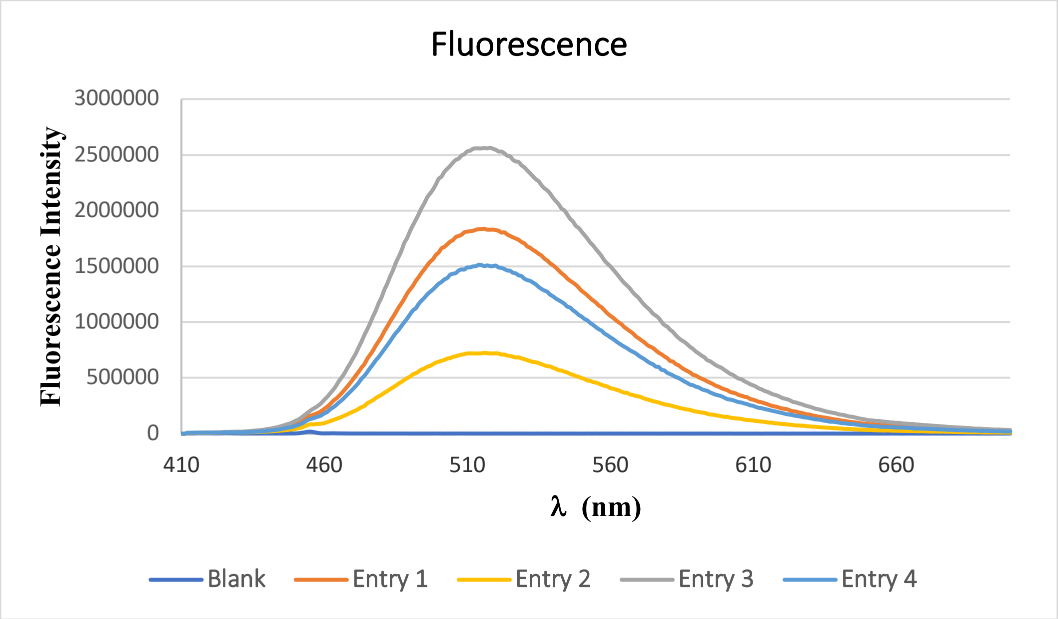
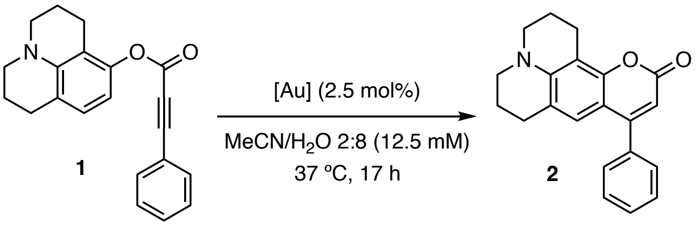


Figure 16. Comparison of fluorescence spectra of entries 1 to 4 (Table 6) (30 μM) in EtOH (2.0 mL) with λ_{exc} = 402 nm.

The different techniques used to value the results obtained in the control experiments (Table 6, entries 1–4) showed that there is a correlation between them as it is observed in Table 7, where the values from the NMR, UV-visible and fluorescence experiments followed the same trend.

Table 7. Comparative table of the results obtained by different techniques.



Entry[a]	**[Au]**	**Conversion (%)**[b]	**NMR yield (%)**[b]	**Absorbance**[c]	**Fluorescence intensity**[d]
1	**A**	17	8	0.053	1830040
2	**C**	30	3	0.018	720960
3	**A**	25	10	0.067	2554920
4	**C**	25	4	0.038	1503100

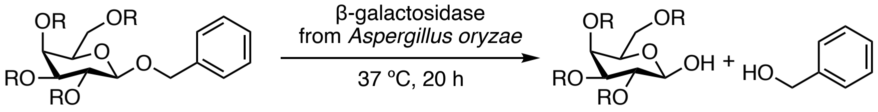
[a] Results from the entries of Table 6. [b] Yield calculated by ^{1}H NMR using diphenylmethane as internal standard. [c] Result from UV-visible absorption experiment (λ_{abs} = 402 nm). [d] Result from fluorescence experiment (λ = 402 nm).

Enzymatic studies using *β*-galactosidase

After proving that catalyst **A** is more active than **C**, the next step of this project was checking if **A** can be generated from **C** using *β*-galactosidase. The enzyme *β*-galactosidase from *Aspergillus oryzae* was used to study the hydrolysis of the glycosidic bond of the precatalyst **C**. The test was performed twice, one with a mixture of acetonitrile/water (2:8) and the other one with acetonitrile/PBS (2:8), both at 37 ºC for 17 h (the PBS is a phosphate-buffered saline aqueous solution used in biological research to mimic human cells). In both test we only observed the precatalyst **C** by ^{1}H NMR (there is a non-identified product in the ^{1}H NMR when the reaction was performed in the mixture of acetonitrile/water), and no deacylated complex was detected.

In order to gain more information about the action of this enzyme, we performed a control experiment in which model substrates derived from benzyl alcohol were subjected to the enzymatic protocol (Table 8). According to these results, *β*-galactosidase from *Aspergillus oryzae* was capable only to hydrolyze the glycosidic bond in galactose-derived substrate **22c** in a mixture of acetonitrile/H$_2$O (Table 8, entry 3). This is a surprising result since *β*-galactosidase is known to be effective in presence of acetylated galactoses. In this regard, the source of *β*-galactosidase might be critical for these transformations, and also for the generation of catalyst **A** from complex **C**.

Table 8. Use of *β*-galactosidase in different model substrates.



22a, R = Piv
22b, R = Ac
22c, R = H

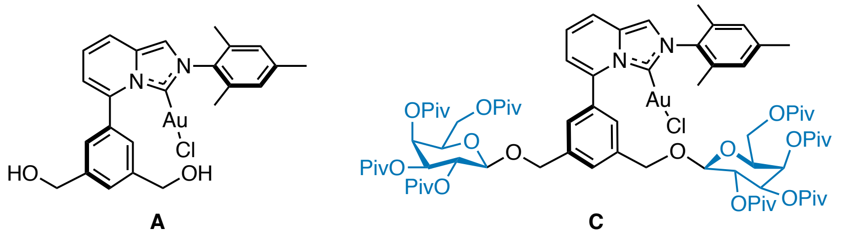
23a, R = Piv
23b, R = Ac
23c, R = H

Entry	Substrate	Solvents 2:8	Results[a]
1	**22a**	MeCN/H$_2$O	No conversion
2	**22b**	MeCN/H$_2$O	No conversion
3	**22c**	MeCN/H$_2$O	Full conversion
4	**22a**	MeCN/PBS	No conversion
5	**22b**	MeCN/PBS	No conversion
6	**22c**	MeCN/PBS	No conversion

[a] Observations by ^{1}H NMR.

Conclusions and outlook

In summary, we have developed a synthesis of N-heterocyclic carbene gold(I) complexes (**A**), which can be decorated with protected galactoses such as in complex **C**. These catalysts have been tested under biologically relevant conditions in a hydroarylation reaction, producing a fluorescent coumarin. We have observed a different reactivity for both complexes under several reaction conditions. Although reactivities are still modest, the differentiated reactivity might serve as *proof-of-concept* for the objective of this project.



A **C**

Figure 17. NHC gold(I) complexes synthesized.

