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Chiral Bifunctional Phosphine Ligand-Enabled Cooperative Asymmetric Coinage Metal Catalysis

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy

in Chemistry

by

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December 2021

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October 2021

Chiral Bifunctional Phosphine Ligands-Enabled Cooperative Gold and Copper Asymmetric Catalysis

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3. T. Li[§], **X. Cheng**[§], P. Qian*, L. Zhang*. Gold-catalysed asymmetric net addition of unactivated propargylic C–H bonds to tethered aldehydes. *Nat. Catal.*, **2021**, *4*, 164-171. *(§ : Both authors contributed equally to this work)*
4. Z. Zheng, X. Ma, **X. Cheng**, K. Zhao, K. Gutman, T. Li, L. Zhang*. Homogeneous Gold-Catalyzed Oxidation Reactions. *Chem. Rev.* **2021**, *121*, 8979-9038.
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8. **X. Cheng,** C. D. Quintanilla, L. Zhang*. Total Synthesis and Structure Revision of Diplobifuranylone B. *J. Org. Chem.* **2019**, *84*, 11054-11060.
9. **X. Cheng,** J. Chen, M. Gainer, L. Zhang*. Gold-Catalyzed Rearrangement of Propargyl Alcohols Using Coupling Constants To Determine Isomeric Ratios. *J. Chem. Educ.* **2019**, *96*, 2348-2351**.**

10. Y. Zheng, J. Zhang, **X. Cheng**, X. Xu, L. Zhang*. Wolff Rearrangement of Oxidatively Generated α-Oxo Gold Carbenes: An Effective Approach to Silylketenes. *Angew. Chem. Int. Ed.* **2019**, *58*,5241–5245.
11. S. Liao, A. Porta, **X. Cheng**, X. Ma, G. Zanoni, L. Zhang*. Bifunctional Ligand Enables Efficient Gold-Catalyzed Hydroalkenylation of Propargylic Alcohol. *Angew. Chem. Int. Ed.* **2018**, *57*, 8250-8254.
12. **X. Cheng,** Y. Wang, L. Zhang*. An Au/Zn-catalyzed Synthesis of N-Protected Indoles via Annulation of *N*-Aylhydroxamic Acids and Alkynes. *Org. Synth.* **2018**, *95*, 15-28.

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National Organic Chemistry Symposium, Bloomington

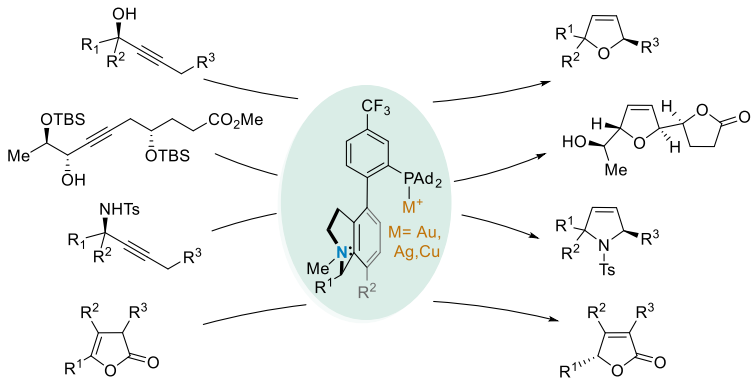
ABSTRACT

Chiral Bifunctional Phosphine Ligand-Enabled Cooperative Asymmetric Coinage Metal Catalysis

by

Xinpeng Cheng

Most ligands used in asymmetric gold(I) catalysis are directly adopted from palladium catalysis. These ligands were initially designed to facilitate the chemistry of square-planar Pd(II) complexes and hence are hardly optimal for Au(I) catalysis, in which the catalysts display linear geometry. For the past several years, the Zhang Lab has designed various bifunctional biphenyl-2-ylphosphine ligands featuring a remote basic group to harness the linear Au(I) structure and enable ligand-metal cooperation. During the research of this dissertation, a new type of bifunctional phosphine ligands possessing a chiral center and a fluxional biphenyl axis were developed to enable asymmetric isomerization of propargylic alcohols and sulfonamides into chiral 2,5-dihydrofurans and chiral 3-pyrrolines, respectively. The synthetic potential of this methodology was demonstrated in a total synthesis of diplobifuranylone B. Notably, this type of chiral ligands is also suitable for Ag(I) and Cu(I) catalysis. β, γ-Butenolides was isomerized into chiral *α, β*-butenolides with high enantiomeric excesses via enantioselective γ-protonation under Cu(I) catalysis.



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1. Chiral Ligand Design in Asymmetric Gold(I) Catalysis

1.1. General Introduction to Asymmetric Gold(I) Catalysis

In the past decade, we have witnessed significant and exciting development in homogeneous gold (I) catalysis. [1] The potent soft Lewis acidity of Au(I) complexes enables the activation of alkynes and allenes and the development of various versatile catalytic methods. These methods are increasingly employed in constructing natural products with complex carbon skeletons that would be otherwise difficult to access. [2-6]

Despite the rapid advancement in gold(I) catalysis, the development of asymmetric gold(I) catalysis remains challenging. As shown in **Figure 1**, gold(I) complex typically favors the linear biscoordination geometry that the chiral ligand (L^*) and the substrate are placed on the opposite sides of the gold center. As a result, the chiral ligand (L*) can not readily reach the reaction site. In addition, the free rotation of ligand-gold bond and gold-alkyne bond make it harder to achieve a rigid structure for enantioinduction.

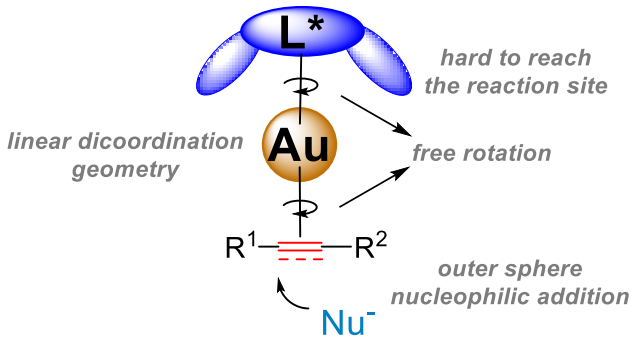


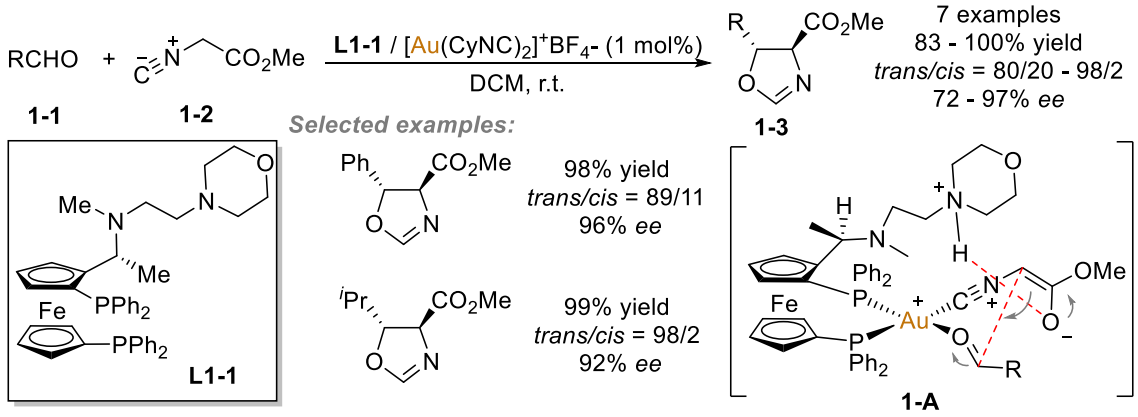
Figure 1. Challenges in Asymmetric Gold (I) Catalysis

Despite these challenges, several strategies have been successfully implemented in asymmetric gold(I) catalysis by employing binuclear gold (I) complexes, monodentate phosphoramidite ligands, and chiral counteranions. The details of them are discussed below.

1.2. Prior art in Asymmetric Gold(I)-Catalysis

In 1986, Ito and Hayashi group[7] reported the first example of asymmetric gold(I) catalysis using the well-designed ferrocenylphosphine ligand **L1-1** (Scheme 1). The chiral gold(I) complex **1-A** permits highly efficient aldol reactions between α-isocyano acetate and aldehydes, producing the oxazoline **1-3** with excellent enantioselectivity and diastereoselectivity. In the proposed transition state **1-A**, the morpholine moiety at the end of the side chain of **L1-1** facilitates the formation of an enolate through deprotonation, and the hydrogen bonding between the protonated morpholine and the enolate permits a favorable arrangement of the enolate and the aldehyde moieties, facilitating high stereoselectivity. In addition, it was found that increasing the distance between the amino group and ferrocene moiety led to a significant decrease in enantioselectivity. Notably, the gold(I) has four coordination sites in this proposed structure, obviously an outlier of well-established gold(I) catalysis.

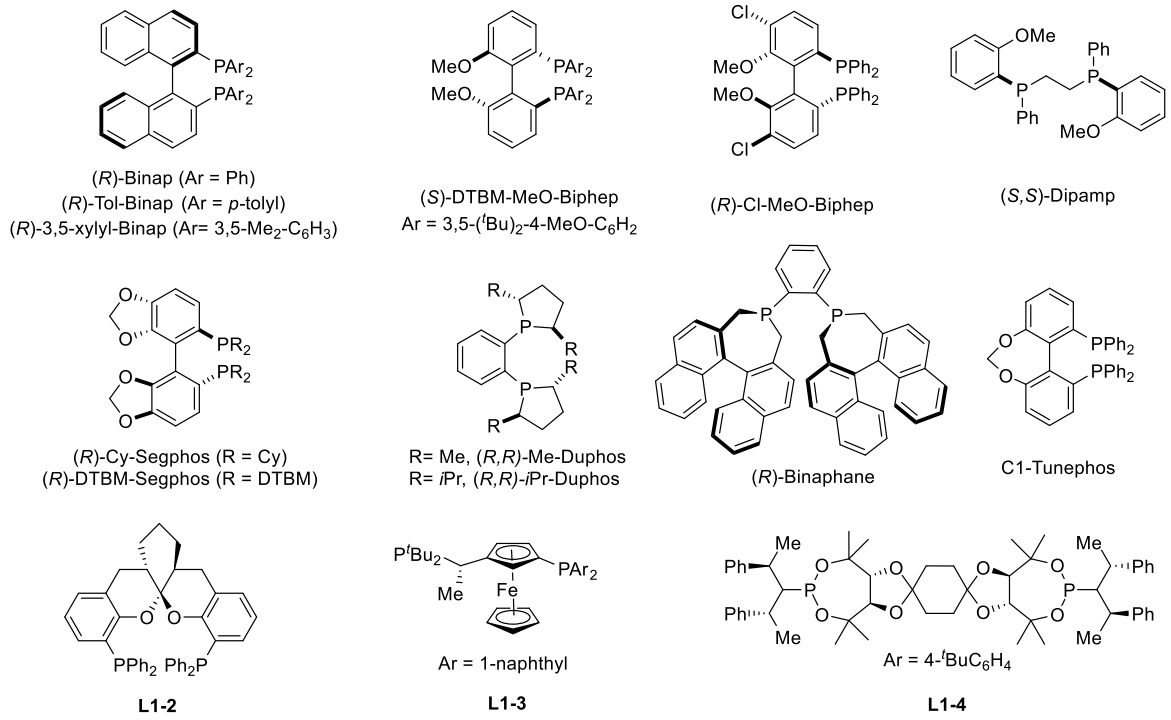
Scheme 1. The First Example of Asymmetric Gold(I) Catalysis



1.2.1. Chiral Bisphosphine Ligands

The usage of the corresponding bimetallic gold(I) complexes of chiral bisphosphine ligands is the most widely investigated strategy in asymmetric gold (I) catalyst. The representative chiral biphosphine ligands are listed in Figure 2. Since this topic has been covered in multiple reviews, only a few selected examples are presented here.[8-12]

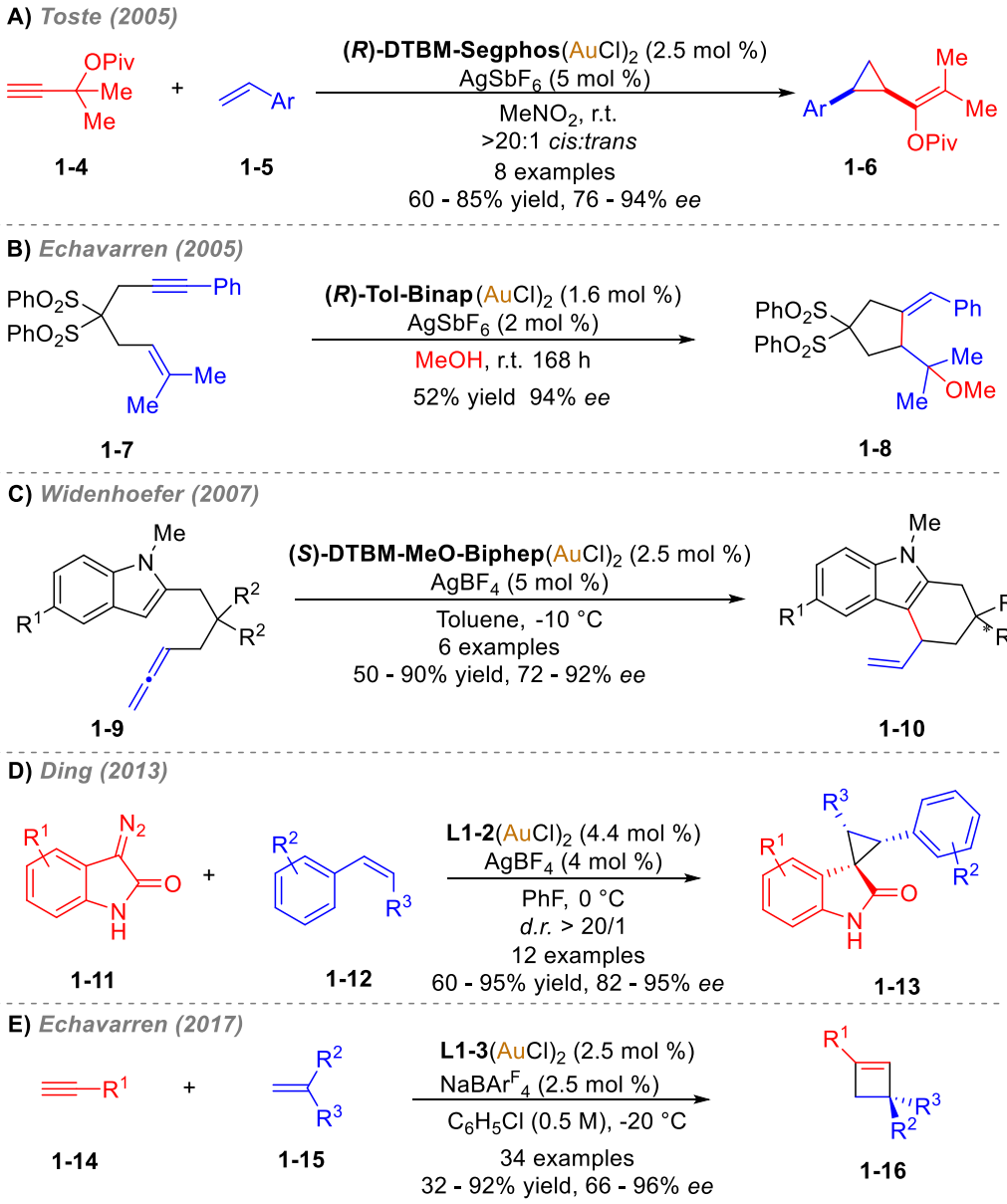
Figure 2. Representative Chiral Bisphosphine Ligands in Asymmetric Gold(I) Catalysis



In 2005, Toste reported the gold(I)-catalyzed enantioselective cyclopropanation of the olefin **1-5** using the propargyl ester **1-4** as the precursor to generated a gold(I)-carbene intermediate.[13] The reaction conditions were mild and the *cis*-cyclopropane **1-6** was formed with >20/1 *cis/trans* selectivity, in good yield, and with moderate to excellent enantioselectivity (Scheme 2A). In the same year, Echavarren disclosed the gold(I)-catalyzed enantioselective cycloisomerization/alcohol addition of the 1,6-enyne **1-7** (Scheme 2B).[14] Albeit the long reaction time, the methylenecyclopentane **1-8** was formed

with 94% ee and in moderate yield. In these two examples, it is noteworthy that chiral bisphosphine ligands were introduced into asymmetric gold(I) catalysis for the first time.

Scheme 2. Selected Synthetic Applications of Chiral Bisphosphine Ligands in Asymmetric Gold(I) Catalysis

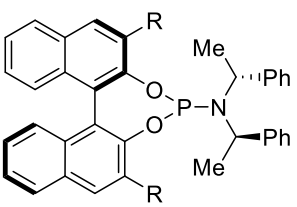


In 2007, Widenhoefer discovered the gold(I)-catalyzed enantioselective intramolecular hydroarylation of allene **1-9**, leading to the formation of chiral tricyclic indole derivatives **1-10** (Scheme 2C).[15] In 2013, Deng reported that the bimetallic gold(I) complex ligated by

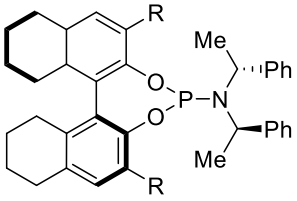
the chiral spiroketal bisphosphine (**L1-2**) derived catalyzed olefin cyclopropanation with the diazooxindole **1-11** to generate the spirocyclopropyloxindole **1-13** (Scheme 2D).[16] The reaction is highly diastereo- and enantioselective, and a range of alkenes including less reactive *cis*- and *trans*-1,2-disubstituted alkenes were accommodated. Later in 2017, Echavarren demonstrated the gold(I)-catalyzed enantioselective intermolecular [2+2] cycloaddition of terminal alkynes **1-14** and alkenes **1-15** using the *non*-C2-symmetric chiral Josiphos **L1-3** as the ligand (Scheme 2E).[17] This reaction offered an expedited synthesis of rumphellaone A in 9 steps.

1.2.2. Monodentate Phosphoramidite Ligands

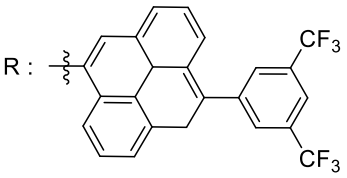
Figure 3. Representative Monodentate Phosphoramidite Ligands in Asymmetric Gold (I) Catalysis



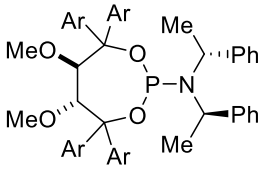
R = H, **L1-9**
R = 9-anthracenyl, **L1-10**
R = 1-pyrenyl, **L1-11**
R = 3,5-$(CF_3)_2C_6H_3$, **L1-12**



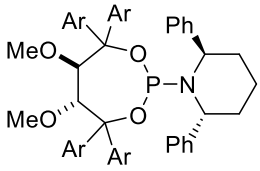
R = H, **L1-13**
R = 1-pyrenyl, **L1-14**
R = 4-pyrenyl, **L1-15**



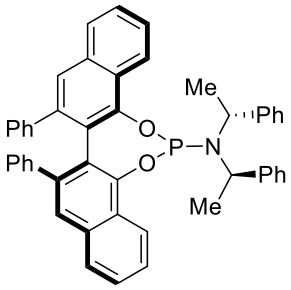
L1-16



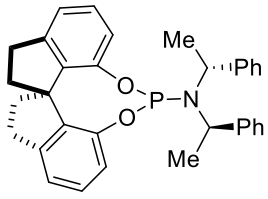
Ar = Ph, **L1-17**
Ar = 4-^{t}BuC$_6$H$_5$, **L1-18**



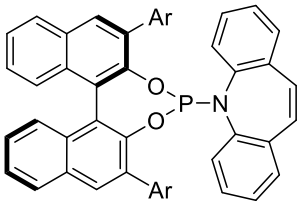
Ar = 2-naphthyl, **L1-19**



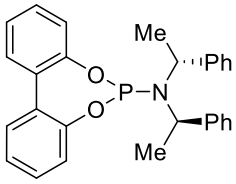
L1-20



L1-21



Ar = 3,5-$(CF_3)_2C_6H_3$, **L1-22**



L1-23

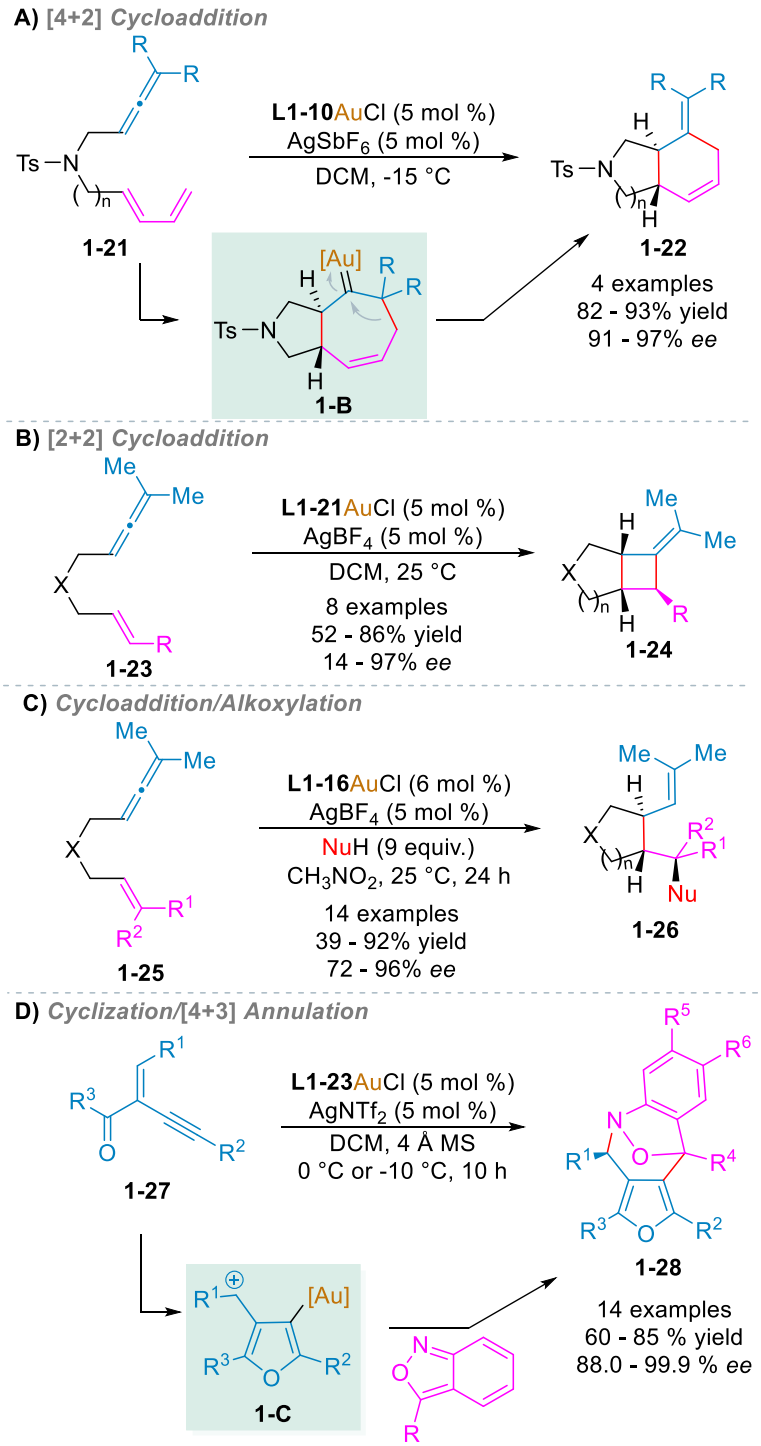
Monodentate phosphoramidite ligand is another type of ligand that has been widely investigated in asymmetric gold (I) catalysis. These ligands are readily available and offer great flexibility in terms of tuning sterics. A list of representative monodentate phosphoramidite ligands are shown in Figure 3.

The first application of monodentate phosphoramidite ligands in asymmetric gold (I) catalysis was reported in 2009 by Macarenas and co-workers.[18] Using the chiral monodentate phosphoramidite **L1-10** as the ligand, the formal intramolecular [4+2] cycloaddition of allenedienes **1-21** was realized with excellent enantioselectivity (Scheme 3A). Mechanistically, the reaction frist undergoes a [4+3] cycloisomerization to generate the cyclopentenyl gold(I)-carbene intermediate **1-B**, which is converted into the observed product upon a 1,2-alkyl migration.