Next, we studied the generation of catalyst **A** from complex **C** by an enzymatic hydrolysis using *β*-galactosidase from *Aspergillus oryzae.* Unfortunately, this specific enzyme does not seem to be active when a protected galactose is employed. So, *β*-galactosidases from other sources will be tested, as well as different group in the galactose residues (including acetyl and free –OH groups).

Encourage by the obtained results, we planned the preparation of:

- Analogues to these gold(I) complexes in order to improve the solubility properties and activity. For example, substituents such as polyethylenglycol chains, terminal-sulfonated chains,26^b triazolylammoniomethyl substituents26^c or ammonium salt groups26^d could be used.
- Other N-heterocyclic carbenes gold(I) complexes with different structures to include more galactoses in order to improve the sterically hinderance around the catalytic site to obtain a more differentiated reactivity.

These complexes will be tested again in the formation of the fluorescent coumarin and the enzyme will be tested in them in order to check if the hydrolysis of the glycosidic bond works. Once that we could manage to do these experiments successfully in the laboratory, they will be tested *in vitro* in senescent cells by Dr. José Alberto López Domínguez from Dr. Manuel Serrano's group at the IRB (Institute for Research in Biomedicine).

In the long term, this methodology could be applied to the targeted generation of bioactive compounds inside senescent cells selectively.

Experimental section

General Information

Unless otherwise stated, all the reactions reported herein were carried out under argon or nitrogen atmosphere. Reactions were carried out in solvents dried by passing through an activated alumina column on a PureSolv^{TM} Solvent Purification System (SPS, Innovative Technologies, Inc., MA), in commercially available anhydrous solvents purchased from ACROS Organics or in HPLC-grade solvents. Yields refer to chromatographically and spectroscopically pure (^{1}H NMR) homogeneous material, unless otherwise stated. Reactions were monitored by TLC (thin layer chromatography), UHPLC-MS or NMR analysis. Thin layer chromatography was carried out using TLC aluminum sheets coated with 0.2 mm of silica gel (Merck 60 F_{254}) using short-wave UV light as visualizing agent and acidic vanillin followed by heat as developing agents. UHPLC-MS was performed in Agilent Technologies 1290 Infinity II, LCMS with single-squad detector InfinityLab (APCI ionization source). Genevac EZ-2 Elite used as multievaporator. Chromatographic purifications were carried out using flash grade silica gel (SDS Chromatogel 60 ACC, 40-60 µm) as the stationary phase manually, or using a CombiFlash® R_f instrument with normal phase disposable columns of different sizes (Teledyne Isco). Preparative TLC was performed on 20 cm x 20 cm silica gel plates (2.0 mm thick, catalogue number 02015, Analtech or 1.0 mm thick, catalogue number P02013 Analtech). NMR spectra were recorded at 298 K on a Bruker Avance 300 Ultrashield, a Bruker Avance 400 Ultrashield (400 MHz for ^{1}H and 101 MHz for ^{13}C) or a Bruker Avance 500 Ultrashield (500 MHz for ^{1}H and 126 MHz for ^{13}C) spectrometers. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane, using as reference residual solvent (^{1}H NMR: $CDCl_3$ at 7.26 ppm, CD_2Cl_2 at 5.31 ppm, CD_3OD at 3.31 ppm, $(CD_3)_2SO$ at 2.50 ppm; for $^{13}C\{^1H\}$ NMR: $CDCl_3$ at 77.16 ppm, CD_2Cl_2 at 54.00 ppm, CD_3OD at 49.00 ppm, $(CD_3)_2SO$ at 39.52 ppm) or tetramethylsilane. Coupling constants (*J*) are reported in hertz (*Hz*). The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintuplet, m = multiplet, br s = broad singlet. Mass spectra were recorded on MicroTOF Focus or Maxis Impact spectrometers (both from Bruker Daltonics). Melting points were determined using a MP70 Melting Point System (Mettler Toledo). Single-crystal X-ray diffraction data were collected at 100 K on a Rigaku MicroMax-007HF, Mo *Kα* rotating anode, equipped with a Pilatus 200 K detector or on a Bruker APEX DUO, Mo *Kα* Microfocus source E025 IuS anode, equipped with an APEX DUO detector using omega scans. 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 2 mL (100 mm pathlength) cells. UV-Vis measurements were carried out on a Shimadzu UV-2401PC spectrophotometer equipped with a photomultiplier detector, double beam optics and D2 and W light sources. Fluorescence measurements were carried out on a Fluorolog Horiba Jobin Yvon spectrofluorimeter equipped with photomultiplier detector, double monochromator and Xenon light source. The fluorescence measurements were made with the following settings: increment 1.0 nm, averaging time 0.1 s, excitation slit width 2.0 nm, emission slit width 2.0 nm.

Reagents were obtained from commercial sources and used without further purification. The preparation of the following compounds has been previously described: **1** and **2**,25 **11**,[45] **23a-b**,[46] **23c**.[47]

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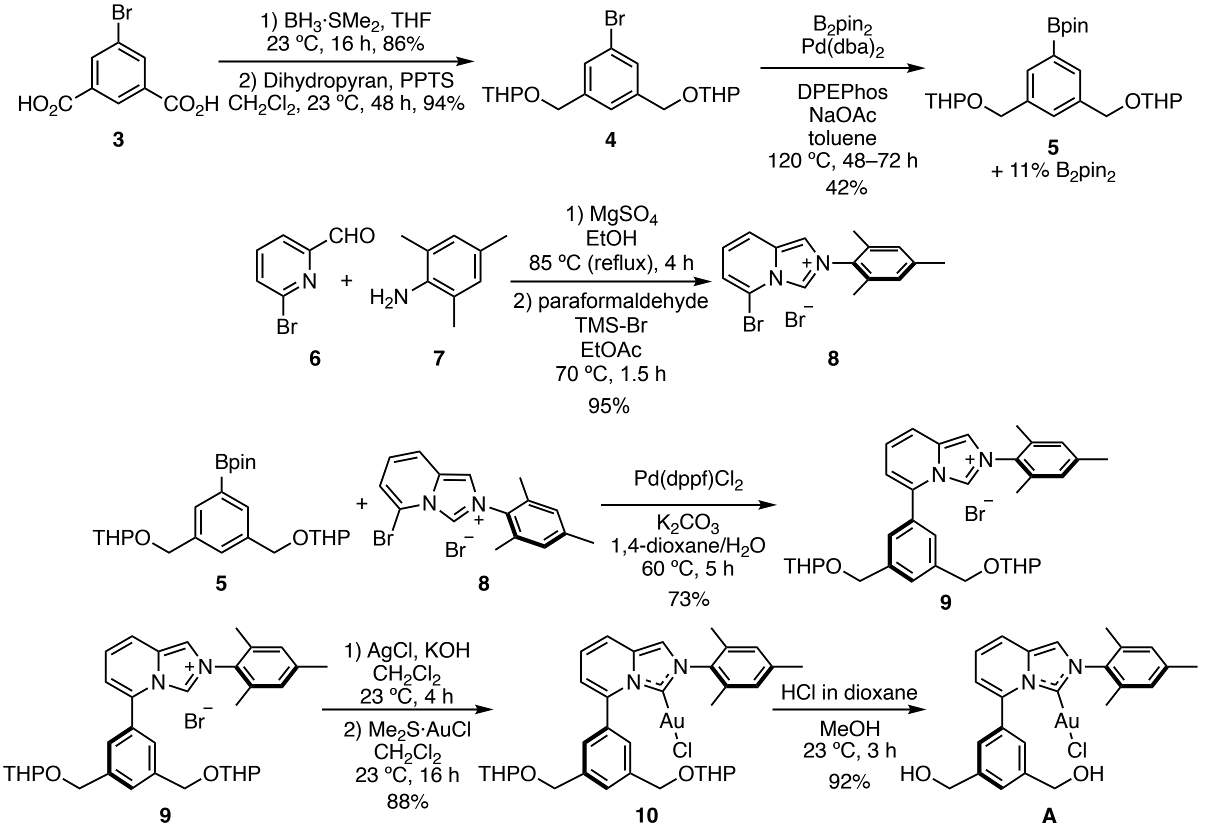
[45] Allman, S. A.; Jensen, H. H.; Vijayakrishnan, B.; Garnett, J. A.; Leon, E.; Liu, Y.; Anthony, D. C.; Sibson, N. R.; Feizi, T.; Matthews, S.; Davis, B. G. *ChemBioChem* **2009**, *10*, 2522–2529.

[46] Cardona, A.; Boutureira, O.; Castillón, S.; Díaz, Y.; Matheu, M. I. *Green Chem.* **2017**, *19*, 2687–2694.

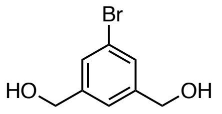
[47] Rye, C. S.; Withers, S. G. *J. Am. Chem. Soc.* **2002**, *124*, 9756–9767.

Synthetic procedures and analytical data

Synthesis of complex A



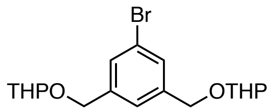
(5-Bromo-1,3-phenylene)dimethanol



It was synthesized according to the reported procedure.38 Under nitrogen atmosphere, 5-bromoisophtalic acid (3.00 g, 12.2 mmol, 1.00 equiv) was dissolved in THF (61 mL, 0.20 M) and the solution was stirred at 0 ºC. Then, borane dimethylsulfide complex (5.81 mL, 61.2 mmol, 5.00 equiv) was added and the mixture was stirred at 24 ºC for 18 h. The reaction was quenched with water and extracted with EtOAc. After separation of the layers, the organic layer was washed with H_2O (3x) and brine. The organic layer was dried over $MgSO_4$ and concentrated under vacuum affording (5-bromo-1,3-phenylene)dimethanol (2.29 g, 10.6 mmol, 86% yield) as a white solid, which was used in the next step without further purification.

^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.39 – 7.32 (m, 2H), 7.28 – 7.22 (m, 1H), 5.30 (s, 2H), 4.49 (s, 4H). **^{13}C{^{1}H} NMR** (101 MHz, $(CD_3)_2SO$) δ 145.2, 127.2, 123.2, 121.3, 62.2. **HRMS** (ESI+) the exact mass calculated for $[C_8H_9BrNaO_2]^+$ is 238.9678 *m/z*; found $[M + Na]^+$ 238.9677 *m/z*. **M.p.** = 75–77 °C.

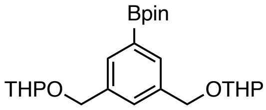
2,2'-(((5-Bromo-1,3-phenylene)bis(methylene))bis(oxy))bis(tetrahydro-2*H*-pyran), 4



It was synthesized according to slightly modified reported procedure.38 Under nitrogen atmosphere, (5-bromo-1,3-phenylene)dimethanol (2.00 g, 9.21 mmol, 1.00 equiv) was dissolved in dichloromethane (77 mL, 0.12 M) and 3,4-dihydro-2H-pyran (2.52 mL, 27.6 mmol, 3.00 equiv) and PPTS (115.8 mg, 460.7 μmol, 0.05 equiv) was added and the mixture was stirred 48 h at 24 ºC. H_2O was added and the product was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated under vacuum. The product was filtered through silica with CH_2Cl_2, affording **4** (3.35 g, 8.69 mmol, 94% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (s, 2H), 7.24 (s, 1H), 4.73 (d, J = 12.3 Hz, 2H), 4.68 (t, J = 3.6 Hz, 2H), 4.44 (d, J = 12.3 Hz, 2H), 3.87 (ddd, J = 11.3, 8.3, 3.2 Hz, 2H), 3.58 – 3.46 (m, 2H), 1.84 (tdd, J = 11.6, 6.6, 3.3 Hz, 2H), 1.78 – 1.69 (m, 2H), 1.69 – 1.44 (m, 8H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 140.7, 129.7, 125.4, 122.5, 97.9, 68.0, 62.2, 30.5, 25.5, 19.3. **HRMS** (ESI+) the exact mass calculated for $[C_{18}H_{25}BrNaO_4]^+$ is 407.0828 *m/z*; found $[M + Na]^+$ 407.0835 *m/z*.

2-(3,5-Bis(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, 5

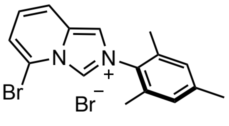


It was synthesized according to the reported procedure.38 Under argon atmosphere, **4** (1.32 g, 3.43 mmol, 1.00 equiv), $Pd(dba)_2$ (19.7 mg, 34.3 μmol, 1 mol%), DPEPhos (18.5 mg, 34.3 μmol, 1 mol%) and NaOAc (562 mg, 6.85 mmol, 2.00 equiv) were added into a microwave vial and it was introduced into the glovebox. B_2pin_2 (1.04 g, 4.11 mmol, 1.20 equiv) toluene (4.9 mL, 0.70 M) were added and the mixture was taken out of the glovebox. The mixture was stirred at 120 ºC for 48 h. It was quenched with water and the product was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The product was purified by flash chromatography with CombiFlash (SiO_2, cyclohexane/EtOAc from 10:0 to 7:3 of EtOAc) affording **5** (704.4 mg, 1.4 mmol, 89% purity, 42% yield) as a colorless oil. After purification 11% of B_2pin_2 was present, the mixture was used in the next step without further purification.

Spectral data in agreement with reported data.38

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 1.8 Hz, 2H), 7.52 (t, J = 1.8 Hz, 1H), 4.79 (d, J = 11.9 Hz, 2H), 4.71 (t, J = 3.6 Hz, 2H), 4.50 (d, J = 11.8 Hz, 2H), 3.93 (ddd, J = 11.5, 8.3, 3.2 Hz, 2H), 3.59 – 3.50 (m, 2H), 1.95 – 1.80 (m, 2H), 1.79 – 1.46 (m, 10H), 1.34 (s, 12H), 1.26 (s, B_2pin_2). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 137.9, 133.8, 130.7, 98.0, 84.0, 83.6 (B_2pin_2), 69.0, 62.2, 30.7, 25.6, 25.2 (B_2pin_2), 25.0, 19.5.