In 2011, Toste expanded the application of this type of ligands to the intramolecular [2+2] cycloaddition of the allene-ene **1-23**, leading to the formation of the 3,4-disubstituted pyrrolidines **1-24** in good yield and with up to 97% *ee* (Scheme 3B).[19] The reaction proceeds through a carbocationic intermediate, which could also be attacked by the exogenous nucleophile to afford the γ-lactams **1-26** (Scheme 3C). A formal synthesis of (-)-isocynometrine was performed to demonstrate the synthetic utility of this chemistry.

In 2020, Liu described the gold-catalyzed cycloisomerization of the 2-(1-alkynyl)-2-alken-1-ones **1-27** to generate 3-furyl methyl cations **1-C**, which is followed by the [4+3] annulation with anthranils to afford the epoxybenzoazepine **1-28** in good yields and with excellent exo diastereoselectivities (*d.r.* > 25/1) and enantioselectivities (up to 99.9% *ee*) (Scheme 3D).[20] A proposed step-wise mechanism was proposed to rationalize the *exo* diastereoselectivity and corroborated by DFT calculations.

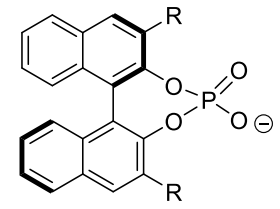
Scheme 3. Selected Synthetic Application of Monodentate Phosphoramidite Ligands in Asymmetric Gold(I) Catalysis



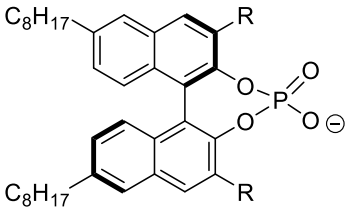
1.2.3. Chiral Counteranions

In 2007, Toste and co-workers reported of the first case of asymmetric couteranion-directed gold catalysis. [21] Instead of relying on the chiral ligands coordinated to gold(I) to create suitable chiral environments for enantioinduction, the stereocontrol of this new strategy is achieved by a chiral counterion. The phosphate counteranions successfully employed in this strategy are shown in Scheme 4.

Scheme 4. Chiral Phosphate Couteranion Used in the Asymmetric Couteranion-Directed Catalysis



R = 2,4,6-^{i}Pr$_3$-C$_6$H$_2$, **L1-24**
R = SiPh$_3$, **L1-25**

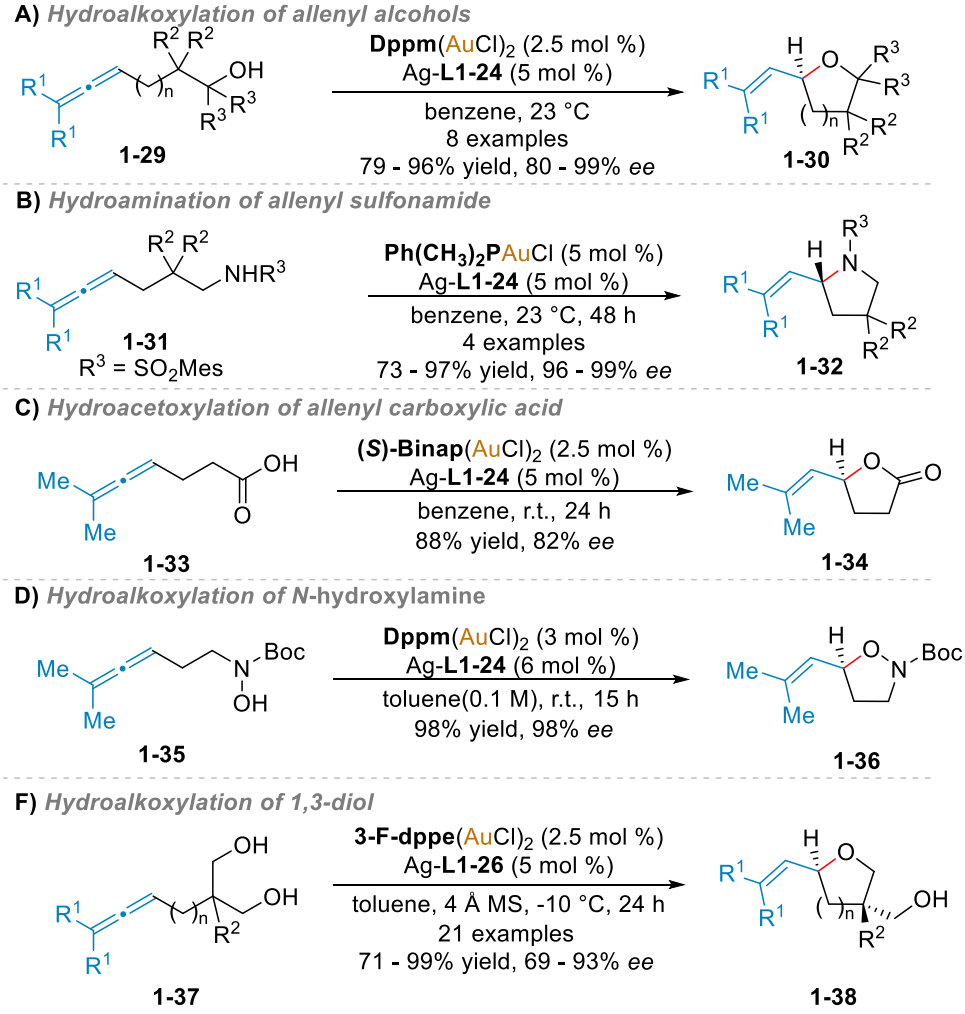


R = 2,4,6-^{i}Pr$_3$-C$_6$H$_2$, **L1-26**

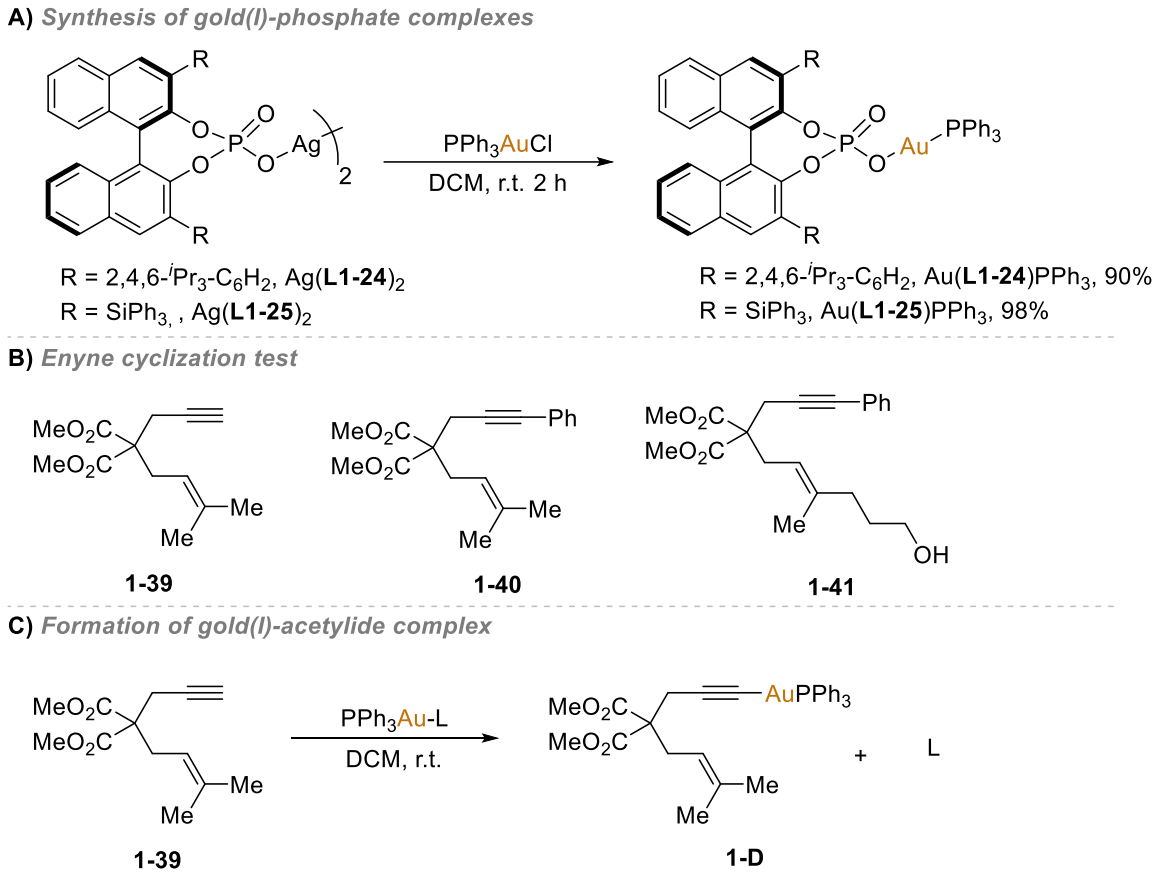
Intramolecular hydroalkoxylation of the γ- or δ-hydroxy allene **1-29** in the presence of catalytic achiral dppm(AuCl)$_2$ and the chiral silver phosphate Ag-**L1-24** in benzene at room temperature resulted in the formation of the chiral tetrahydrofuran **1-30** in good yields and excellent enantioselectivities. Notably, the enantioselectivity decreased significantly in polar solvents such as nitromethane, signaling the importance of ion-pair in enantioinduction (Scheme 5A). In addition, this chiral anion strategy could also be applied to the hydroamination of allenyl sulfonamides **1-31**, leading to the formation of the chiral pyrrolidine **1-32** with >95% *ee* (Scheme 5B). Furthermore, the chiral counterion and chiral ligands can be combined together to enhance enantioselectivity. Hydroacetoxylation of allenyl carboxylic acid **1-33** catalyzed by the gold complexes incorporating chiral ligands or chiral counterions gave poor enantioselectivities, i.e., <40% *ee*. However, combining

these two strategies led to the formation of γ-lactone **1-34** in 82% *ee* (Scheme 5C). Later, in 2010, the same strategy was adopted to access isoxazolidines **1-36** from *N*-hydroxylamine **1-35** (Scheme 5D).[22] In 2015, Toste further expanded the scope of this strategy and achieved the first example of gold(I)-catalyzed enantioselective desymmetrization of the 1,3-diols **1-37** (Scheme 5F). [23] To note, a clear linear relationship was observed between the *ee* value of the silver phosphate catalyst and the desired product **1-38**, suggesting that the second gold center does not participate in the chiral induction.

Scheme 5. Application of Asymmetric Couteranion-Directed Catalysis



Scheme 6. Limitation of Chiral Couteranion Statgies.



It is noteworthy that in this chiral counterion strategy the substrates are limited to those allenes discussed above. The concept of couteranion-directed catalysis has not been extended to the activation of alkynes. In 2012, Echavarren explored implementing this concept in the gold(I)-catalyzed activation of enynes (Scheme 6).[24] The gold(I)-phosphate complexes were prepared in good yields by the reaction of silver(I) phosphate complexes with PPh_3AuCl at room temperature (Scheme 6A). Compared with the *in*-situ generated complexes, these gold(I)-phosphate complexes showed similar reactivity toward the cyclization of allenol. However, they were inactive in the cyclization of enyne **1-39**, **1-40,** and **1-41** (Scheme 6B). These enynes have been demonstrated to be highly reactive toward gold(I) catalyst, especially the enyne **1-39**, which the cyclization could happen as low as -

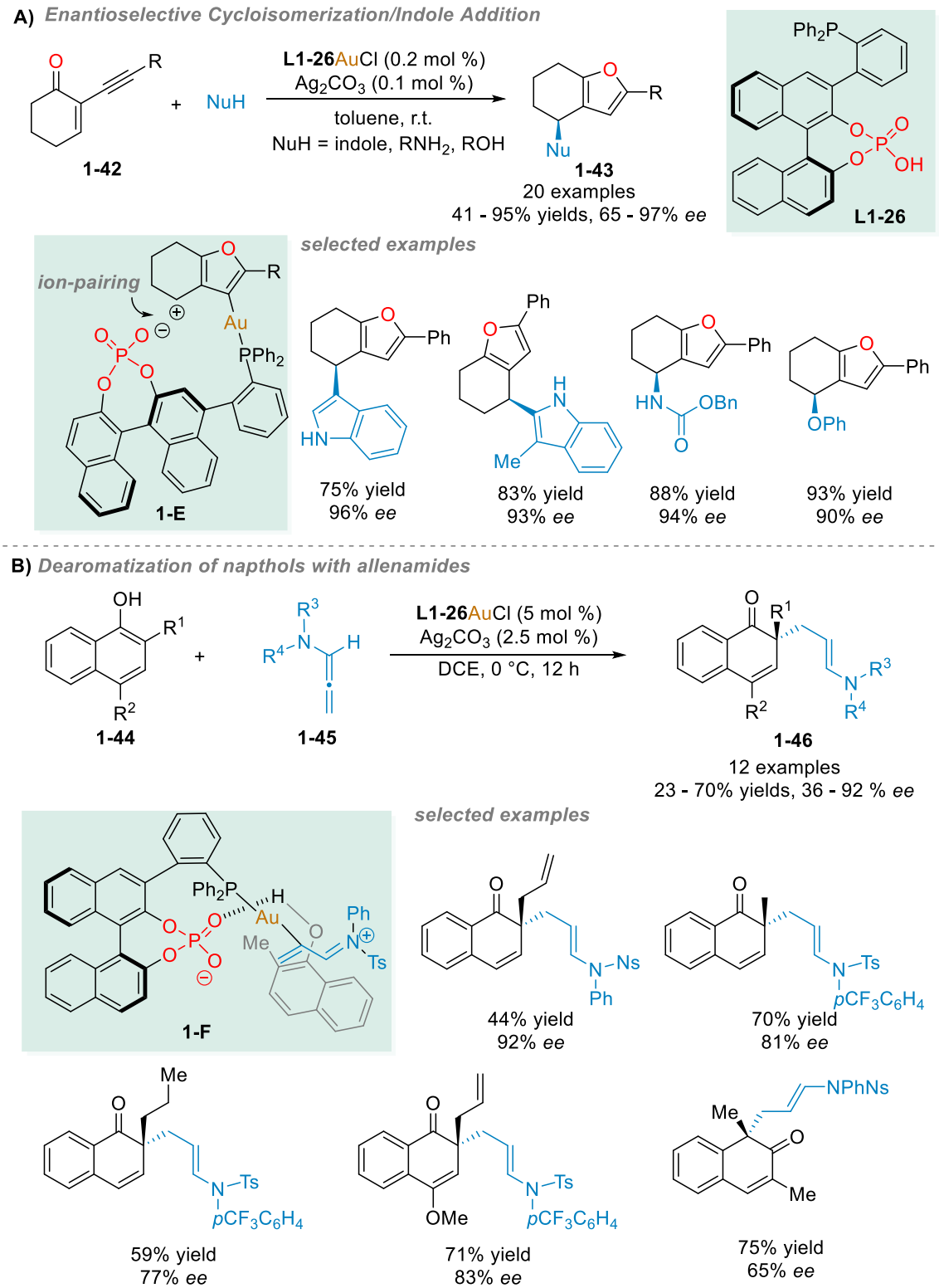
63 ˚C. [25] Interestly, the addition of an equimolar amount of Ag(I) complexes or excess amount of MeOH could restore the gold(I)-phosphate complex reactivity. Gold(I) complexes with phosphates were sufficiently basic to deprotonate terminal alkyne hydrogens and form gold(I)-acetylide complexes **1-D**, leading to a catalytic dead-end (Scheme 6C).

In 2020, Marinetti and Guinchard reported a new strategy in asymmetric counteranion-directed catalysis, in which the gold center is tethered to a BINOL-derived chiral phosphate counterion via a bifunctional monophosphine ligand, *e.g.* **L1-26** (Scheme 7).[26] Compared with the previous strategy in which the stereochemical control suffers from the poorly defined and flexible spatial arrangement of the phosphate-carbocation pair, tethering the chiral phosphate moiety to a gold complex via a covalent bond offers geometrical constraints and molecular organization for efficient enantioinduction.

The thus-designed ligand **L1-26** was examined in the enantioselective cycloisomerization/indole addition of 2-alkynylenones **1-42** (Scheme 7A) to generate chiral bicyclic furan **1-43** with a low catalyst loading, i.e., 0.2 mol %. The stereocontrol is thought to be achieved by an electrostatic pairing between the carbocation and the tethered phosphate group in the intermediate **1-E**.

In 2021, Marinetti and Guinchard further explored this reaction design and demonstrated enantioselective gold(I)-catalyzed dearomatization of 1-naphthols **1-44** with allenamides **1-45** to generate the benzocyclohexenone **1-45** in moderate to high enantioselectivities (Scheme 7B).[27] In the key intermediate **1-F** responsible for the stereocontrol, the phosphate unit not only forms the intramolecular ion-pairing with an iminium unit but also directs the addition of the naphthol via hydrogen bonding.

Scheme 7. Tethered Couterion-Directed Gold Catalysis



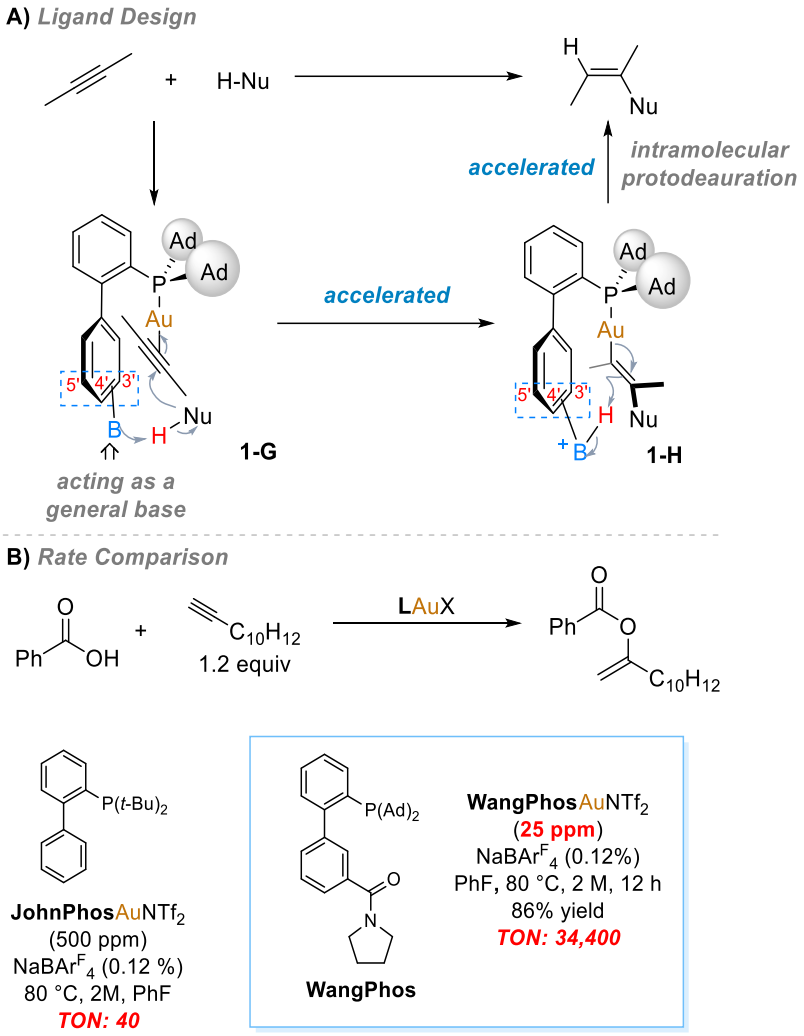
1.3. Chiral Ligands Developed for Homogeneous Gold Catalysis

1.3.1. Biaryl Monophospine Ligands

In 2014, our group started the journey of developing new biphenyl-2-ylphosphine ligands based on the linear gold(I) structure. Two types of chiral bifunctional ligands, amide-functionalized and amine-functionalized ligands, have been successfully developed.[28] This section will only cover amide-functionalized ligands, and the details about amine-functionalized ligands will be discussed in **Chapter 3**.

In our initial foray into the ligand design,[29] as shown in Scheme 8A, we envisioned that the basic B group could partially deprotonate the protic nucleophile in the transition state **1-G**, which would result in a lowered barrier and hence accelerated nucleophilic attack at the gold-activated C-C triple bond via general base catalysis. Furthermore, subsequent protodeauration via **1-H** could also be accelerated due to its intramolecular nature. Such an addition to allenes should be similarly accelerated. This would lead to accelerated reaction and increased catalyst turnover frequency, which would likely result in improved turnover numbers and, in turn, lower catalyst loadings. We examined the gold-catalyzed addition of carboxylic acids to alkynes based on this design.[29] A carboxamide was found to be a suitable B group for achieving anticipated reaction acceleration. Moreover, **WangPhos** featuring a 3'-pyrrolidine-1-carbonyl turned out to be particularly efficacious. With its cationic gold complex as the catalyst (Scheme 8B), the addition of benzoic acid to 1-dodecyne is accelerated by an estimated 860 times when compared to that by the gold(I) catalyst prepared from **JohnPhos**, an electronically and sterically similar ligand but only missing the remote amide group.

Scheme 8. Ligand Designed for Accelerated Nucleophilic Attack

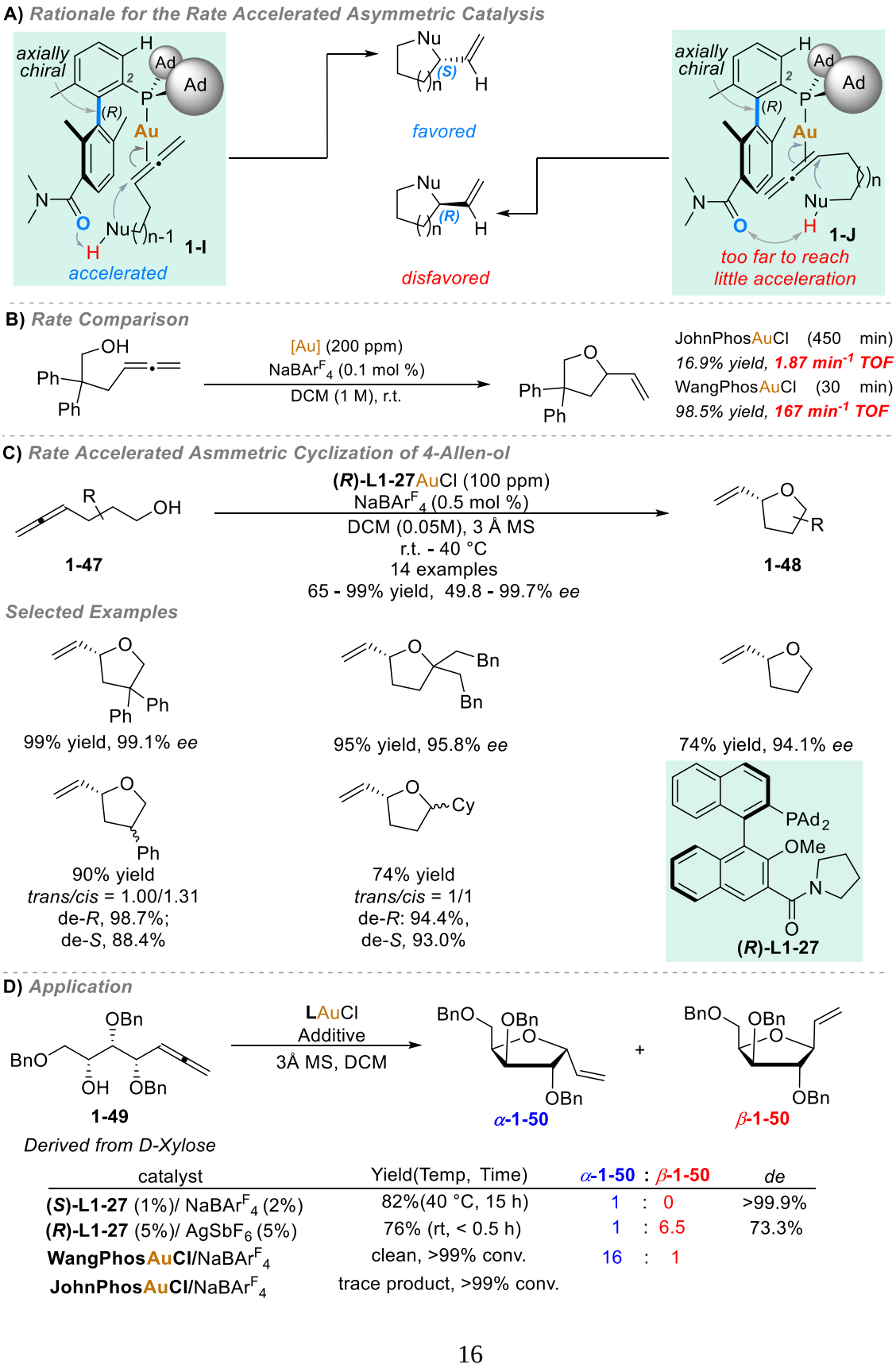


With the success of Wangphos in rate-accelerated nucleophilic addition, we further design a chiral version of WangPhos, i.e. (*R*)-**L1-27**, to achieve ligand-accelerated asymmetric gold-catalysis.[30] As shown in **Scheme *9***, the cyclization of an allenyl nucleophile can generate a new chiral center. With a chiral version of WangPhos featuring a restricted biaryl axis, the corresponding cationic Au(I) complex can bind to a monosubstituted allene to form two competing complexes **1-I** and **1-J,** prior to cyclization. With the 3'-amide group positioned optimally to direct the attack of the tethered nucleophile in the case of **1-I**, the cyclization should be much accelerated. On the contrary,

the amide group is far away from the nucleophile in **1-J**, and hence little rate increase could be expected. As a result, the cyclization would mostly go through **1-I** and thereby become enantioselective or diastereoselective. This anticipated acceleration was confirmed with WangPhos as the ligand (Scheme 9B), leading to >88 fold of increase on TOF over JohnPhos. As shown in Scheme 9C, (*R*)-**L1-27**, an axially chiral version of WangPhos prepared in a 4-step sequence from commercially available (*R*)-binol indeed enables highly enantioselective cyclization of achiral allenyl alcohols **1-47**, affording tetrahydrofurans **1-48** with >94% ee. Moreover, with chiral substrates, high diastereomeric excesses are achieved with each substrate enantiomer regardless of the configuration. This chemistry constitutes the first accelerated asymmetric gold catalysis,[9, 31] and due to the fast reaction rate, the catalyst loadings can be as low as 100 ppm.

To examine the synthetic utility of this chemistry, the allenyl polyol **1-49** prepared from $_{D}$-xylose was subjected to the chemistry (Scheme 9D). With WangPhos as the ligand, an intrinsic preference for the α-*C*-glycoside α-**1-50** over its β-anomer (16:1) was observed. In a matched scenario with (*S*)-**L1-27** as the ligand, α-**1-50** was formed exclusively. On the other hand, in the mismatched scenario with (*R*)-**L1-27**, the large intrinsic preference for the α-anomer was reverted to favor *β*-**1-50** by a ratio of 6.5/1. This is valuable in stereoselective access to *C*-glycosides. In addition, the reaction was messy when Johnphos was used as the ligand, revealing that due to the accelerated cyclization, these amide-functionalized ligands also enable valuable chemoselectivity as side reactions are no longer kinetically competitive.

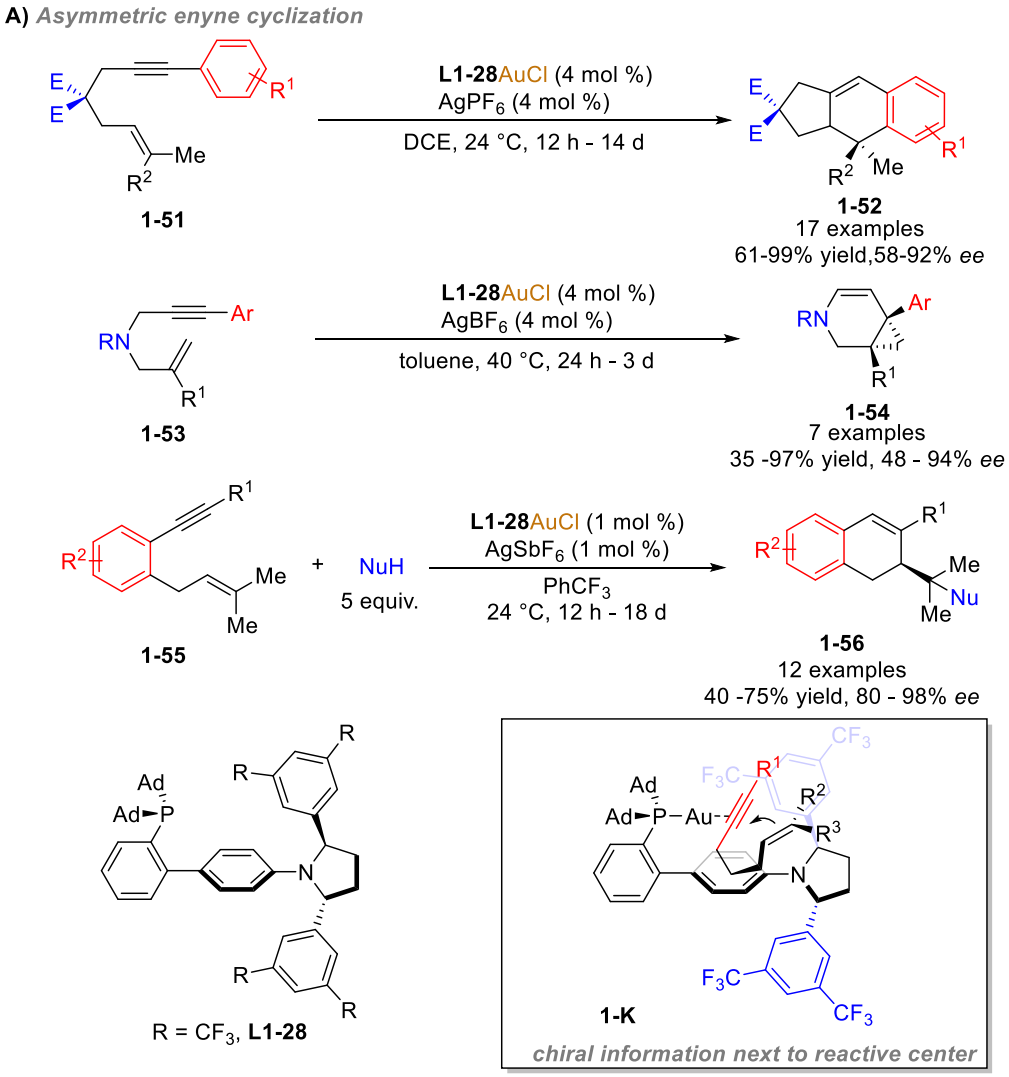
Scheme 9. Ration Accelerated Asymmetric Cyclization of 4-Allen-1-ol



catalyst	Yield(Temp, Time)	α-1-50 : β-1-50	de
(*S*)-L1-27 (1%)/ NaBAr$^F_4$ (2%)	82%(40 °C, 15 h)	1 : 0	>99.9%
(*R*)-L1-27 (5%)/ AgSbF$_6$ (5%)	76% (rt, < 0.5 h)	1 : 6.5	73.3%
WangPhosAuCl/NaBAr$^F_4$	clean, >99% conv.	16 : 1	
JohnPhosAuCl/NaBAr$^F_4$	trace product, >99% conv.		

In 2019, Echavarren prepared a series of chiral modified JohnPhos-type ligands featuring a C_2-symmetric *trans-2,5*-diaryl pyrrolidine at the para position of the biphenyl scaffold, e.g., **L1-28**, in a 3-step sequence from enantiopure benzylic diols and biphenylamines (Scheme 10).[32] Similar to our design, the bulky substituents on the phosphine, i.e., adamantyl group, were deployed to prevent rotation around the C-P bond. Thus it forces the P-Au-Cl axial to be paralleled to the biphenyl axis because of the linear structure of Au(I) catalyst and positioned proximal to the *trans*-2,5-pyrrolidine moiety for enantioinduction (**1-K**). Facilitated by the chiral ligand **L1-28, the** 1,6-enyne **1-51** was converted into the cyclopenta[b]naphthalenes **1-52** in good yields and with moderate to high enantioselectivities via the formal [4+2] reaction.[33] In addition, *N*-tethered 1,6-enynes **1-53** went through the 6-*endo-dig* cyclization to afford azabicyclo[4.1.0]hept-4-enes **1-54** in moderate to good yields and with medium to excellent enantioselectivities.[34] Moreover, in the presence of nucleophiles, a tandem gold(I)-catalyzed *6-endo-dig* cyclization/nucleophilic addition of the 7-substituted-1,6-enynes **1-55** was conducted to give the 1,2-dihydronaphthalenes **1-56** in moderate to good yields and with excellent enantioselectivities.[35] To note, despite the structural similarity between **1-51** and **1-55**, opposite enantioselectivities were found in the final product **1-52** and **1-56** using the same ligand enantiomer. DFT calculations revealed that the opposite enantioselectivities could be attributed to the difference in the energy barriers between the respective *Si* and *Re* faces of alkenes. Additionally, the first enantioselective total synthesis of the Carexane O, Carexane I, and Carexane P were achieved in 3-6 steps from the product **1-57**.

Scheme 10. Asymmetric Enyne Cyclization

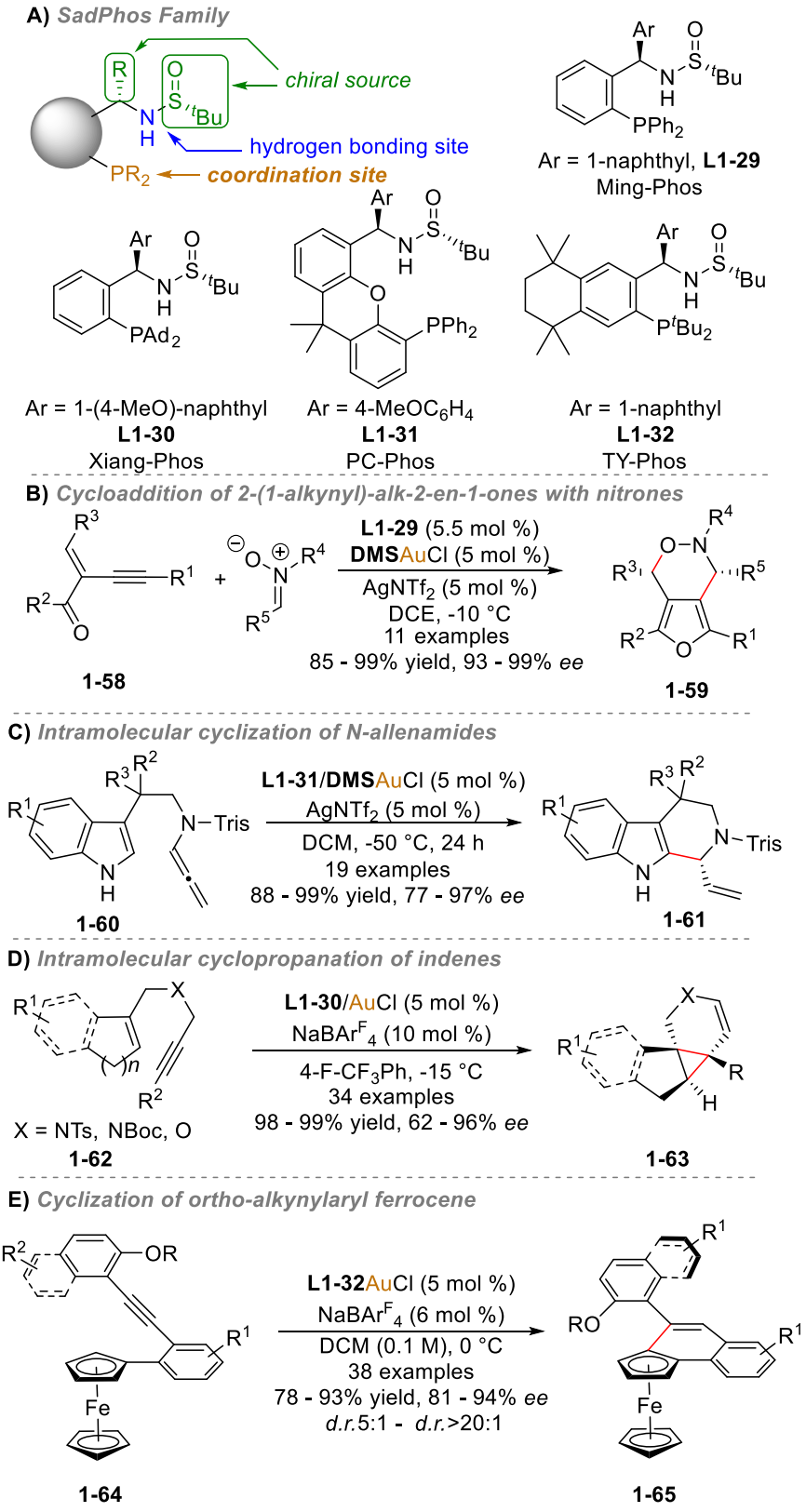


1.3.2. Chiral Sulfinamide Monophosphine Ligands

Starting from 2014, the group of Juliang Zhang began the development of the so-called SadPhos (sulfinamidephosphine) family of chiral ligand,[36-40] in which Ellman's sulfinamides[41] served as the key starting material to introduce a new chiral center. As shown in Scheme 11A, the general structure of Sadphos features dialkyl phosphine motif to provide a coordination site for Au(I) and two chiral centers, i.e., *tert*-butylsulfinyl group and the benzylic position α to the sulfinamide moiety, for efficient enantioinduction. In addition, the *tert*-butylsulfinamide motif offers a hydrogen bonding site for non-covalent interactions. The Sadphos ligands used in gold catalysis include Ming-Phos (**L1-29**), Xiang-Phos (**L1-30**), PC-Phos (**L1-31**), and TY-Phos (**L1-32**). In addition, Sadphos ligands are also be widely adopted in palladium catalysis. However, that is beyond the coverage of this dissertation.

In 2014, J. Zhang reported their initial foray into the development and application of the SadPhos ligands.[40] Enantioselective gold-catalyzed cycloaddition of the 2-(1-alkynyl)-alk-2-en-1-ones **1-58** with nitrones afforded the fused-furan **1-59** in good yields and with excellent enantioselectivities by using Ming-Phos (**L1-29**) as the ligand in gold catalysis (Scheme 11B). Later, the same group developed a new Sadphos ligand, i.e., PC-Phos (**L1-31**),[38] with the chiral center and dialkyl phosphine positioned further apart than in MingPhos (**L1-29**). Utilizing this new ligand (PC-Phos), the chiral tetrahydrocarbolines **1-61** was synthesized via gold-catalyzed enantioselective intramolecular cyclization of the *N*-allenamides **1-60** (Scheme 11C). The synthetic potential of this reaction was demonstrated in the total synthesis of (*R*)-desbromoarborescidine A and formal synthesis of (*R*)-desbromoarborescidine C and (*R*)-deplancheine.

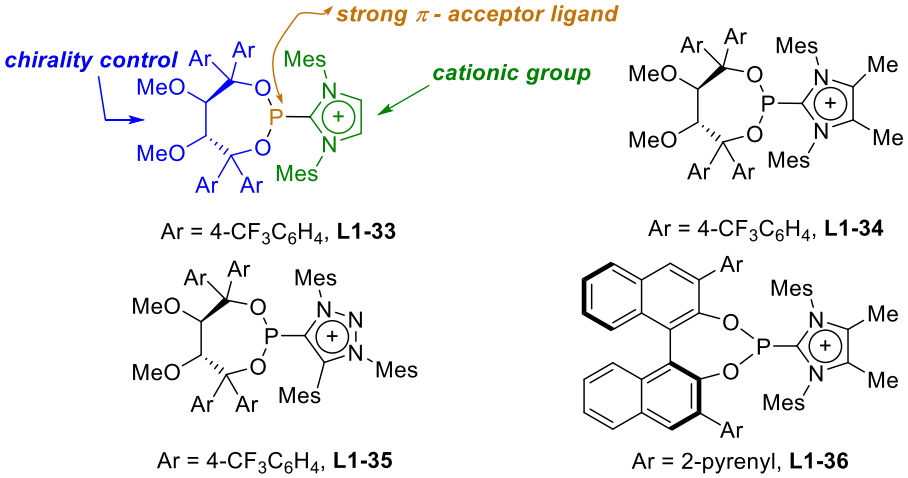
Scheme 11. SadPhos Ligand Design and Application in Gold Catalysis



In 2018, the J. Zhang lab reported an intramolecular enantioselective cyclopropanation of indenes and trisubstituted alkenes.[37] With Xiang-Phos (**L1-30**) as the ligand, the 1,6-enynes **1-62** were converted into the desired products **1-63** with [5,3,6] fused-ring systems containing two vicinal all-carbon quaternary stereogenic centers (Scheme 11D). In 2021, they developed a gold-catalyzed asymmetric hydroarylation of the ortho-alkynylaryl ferrocenes derivatives **1-64** to access the desired product **1-65** with two different chiralities, i.e., axial and planar chirality, by using TY-Phos **L1-32** (Scheme 11E).[36]

1.3.3. α-Cationic Phosphonites Ligands

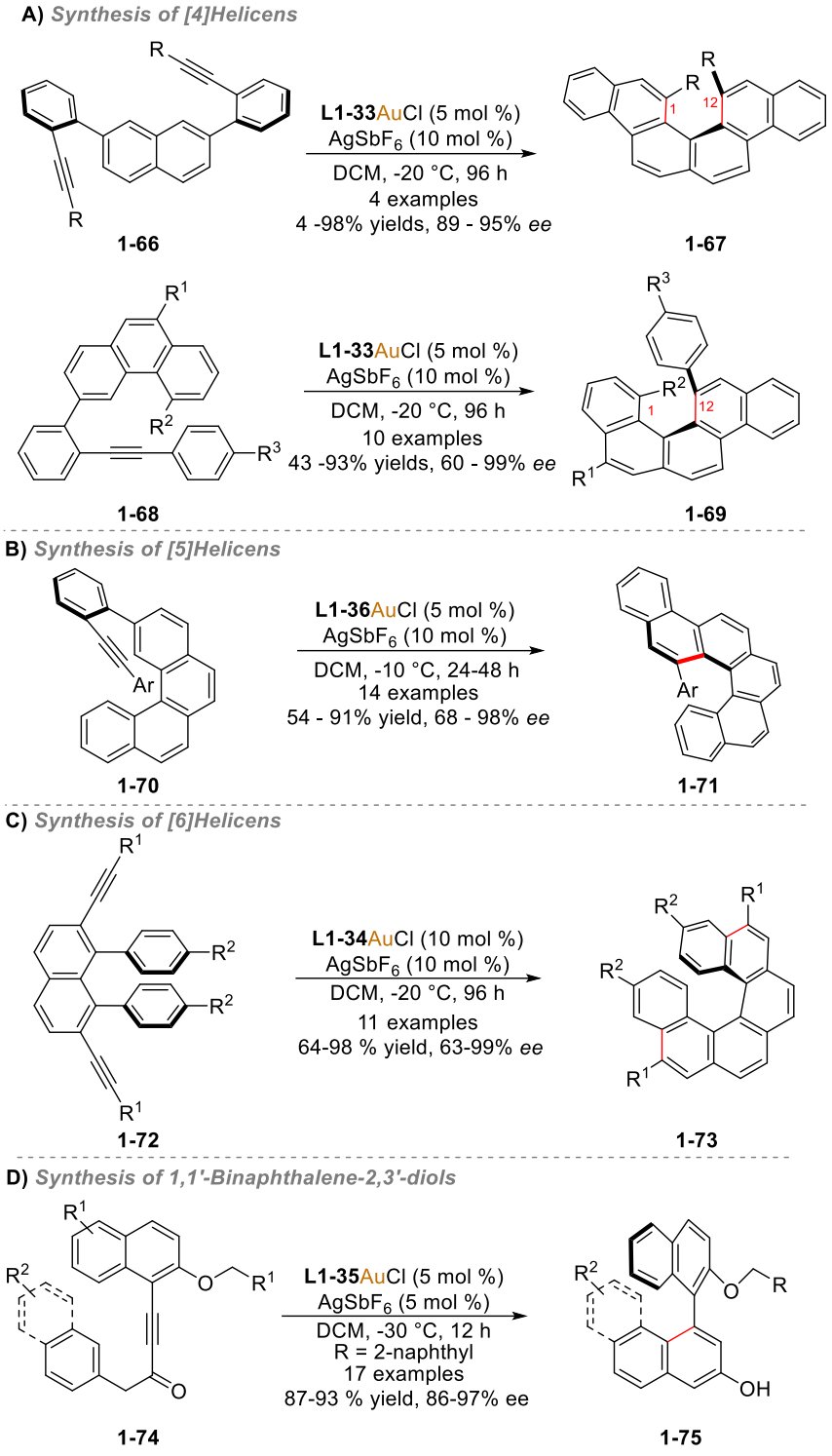
Scheme 12. Design of Chiral α-Cationic Phosphonites Ligands



Since 2014, the group of Alcarazo began the journey of developing a library of chiral α-cationic phosphonites ligands derived from TADDOL or BINOL (Scheme 12). [42-45] In this ligand design, the enantioinduction is achieved via well-precedented TADOL, or BINOL derived moieties, which is readily available to access and modify, and has well-documented in enantioselective gold(I) catalysis.[46-49] An imidazolium unit is introduced to

increase the π-acceptor ability of the ligand and, in turn, the π-acidity of the corresponding gold complexes.

Scheme 13. Application of Chiral α-Cationic Phosphonites Ligands



[4]helicene is typically configurationally unstable under ambient conditions because of the low activation energy of racemization. [50] However, installing appropriate substituents at the 1 and 12 positions [4]helicene can dramatically increase the energy barrier due to the steric clash and thus fix the configuration of [4]helicene. In 2020, Alcarazo described the first enantioselective preparation the 1,12-disubstituted [4]helicenes **1-67** or **1-69** via intramolecular hydroarylation of diyne **1-66** or **1-68** using the chiral α-cationic phosphonite **L1-33** as the ligand (Scheme 13A).[44] The synthetic utility is demonstrated by accommodating the [4]helicens with the different substitution patterns.

The parent [5]helicene is also not configurationally stable, and its racemization occurs at room temperature.[51] Using the same strategy, the configuration of [5]helicene is locked by installing substituents at the 1 position. With the BINOL-derived cationic phosphonite **L1-36** as the ligand, the alkyne **1-70** were converted into the 1-(aryl)benzo[5]carbohelicene **1- 71** in moderate and high yields and with good to excellent enantioselectivities under gold catalysis (Scheme 13B).[43]

[6]helicene is the smallest helicene with configuration stability, albeit the racemization still occurs at high temperatures [$t_{1/2}$(*rac*) = 48 min at 205 ºC]. The chiral α-cationic phosphonite **L1-34** enables the gold-catalyzed intramolecular hydroarylation of cyclization of the diyne **1-72** to afford the [6]helicene **1-73** in moderate to good yields and with medium to excellent enantioselectivities (Scheme 13C).[45] Notably, no catalytic activity was observed using the structurally related phosphoramidite gold complex under the same reaction conditions, thus demonstrating the essential rule of the imidazolium moiety. In addition to the preparation of enantiopure carbohelicenes, chiral α-cationic phosphonites

the ligand **L1-35** was also utilized in the highly atroposelective synthesis of the 1,1'-binaphthalene-2,3'-diols **1-75** from the alkynones **1-74** (Scheme 13D).[42]

1.4. Reference

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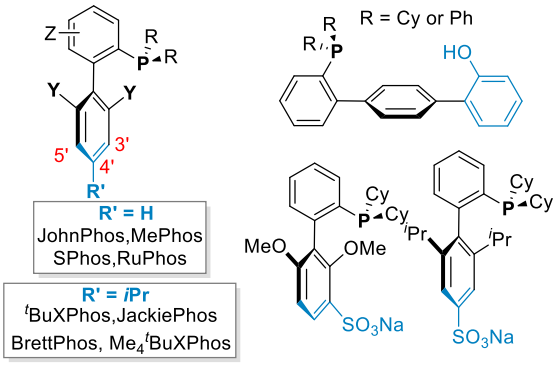
2. Design of Bifunctional Biaryl-2-yl Phosphine Ligands

2.1. Ligand Design Consideration

Currently, most biaryl-2-yl-phosphine ligands used in gold(I) catalysis are directly adopted from palladium catalysis. These ligands were initially designed to facilitate the chemistry of square-planar Pd(II) complexes and hence are hardly optimal for Au(I) catalysis, in which the catalysts display distinct linear geometry. As shown in Figure 4, most reported biphenyl-2-ylphosphine ligands are barely functionalized at the C3', C4', and C5' positions. The only exceptions are a sulfonate group for increasing catalyst aqueous solubility[1] and a phenol moiety for regioselective Pd-catalyzed Kumada coupling.[2]

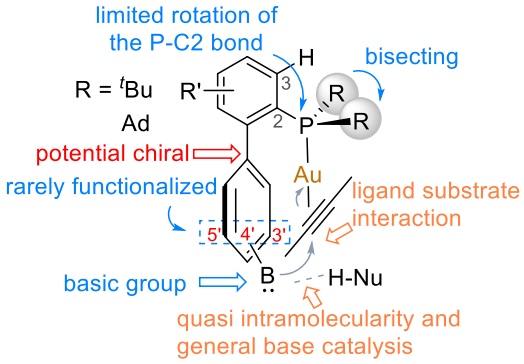
Figure 4. Known Biaryl-2-yl-Phosphine Ligands



Starting from 2014, we embarked on the journey to design new biaryl-2-yl-phosphine ligands tailored to the linear gold(I) structure (Figure 5). To begin with, we installed a bulky group (*tert*-butyl or 1-adamantyl) on the phosphorus to increase the rotation barrier and restrict the free rotation of the P-C2 bond. Thus, the linear P-Au-alkyne centroid axis should be parallel to the ligand pendant phenyl ring, and the gold-coordinated C-C triple bond would lie proximal to C3', C4', and C5' positions. Next, C3', C4', and C5'

positions are functionalized with a basic group (i.e., **B**), which can be an amide, aniline or amino group to interact with the substrate or the approaching nucleophile and enable new transformations, enhance reaction efficiency, and/or achieve unprecedented selectivity.