5-Bromo-2-mesitylimidazo[1,5-*a*]pyridin-2-ium bromide, 8

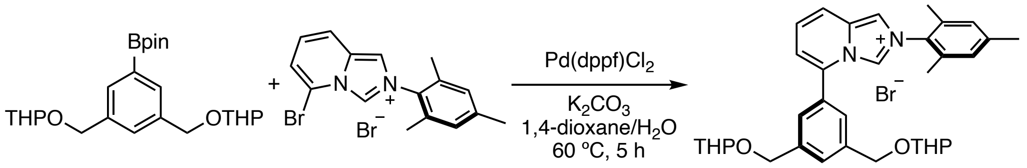


Under nitrogen atmosphere, 6-bromopicolinaldehyde **6** (500 mg, 2.69 mmol, 1.0 equiv) and mesitylamine **7** (0.40 mL, 2.8 mmol, 1.05 equiv) in HPLC-grade EtOH (15 mL, 0.18 M) was refluxed at 80 ºC for 4 h. Solvents were removed under reduced pressure and HPLC-grade EtOAc (30 mL, 0.09 M) and paraformaldehyde (88.8 mg, 2.96 mmol, 1.10 equiv) were added and the mixture was stirred at 70 ºC for 5 min under nitrogen atmosphere. Then TMSBr (0.380 mL, 2.96 mmol, 1.10 equiv) was added dropwise and was stirred at 70 ºC for 1.5 h. The suspension was filtered, washed with Et_2O and dried, affording **8** (1.013 g, 2.557 mmol, 95% yield) as a yellowish solid.

Spectral data in agreement with reported data.39

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.86 (s, 1H), 8.75 (s, 1H), 8.49 (d, *J* = 9.2 Hz, 1H), 7.48 (d, *J* = 7.1 Hz, 1H), 7.28 (dd, *J* = 9.2, 7.2 Hz, 1H), 7.03 (s, 2H), 2.35 (s, 3H), 2.07 (s, 6H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 141.9, 134.1, 132.6, 131.1, 130.1, 126.2, 125.9, 123.4, 119.8, 118.6, 112.7, 21.3, 17.9.

5-(3,5-Bis(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)phenyl)-2-mesitylimidazo[1,5-*a*]pyridin-2-ium bromide, 9

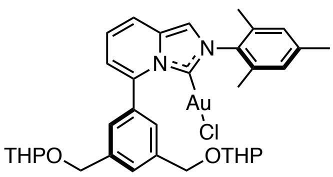


Under argon atmosphere, a mixture of **5** (613.2 mg, 1.262 mmol, 1.000 equiv, 89% purity), **8** (500.0 mg, 1.262 mmol, 1.000 equiv), $Pd(dppf)Cl_2$ (92.4 mg, 0.126 mmol, 10 mol%) and K_2CO_3 (523.3 mg, 3.787 mmol, 3.000 equiv) in 1,4-dioxane (4.2 mL) and water (2.1 mL) (total concentration of 0.2 M) (both HPLC-grade and degassed with argon) was stirred at 60 ºC for 5 h. The reaction was quenched with H_2O and EtOAc was added, both layers were separated and the organic layer was washed with H_2O (3x). The combined aqueous layers were combined and the product was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under vacuum. Product **9** (706.2 mg, 0.920 mmol, 81% purity, 73% yield) was afforded as a brown oil. After purification 19% of B_2pin_2 was present, the mixture was used in the next step without further purification.

Product not stable under storage. Only ^{1}H NMR and HRMS are here reported:

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (s, 1H), 8.86 (d, *J* = 1.4 Hz, 1H), 8.68 (d, *J* = 9.3 Hz, 1H), 7.62 (d, *J* = 1.5 Hz, 2H), 7.51 (s, 1H), 7.43 (dd, *J* = 9.3, 6.9 Hz, 1H), 7.16 (dd, *J* = 6.9, 1.0 Hz, 1H), 7.03 (s, 2H), 4.87 (d, *J* = 12.6 Hz, 2H), 4.70 (dd, *J* = 4.6, 2.7 Hz, 2H), 4.61 (d, *J* = 12.7 Hz, 2H), 3.83 (ddd, *J* = 11.1, 7.7, 3.3 Hz, 2H), 3.55 – 3.44 (m, 2H), 2.36 (s, 3H), 2.07 (d, *J* = 3.0 Hz, 6H), 1.86 – 1.71 (m, 6H), 1.61 – 1.40 (m, 6H), 1.26 (s, B_2pin_2). **HRMS** (ESI+) the exact mass calculated for $[C_{34}H_{41}N_2O_4]^+$ is 541.3061 *m/z*; found $[M–Br]^+$ 541.3070 *m/z*.

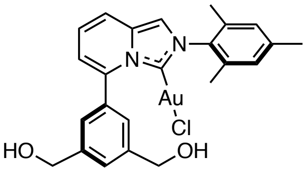
Complex 10



Under argon atmosphere, a mixture of **9** (614.0 mg, 711.2 μmol, 72% purity, 1.0 equiv), AgCl (122.3 mg, 853.4 μmol, 1.200 equiv) and KOH (47.9 mg, 853 μmol, 1.20 equiv) in dichloromethane (10.2 mL, 0.07 M) was stirred at 23 ºC for 4 h. Then, it was filtered through celite with CH_2Cl_2 and concentrated under reduced pressure. (Dimethylsulfide)gold(I) chloride (209.5 mg, 711.2 μmol, 1.000 equiv) was added to the crude and, under argon, dichloromethane (7.9 mL, 0.090 M) was added and the mixture was stirred at 23 ºC for 16 h. The crude was filtered through celite and concentrated. The crude was further purified by flash chromatography with CombiFlash (SiO_2, cyclohexane/EtOAc from 10:0 to 6:4 of EtOAc) affording gold(I) complex **10** (486.3 mg, 629.0 μmol, 88% yield) as a white solid.

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.54 – 7.40 (m, 4H), 7.36 (s, 1H), 7.10 – 7.04 (m, 1H), 7.03 (s, 2H), 6.64 (dq, *J* = 6.4, 2.4 Hz, 1H), 4.81 (dd, *J* = 12.7, 3.1 Hz, 2H), 4.77 (t, *J* = 3.5 Hz, 2H), 4.58 (d, *J* = 13.4 Hz, 2H), 3.95 – 3.83 (m, 2H), 3.60 – 3.46 (m, 2H), 2.36 (s, 3H), 1.98 (s, 6H), 1.90 – 1.78 (m, 2H), 1.78 – 1.67 (m, 2H), 1.67 – 1.46 (m, 8H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 164.8, 140.3, 140.1 – 139.9 (m), 136.9, 134.8, 134.8, 132.6, 129.6, 128.2, 128.1, 128.0, 123.6, 117.6, 116.8, 113.1, 98.3, 98.3, 68.6, 68.6, 62.7, 62.6, 31.1, 31.0, 26.0, 21.3, 20.0, 19.9, 17.9. **HRMS** (ESI+) the exact mass calculated for $[C_{34}H_{40}AuClN_2NaO_4]^+$ is 795.2234 *m/z*; found $[M + Na]^+$ 795.2241 *m/z*. **M.p.** = >91 °C (decomposition).