Figure 5. Biphenyl-2-yl-Phosphine with Remote Basic Group

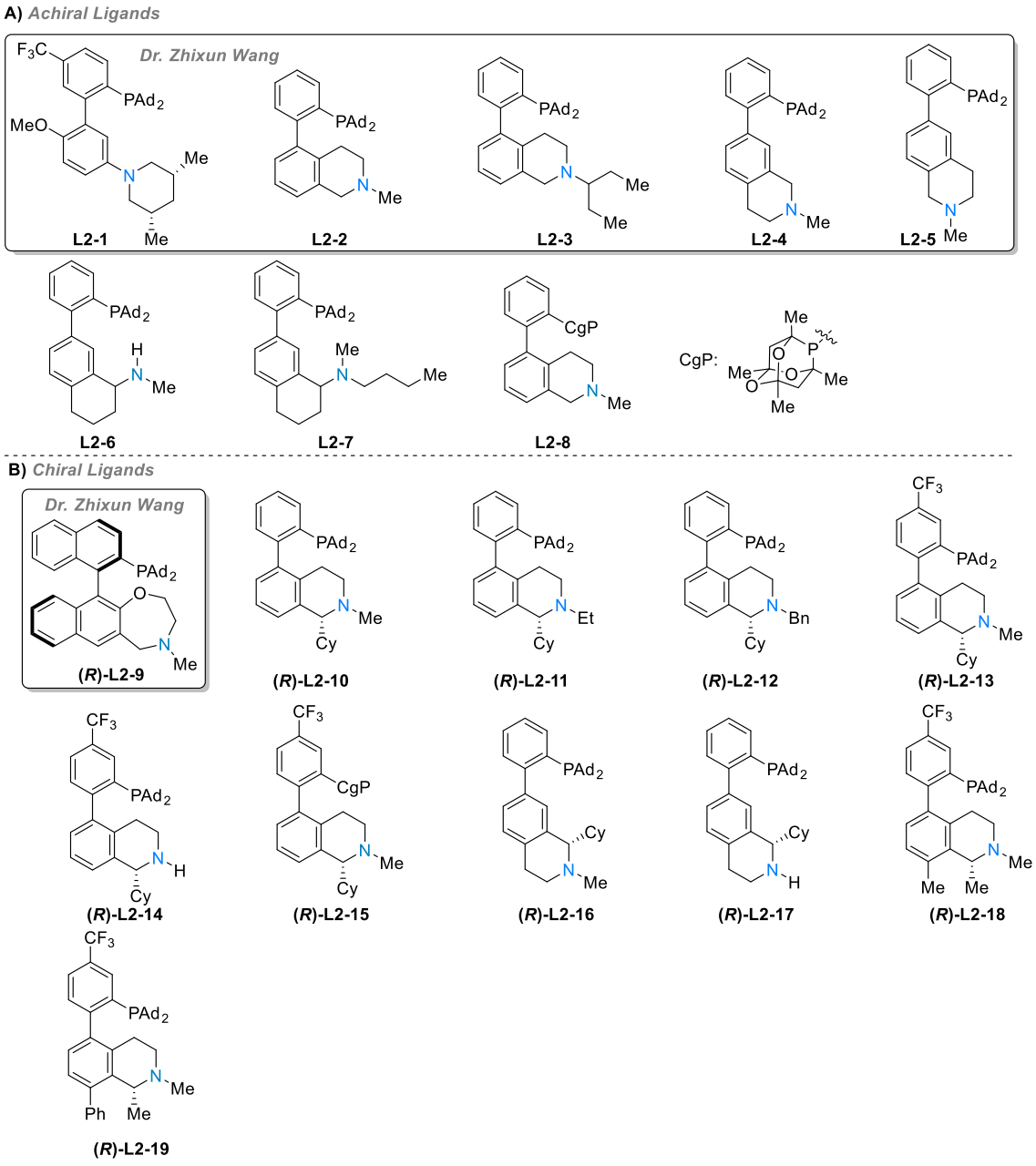


For the past eight years, the Zhang group has prepared a series of bifunctional biaryl-2-yl-phosphine ligands that can be divided into two subtypes: the amide-functionalized ligands for accelerated nucleophilic addition and the amine-functionalized ligands for unprecedented deprotonative processes. Amide-functionalized ligands have been discussed in **Chapter 1.3.1**, and this chapter will only focus on the amine-functionalized ligands.

As shown in Figure 6A, members of Zhang group synthesized a series of achiral ligands (**L2-1** – **L2-8**) featuring the nitrogen at different positions.[3, 4] In addition, the steric hindrance around nitrogen is tuned to achieve regioselectivity. Moreover, the di-adamantyl phosphoryl group of the ligands was replaced by the cage phosphine (**L2-8**) to increase the gold(I) π-acidity. The reactivities of these achiral ligands are discussed in **Chapter 2.2**. Built on these achiral ligands, we designed two types of chiral ligands with either an axial chirality or a central chirality and will be discussed them in **Chapter 2.3.** The application of these chiral ligands will be discussed in **Chapter 3, 4, 5, and 6**. Notably, **L2-1 - L2-5**

and **(*R*)-L2-9** were developed by the previous group member Dr. Zhixun Wang and the other ligands in this library were developed by myself.

Figure 6. Aniline/Amine-Functionalized Bifunctional Phosphine Ligands

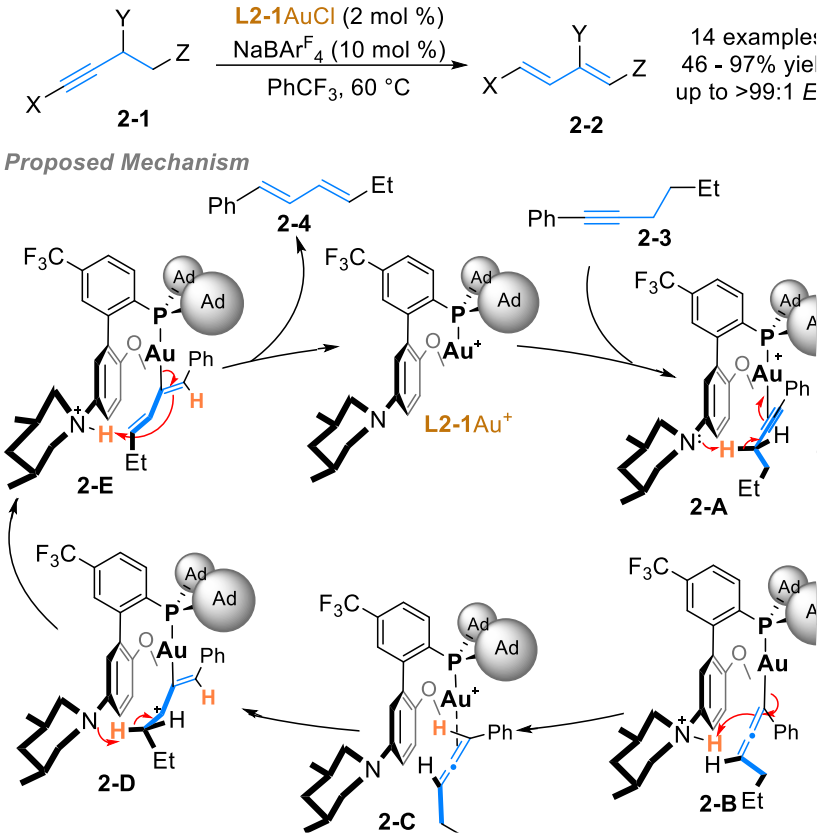


2.2. Application of Achiral Amine-Functionalized Bifunctional Phosphine Ligands

2.2.1. Isomerization of alkynes into 1,3-dienes

In 2014, the previous group member, Dr. Zhixun Wang, demonstrated the first implementation of this ligand design (Scheme 14).[4] Using only 2 mol % piperidine-functionalized **L2-1** as the ligand, internal alkynes can be isomerized into 1,3-dienes with good to excellent *E*-selectivities. Using 1-phenyl-1-hexyne (**2-3**) as an example, the proposed mechanism begins with the *soft propargylic deprotonation* of a weakly acidic propargylic proton (*p*Ka > 30) by the aniline moiety of the ligand (*p*Ka ~4), as depicted in the structure **2-A** following an orthogonal process. This transformation necessitates the synergy between ligand nitrogen and cationic gold. The allenyl gold intermediate **2-B** generated after propargylic deprotonation goes through *ipso*-protodeauration to give the allene **2-C**, which is followed by its activation by the cationic gold to form the allenyl cation **2-D**. The second deprotonation of γ-proton by the same aniline moiety generates 1,3-diene (**2-4**) upon protodeauration. The overall transformation involves gold-ligand cooperation in two proton transfer processes. A DFT study[5] largely supports the proposed mechanism, and additionally reveals that the *soft propargylic deprotonation* follows a *syn-periplanar* process.

Scheme 14. Ligand-Enabled Isomerization of Alkyne into 1,3-Diene

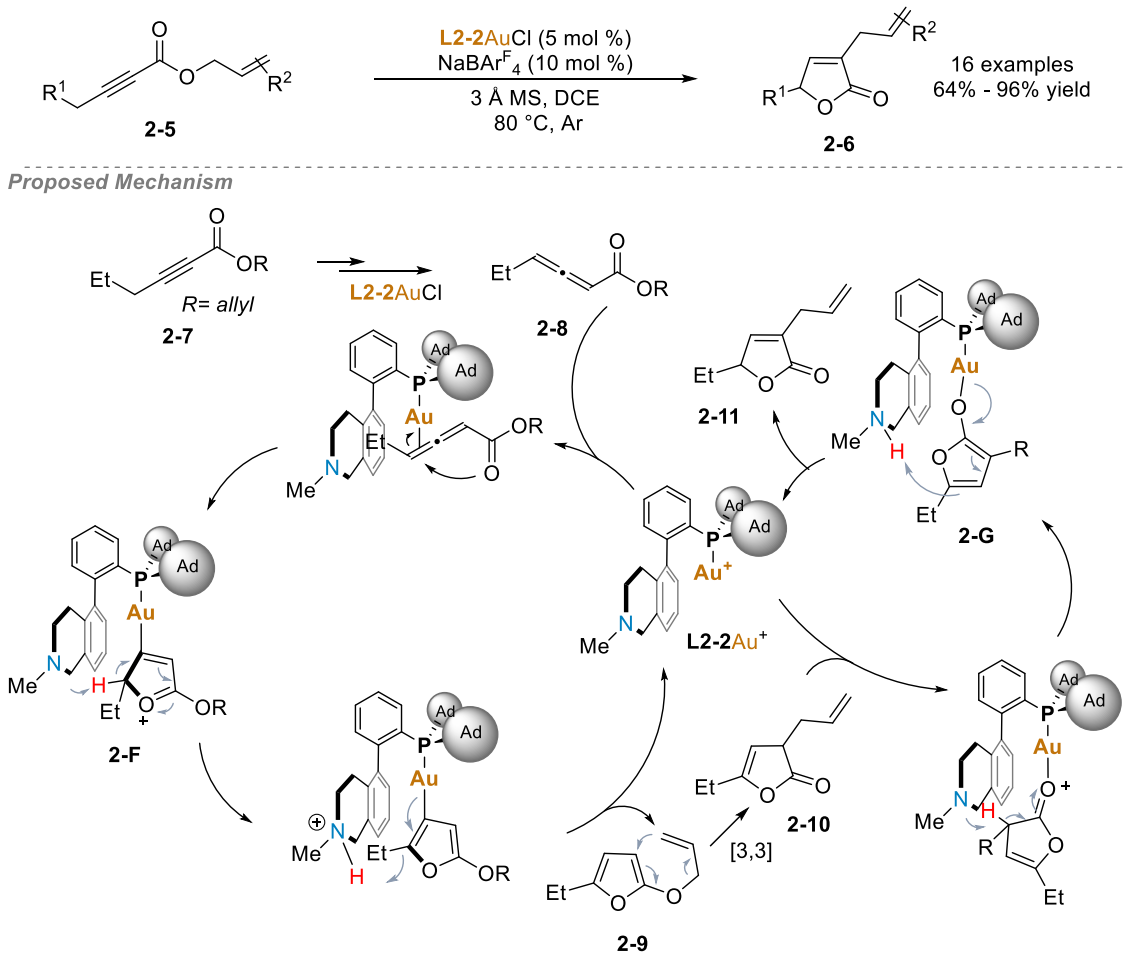


2.2.2. Synthesis of α-Allylbutenolides

In 2018, our group reported the cycloisomerization of allylic alkynoate to α-allylbutenolides with good to excellent yields using the tertiary-amino functionalized **L2-2** as the ligand (Scheme 15). [6] Using allyl hex-2-ynoate (**2-7**) as an example, mechanically, it undergoes the first proton transfer process as depicted in Scheme 15 to generate the allene intermediate **2-8**. Instead of further isomerization to 1,3-dienes, the *5-endo-trig* cyclization is favored because the electron-withdrawing ester group destabilized the formation of the allylic cation intermediate **2-D**, leading to the formation of the cationic species **2-F**. The γ-deprotonative aromatization of **2-F** and *ipso*-protodeauration delivers the allyloxyfuran **2-9**, which undergoes the [3,3]-sigmatropic rearrangement to form the unconjugated

butenolide **2-10**. Promoted by the same catalyst, the unconjugated butenolide **2-10** goes through α-deprotonation to generate alkoxyfuran intermediate **2-G**, followed by γ-protonation to afford α-allyl alkynoate **2-11**. The overall process involves three gold-ligand cooperative proton migrations.

Scheme 15. Synthesis of Butenolides from Allyl Alkynoates

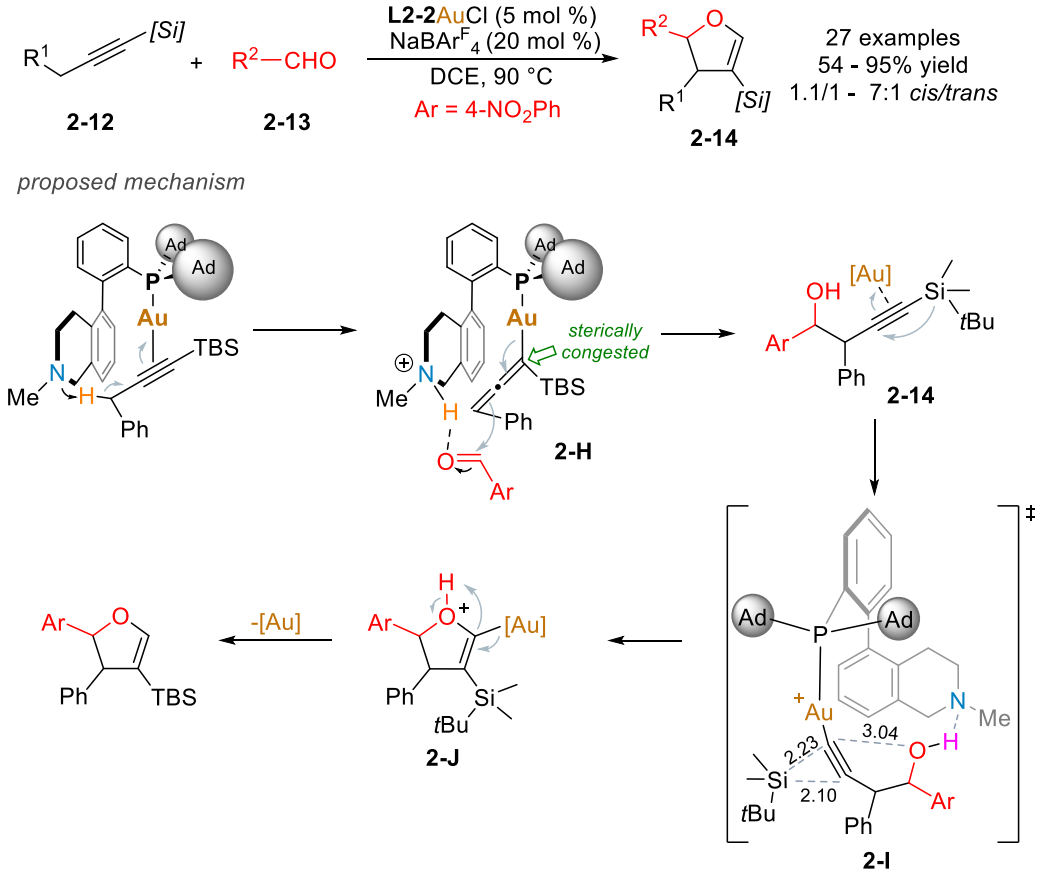


2.2.3. Nucleophilic Reaction of Catalytically Generated σ-Allenylgold

In 2019, our group reported that the facile *ipso*-protodeauration of the σ-allenylgold, as depicted in Scheme 14, could be slowed down by installing a bulky silyl group, e.g., a TBS group, at the alkyne terminus.[7] The allenyl gold intermediate **2-H** generated from the *soft propargylic deprotonation* can serve as a nucleophile to intermolecularly attack aldehyde

and deliver the homopropargylic alcohol **2-14** intermediate. Its subsequent gold-catalyzed cyclization entails an unexpected silyl migration to afford the 3-silylated dihydrofuran (**2-14**) in moderate to high yields and with a moderate *cis/trans* ratio (Scheme 16). The reaction scope is relatively limited. The aldehyde needs to be activated with electron-withdrawing groups and without α-C(sp^3)-H. A π-substituent at the propargylic position is necessary for the alkynes. The DFT calculation suggests the cyclization and the silyl migration go through a concerted process as depicted in **2-I**, and the bulky silyl group, as well as the tertiary amino group of the ligand, play critical roles during this transformation.

Scheme 16. Intermolecular Propargylation of Aldehyde and Silyl-Migrative Cyclization

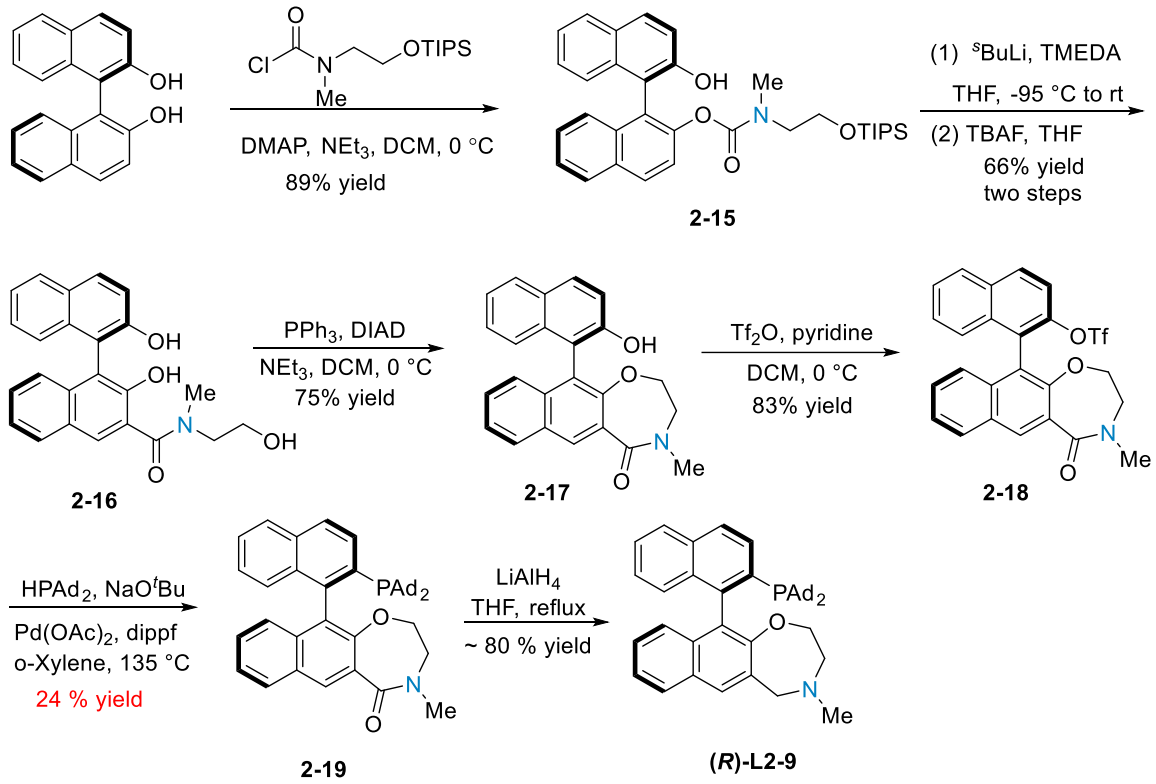


2.3. Design and Synthesis of Chiral Amine-Functionalized Bifunctional Phosphine Ligands

As we described in ***Chapter 2.2***, the achiral ligand **L2-2** has demonstrated versatile synthetic utility in the gold-ligand cooperation chemistry. In 2018, we began the journey to design the chiral version of the **L2-2** ligand for harvesting the great potential of utilizing gold-ligand cooperation in asymmetric transformations.

Dr. Zhixun Wang achieved our first foray into the chiral ligand design by utilizing axial chirality. As shown in Scheme 17, the synthesis started with acylation of (*R*)-BINOL to afford the carbamate (**2-15**) in 89% yield. The ^{s}BuLi-promoted Snieckus−Fries rearrangement[8] of the carbamate (**2-15**) and the deprotection of the TIPS group gave binol (**2-16**) in 66% overall yield. The ring closure was achieved via Mitsunobu reaction to afford 7-membered ring binol (**2-17**) in 75% yield, which then went through triflation to give the triflate (**2-18**) in 83% yield. The installation of PAd_2 using palladium-catalyzed cross-coupling reactions turned out to be very inefficient. The reaction was sluggish, and a high reaction temperature was required. The highest yield we can achieve is 24% yield with low conversion and hydration of triflate. Reduction of the amide (**2-19**) finished the synthesis of **(*R*)-L2-9** in 80% yield. Overall, we synthesized **(*R*)-L2-9** in 7 steps and 7% yield. At that time, we believed the low yield in the cross-coupling step was caused by the steric congestion around a stable chiral axis. Recently, after the attempts of our group member Ke Zhao, we achieved the Pd-catalyzed cross-coupling reaction in high yield, i.e., ~80% yield, by replacing the triflate with bromide.

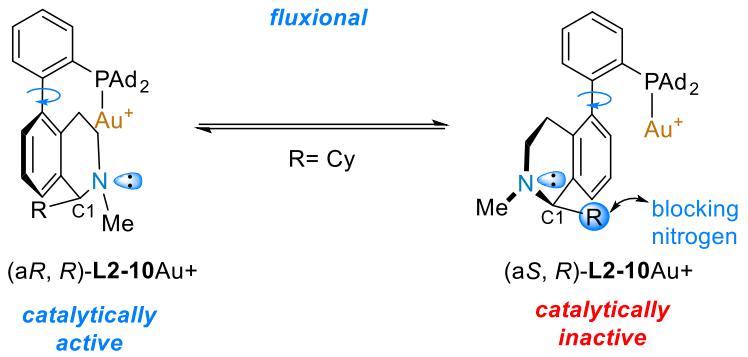
Scheme 17. Synthesis of the Chiral Version of L2-2 ligand Using Axial Chirality



Due to the low yield in the installation of the bulky PAd_2 group, we envisioned a new ligand design featuring central chirality, which is depicted in Figure 7. The axial fluxional chiral ligand **L2-10** features a chiral center at the C1 position of the tetrahydroisoquinoline ring.[9] The bulky *R* group in (*aR*, *R*)-**L2-10** would largely not affect the catalytic activity of the gold complex as it points away from the catalytic site. On the other hand, the axial rotation of (*aR*, *R*)-**L2-10** by 180˚ would afford (a*S*, *R*)-**L2-10**, which has the R group pointing to the catalytic site. A bulky and/or pseudo axially oriented R group would provide sufficient steric shielding of the nitrogen lone pair electrons to block its participation in the key deprotonation step. As such, similar to the stable axial chirality in (*R*)-**L2-9**, this center chirality could also make the remote tertiary amino group only available for deprotonation when it is behind the biphenyl framework. Compared with the

previous design, this new design increases the efficiency in installing PAd_2 due to the decrease in steric congestion and offers flexability for ligand modification.

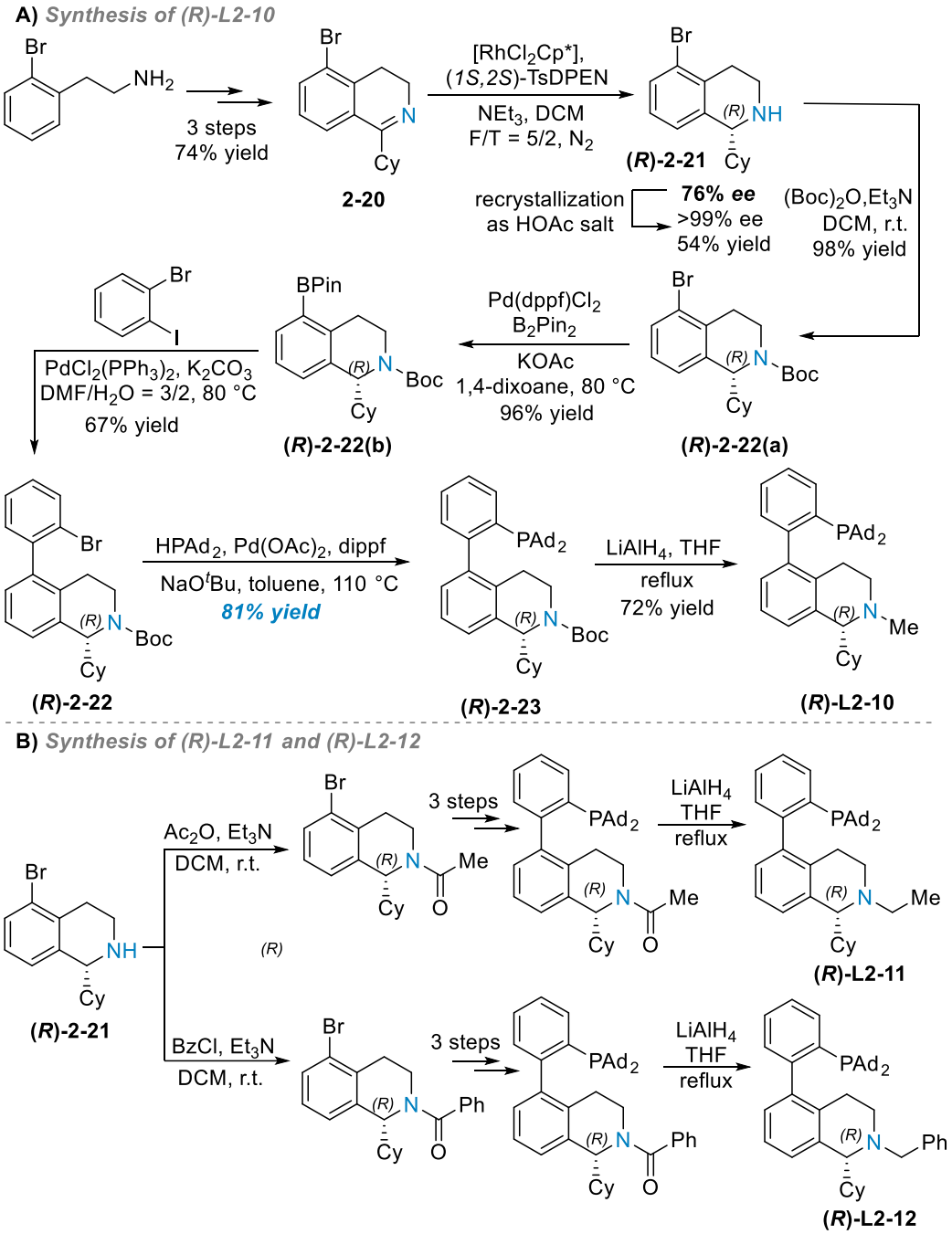
Figure 7. Design Chiral Version of L2-2 Ligand Using Central Chirality



As shown in Scheme 18A, the ligand synthesis of (*R*)-**L2-10** commenced with a straightforward 3-step, two-pot preparation of the dihydroisoquinoline **2-20** in 74% yield.[10] The Noyori asymmetric reduction of **2-20** yielded the tetrahydroisoquinoline **(*R*)-2-21** in quantitative yield and 76% *ee*. Double recrystallizations of the HOAc salt of **(*R*)-2-21** increased the enantiopurity of **(*R*)-2-21** to >99% ee, and the overall yield was a respectable 54%. The cross-coupling precursor **(*R*)-2-22** was obtained in a 3-step routine sequence, i.e., Boc group protection, Miyaura borylation, and Suzuki coupling, from **(*R*)-2-21** in a 63% combined yield. The previously challenging installation of the PAd_2 group was, as anticipated, uneventful, and the phosphine **(*R*)-2-23** was isolated in 81% yield. The chiral ligand **(*R*)-L2-10** was prepared from **(*R*)-2-23** through reduction of Boc group in 72% yield.

As shown in Scheme 8B, the chiral ligand **(*R*)-L2-11** and **(*R*)-L2-12** were prepared in a similar way from **(*R*)-2-21**. The acetyl group and benzoyl group were installed on the secondary amine **(*R*)-2-21** to access **(*R*)-L2-11** and **(*R*)-L2-12** respectfully.

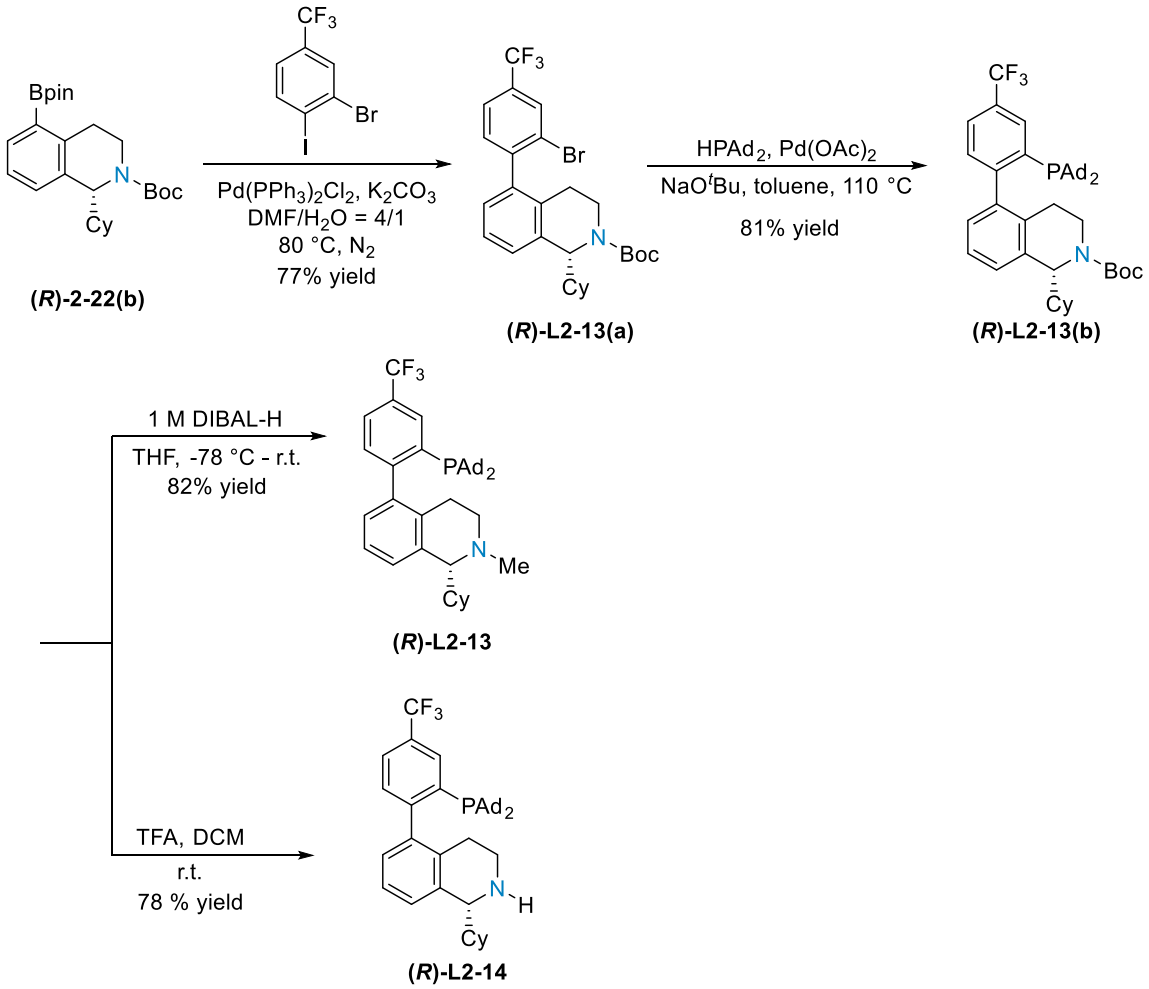
Scheme 18. Synthesis of Chiral Ligand (*R*)-L2-10, (*R*)-L2-11, and (*R*)-L2-12.



To decrease the σ-donating ability of phosphine ligand and further increase the π-acidity of the gold complex, the chiral ligand **(*R*)-L2-13** was synthesized featuring an additional electron-withdrawing CF_3 group at the meta position of the benzene ring (Scheme 19). The synthesis of **(*R*)-L2-13** started with the Suzuki coupling between **(*R*)-2-**

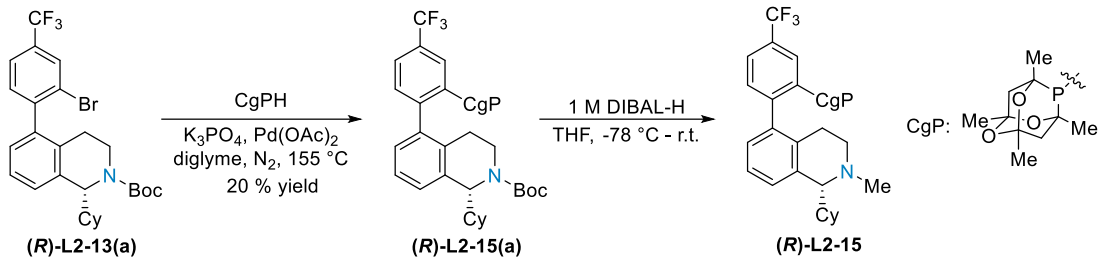
22(b) and 2-bromo-1-iodo-4-(trifluoromethyl)benzene to afford biphenyl **(*R*)-L2-13(a)** in 77% yield, followed by the installation of PAd_2 to give **(*R*)-L2-13(b)** in 81% yield. Notably, reducing the Boc group using $LiAlH_4$ under reflux in THF also led to the reduction of the trifluoromethyl group. Thus, a milder condition, i.e., 1 M DIBAL-H in THF, -78 ˚C -r.t., was used to circumvent this problem, affording chiral ligand **(*R*)-L2-13** in 82% yield.

Scheme 19. Synthesis of Chiral Ligand (*R*)-L2-13 and (*R*)-L2-14.



To further study the influence of different subsistuents on ligand basic nitrogen, we also synthesized the chiral ligand **(*R*)-L2-14** with a secondary amine in 78% yield from deprotecting the Boc group of **(*R*)-L2-13(b)** (Scheme 19).

Scheme 20. Synthesis of Chiral Ligand (*R*)-L2-15

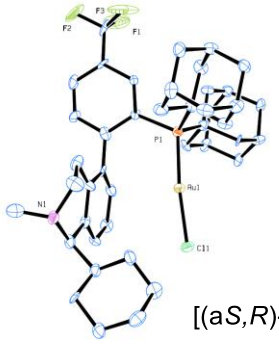


Phospha-adamantane (CgPH) was first reported by Buckler and Epstein in 1961.[11] They found that this cage structure could be accessed via acid-catalyzed condensation between PH_3 and acetylacetone. This adamantane cage offers unique features such as strong steric hindrance, rigidity, and phosphonite-like electronic properties.[12] Thus, we thought CgP ligand **(*R*)-L2-15** could further increase the π-acidity of the corresponding gold complex without compromising the steric hindrance. To this end, we synthesized **(*R*)-L2-15** in two steps from **(*R*)-L2-13(a)** (Scheme 20). To note, the Pd-catalyzed cross-coupling reaction to install CgPH is relatively inefficient because of the high reaction temperature and low yield. In addition, the product **(*R*)-L2-15(a)** was co-eluted with the solvent diglyme in the column separation.

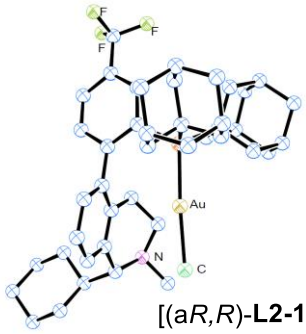
Notably, the ^{1}H, ^{13}C, and ^{31}P NMR spectra of the **(*R*)-L2-10**AuCl exhibited two sets of signals and hence revealed that the half time of biphenyl axis rotation is longer than the NMR time scale. Using the ligand analog **(*R*)-L2-13** with an additional CF_3 group, we managed to separate the two pre-catalyst atropisomers because they form crystals of different shapes and could be manually separated. X-ray diffraction studies confirmed their structures (Figure 8). In the case of [(a*S*, *R*)-**L2-13**]AuCl, the cyclohexyl group clearly intrudes into the space occupied by Cl and should block the binding of π-substrates during catalysis. In the case of [(a*R*, *R*)-**L2-13**]AuCl, the cyclohexyl group points away from the

metal. Though an inversion of the pyramidal nitrogen in [(a*R*, *R*)-**L2-13**]AuCl is needed to point its lone pair electrons to gold, and such a process should have an easily surmountable barrier.

Figure 8. X-ray Diffraction of [(a*S*, *R*)-L2-13]AuCl and [(a*R*, *R*)-L2-13]AuCl



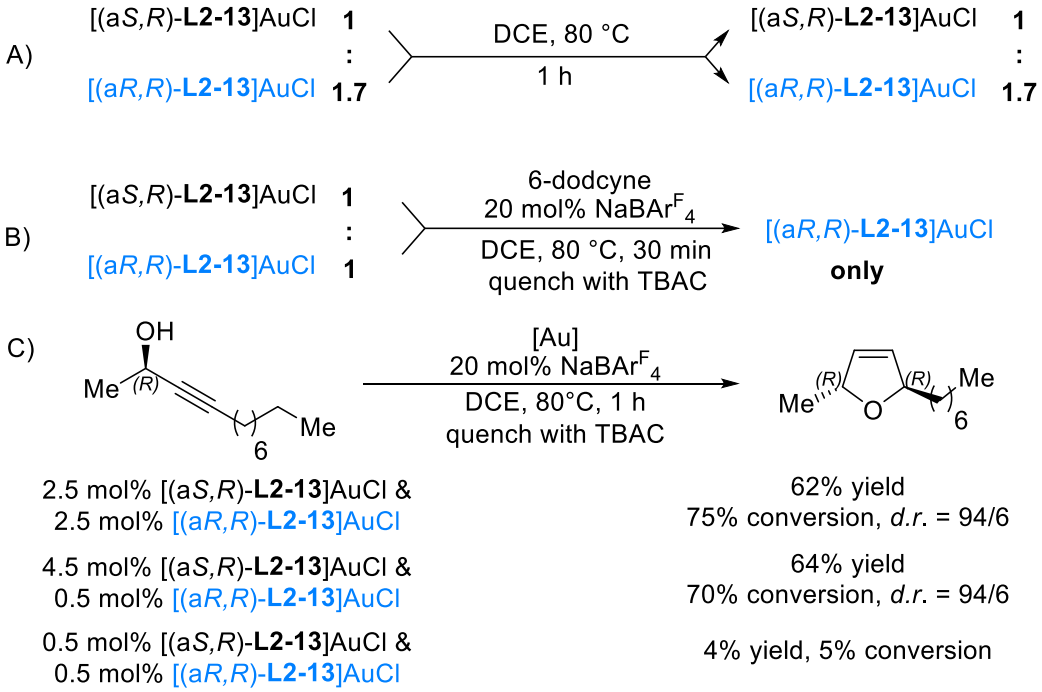
[(a*S*,*R*)-**L2-13**]AuCl



[(a*R*,*R*)-**L2-13**]AuCl

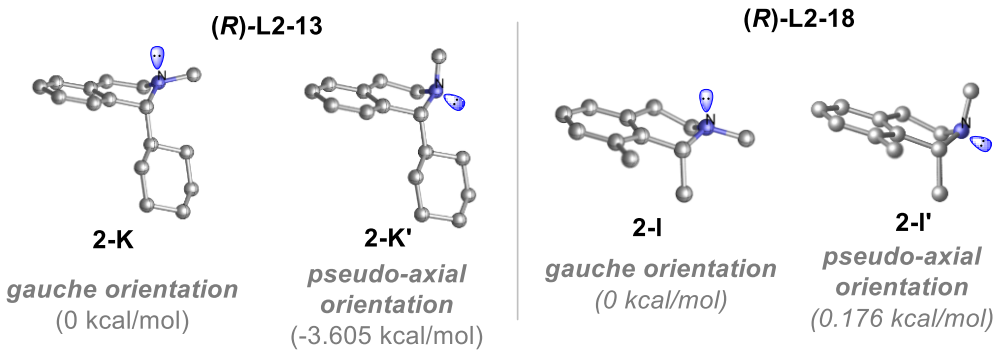
As shown in Scheme 21A, when a 1:1.7 mixture of [(a*R*, *R*)-**L2-13**]AuCl and [(a*S*, *R*)-**L2-13**]AuCl was heated at 80 ˚C in DCE for 1 h, the ratio did not change, revealing that the ligand axial configuration is stable when ligated to AuCl. Interestingly, as shown in Scheme 21B, a 1:1 mixture of [(a*R*, *R*)-**L2-13**]AuCl and [(a*S*, *R*)-**L2-13**]AuCl was completely converted into [(a*R*, *R*)-**L2-13**]AuCl when a solution of it in DCE was first treated with $NaBAr^F_4$, i.e., a chloride abstractor, and 6-dodecyne, i.e., a cationic gold stablizater, then heated at 80 ˚C and at last quenched with tetrabutylammonium chloride. This experiment revealed that the biphenyl axis of cationic (*R*)-**L2-13**Au^+ can freely rotate at 80 ˚C and moreover, [(a*R*, *R*)-**L2-13**]Au^+ with the requisite axial configuration for our chemistry is thermodynamically much favored. This result suggests that the existence of stable pre-catalyst axial isomers is inconsequential. This conclusion is nicely supported by the experiments shown in Scheme 21C, where the conversions and the yields correlate to the total amounts of (*R*)-**L2-13**AuCl instead of that of [(a*R*, *R*)-**L2-13**]AuCl alone.

Scheme 21. Study of the Axial Chirality of Gold Catalysts



As indicated in the X-ray structure of [(a*R*, *R*)-**L2-13**]AuCl, the deprotonation process requires overcoming an energy barrier to inverse the pyramidal nitrogen so that its lone pair electrons points to gold. As shown in Figure 9, our DFT calculation of the tetrahydroisoquinoline portion of **(*R*)-L2-13** at M06-2x/cc-pVDZ level revealed the pseudo-axial orientation **2-K'** is 3.605 kcal/mol less stable than the gauche orientation **2-K**.[13] To lower the energy battier and make the exposed conformer energetically less disfavored, we envisioned that minimizing the cyclohexyl group into a methyl group would decrease the destabilizing gauche interaction. To maintain a pseudo-axial orientation of the methyl group, we installed an 8-methyl group in order to enhance the $A^{1,3}$-strain when it is pseudo equatorially oriented. To our delight, our DFT calculation confirmed that two conformations of **(*R*)-L2-18**, i.e., **2-I** and **2-I'**, are energetically nearly equal.

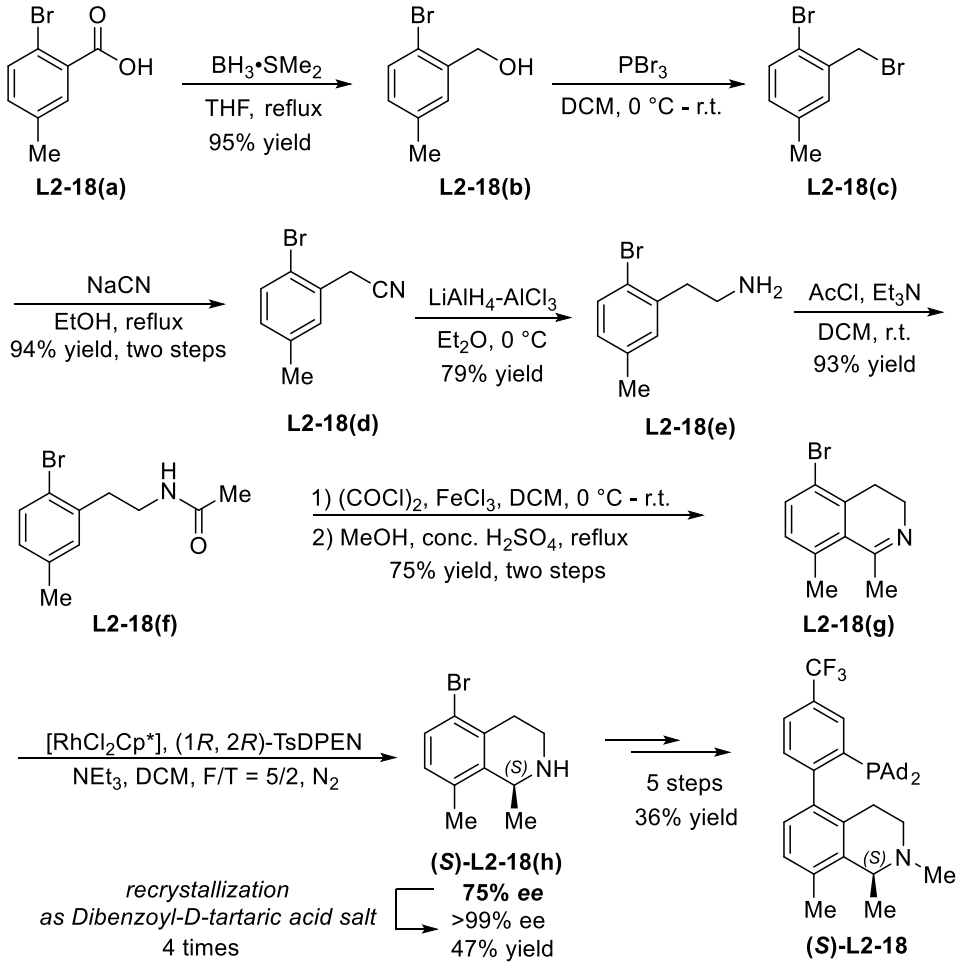
Figure 9. Ligand Design Iteration



To this end, we commended the journey to synthesize chiral ligand **(*S*)-L2-18** (Scheme 22). The synthesis began with the reduction of commercial available benzoic acid **L2-18(a)** into benzyl alcohol **L2-18(b)** in 95% yield, followed by bromination of alcohol and SN2-type cyanation to afford benzyl cyanide **L2-18(d)** in 94% overall yield. A mixture of lithium aluminum hydride and aluminum trichloride reduced benzyl cyanide **L2-18(d)** at room temperature in ether solution, affording primary amine **L2-18(e)** in 79% yield. The primary amine **L2-18(e)** was converted into dihydroisoquinoline **L2-18(g)** via acylation, Friedel-Crafts annulation, and acid-catalyzed elimination. The Noyori asymmetric reduction of **L2-18(g)** yielded the tetrahydroisoquinoline **(*S*)-L2-18(h)** in quantitative yield and 75% ee. To our surprise, the HOAc salt of **(*S*)-L2-18(h)** has good solubility in common solvents such as Et_2O, EtOAc, DCM, and MeOH. In addition, adding hexane into the salt solution could not precipitate the salt out. After screening different acids, we chose to use dibenzoyl-D-tartaric acid because it has good solubility in EtOAc while the corresponding salt could hardly dissolve in EtOAc, making the salt crash out of the solution easily. After four times recrystallization of the dibenzoyl-D-tartaric acid salt of **(*S*)-L2-18(h)** in MeOH/*i*PrOH/hexane solution, the *ee* value of **(*S*)-L2-18(h)** was enriched to 99% yield, and the overall yield is 47%. Followed the similar 5 steps transformation in the synthesis

of ligand **(*R*)-L2-10**, **(*S*)-L2-18(h)** was transformed into the chiral ligand **(*S*)-L2-18** in 36% overall yield.