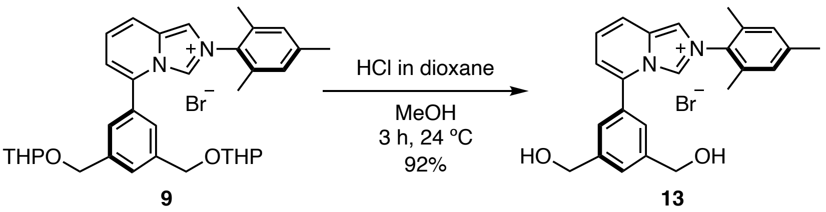
Complex A



A dilution of HCl in 1,4-dioxane 3.5 M (0.37 mL, 5.0 equiv) was added into a solution of complex **10** (200 mg, 0.259 mmol, 1.00 equiv) in HPLC-grade MeOH (12.9 mL, 0.020 M) and the mixture was stirred at 24 ºC for 3 h. Volatiles were removed and the crude was purified by flash column chromatography (SiO_2, dichloromethane/MeOH from 10:0 to 9.7:0.3 of MeOH) affording gold(I) complex **A** (143.6 mg, 237.4 μmol, 92% yield) as a white solid.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.57 (d, *J* = 1.5 Hz, 2H), 7.55 – 7.51 (m, 1H), 7.51 (dd, *J* = 9.3, 1.2 Hz, 1H), 7.38 (s, 1H), 7.07 (dd, *J* = 9.3, 6.7 Hz, 1H), 7.03 (s, 2H), 6.66 (dd, *J* = 6.7, 1.2 Hz, 1H), 4.68 (s, 4H), 2.65 (s, 2H), 2.35 (s, 3H), 1.98 (s, 6H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 163.8, 142.7, 140.3, 139.7, 136.8, 134.8, 134.8, 132.6, 129.6, 128.6, 128.1, 123.7, 117.8, 117.0, 113.3, 65.3, 21.3, 18.0. **HRMS** (ESI+) the exact mass calculated for $[C_{24}H_{24}AuClN_2NaO_2]^+$ is 627.1084 *m/z*; found $[M + Na]^+$ 627.1093 *m/z*. **M.p.** = >237 °C (decomposition).

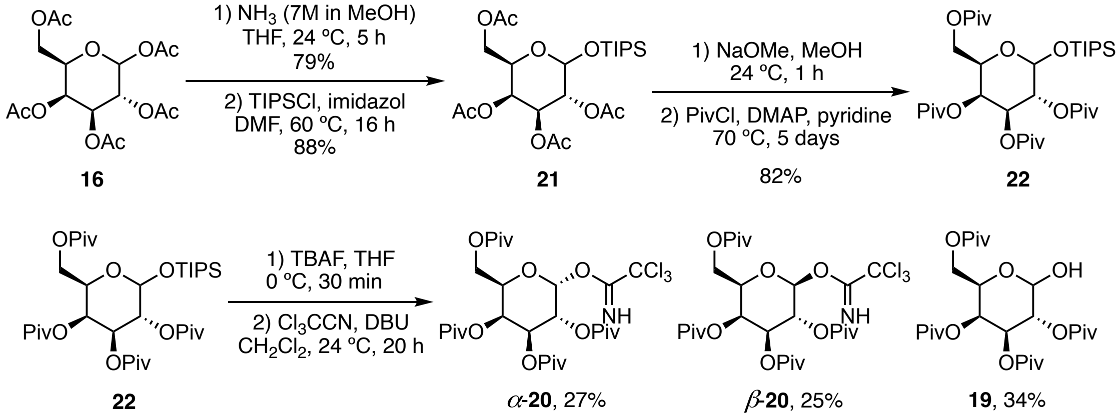
Synthesis of 5-(3,5-Bis(hydroxymethyl)phenyl)-2-mesitylimidazo[1,5-*a*]pyridin-2-ium bromide, 13



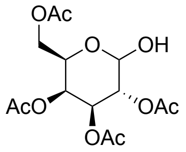
A dilution of HCl 3.5 M in 1,4-dioxane (0.17 mL, 5.00 equiv) was added into a solution of **9** (111.4 mg, 118.3 µmol, 1.000 equiv, 66% purity) in HPLC-grade MeOH (5.9 mL, 0.020 M) and the mixture was stirred at 24 ºC for 3 h. Volatiles were removed and the crude was washed with pentane and Et_2O affording **13** (60.7 mg, 0.110 mmol, 82% purity, 92% yield) as a white solid.

^{1}H NMR (400 MHz, CD_3OD) δ 9.79 (d, *J* = 1.5 Hz, 1H), 8.30 (t, *J* = 2.1 Hz, 1H), 7.98 – 7.92 (m, 1H), 7.68 (d, *J* = 1.6 Hz, 2H), 7.57 (s, 1H), 7.52 (dd, *J* = 9.3, 6.9 Hz, 1H), 7.28 (dd, *J* = 7.0, 0.9 Hz, 1H), 7.16 (s, 2H), 4.72 (s, 4H), 2.38 (s, 3H), 2.08 (s, 6H), 1.20 (B_2pin_2). **^{13}C{^{1}H} NMR** (126 MHz, CD_3OD) δ 144.8, 142.8, 137.7, 135.7, 133.5, 133.1, 132.8, 130.7, 129.1, 127.4, 126.9, 119.9, 118.6, 117.0, 75.8 (B_2pin_2), 64.6, 25.0 (B_2pin_2), 21.1, 17.3. **HRMS** (ESI+) the exact mass calculated for $[C_{24}H_{25}N_2O_2]^+$ is 373.1911 *m/z*; found $[M – Br]^+$ 373.1915 *m/z*.

Synthesis of *α*-20 and *β*-20 TCA donors



(2*R*,3*S*,4*S*,5*R*)-2-(Acetoxymethyl)-6-hydroxytetrahydro-2*H*-pyran-3,4,5-triyl triacetate

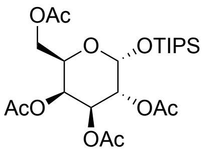


Per-acetylated galactose (1.00 g, 2.56 mmol, 1.00 equiv) was dissolved in THF (36.6 mL, 70.0 mM). The mixture was cooled to 0 ºC and NH_3 (7.0 M in MeOH, 7.32 mL, 51.2 mmol, 20.0 equiv) was added. The reaction was stirred at this temperature for 10 min and then it was warmed to 24 ºC and stirred for 5 h. Then, the volatiles were evaporated in vacuum and the crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 1:1) affording the desired product (2*R*,3*S*,4*S*,5*R*)-2-(acetoxymethyl)-6-

hydroxytetrahydro-2*H*-pyran-3,4,5-triyl triacetate (707 mg, 2.03 mmol, 79% yield) as a white foam. The data spectra match the one in the literature.[48]

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.51 (d, *J* = 3.6 Hz, 1H), 5.47 (dd, *J* = 3.4, 1.4 Hz, 1H), 5.44 – 5.36 (m, 1H), 5.15 (dd, *J* = 10.8, 3.6 Hz, 1H), 4.49 – 4.43 (m, 1H), 4.11 – 4.07 (m, 2H), 2.14 (s, 3H), 2.09 (s, 3H), 2.05 (s, 3H), 1.99 (d, *J* = 1.4 Hz, 3H).