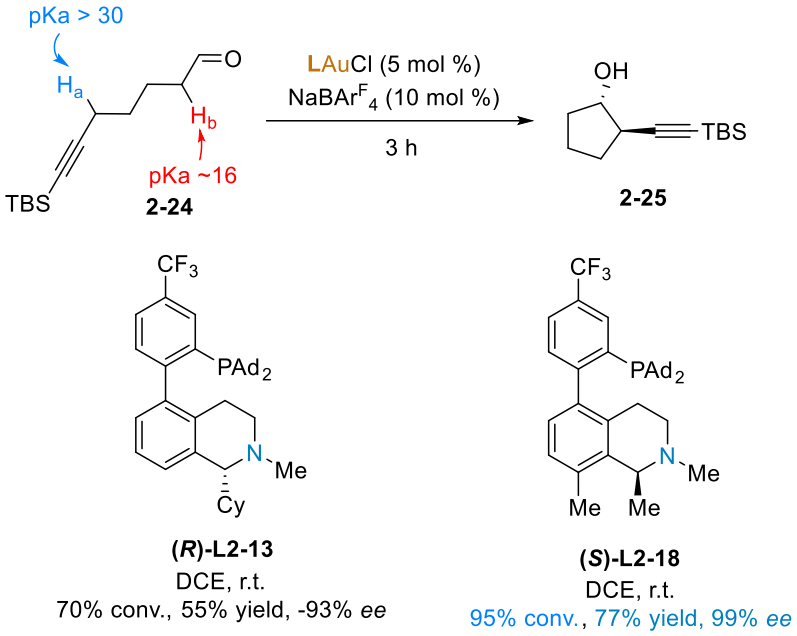
Scheme 22. Synthesis of Chiral Ligand (*S*)-L2-18



As discussed in Chapter 2.2.3, we discovered intermolecular propargylation of aldehydes via a nucleophilic σ-allenyl gold intermediate. Two years later, we reported the intramolecular version of this transformation. As depicted in Scheme 23, TBS-terminated hept-6-ynal **2-24** went through *soft propargylic deprotonation* to generate nucleophilic σ-allenyl gold intermediate, followed by intramolecular cyclization with an aldehyde to form the *trans*-ring-fused homopropargylic alcohol **2-25**. Of note, cooperative deprotonation of propargylic C-H bonds by the mild basic ligand tertiary amine played a key role in the

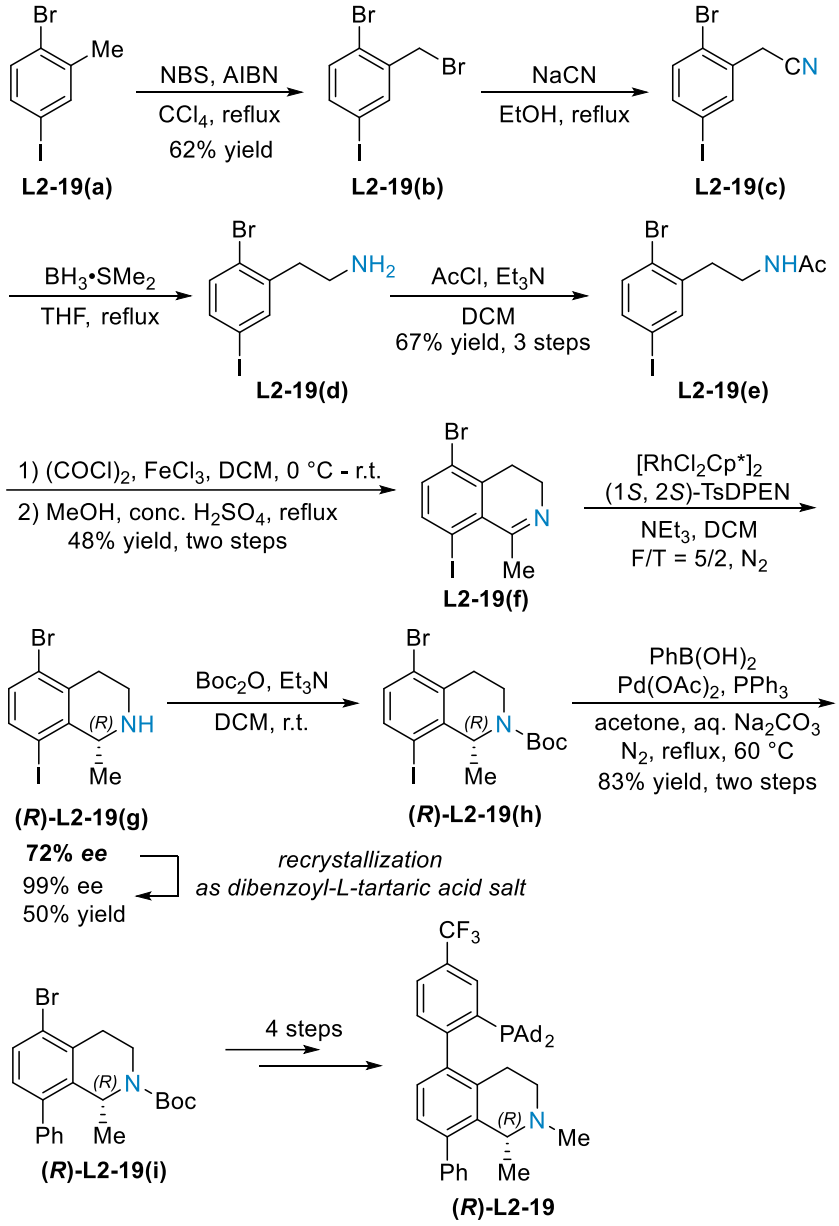
chemoselective deprotonation of the propargylic H_a (*pKa* >30) over the aldehydic Hb (*pKa* ~16). With **(*R*)-L2-13** as the catalyst, the cyclization gave **2-25** in 70% conversion, 55% yield, and -93% *ee*. To our delight, our newly designed ligand **(*S*)-L2-18** led to a higher conversion (95%), a better yield of **2-25** (77%), and an excellent *ee* (99%).

Scheme 23. Intramolecular Asymmetric Propargylation of Aldehydes



In addition to the methyl group, we installed a phenyl group at the 8-position of the tetrahydroisoquinoline motif and generated chiral ligand **(*R*)-L2-19** (Scheme 24). The synthesis of this ligand followed a very similar route of **(*S*)-L2-18** synthesis. 1-Bromo-4-iodo-2-methylbenzene **L2-19(a)** was used as the starting material, and the phenyl group was installed in the late-stage via Suzuki coupling. Moreover, with an iodide group at the 8-position, this synthesis offers expedient access to other substituents via Pd-catalyzed cross-coupling reaction and enriches our ligand library.

Scheme 24. Synthesis of Chiral Ligand (*R*)-L2-19



2.4. Experimental Section

General Information

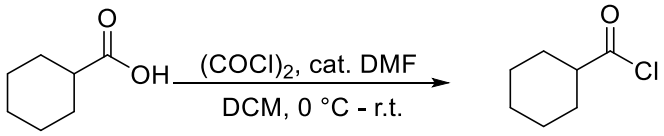
Ethyl acetate (ACS grade), hexanes (ACS grade), dichloromethane (ACS grade) were purchased from Fisher Scientific and used without further purification. ACS grade 1,2-dichloroethane was purchased from Acros Organics and used directly. Commercially

available reagents were used without further purification. Reactions were monitored by thin-layer chromatography (TLC) using Silicycle precoated silica gel plates. Flash column chromatography was performed over Silicycle silica gel (230-400 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 400 MHz, 500 MHz and 600 MHz spectrometers using residue solvent peaks as internal standards ($CDCl_3$, ^{1}H: 7.26 ppm; ^{13}C: 77.00 ppm. CD_2Cl_2, ^{1}H: 5.32 ppm; ^{13}C: 53.84 ppm) (multiplicity: s = singlet, d = doublet, t = triplet, q = quadruplet, quint = quintuplet, sext = sextuplet, sept = septuplet, oct = octuplet, non = nonuplet, m = multiplet).^{31}P NMR spectra were recorded on Agilent 400MHz spectrometer calibrated by phosphoric acid peak (H_3PO_4, ^{31}P: 0.00 ppm). ^{19}F NMR spectra were recorded on an Agilent 400MHz spectrometer calibrated by trifluoroacetic acid peak (CF_3COOH, ^{19}F: -76.55 ppm). Mass spectra were recorded with Waters micro mass ZQ detector using the electrospray method.

Synthesis of Ligands and Gold Catalysts

Synthesis of 5-bromo-1-cyclohexyl-1,2,3,4-tetrahydro-isoquinoline (2-21)

Cyclohexanecarbonyl chloride [2-20(b)]

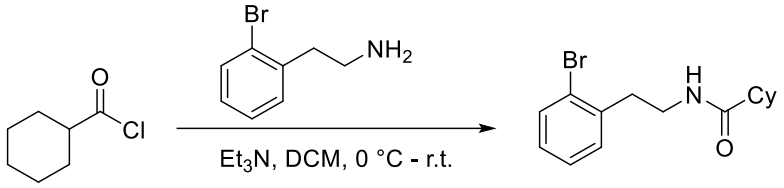


2-20(a) **2-20(b)**

To a solution of cyclohexanecarboxylic acid (16.92 g, 132 mmol) in 160 mL DCM solution at 0 ℃, 1-2 drops of DMF were added. Oxalyl chloride (14.4 mL, 168 mmol) was slowly added to the reaction mixture. After adding oxalyl chloride, the mixture was allowed to warm up and stir at room temperature for 5 h. Then the mixture was concentrated to

remove the solvent and excess oxalyl chloride to afford the crude cyclohexanecarbonxyl chloride, which was used in the next step without purification.

***N*-[2-(2-bromo-phenyl)ethyl]cyclohexanecarboxamide [2-20(c)]**

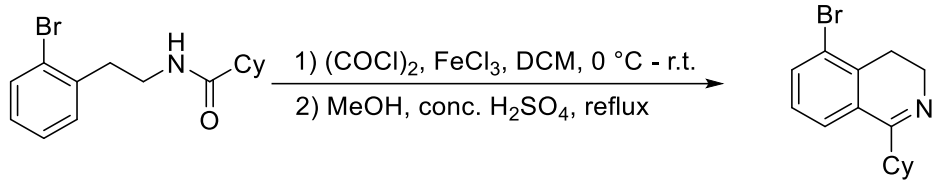


2-20(b) **2-20(c)**

The crude cyclohexanecarbonxyl chloride[**2-20(b)**] was dissolved in 160 mL DCM and cool to 0 ℃, followed by the addition of triethylamine (33.5 mL, 240 mml) and 2-bromophenethylamine (17.2 mL, 120 mmol). The mixture was stirred overnight at room temperature. Then water was added to quench the reaction. The reaction mixture was extracted with DCM for three times, washed with brine. The combined organic layer was dried over Na_2SO_4. After filtration and concertation, the residue was purified by flash column chromatography (hexane/EtOAc = 7:1 to hexane/EtOAc = 1: 1) to afford **2-20(c)** (32.45g, 87% yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.0 Hz, 1H), 7.28 – 7.19 (m, 2H), 7.14 – 7.07 (m, 1H), 3.53 (q, *J* = 6.8 Hz, 2H), 2.97 (t, *J* = 6.9 Hz, 2H), 2.03 (tt, *J* = 11.8, 3.4 Hz, 1H), 1.80 (dd, *J* = 23.6, 12.3 Hz, 4H), 1.67 (s, 1H), 1.39 (q, *J* = 12.0 Hz, 2H), 1.29 – 1.15 (m, 3H); **^{13}C NMR (151 MHz, $CDCl_3$)** δ 176.08, 138.37, 132.87, 131.07, 128.21, 127.53, 124.55, 45.51, 38.95, 35.75, 29.64, 25.71; **HRMS (ESI-TOF)**: calculated for $[M+Na]^+$ ($C_{15}H_{20}NONaBr$) requires *m/z* 332.0626, found *m/z* 332.0626.

5-bromo-1-cyclohexyl-3,4-dihydroisoquinoline (2-20)



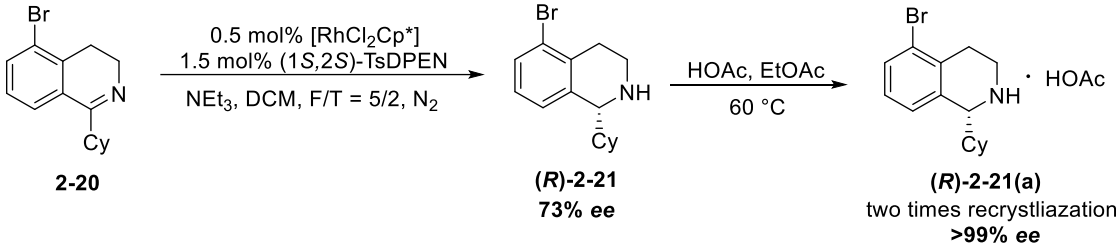
2-20(c) **2-20**

Oxalyl chloride (10.8 mL, 125.3 mmol) was slowly added into a solution of **2-20(c)** (32.45 g, 104.6 mmol) in 500 mL DCM solution at 0 ℃. The mixture was warm up to room temperature and stirred for 1 h. During this process, gas evolution was observed, and the reaction mixture turned from colorless to yellow. Then anhydrous ferric chloride (20.36 g, 125.5 mmol) was added into this mixture and stirred for 24 h. 1M HCl was added to the reaction mixture to quench the reaction. The aqueous phase was separated and extracted with DCM for three times. The combined organic layer was washed with *saq*. $NaHCO_3$ and brine, dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure to afford crude 7-bromo-10b-cyclohexyl-6,10b-dihydro-5H-oxazolo[2,3-a]isoquinoline-2,3-dione as a brown sold. The solid was dissolved in 400 mL MeOH and 110 mL conc. H_2SO_4 was slowly added into the reaction mixture, and the mixture was heated to reflux. After 24 h, the mixture was cooled down to room temperature, and methanol was removed under reduced pressure. The residue was diluted with water, cool down to 0 ℃, and *saq.* NaOH solution was slowly added into this mixture until pH > 10. The mixture was extracted with DCM for three times, the combined organic layer was washed with brine, dried over Na_2SO_4. After filtration and removing the solvent under reduced pressure, the residue was purified by flash column chromatography (hexane/EtOAC = 10/1) to afford **2-20** (22.60 g, 74% yield) as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.46 (d, *J* = 7.7 Hz, 1H), 7.16 (t, *J* = 7.9 Hz, 1H), 3.65 (t, *J* = 7.5 Hz, 2H), 2.89 – 2.79 (m, 1H), 2.73 (t, *J* = 7.5

Hz 2H), 1.88 – 1.78 (m, 4H), 1.77 – 1.68 (m, 1H), 1.47 – 1.30 (m, 4H), 1.30 – 1.19 (m, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 170.08, 137.98, 133.92, 130.72, 127.77, 123.76, 123.66, 46.43, 42.05, 31.25, 26.45, 26.16, 25.76; **HRMS (ESI-TOF)**: calculated for $[M+H]^+$ ($C_{15}H_{19}BrN$) requires *m/z* 292.0701, found *m/z* 292.0710.

(*R*)-5-bromo-1-cyclohexyl-1,2,3,4-tetrahydro-isoquinoline acetic acid salt [(*R*)-2-21(a)]



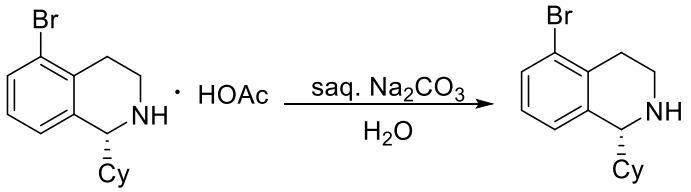
Following a modified literature procedure, [14] a solution of $[RhCl_2Cp^*]_2$ (30.9 mg, 0.05 mmol), (1*S*, 2*S*)-TsDPEN (55.0 mg, 0.15 mmol) and triethylamine (16 μL, 0.12 mmol) in 10 mL dry dichloromethane was stirred for 20 min under nitrogen at room temperature. A solution of **2-20** (2.92 g, 10 mmol) in 10 mL dichloromethane and an azeotropic mixture of 5:2 formic acid-triethylamine (10 mL) was added to the mixture. The mixture was stirred until the substrate disappeared as determined by TLC. *Saq*. Na_2CO_3 was added to render the mixture basic, and the mixture was extracted with DCM three times, washed with brine and dried over Na_2SO_4, and concentrated to give a crude product **(*R*)-2-21** as a brown oil. Chiral HPLC analysis indicated 73% *ee*.

Acetic acid (0.52 mL, 9 mmol) was added into a crude product solution in 16 mL EtOAc. Solid was formed after stirring for few minutes. The mixture was heated to 60 ℃ and continued stirring until all solid dissolved. Hexane (21 mL) was added to the mixture. Then the solution was slowly cool back to room temperature. The solvent was removed

under vacuum filtration to afford a white solid. Recrystallization of the white solid again to afford **(*R*)-2-21(a)** (1.91 g, 54% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09 (br s, 2H), 7.44 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.11 (d, *J* = 7.7 Hz, 1H), 7.06 (t, *J* = 7.8 Hz, 1H), 4.06 (d, *J* = 4.8 Hz, 1H), 3.41 (ddd, *J* = 12.6, 5.7, 4.5 Hz, 1H), 3.01 (ddd, *J* = 12.6, 9.2, 5.0 Hz, 1H), 2.91 (dt, *J* = 17.2, 4.7 Hz, 1H), 2.79 (ddd, *J* = 17.1, 9.2, 5.8 Hz, 1H), 1.98 (s, 3H), 1.90 (dtd, *J* = 11.4, 8.1, 4.2 Hz, 1H), 1.84 – 1.79 (m, 1H), 1.75 – 1.70 (m, 2H), 1.69 – 1.64 (m, 1H), 1.44 – 1.38 (m, 1H), 1.36 – 1.24 (m, 2H), 1.21 – 1.05 (m, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 176.74, 138.33, 134.42, 130.53, 127.20, 125.66, 125.46, 59.95, 42.50, 40.51, 30.42, 29.01, 26.70, 26.56, 26.37, 26.16, 22.39.

(*R*)-5-bromo-1-cyclohexyl-1,2,3,4-tetrahydro-isoquinoline [(*R*)-2-21]



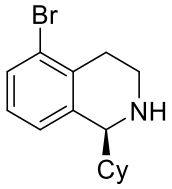
(*R*)-2-21(a) **(*R*)-2-21**

Saq. Na_2CO_3 (10 mL) was added into the solution of **(*R*)-2-21(a)** (1.91 g) in water (50 mL) and stirred for 10 min. Oil was formed, and DCM (20 mL) was added to the mixture to dissolve the oil. The aqueous layer was separated and exacted three times with DCM. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated to afford **(*R*)-2-21** (1.59 g, 100% yield) as a yellow oil.

$[\alpha]_D^{20}$ = +49.6° (*c* = 0.99, $CHCl_3$); **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.39 (d, *J* = 7.8 Hz, 1H), 7.11 (d, *J* = 7.7 Hz, 1H), 7.02 (t, *J* = 7.8 Hz, 1H), 3.84 (d, *J* = 4.5 Hz, 1H), 3.30 (ddd, *J* = 12.5, 5.9, 4.1 Hz, 1H), 2.92 (ddd, *J* = 12.5, 9.1, 4.9 Hz, 1H), 2.79 (dt, *J* = 17.0, 4.4 Hz, 1H), 2.68 (ddd, *J* = 16.4, 9.1, 6.0 Hz, 1H), 1.92 – 1.79 (m, 2H), 1.74 – 1.60 (m,

4H), 1.42 – 1.23 (m, 3H), 1.21 – 1.00 (m, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 141.32, 135.67, 129.75, 126.62, 125.74, 125.28, 60.91, 42.60, 41.81, 30.97, 30.78, 26.95, 26.52, 26.51, 26.47; **HRMS (ESI-TOF)**: calculated for $[M+H]^+$ ($C_{15}H_{19}BrN$) requires *m/z* 294.0857, found *m/z* 294.0848; **>99.9% *ee*** [determined by HPLC: Chiralcel® Chiral IC column, Hexane/^{i}PrOH/$HNEt_2$ = 97/3/0.1, 1.0 mL/min, λ = 225 nm; t_R(major) = 5.26 min, t_R(minor) = 6.45 min].

(*S*)-5-bromo-1-cyclohexyl-1,2,3,4-tetrahydro-isoquinoline [(*S*)-2-21]

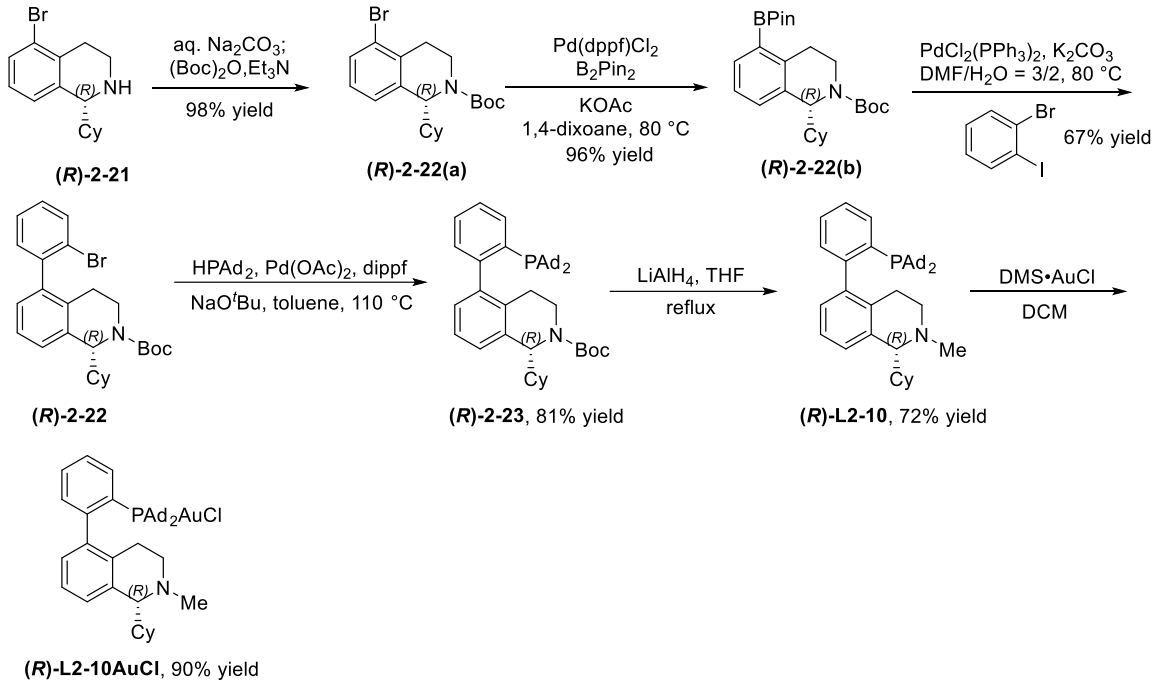


(*S*)-2-21

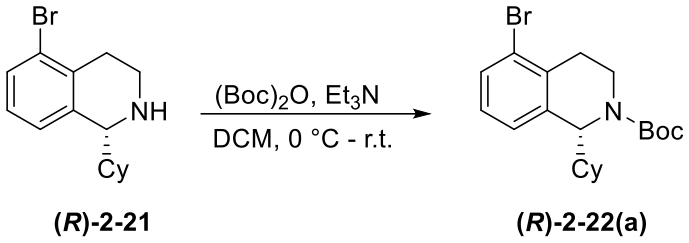
(*S*)-2-21 was prepared like **(*R*)-2-21**, using (1*R*, 2*R*)-TsDPEN instead of (1*S*, 2*S*)-TsDPEN in the asymmetric hydrogen transformation step.

$[\alpha]_D^{20}$ = -49.4° (*c* = 1.01, $CHCl_3$); **>99.9% *ee*** [determined by HPLC: Chiralcel® Chiral IC column, Hexane/^{i}PrOH/$HNEt_2$ = 97/3/0.1, 1.0 mL/min, λ = 225 nm; t_R(major) = 6.44 min, t_R(minor) = 5.26 min].

Synthesis of Gold Complexes



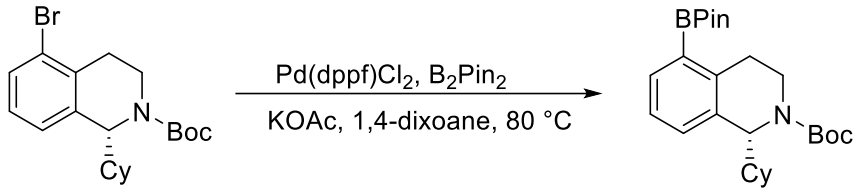
tert-butyl (*R*)-5-bromo-1-cyclohexyl-3,4-dihydroisoquinoline-2(1H)-carboxylate [(*R*)-2-22(a)]



To a solution of **(*R*)-2-21** (1.47g, 5 mmol) and Et_3N (1.39 mL, 10 mmol) in dichloromethane at 0 ℃, $(Boc)_2O$ (1.15 mL, 5 mmol) were slowly added. Gas evolution was observed after adding $(Boc)_2O$. The reaction mixture was stirred overnight at room temperature. After removing the solvent under reduced pressure, the residue was purified by flash column chromatography (hexane/EtOAc = 20/1) to afford **(*R*)-2-22(a)** (1.93 g, 98% yield) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 – 7.40 (m, 2H), 7.08 – 6.97 (m, 4H), 4.82 (d, *J* = 9.1 Hz, 1H), 4.67 (d, *J* = 8.4 Hz, 1H), 4.18 (ddd, *J* = 12.5, 7.2, 4.3 Hz, 1H), 3.91 (dt, *J* = 12.9, 6.3 Hz, 1H), 3.42 (ddd, *J* = 13.7, 8.1, 6.2 Hz, 1H), 3.30 (ddd, *J* = 13.6, 9.1, 6.1 Hz, 1H), 2.95 (ddd, *J* = 16.7, 12.0, 8.2 Hz, 2H), 2.83 (ddd, *J* = 16.8, 7.8, 3.7 Hz, 2H), 1.83 – 1.53 (m, 12H), 1.46 (s, 18H), 1.20 – 1.01 (m, 10H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 155.21, 154.97, 139.52, 139.07, 134.37, 134.12, 130.75, 130.64, 127.71, 127.25, 126.44, 126.28, 125.29, 124.74, 79.80, 79.48, 59.87, 58.93, 43.15, 42.78, 39.19, 37.64, 30.87, 30.66, 29.89, 29.54, 28.51, 28.45, 26.42, 26.39, 26.26, 26.21, 26.14.