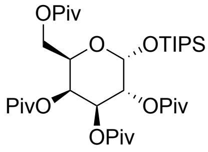
(2*R*,3*S*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-((triisopropylsilyl)oxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate, 21



(2*R*,3*S*,4*S*,5*R*)-2-(acetoxymethyl)-6-hydroxytetrahydro-2*H*-pyran-3,4,5-triyl triacetate (3.00 g, 8.60 mmol, 1.00 equiv) was dissolved in DMF (22.0 mL, 0.40 M). Then imidazole (1.50 g, 22.0 mmol, 2.50 equiv) and TIPSCl (3.70 mL, 17.0 mmol, 2.00 equiv) were added. The mixture was stirred at 60 °C for 16 h. Then the reaction was quenched by addition of water and the aqueous layer was extracted with EtOAc (3x). The organic layer was washed with water (3x), brine, dried over $MgSO_4$ and concentrated under vacuum. Purification by flash chromatography with CombiFlash (SiO_2, cyclohexane) afforded the title product **21** (3.60 g, 7.1 mmol, 83% yield) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.36 (dd, *J* = 3.5, 1.2 Hz, 1H), 5.16 (dd, *J* = 10.6, 7.5 Hz, 1H), 4.98 (dd, *J* = 10.5, 3.5 Hz, 1H), 4.77 (d, *J* = 7.5 Hz, 1H), 4.16 – 4.04 (m, 2H), 3.89 (ddd, *J* = 7.0, 6.1, 1.2 Hz, 1H), 2.14 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H), 1.96 (s, 3H), 1.13 – 1.05 (m, 3H), 1.05 – 1.00 (m, 18H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 170.5, 170.5, 170.3, 169.4, 96.1, 71.2, 71.0, 70.9, 67.5, 61.9, 20.9, 20.8, 20.7, 20.7, 17.8, 17.7, 12.2. **HRMS** (ESI+) the exact mass calculated for $[C_{23}H_{40}NaO_{10}Si]^+$ is 527.2283 *m/z*; found $[M + Na]^+$ 527.2276 *m/z*. $\boldsymbol{\alpha_D^{589}}$ = 9.7 deg·cm^2·g^{-1} (CH_2Cl_2, c 0.1, 297 K).

(2*R*,3*S*,4*S*,5*R*,6*R*)-2-((Pivaloyloxy)methyl)-6-((triisopropylsilyl)oxy)tetrahydro-2*H*-pyran-3,4,5-triyl tris(2,2-dimethylpropanoate), 22



NaOMe (152.0 mg, 2.81 mmol, 0.400 equiv) was added to a solution of tri-O-acetyl-D-glucal **21** (3.55 g, 7.03 mmol, 1.00 equiv) in MeOH (7.7 mL, 0.91 M) at 0 °C under an argon atmosphere. The solution was allowed to warm to 24 ºC and stirred for 1 h. The reaction mixture was neutralized (~pH 7) with amberlyst® 15 hydrogen form (wet) (prewashed with MeOH), filtered and evaporated to dryness. Then, the residue was dissolved in pyridine (38.0 mL, 0.185 M) and DMAP (6.88 g, 56.3 mmol, 6.00 equiv) and PivCl (6.79 mL, 56.3 mmol, 6.00 equiv) were added. The suspension was warmed to 70 ºC and stirred for 2 days. TLC shows the di protected starting material, the tri protected and the desired product. The reaction was cooled to room temperature and 4.0 equiv more or PivCl were added, and the reaction was stirred at 70 ºC for 2

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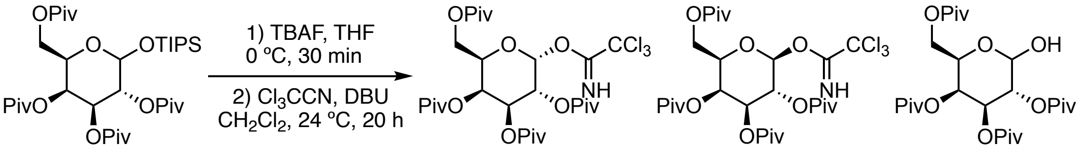
[48] Wang, R.; Chen, J.-Z.; Zheng, X.-A.; Kong, R.; Gong, S.-S.; Sun, Q. *Carbohydrate Research* **2018**, *455*, 114–118.

days. TLC showed no full conversion, addition of 2.0 equiv of PivCl and the reaction mixture was stirred at the same temperature overnight. The reaction was diluted with water and CH_2Cl_2. The two phases were separated and the aq. layer was extracted with CH_2Cl_2 (3x). The combined organic phases were dried over $MgSO_4$ and evaporated to dryness. Purification by flash chromatography with CombiFlash (SiO_2, cyclohexane) afforded the desired compound **22** (3.90 g, 5.79 mmol, 82% yield over two steps) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.40 (dd, *J* = 3.3, 1.1 Hz, 1H), 5.21 (dd, *J* = 10.5, 7.4 Hz, 1H), 5.08 (dd, *J* = 10.5, 3.3 Hz, 1H), 4.92 (d, *J* = 7.5 Hz, 1H), 4.09 – 4.02 (m, 2H), 3.96 (td, *J* = 6.6, 1.1 Hz, 1H), 1.26 (s, 9H), 1.18 (s, 9H), 1.16 (s, 9H), 1.11 (s, 9H), 1.12 – 1.06 (m, 3H) 1.06 – 1.02 (m, 18H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 178.2, 177.6, 177.1, 176.8, 96.6, 77.4, 71.3, 71.3, 71.0, 67.3, 61.9, 39.2, 38.9, 38.9, 27.4, 27.3, 27.3, 27.2, 18.1, 18.1, 12.7. **HRMS** (ESI+) the exact mass calculated for $[C_{35}H_{64}NaO_{10}Si]^+$ is 695.4161 *m/z*; found $[M + Na]^+$ 695.4186. *m/z*. $\boldsymbol{\alpha}_D^{589}$ = 2.3 deg·cm^2·g^{-1} (CH_2Cl_2, c 0.1, 298 K).

Synthesis of *α*-20 and *β*-20 TCA donors

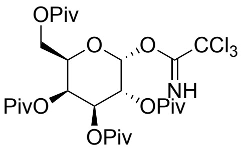


22 *α*-**20**, 27% *β*-**20**, 25% **19**, 34%

Compound **22** (284.0 mg, 422.0 µmol. 1.000 equiv) was dissolved in THF (8.44 mL, 0.050 M) under argon atmosphere. The mixture was cooled to 0 ºC and TBAF (1.00 M in THF, 844 µL, 2.00 equiv) was added. The reaction was stirred at this temperature for 30 min. The reaction was quenched using sat. $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3x) and the combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated in vacuum. The crude was obtained as a colorless oil and used directly in the next step without further purification.

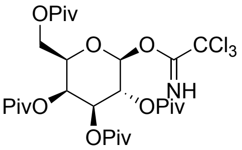
The obtained crude material was dissolved in dry CH_2Cl_2 (8.44 mL, 0.050 M) under argon atmosphere. The solution was cooled to 0 ºC. Then, tricholoroacetonitrile (423 µL, 4.22 mmol, 10.0 equiv) and DBU (6.31 µL, 42.2 µmol, 0.100 equiv) were added. The mixture was slowly warmed to 24 ºC and stirred 20 h. The volatiles were evaporated in vacuum and the crude was purified by flash chromatography with CombiFlash (SiO_2, cyclohexane) to afford compounds *α*-**20** (75 mg, 0.11 mmol, 27% yield over two steps) as a colorless oil, *β*-**20** (70 mg, 0.11 mmol, 25% yield over two steps) as a white foam, and **19** (75 mg, 0.15 mmol, 34% recovered) as a colorless oil.

(2*R*,3*S*,4*S*,5*R*,6*R*)-2-((Pivaloyloxy)methyl)-6-(2,2,2-trichloro-1-iminoethoxy)tetrahydro-2*H*-pyran-3,4,5-triyl tris(2,2-dimethylpropanoate), *α*-20



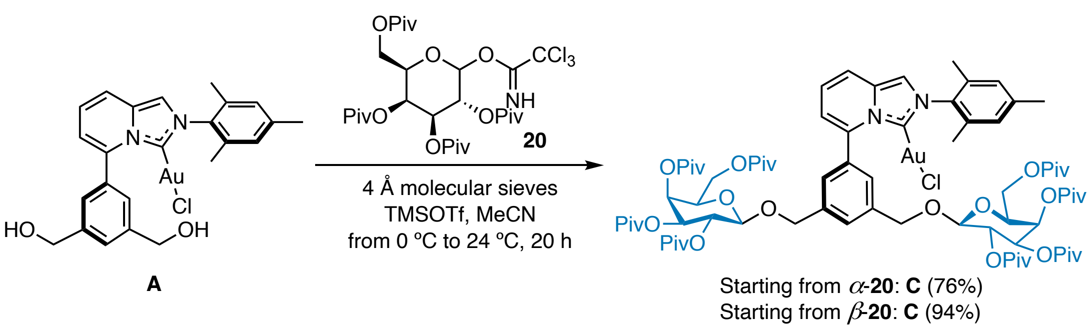
^{1}H NMR. (400 MHz, CD_2Cl_2) δ 8.72 (s, 1H), 6.60 (d, *J* = 3.6 Hz, 1H), 5.57 (dd, *J* = 3.2, 1.3 Hz, 1H), 5.50 (dd, *J* = 10.8, 3.2 Hz, 1H), 5.39 (dd, *J* = 10.9, 3.6 Hz, 1H), 4.53 – 4.45 (m, 1H), 4.12 – 3.99 (m, 2H), 1.27 (s, 9H), 1.14 (s, 9H), 1.13 (s, 9H), 1.12 (s, 9H). **^{13}C{^{1}H} NMR** (101 MHz, CD_2Cl_2) δ 178.0, 177.7, 177.4, 177.2, 161.1, 93.9, 91.3, 70.2, 68.2, 67.8, 67.3, 62.0, 39.4, 39.2, 39.1, 39.0, 27.4, 27.3, 27.2, 27.2. **HRMS** (ESI+) the exact mass calculated for $[C_{28}H_{44}Cl_3NNaO_{10}]^+$ is 682.1923 *m/z*; found $[M + Na]^+$ 682.1911 *m/z*. **α_D^{589}** = 71.1 deg·cm^2·g^{-1} (CH_2Cl_2, c 0.1, 298K).

(2*R*,3*S*,4*S*,5*R*,6*S*)-2-((Pivaloyloxy)methyl)-6-(2,2,2-trichloro-1-iminoethoxy)tetrahydro-2*H*-pyran-3,4,5-triyl tris(2,2-dimethylpropanoate), *β*-20



^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.79 (s, 1H), 6.01 (d, *J* = 8.3 Hz, 1H), 5.48 – 5.43 (m, 2H), 5.22 (dd, *J* = 10.4, 3.4 Hz, 1H), 4.19 – 4.13 (m, 2H), 4.08 – 4.00 (m, 1H), 1.28 (s, 9H), 1.16 (s, 9H), 1.12 (s, 9H), 1.11 (s, 9H). **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ 178.0, 177.4, 177.2, 176.6, 161.3, 96.3, 90.8, 72.5, 71.4, 68.2, 67.0, 61.2, 39.40, 39.1, 39.1, 39.0, 27.3, 27.3, 27.2, 27.2. **HRMS** (ESI+) the exact mass calculated for $[C_{28}H_{44}Cl_3NNaO_{10}]^+$ is 682.1923 *m/z*; found $[M + Na]^+$ 682.1908 *m/z*. **M.p.** = 58–72 ºC. **α_D^{589}** = 21.3 deg·cm^2·g^{-1} (CH_2Cl_2, c 0.1, 298K).

Synthesis of complex C



A suspension of *α*-**20** (109 mg, 165 µmol, 2.50 equiv) and complex **A** (40.0 mg, 66.1 µmol, 1.00 equiv) in dry MeCN (1.32 mL, 0.050 M) under argon atmosphere, was sonicated and placed to an ice bath. The suspension was treated with a solution of TMSOTf (0.2 M in MeCN, 66.1 µL, 13.2 µmol, 0.200 equiv) and it was slowly warmed to 24 ºC and stirred for 20 h. Then the solution was concentrated in vacuum. The crude material was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 5:1) followed by dissolving the obtained solid in CH_2Cl_2 and washing the organic layer with HCl (1M, 3x), affording compound **C** (81 mg, 51 µmol, 76% yield) as a white solid.

Same conditions were done using *β*-**20** (60.1 mg, 90.9 µmol, 2.50 equiv) as a starting material and **A** (22.0 mg, 36.4 µmol, 1.00 equiv). Complex **C** was also obtained (55 mg, 34 µmol, 94% yield) as a white solid.

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.53 (br s, 1H), 7.51 (dd, *J* = 9.4, 1.4 Hz, 1H), 7.42 (t, *J* = 1.7 Hz, 1H), 7.37 (s, 1H), 7.30 (t, *J* = 1.6 Hz, 1H), 7.08 – 7.00 (m, 3H), 6.62 (dd, *J* = 6.7, 1.2 Hz, 1H), 5.39 (t, *J* = 3.7 Hz, 2H), 5.23 (dd, *J* = 7.5, 1.5 Hz, 1H), 5.20 (dd, *J* = 8.2, 2.2 Hz, 1H), 5.14 (dd, *J* = 10.5, 3.3 Hz, 1H), 5.03 (dd, *J* = 10.5, 3.4 Hz, 1H), 4.93 – 4.79 (m, 4H), 4.76 (d, *J* = 7.8 Hz, 1H), 4.69 (d, *J* = 12.3 Hz, 1H), 4.20 – 4.08 (m, 3H), 4.06 – 3.97 (m, 3H), 2.37 (s, 3H), 1.97 (d, *J* = 2.1 Hz, 6H), 1.25 (s, 18H), 1.17 (s, 9H), 1.14 (s, 9H), 1.11 (s, 9H), 1.08 (s, 9H), 1.07 (s, 9H), 0.93 (s, 9H). **^{13}C{^{1}H} NMR** (101 MHz, CD_2Cl_2) δ 178.0, 177.4, 177.3, 177.2, 177.2, 177.1, 176.9, 164.8, 140.4, 139.3, 138.8, 138.4, 136.7, 135.2, 134.8, 134.7, 132.4, 129.7, 129.6, 129.0, 128.5, 128.2, 123.6, 117.9, 117.0, 113.2, 99.9, 98.9, 71.67, 71.5, 71.4, 71.2, 70.4, 69.6, 69.4, 69.3, 67.5, 67.45, 61.7, 61.6, 39.4, 39.1, 39.0, 39.0, 38.9, 27.4, 27.3, 27.3, 27.3, 27.2, 21.4, 18.2, 18.0. **HRMS** (ESI+) the exact mass calculated for $[C_{76}H_{108}AuClN_2NaO_{20}]^+$ is 1623.6742 *m/z*; found $[M + Na]^+$ 1623.6716 *m/z*. **M.p.** = 112–127 ºC. $\boldsymbol{\alpha_D}^{\mathbf{589}}$ = –38.3 deg·cm^2·g^{-1} (CH_2Cl_2, c 0.1, 298K).