***tert*-butyl (*R*)-1-cyclohexyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroiso-quinoline-2(1H)-carboxylate [(*R*)-2-22(b)]**

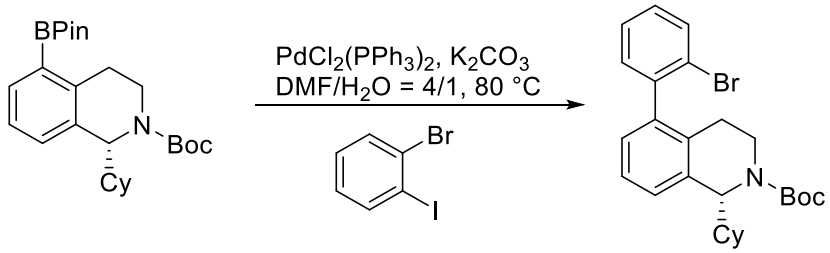


(*R*)-2-22(a) **(*R*)-2-22(b)**

$Pd(dppf)Cl_2$•CH_2Cl_2 (204.1 mg, 0.25 mmol), B_2Pin_2 (1.52g, 6 mmol), KOAc (2.45g, 25 mmol) and **(*R*)-2-22(a)** (1.97 g, 5 mmol) in 25 mL dry 1,4-dioxane was added into a flamed dried Schlenk flask under nitrogen. The mixture was degassed under N_2 for 30 min, then heated to 80 ℃ for 24 h. The mixture was cooled down to room temperature and filtrate through celite using DCM as eluent. The solvent was removed, and the residue was purified by flash column chromatography (hexane/EtOAc = 20/1) to afford **(*R*)-2-22(b)** (1.50 g, 96% yield) as a colorless oil, which solidified under high vacuum as a white solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 – 7.67 (m, 2H), 7.19 – 7.10 (m, 4H), 4.79 (d, *J* = 9.3 Hz, 1H), 4.65 (d, *J* = 8.6 Hz, 1H), 3.91 (dt, *J* = 13.1, 6.8 Hz, 1H), 3.67 – 3.53 (m, 2H), 3.48 – 3.31 (m, 3H), 3.17 – 3.02 (m, 2H), 1.79 (d, *J* = 12.2 Hz, 4H), 1.72 – 1.52 (m, 8H), 1.46 (d, *J* = 6.9 Hz, 18H), 1.33 (d, *J* = 5.7 Hz, 24H), 1.25 – 1.00 (m, 10H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 155.59, 155.19, 141.40, 141.33, 137.21, 136.54, 134.56, 134.54, 131.20, 130.80, 124.45, 124.27, 83.44, 83.43, 79.27, 78.92, 60.70, 59.97, 43.32, 43.18, 40.99, 39.27, 30.92, 30.78, 30.08, 29.74, 28.43, 28.41, 27.01, 26.81, 26.42, 26.39, 26.22, 26.18, 26.12, 24.92, 24.87, 24.85, 24.75, 24.68.

***tert*-butyl (*R*)-5-(2-bromophenyl)-1-cyclohexyl-3,4-dihydroisoquinoline-2(1H)-carboxylate [(*R*)-2-22]**

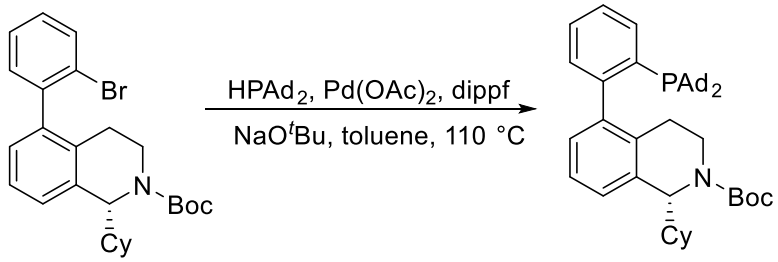


(*R*)-2-22(b) **(*R*)-2-22**

$PdCl_2(PPh_3)_2$ (280.7 mg, 0.4 mmol), K_2CO_3 (2.21 g, 16 mmol), **(*R*)-2-22(b)** (1.76 g, 4 mmol) were added into a Schlenk flask under nitrogen, followed by the addition of DMF (12 mL), H_2O (3 mL) and 1-bromo-2-iodobenzene (2.26 g, 8 mmol). The resulting mixture was degassed under N_2 for 30 min, then heated to 80 ℃ for 24 h. The mixture was cooled down to room temperature and diluted with DCM. The organic layer was extracted three times with water, dried over MgSO4. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (hexane/EtOAc = 20/1) to afford **(*R*)-2-22** (1.26 g, 67% yield) as a colorless oil, which solidified under high vacuum as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.2 Hz, 2H), 7.39 – 7.32 (m, 2H), 7.26 – 7.20 (m, 6H), 7.19 – 7.12 (m, 2H), 7.08 – 7.02 (m, 2H), 4.90 (dd, *J* = 13.0, 8.9 Hz, 1H), 4.76 (dd, *J* = 16.9, 8.2 Hz, 1H), 3.83 (dq, *J* = 13.0, 6.4 Hz, 1H), 3.67 – 3.35 (m, 3H), 2.79 – 2.40 (m, 4H), 1.86 – 1.60 (m, 12H), 1.53 – 1.43 (m, 18H), 1.24 – 1.00 (m, 10H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 155.67, 155.55, 155.30, 155.26, 141.96, 141.84, 141.80, 141.72, 140.69, 140.53, 140.24, 140.10, 137.81, 137.56, 137.38, 137.13, 133.18, 133.12, 132.93, 132.74, 132.55, 132.48, 132.41, 131.15, 131.02, 130.85, 130.81, 128.88, 128.84, 128.81, 128.79, 128.21, 128.02, 127.81, 127.74, 127.68, 127.57, 127.52, 127.40, 127.32, 127.25, 127.13, 127.11, 125.07, 124.96, 124.85, 124.76, 124.00, 123.81, 123.69, 79.54, 79.16, 79.12, 60.83, 60.51, 59.96, 59.73, 44.00, 43.82, 43.77, 43.58, 40.87, 40.69, 39.72, 39.21, 31.01, 30.93, 30.80, 30.75, 30.25, 30.17, 29.85, 29.80, 28.48, 28.46, 28.45, 26.55, 26.51, 26.48, 26.47, 26.37, 26.33, 26.30, 26.28, 26.22, 26.19, 25.61, 25.58, 25.47, 25.26.

***tert*-butyl (*R*)-1-cyclohexyl-5-(2-(di((1*S*,3*R*,5*R*,7*S*)-adamantan-1-yl)phosphanyl)phenyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate [(*R*)-2-23]**



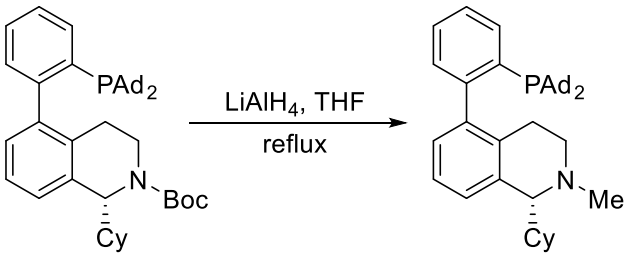
(*R*)-2-22 **(*R*)-2-23**

Under nitrogen atmosphere, **(*R*)-2-22** (470.4 mg, 1.0 mmol, 1 equiv.), $Pd(OAc)_2$ (22.4 mg, 0.1 mmol),1,1'- bis(diisopropylphosphino)ferrocene (dippf, 50.2 mg, 0.12 mmol), NaO*t*Bu (288.3 mg, 3 mmol) and 3 mL dry toluene were added to a flamed dried Schlenk flask and the resulting suspension was stirred until apparently homogeneous (around 15 min). After adding di(1-adamantyl)phosphine (362.9 mg, 1.2 mmol), the flask

was heated at 110 °C in an oil bath for 24h, then cooled to room temperature, and filtrated through a pad of silica gel using DCM as eluent. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (hexane only to hexane/EtOAc = 20/1) to afford **(*R*)-2-23** (560.5 mg, 81% yield) as a colorless oil, which solidified under high vacuum as a white solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.91 – 7.84 (m, 1H), 7.38 – 7.29 (m, 2H), 7.20 – 7.08 (m, 2H), 7.08 – 7.00 (m, 2H), 4.90 – 4.65 (m, 1H), 3.67 – 3.32 (m, 2H), 2.72 – 2.42 (m, 2H), 2.01 – 1.54 (m, 36H), 1.50 – 1.38 (m, 9H), 1.31 – 0.96 (m, 5H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 155.79, 155.49, 155.21, 150.01, 149.95, 149.89, 149.77, 149.68, 149.61, 149.56, 149.45, 142.08, 142.01, 141.78, 141.71, 141.62, 141.56, 137.68, 137.18, 137.09, 136.97, 136.94, 136.80, 136.79, 136.65, 134.49, 134.26, 134.20, 133.98, 133.79, 133.51, 133.14, 132.57, 132.24, 131.28, 131.22, 130.61, 130.57, 130.41, 130.39, 130.35, 130.33, 130.26, 130.22, 128.08, 127.99, 127.96, 127.22, 126.80, 126.74, 126.29, 125.50, 125.41, 125.38, 123.90, 123.82, 123.70, 123.52, 79.45, 79.27, 79.02, 78.84, 61.49, 60.76, 60.13, 45.02, 44.69, 43.91, 43.21, 42.14, 42.04, 42.01, 41.96, 41.90, 41.88, 41.83, 41.77, 41.70, 41.67, 40.72, 40.48, 37.64, 37.59, 37.54, 37.40, 37.37, 37.34, 37.28, 37.12, 37.01, 36.91, 36.84, 36.70, 36.61, 36.56, 36.54, 30.99, 30.94, 30.87, 30.77, 30.53, 30.27, 30.07, 29.68, 28.84, 28.76, 28.67, 28.49, 28.44, 26.84, 26.77, 26.61, 26.55, 26.45, 26.36, 26.34, 26.31, 26.28, 26.23, 25.75, 25.45 (As the coupling patterns could not be determined, all peaks were shown); ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.20, 22.04, 22.03, 21.83.

Chiral Phosphine Ligand (*R*)-L2-10

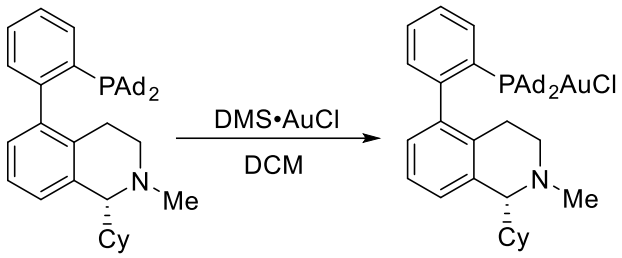


(*R*)-2-23 **(*R*)-L2-10**

To a solution of **(*R*)-2-23** (692.0 mg, 1.0 mmol) in dry THF (10 mL), $LiAlH_4$ (379.5 mg, 10 mmol) was slowly added under nitrogen atmosphere at 0 ℃. After refluxing for 12 h, the reaction was diluted with ether, quenched carefully with water and aqueous NaOH, dried over anhydrous $MgSO_4$. The crude product was purified by recrystallization from DCM/MeOH to give **(*R*)-L2-10** (436.2 mg, 72% yield) as a white solid.

^{1}H NMR (600 MHz, CD_2Cl_2) δ 8.04 – 7.81 (m, 1H), 7.48 – 7.28 (m, 2H), 7.25 – 6.89 (m, 4H), 3.49 – 3.24 (m, 1H), 3.09 – 2.86 (m, 1H), 2.53 – 2.22 (m, 6H), 2.07 – 1.48 (m, 36H), 1.35 – 0.96 (m, 5H); **^{13}C NMR (101 MHz, CD_2Cl_2)** δ 150.33, 150.30, 149.99, 149.96, 141.84, 141.78, 141.74, 141.67, 137.29, 137.06, 136.86, 136.84, 136.78, 136.75, 134.68, 134.34, 134.07, 133.94, 133.58, 133.31, 131.17, 131.11, 130.48, 130.42, 129.22, 129.17, 128.87, 128.83, 127.91, 127.76, 127.23, 126.74, 125.22, 125.16, 123.41, 123.06, 69.77, 69.71, 50.66, 49.51, 46.68, 45.47, 45.30, 45.04, 42.08, 41.96, 41.93, 41.84, 41.81, 37.64, 37.57, 37.39, 37.31, 37.28, 37.03, 36.85, 36.81, 36.52, 30.82, 30.61, 29.82, 29.34, 29.00, 28.97, 28.91, 28.89, 28.87, 26.90, 26.86, 26.81, 26.77, 26.66, 26.34. (As the coupling patterns could not be determined, all peaks were shown); ^{31}P NMR (162 MHz, CD_2Cl_2) δ 22.74, 22.40; **HRMS (ESI-TOF)**: calculated for $[M+H]^+$ ($C_{42}H_{57}NP$) requires *m/z* 605.4229, found *m/z* 605.4223.

Chiral Gold Catalyst (*R*)-L2-10AuCl



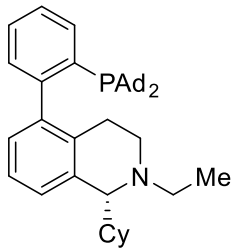
(*R*)-L2-10 **(*R*)-L2-10AuCl**

To a solution of **(*R*)-L2-10** (302.9 mg, 0.5 mmol) in 5 mL anhydrous DCM was added chloro(dimethylsulfide)gold(I) (144.3 mg, 0.49 mmol). The mixture was stirred for 30 min at room temperature, and the solvent was evaporated off. The crude mixture was dissolved again in DCM and filtrated through a short pad of celite to remove gold participation. The solvent was removed under the reduced pressure, and the resulting solid was recrystallized from DCM/pentane to afford **(*R*)-L2-10AuCl** (377.2 mg, 90% yield) as a white solid.

^{1}H NMR (600 MHz, CD_2Cl_2) δ 8.03 – 7.78 (m, 1H), 7.59 – 7.38 (m, 2H), 7.30 – 7.04 (m, 3H), 6.97 – 6.77 (m, 1H), 3.57 – 3.20 (m, 1H), 3.07 – 2.86 (m, 1H), 2.81 – 2.48 (m, 2H), 2.44 – 1.45 (m, 40H), 1.37 – 0.97 (m, 5H); **^{13}C NMR (101 MHz, CD_2Cl_2)** δ 149.35, 149.22, 140.25, 140.18, 140.13, 140.07, 138.13, 134.86, 134.84, 134.82, 134.80, 134.50, 133.97, 133.51, 133.43, 133.21, 133.13, 130.43, 130.41, 130.30, 130.27, 129.01, 128.56, 127.61, 127.46, 126.17, 126.10, 126.03, 125.96, 125.17, 124.57, 124.55, 124.14, 124.12, 124.10, 69.90, 69.43, 49.72, 49.66, 45.71, 45.14, 45.11, 44.74, 43.09, 42.95, 42.86, 42.71, 42.53, 42.50, 42.44, 42.22, 42.20, 42.14, 42.11, 41.98, 41.80, 41.78, 36.17, 36.15, 36.13, 36.12, 30.79, 30.44, 29.72, 28.83, 28.79, 28.72, 28.69, 28.64, 28.62, 28.59, 28.54, 28.49, 26.83, 26.74, 26.57, 26.54, 26.29, 25.57 (As the coupling patterns could not be determined, all peaks were shown); **^{31}P NMR (162 MHz, CD_2Cl_2)** δ 61.79, 61.56; **HRMS**

(ESI-TOF): calculated for $[M+H]^+$ ($C_{42}H_{57}AuClNP$) requires *m/z* 838.3583, found *m/z* 838.3574.

Chiral Phosphine Ligand (*R*)-L2-11



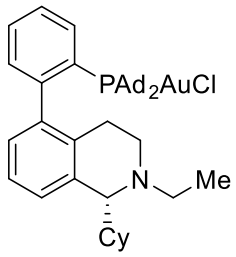
(*R*)-L2-11

(*R*)-L2-11 was synthesized similar to **(*R*)-L2-10**. In the nitrogen protection step, acetyl chloride was used instead of $(Boc)_2O$.

^{1}H NMR (600 MHz, CD_2Cl_2) δ 7.93 – 7.87 (m, 2H), 7.38 – 7.30 (m, 4H), 7.18 (ddd, *J* = 7.3, 3.9, 1.8 Hz, 1H), 7.14 (ddd, *J* = 7.2, 3.9, 1.9 Hz, 1H), 7.11 – 7.07 (m, 2H), 7.01 – 6.94 (m, 4H), 3.40 (d, *J* = 5.6 Hz, 1H), 3.34 (d, *J* = 7.1 Hz, 1H), 3.13 – 3.00 (m, 2H), 2.67 – 2.43 (m, 7H), 2.35 (dt, *J* = 16.7, 6.4 Hz, 1H), 2.26 (dt, *J* = 17.0, 6.3 Hz, 1H), 2.14 (ddd, *J* = 17.3, 7.6, 4.7 Hz, 1H), 2.02 – 1.47 (m, 72H), 1.22 – 1.09 (m, 10H), 1.06 (t, *J* = 7.1 Hz, 3H), 1.02 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR (101 MHz, CD_2Cl_2)** δ 150.93, 150.85, 150.60, 150.52, 142.71, 142.64, 142.27, 142.19, 137.95, 137.49, 137.42, 137.39, 137.33, 137.30, 135.21, 134.75, 134.47, 134.26, 134.14, 133.87, 131.66, 131.60, 130.99, 130.92, 129.79, 129.74, 129.56, 129.52, 128.45, 128.28, 128.18, 127.55, 125.70, 123.77, 123.35, 68.38, 67.97, 50.86, 50.17, 46.95, 46.53, 45.00, 44.82, 42.59, 42.53, 42.47, 42.40, 42.33, 38.25, 38.06, 38.00, 37.80, 37.72, 37.46, 37.39, 37.34, 37.14, 31.55, 31.39, 31.00, 30.62, 30.14, 29.53, 29.50, 29.44, 29.42, 27.49, 27.35, 27.29, 27.23, 27.21, 25.80, 25.28, 13.60, 13.48 (As the coupling patterns could not be determined, all peaks were shown); **^{31}P NMR**

(162 MHz, CD_2Cl_2) δ 22.94, 22.15; **HRMS (ESI-TOF)**: calculated for $[M+H]^+$ ($C_{43}H_{59}NP$) requires *m/z* 620.4385, found *m/z* 620.4385.

Chiral Gold Catalyst (*R*)-L2-11AuCl

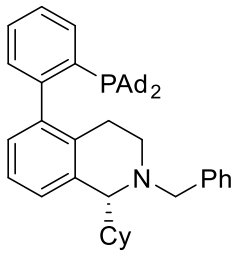


(*R*)-L2-11AuCl

Gold complex **(*R*)-L2-11AuCl** was prepared the same way as **(*R*)-L2-10AuCl.**

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.00 – 7.82 (m, 1H), 7.64 – 7.46 (m, 2H), 7.36 – 7.07 (m, 3H), 7.04 – 6.75 (m, 1H), 3.58 – 3.31 (m, 1H), 3.21 – 3.02 (m, 1H), 2.87 – 2.43 (m, 3H), 2.39 – 1.80 (m, 19H), 1.80 – 1.54 (m, 16H), 1.38 – 0.75 (m, 11H); **^{13}C NMR (101 MHz, CD_2Cl_2)** δ 150.06, 149.93, 141.13, 141.06, 140.95, 140.89, 138.85, 135.44, 135.42, 135.41, 135.00, 134.06, 133.98, 133.80, 133.73, 131.00, 130.98, 130.87, 130.85, 129.86, 129.64, 128.41, 128.14, 126.68, 126.61, 126.55, 126.48, 125.38, 125.17, 125.00, 124.74, 124.57, 67.94, 67.79, 50.33, 50.03, 45.95, 44.88, 43.54, 43.46, 43.30, 43.22, 43.10, 43.08, 42.90, 42.87, 42.75, 42.73, 42.66, 42.64, 42.40, 42.38, 36.70, 36.69, 31.99, 31.55, 31.21, 31.01, 30.09, 30.06, 29.36, 29.28, 29.26, 29.24, 29.18, 29.14, 29.08, 27.35, 27.22, 27.18, 27.09, 26.94, 25.23, 25.16 (As the coupling patterns could not be determined, all peaks were shown). **^{31}P NMR (162 MHz, CD_2Cl_2)** δ 61.76, 61.48; **HRMS (ESI-TOF)**: calculated for $[M+H]^+$ ($C_{43}H_{59}AuClNP$) requires *m/z* 852.3739, found *m/z* 852.3750.

Chiral Phosphine Ligand (*R*)-L2-12

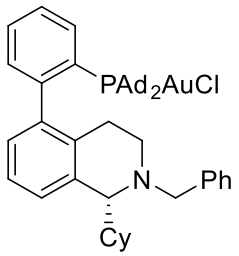


(*R*)-L2-12

(*R*)-L2-12 was synthesized similar to **(*R*)-L2-10**. In the nitrogen protection step, benzoyl chloride was used instead of $(Boc)_2O$.

^{1}H NMR (600 MHz, CD_2Cl_2) δ 7.94 (d, *J* = 7.5 Hz, 2H), 7.43 – 7.28 (m, 12H), 7.27 – 7.20 (m, 4H), 7.18 – 7.12 (m, 2H), 7.08 – 6.99 (m, 4H), 3.85 (d, *J* = 13.5 Hz, 1H), 3.82 (d, *J* = 13.9 Hz, 1H), 3.71 (d, *J* = 13.5 Hz, 1H), 3.65 (d, *J* = 13.9 Hz, 1H), 3.49 (d, *J* = 6.0 Hz, 1H), 3.45 (d, *J* = 7.2 Hz, 1H), 3.12 (dt, *J* = 12.8, 6.7 Hz, 1H), 3.04 (ddd, *J* = 12.6, 7.8, 4.8 Hz, 1H), 2.60 – 2.42 (m, 4H), 2.37 (dt, *J* = 16.8, 6.0 Hz, 1H), 2.17 (t, *J* = 5.4 Hz, 1H), 2.09 – 1.52 (m, 72H), 1.30 – 1.03 (m, 10H); **^{13}C NMR (101 MHz, CD_2Cl_2)** δ 150.88, 150.76, 150.54, 150.43, 142.88, 142.82, 142.46, 142.39, 141.01, 140.81, 137.66, 137.41, 137.39, 137.34, 137.32, 137.30, 134.60, 134.33, 134.04, 133.87, 133.77, 131.70, 131.63, 130.91, 130.84, 130.06, 130.02, 129.71, 129.68, 129.15, 129.10, 129.04, 129.02, 128.85, 128.46, 128.42, 128.38, 128.30, 128.20, 127.75, 127.07, 126.94, 125.72, 123.74, 123.39, 68.35, 67.93, 60.79, 60.51, 46.20, 46.16, 45.12, 44.67, 42.57, 42.53, 42.50, 42.45, 42.40, 42.37, 42.27, 38.24, 38.00, 37.99, 37.75, 37.70, 37.45, 37.35, 37.27, 37.12, 31.61, 31.34, 30.88, 30.54, 29.50, 29.50, 29.45, 29.43, 29.42, 29.41, 29.36, 29.35, 27.45, 27.35, 27.27, 27.21, 25.14, 25.08 (As the coupling patterns could not be determined, all peaks were shown); **^{31}P NMR (162 MHz, CD_2Cl_2)** δ 22.97, 22.02; **HRMS (ESI-TOF)**: calculated for $[M+H]^+$ ($C_{48}H_{61}NP$) requires *m/z* 682.4536, found *m/z* 682.4542.