Crystallographic Data

Complex A

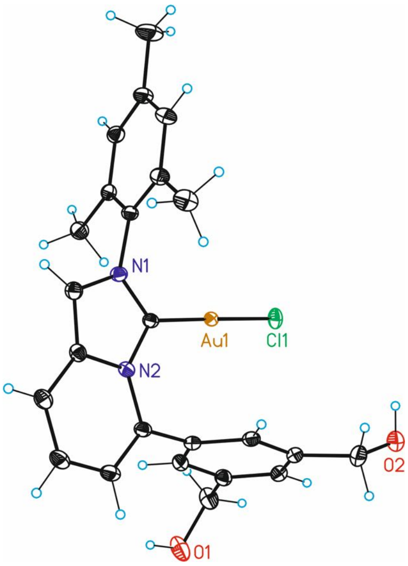


Table 1. Crystal data and structure refinement for **Complex A**.

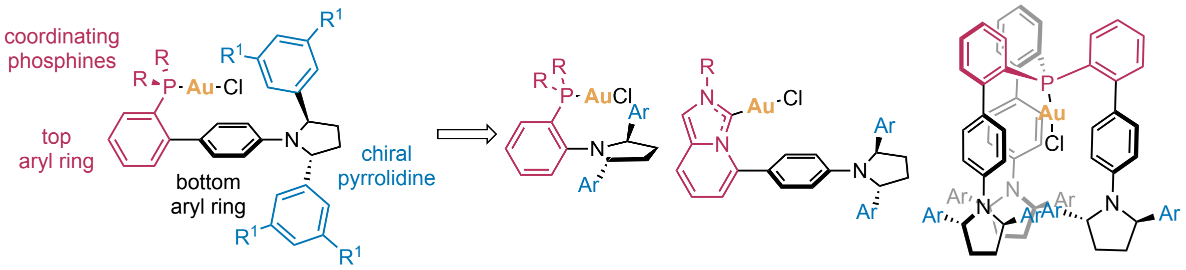
Identification code	AAB-5-014_a	
Empirical formula	C48 H48 Au2 Cl2 N4 O4 P0	
Formula weight	1209.73	
Temperature	100(2)K	
Wavelength	0.71073 Å	
Crystal system	orthorhombic	
Space group	P b c a	
Unit cell dimensions	a = 12.66410(10)Å	a= 90°.
	b = 15.15410(10)Å	b = 90°.
	c = 22.41410(10)Å	g = 90°.
Volume	4301.56(5) Å^3	
Z	4	
Density (calculated)	1.868 Mg/m^3	
Absorption coefficient	6.988 mm^{-1}	
F(000)	2352	
Crystal size	0.400 x 0.200 x 0.050 mm^3	
Theta range for data collection	3.440 to 33.606°.	
Index ranges	-19<=h<=19,-23<=k<=22,-34<=l<=34	
Reflections collected	179734	
Independent reflections	8347[R(int) = 0.0371]	
Completeness to theta =33.606°	98.0%	
Absorption correction	Multi-scan	
Max. and min. transmission	1.00 and 0.38	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	8347/ 0/ 276	
Goodness-of-fit on F^2	1.080	
Final R indices [I>2sigma(I)]	R1 = 0.0141, wR2 = 0.0366	
R indices (all data)	R1 = 0.0166, wR2 = 0.0374	
Largest diff. peak and hole	1.002 and -0.673 e.Å^{-3}	

General Conclusions

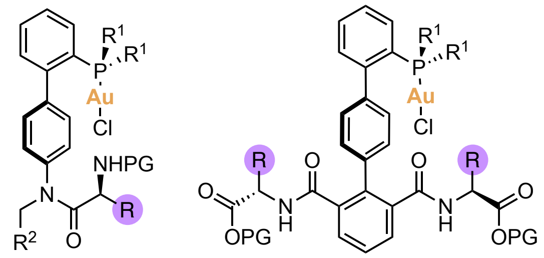
The research developed in this doctoral thesis has led to the following conclusions:

The synthesis of new families of chiral gold(I) complexes has been achieved derived from a previous design reported in our group, based on dialkylbiphenyl phosphine ligands bearing a C_2-asymmetric 2,5-disubstituted pyrrolidines. Modifications in this structure have allowed the studied and comparation of these catalysts in different transformations. The new families can be divided by:

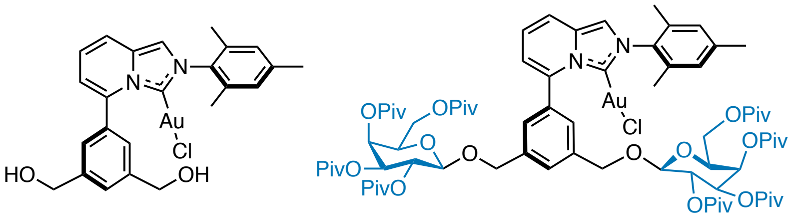
- Shorter complexes: approaching the chiral information to the gold(I) metal by removing the bottom aryl ring of the biphenyl scaffold. These chiral gold(I) complexes have been proved to be valuable in the atroposelective cyclization reaction of sulfonamides to afford 2-arylindoles, obtaining the opposite enantiomer than the model ligand. However, they did not accomplish the Au(I)/Au(III) redox catalysis.
- N-heterocyclic carbene complexes: the synthesis of these chiral complexes has been successfully achieved and their reactivities studied. They have showed good results in terms of yields and enantioselectivities. However, the enantioselectivity is not improved compared to the results obtained with the phosphine gold(I) complexes, probably due to the higher angle of the gold(I) regarding to the biphenyl moiety.
- Sterically hindered complexes: the synthesis of new sterically hindered chiral gold(I) complexes has been successfully prepared and they have been tested in catalysis, in general obtaining good yields, but low enantioselectivities. This behavior has been theoretically studied and could be explained by the opening of the pocket when a substrate is coordinated to the gold(I).



Other type of JohnPhos-gold(I) complexes has been synthesized bearing one or two amino acids and they have tested in different transformations, in general giving good reactivity. However, these complexes have not presented any enantioinduction, probably because the asymmetry of the ligands (when only one amino acid is present) and/or the free rotation of the bonds of the amino acids.



On the other hand, the synthesis of an N-heterocyclic carbene gold(I) complex has been carried out and this complex was also decorated with protected *β*-galactoses. Both complexes have been tested in a hydroarylation reaction, producing a fluorescent coumarin, under biological conditions. A modest different reactivity has been observed that might serve as *proof-of-concept* for the objective of this project.



The enzymatic hydrolysis of the glycosidic bonds of the complex using *β*-galactosidase from *Aspergillus oryzae* has been studied. Unfortunately, this specific enzyme does not seem to be active when a protected galactose is employed. Further work could be done in this field, by testing again the formation of the fluorescent coumarin and testing the enzyme in order to check if the hydrolysis of the glycosidic bond works. The successful results of these experiments would allow testing this system *in vitro* in senescent cells by Dr. José Alberto López Domínguez from Dr. Manuel Serrano's group at the IRB (Institute for Research in Biomedicine).

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