Chiral Gold Catalyst (*R*)-L2-12AuCl

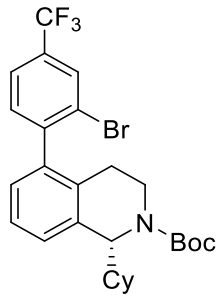


(*R*)-L2-12AuCl

Gold complex **(*R*)-L2-12AuCl** was prepared the same way as **(*R*)-L2-10AuCl.**

^{1}H NMR (600 MHz, CD_2Cl_2) δ 7.94 – 7.85 (m, 1H), 7.55 – 7.40 (m, 3H), 7.34 (d, *J* = 7.5 Hz, 1H), 7.29 – 7.12 (m, 6H), 6.99 – 6.84 (m, 1H), 4.01 – 3.76 (m, 1H), 3.75 – 3.58 (m, 1H), 3.58 – 3.33 (m, 1H), 3.16 – 2.92 (m, 1H), 2.73 – 2.43 (m, 2H), 2.41 – 2.28 (m, 1H), 2.27 – 1.94 (m, 20H), 1.79 – 1.56 (m, 16H), 1.35 – 1.07 (m, 5H); **^{13}C NMR (101 MHz, CD_2Cl_2)** δ 149.98, 149.85, 141.50, 141.44, 141.28, 141.22, 135.43, 135.40, 135.38, 134.39, 134.11, 134.03, 133.72, 133.65, 131.01, 130.99, 130.93, 130.91, 130.05, 129.73, 129.34, 129.11, 128.62, 128.37, 128.27, 127.06, 126.68, 126.61, 126.59, 126.52, 125.24, 125.02, 124.84, 124.59, 124.46, 124.41, 68.24, 68.16, 60.20, 60.04, 45.01, 44.30, 43.46, 43.34, 43.23, 43.11, 43.09, 43.03, 43.00, 42.87, 42.72, 42.69, 42.64, 42.55, 42.53, 42.38, 42.35, 36.67, 36.65, 36.63, 36.60, 36.58, 34.49, 31.61, 30.88, 30.05, 29.24, 29.20, 29.17, 29.14, 29.13, 29.10, 29.07, 29.03, 27.21, 27.12, 27.08, 27.05, 26.94, 24.55, 24.39 (As the coupling patterns could not be determined, all peaks were shown); **^{31}P NMR (162 MHz, CD_2Cl_2)** δ 61.89, 61.51; **HRMS (ESI-TOF)**: calculated for $[M+H]^+$ ($C_{48}H_{61}AuClNP$) requires *m/z* 914.3896, found *m/z* 914.3880.

***tert*-butyl (*R*)-5-(2-bromo-4-(trifluoromethyl)phenyl)-1-cyclohexyl-3,4-dihydroisoquinoline-2(1H)-carboxylate [(*R*)-L2-13(a)]**

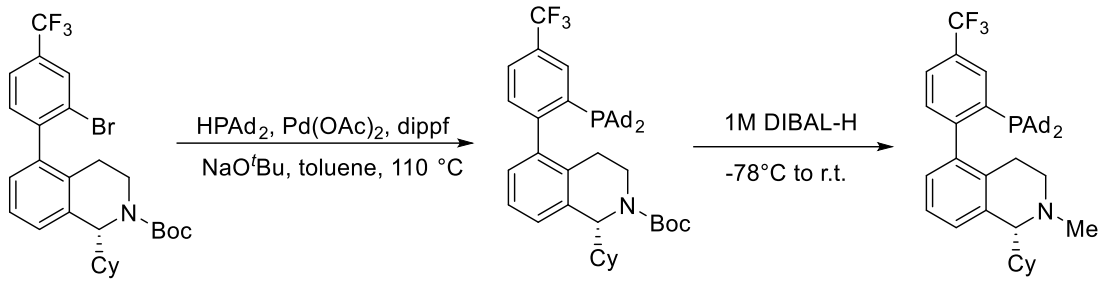


(*R*)-L2-13(a)

[(*R*)-L2-13(a)] was prepared the same way as **(*R*)-2-22**. 2-Bromo-1-iodo-4-(trifluoromethyl)benzene was used instead of 1-bromo-2-iodobenzene.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.91 (s, 2H), 7.61 (d, *J* = 7.8 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.33 (t, *J* = 7.8 Hz, 1H), 7.27 – 7.19 (m, 2H), 7.20 – 7.13 (m, 2H), 7.03 – 6.96 (m, 2H), 4.90 (dd, *J* = 16.1, 8.9 Hz, 1H), 4.75 (dd, *J* = 21.2, 8.2 Hz, 1H), 3.82 (td, *J* = 10.4, 9.2, 3.8 Hz, 1H), 3.60 (ddt, *J* = 31.2, 13.7, 7.3 Hz, 1H), 3.51 – 3.32 (m, 2H), 2.68 (dt, *J* = 14.7, 7.0 Hz, 1H), 2.64 – 2.42 (m, 2H), 2.38 (dt, *J* = 16.2, 6.2 Hz, 1H), 1.83 – 1.53 (m, 12H), 1.52 – 1.38 (m, 18H), 1.34 – 1.00 (m, 10H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 155.60, 155.48, 155.25, 155.20, 145.79, 145.70, 145.64, 145.58, 139.45, 139.28, 139.02, 138.90, 138.03, 137.79, 137.65, 137.37, 132.84, 132.79, 132.60, 132.41, 131.50, 131.41, 131.33, 131.26, 131.21, 131.01, 130.98, 130.93, 129.58, 129.55, 129.53, 129.49, 129.47, 129.43, 129.41, 129.38, 128.77, 128.58, 128.30, 128.14, 127.41, 127.26, 127.16, 127.03, 125.29, 125.19, 125.07, 125.00, 124.45, 124.31, 124.25, 124.21, 124.16, 124.08, 124.04, 124.01, 123.97, 121.74, 79.67, 79.30, 79.26, 60.75, 60.40, 59.82, 59.57, 43.95, 43.71, 43.46, 40.57, 40.42, 39.48, 38.95, 34.59, 34.46, 31.53, 30.98, 30.89, 30.77, 30.72, 30.20, 30.10, 29.77, 29.72, 28.43, 28.41, 28.39, 26.50, 26.44, 26.42, 26.34, 26.29, 26.26, 26.24, 26.22, 26.17, 26.13, 25.67, 25.61, 25.47, 25.23, 25.21; **^{19}F NMR (376 MHz, $CDCl_3$)** δ -61.45.

Chiral Phosphine Ligand (*R*)-L2-13



(*R*)-L2-13(a) **(*R*)-L2-13(b)** **(*R*)-L2-13**

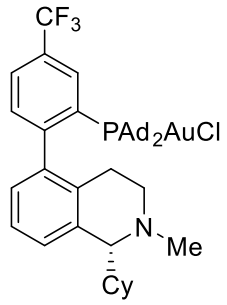
(*R*)-L2-13(b) was prepared the same way as **(*R*)-2-23.**

To a solution of **(*R*)-L2-13(b)** (760.0 mg, 1.0 mmol) in dry THF (10 mL), DIBAL-H (1M in hexane, 20 mL, 20 mmol) was slowly added under nitrogen atmosphere at -78 ℃. After stirring at -78 ℃ for 2 h, the reaction mixture was slowly raised to room temperature and further stirring for 24 h. The reaction was diluted with ether, quenched carefully with water and aqueous NaOH, dried over anhydrous $MgSO_4$. The crude product was purified by recrystallization from DCM/MeOH to give **(*R*)-L2-13** (552. 6 mg, 82% yield) as a white solid. [Note: using $LiAlH_4$/THF/reflux condition could reduce CF_3 group]

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15 (d, *J* = 12.9 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.32 (dd, *J* = 26.8, 7.9 Hz, 1H), 7.14 (d, *J* = 7.7 Hz, 1H), 7.07 – 6.92 (m, 2H), 3.44 – 3.30 (m, 1H), 3.13 – 2.95 (m, 1H), 2.56 – 2.31 (m, 6H), 2.03 – 1.52 (m, 36H), 1.32 – 0.95 (m, 5H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 153.86, 153.54, 140.32, 140.26, 140.19, 137.08, 136.61, 136.22, 135.89, 135.33, 135.01, 134.34, 133.39, 133.36, 133.33, 133.23, 133.20, 133.17, 133.10, 133.09, 131.60, 131.54, 130.85, 130.79, 129.25, 129.21, 128.77, 128.74, 128.20, 127.51, 127.44, 127.19, 125.69, 124.61, 124.58, 124.54, 124.51, 123.86, 123.48, 122.98, 70.12, 50.94, 49.14, 46.69, 45.78, 45.11, 45.00, 42.03, 41.94, 41.90, 41.81, 41.69, 37.88, 37.85, 37.62, 37.59, 37.52, 37.26, 36.97, 36.80, 36.70, 30.60, 30.53, 30.19, 29.49, 28.79, 28.75, 28.71, 28.67, 26.87, 26.80, 26.72, 26.51, 26.05 (As the coupling patterns

could not be determined, all peaks were shown); **^{19}F NMR (376 MHz, $CDCl_3$)** δ -61.13; **^{31}P NMR (162 MHz, $CDCl_3$)** *δ* 22.45, 22.00; **HRMS (ESI-TOF)**: calculated for $[M+H]^+$ ($C_{43}H_{56}F_3NP$) requires *m/z* 674.4097, found *m/z* 674.4103.

Chiral Gold Catalyst (*R*)-L2-13AuCl



(*R*)-L2-13AuCl

Gold complex (***R***)-**L2-13AuCl** was prepared the same way as (***R***)-**L2-10AuCl.**

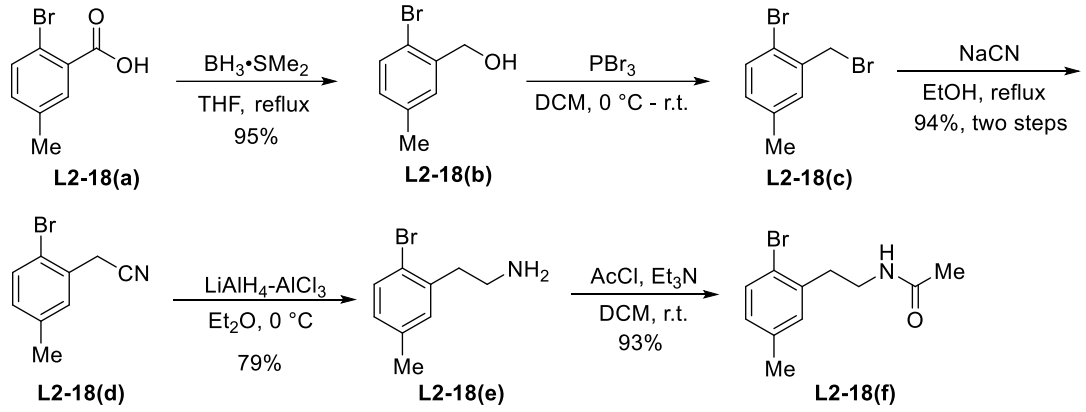
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.19 – 8.01 (m, 2H), 7.79 – 7.64 (m, 2H), 7.46 – 7.37 (m, 1H), 7.34 – 7.26 (m, 1H), 7.22 – 7.19 (m, 3H), 7.18 – 7.12 (m, 1H), 6.92 – 6.83 (m, 1H), 6.79 – 6.70 (m, 1H), 3.55 – 3.45 (m, 1H), 3.35 – 3.28 (m, 1H), 3.07 – 2.91 (m, 2H), 2.85 – 2.69 (m, 1H), 2.60 – 2.34 (m, 7H), 2.31 – 1.84 (m, 44H), 1.76 – 1.46 (m, 32H), 1.38 – 0.88 (m, 10H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 153.34, 153.27, 153.18, 138.69, 138.64, 138.51, 138.50, 138.47, 134.26, 134.21, 134.06, 133.96, 133.90, 133.52, 131.50, 131.47, 131.45, 131.40, 131.37, 131.35, 129.76, 129.37, 128.67, 128.62, 128.57, 128.52, 128.42, 128.36, 128.31, 128.26, 128.15, 128.10, 127.26, 127.12, 126.95, 126.80, 126.24, 126.17, 125.93, 125.85, 124.79, 124.73, 124.68, 122.56, 120.39, 70.19, 69.61, 50.00, 49.73, 45.77, 45.37, 45.22, 43.43, 43.27, 43.09, 42.71, 42.62, 42.61, 42.53, 42.45, 42.29, 42.20, 42.14, 42.12, 41.78, 36.10, 36.05, 30.85, 30.31, 29.96, 28.89, 28.60, 28.54, 28.46, 28.40, 28.37, 28.32, 26.88, 26.76, 26.67, 26.54, 26.49, 26.44, 26.15, 25.95 (As the coupling patterns could not be determined, all peaks were shown); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -

61.47, -61.50; **^{31}P NMR** (162 MHz, $CDCl_3$) δ 61.80, 61.50; **HRMS (ESI-TOF)**: calculated for $[M+H]^+$ ($C_{43}H_{56}AuClF_3NP$) requires *m/z* 906.3456, found *m/z* 906.3445.

Chiral Gold Catalyst (*S*)-L2-13AuCl

(*S*)-L2-13AuCl was prepared similar to **(*R*)-L2-13AuCl.** (*S*)-5-bromo-1-cyclohexyl-1,2,3,4-tetrahydro-isoquinoline **(*S*)-2-21** was used as starting material instead of (*R*)-5-bromo-1-cyclohexyl-1,2,3,4-tetrahydro-isoquinoline **(*R*)-2-21**.

***N*-(2-bromo-5-methylphenethyl)acetamide [L2-18(f)]**



To a solution of 2-bromo-5-methylbenzoic acid **L2-18(a)** (21.5 g, 100 mmol) in 150 mL THF solution at 0 ˚C, $BH_3{\cdot}SMe_2$ (9.5 mL, 100 mmol) was slowly added into the solution. The reaction mixture was heated to reflux for four h and then cooled down to 0 ℃. 1M HCl solution was added to quench the reaction. Then the mixture was diluted with water, extracted with Et_2O three times, and washed with brine. The combined organic layer was dried over Na_2SO_4. The solution was filtrated, and the solvent was removed under reduced pressure to afford **L2-18(b)** (19.18 g, 95% yield) as a white solid. **L2-18(b)** was directly used in the next step without further purification.

To a solution of 2-bromo-5-methylbenzyl alcohol **L2-18(b)** (19.18 g, 95 mmol) in 100 mL dichloromethane solution at 0 ℃, PBr_3 (4.5 mL, 47.5 mmol) was slowly added into the solution. The reaction mixture was warmed to room temperature and stirred overnight. A saturated $NaHCO_3$ solution was added to the reaction mixture to quench the reaction. Then the mixture was diluted with water, extracted with DCM three times, and washed with brine. The combined organic layer was dried over Na_2SO_4. The solution was filtrated, and the solvent was removed under reduced pressure to afford **L2-18(c)** as a colorless oil. **L2-18(c)** was directly used in the next step without further purification.

To a solution of 1-bromo-2-(bromomethyl)-4-methylbenzene **L2-18(c)** in 27 mL EtOH, NaCN solution (5.59g, 114 mmol, dissolved in 6.3 mL H_2O) was added. NaCN precipitated out due to its low solubility in EtOH. The reaction mixture was heated to reflux for 1 h and cooled down to room temperature. After the reaction, all solid was dissolved, and the color of the reaction mixture turned orange. The reaction mixture was diluted with water, extracted with Et_2O three times, and washed with brine. The combined organic layer was dried over Na_2SO_4. The solution was filtrated, and the solvent was removed under reduced pressure to afford **L2-18(d)** (18.73g, 94% yield over two steps) as a yellow oil. **L2-18(d)** was directly used in the next step without further purification.

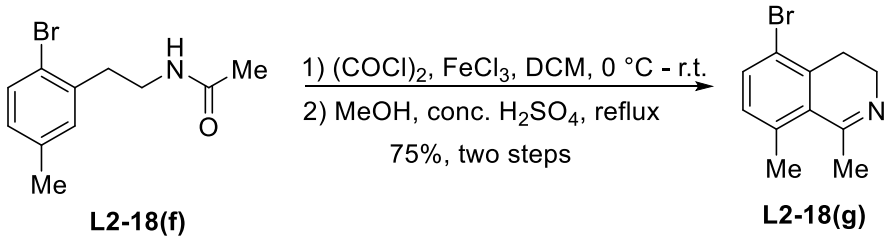
$LiAlH_4$ (5.075g, 133.7 mmol) was added into a solution of $AlCl_3$ (12.25g, 91.9 mmol) in 100 mL Et_2O at 0 ℃. The reaction mixture was stirred at 0 ℃ for 10 min. Then a solution of 2-(2-bromo-5-methylphenyl)acetonitrile **L2-18(d)** (18.73g, 89.16 mmol) in 50 mL Et_2O was slowly added into the reaction mixture at 0 ℃. The reaction mixture was allowed to warm up to room temperature and stirred for 1 h. The mixture was cool down in the iced bath, diluted with Et_2O, quenched with concentrated H_2SO_4 solution until pH ~1, and

basified with 6M NaOH solution until pH ~13. The reaction mixture was extracted with Et_2O three times and washed with brine. The combined organic layer was dried over Na_2SO_4. The solution was filtrated, and the solvent was removed under reduced pressure to afford **L2-18(e)** (15.12g, 79% yield) as light brown oil. **L2-18(e)** was directly used in the next step without further purification.

To a solution of 2-(2-bromo-5-methylphenyl)ethan-1-amine **L2-18(e)** (15.11 g, 70.6 mmol) in 140 mL DCM solution at 0 ℃, Et_3N (19.69 mL, 141.6 mmol) and acetyl chloride (6.02 mL, 84.2 mmol) were added into the solution. The reaction mixture was warmed to room temperature and stirred overnight. Then the mixture was diluted with water, extracted with DCM three times, and washed with $NaHCO_3$ and brine. The combined organic layer was dried over Na_2SO_4. After filtration and concertation, the residue was purified by flash column chromatography (hexane/EtOAc = 1/1) to afford **L2-18(f)** (16.77 g, 93% yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.1 Hz, 1H), 7.03 (d, *J* = 2.2 Hz, 1H), 6.89 (dd, *J* = 8.0, 2.2 Hz, 1H), 5.79 (s, 1H), 3.48 (q, *J* = 6.7 Hz, 2H), 2.90 (t, *J* = 7.1 Hz, 2H), 2.26 (s, 3H), 1.94 (s, 3H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 170.14, 137.86, 137.48, 132.50, 131.62, 129.02, 121.05, 39.47, 35.54, 23.23, 20.75; **HRMS (ESI-TOF)**: calculated for $[M+Na]^+$ ($C_{11}H_{14}BrNONa$) requires *m/z* 278.0157, found *m/z* 278.0154.

5-Bromo-1,8-dimethyl-3,4-dihydroisoquinoline [L2-18(g)]

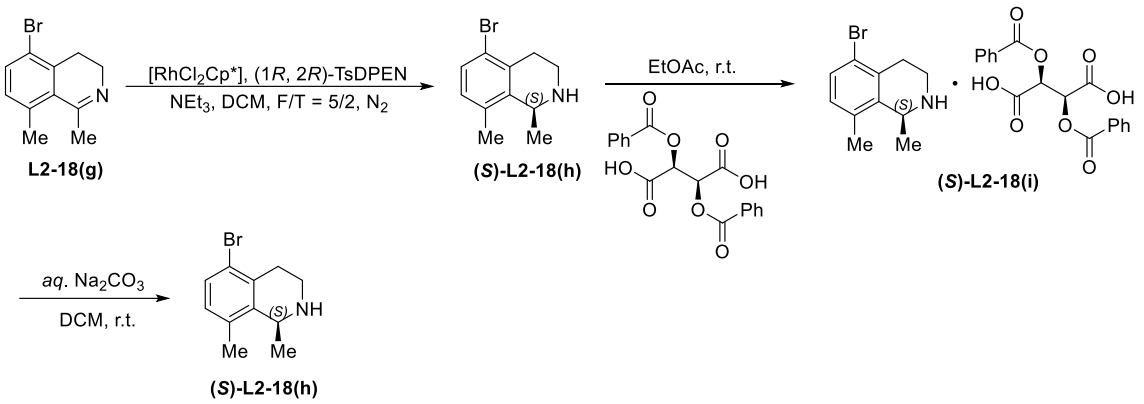


L2-18(f) **L2-18(g)**

Oxalyl chloride (7.3 mL, 78.7 mmol) was slowly added into a solution of **L2-18(f)** (16.77 g, 65.6 mmol) in 140 mL DCM solution at 0 ℃. The mixture was warmed up to room temperature and stirred for 1 h. During this process, gas evolution was observed, and the reaction mixture was turned from colorless to yellow. Then anhydrous ferric chloride (20.36 g, 125.5 mmol) was added into this mixture and stirred for 24 h. 1M HCl was added to the reaction mixture to quench the reaction. The aqueous phase was separated and extracted with DCM three times. The combined organic layer was washed with saq. $NaHCO_3$ and brine, dries over Na_2SO_4. After filtration and remove the solvent under reduced pressure. The residue was dissolved in 200 mL MeOH, and 55 mL concentrated H_2SO_4 was slowly added into the reaction mixture, and the mixture was heated to reflux. After 24 h, the mixture was cooled down to room temperature, and methanol was removed under reduced pressure. The residue was diluted with water, cool down to 0 ℃, and saq. NaOH solution was slowly added into this mixture until pH > 10. The mixture was extracted with DCM three times, the combined organic layer was washed with brine, dried over Na_2SO_4. After filtration and removing the solvent under reduced pressure, the residue was purified by flash column chromatography (hexane/EtOAc = 5/1 to hexane/EtOAc = 1/1) to afford **L2-18(g)** (11.71 g, 75% yield) as a brown oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.2 Hz, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 3.43 – 3.35 (m, 2H), 2.64 – 2.56 (m, 2H), 2.39 (s, 3H), 2.34 (d, *J* = 1.3 Hz, 3H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 164.88, 139.02, 133.96, 133.11, 132.18, 131.49, 120.37, 46.18, 27.27, 27.14, 22.66; **HRMS (ESI-TOF)**: calculated for $[M+H]^+$ ($C_{11}H_{13}BrN$) requires *m/z* 238.0231, found *m/z* 238.0238.

(*S*)-5-Bromo-1,8-dimethyl-1,2,3,4-tetrahydroisoquinoline [(*S*)-L2-18(h)]



Following a modified literature procedure, [14] a solution of $[RhCl_2Cp^*]_2$ (123.6 mg, 0.2 mmol), (1*R*, 2*R*)-TsDPEN (219.9 mg, 0.6 mmol) and triethylamine (16 μL, 0.12 mmol) in 10 mL dry dichloromethane was stirred for 20 min under nitrogen at room temperature. A solution of **L2-18(g)** (2.38 g, 10 mmol) in 10 mL dichloromethane and an azeotropic mixture of 5:2 formic acid-triethylamine (10 mL) was added to the mixture. The mixture was stirred until the reaction completion as determined by TLC. Saturated Na_2CO_3 was added to render the mixture basic, and the mixture was extracted with DCM three times, washed with brine and dried over Na_2SO_4, and concentrated to give a crude product **(*S*)-L2-18(h)** as a brown oil. Chiral HPLC analysis indicated 75% *ee*.

A solution of Dibenzoyl-*D*-tartaric acid (3.59g, 10 mmol) in 20 mL EtOAc was added into a solution of the crude product **(*S*)-L2-18(h)** in 20 mL EtOAc. Solid was formed after stirring for a few minutes. The precipitate was collected using filtration and washed with EtOAc three times to afford a yellow solid. Recrystallization of the yellow solid (hexane/^{i}PrOH/MeOH) four times to afford **(*S*)-L2-18(i)** (2.80 g, 47% yield) as a white solid. Chiral HPLC analysis indicates 99.5% *ee* for the corresponding amine.

^{1}H NMR (500 MHz, CD_3OD) δ 8.20 – 8.07 (m, 4H), 7.62 (t, *J* = 7.6 Hz, 2H), 7.56 – 7.42 (m, 5H), 7.02 (d, *J* = 8.1 Hz, 1H), 5.90 (s, 2H), 4.91 (br s, 3H), 4.74 (q, *J* = 6.6 Hz,

1H), 3.60 – 3.43 (m, 2H), 3.08 (ddd, *J* = 18.2, 5.5, 2.4 Hz, 1H), 2.96 (ddd, *J* = 18.5, 11.2, 7.9 Hz, 1H), 2.25 (s, 3H), 1.51 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR (126 MHz, CD_3OD)** δ 171.58, 167.32, 135.75, 135.66, 134.41, 132.89, 131.83, 131.32, 131.15, 130.96, 129.50, 123.55, 75.00, 49.29, 36.41, 27.47, 18.40, 17.95.

(*S*)-L2-18(i) (2.57g, 4.5 mmol) was added into a saturated Na_2CO_3 solution (50 mL). The resulting mixture was stirred vigorously until all solid was dissolved. Then the solution was exacted three times with DCM. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated to afford **(*S*)-L2-18(h)** (1.08 g, 100% yield) as a yellow oil.

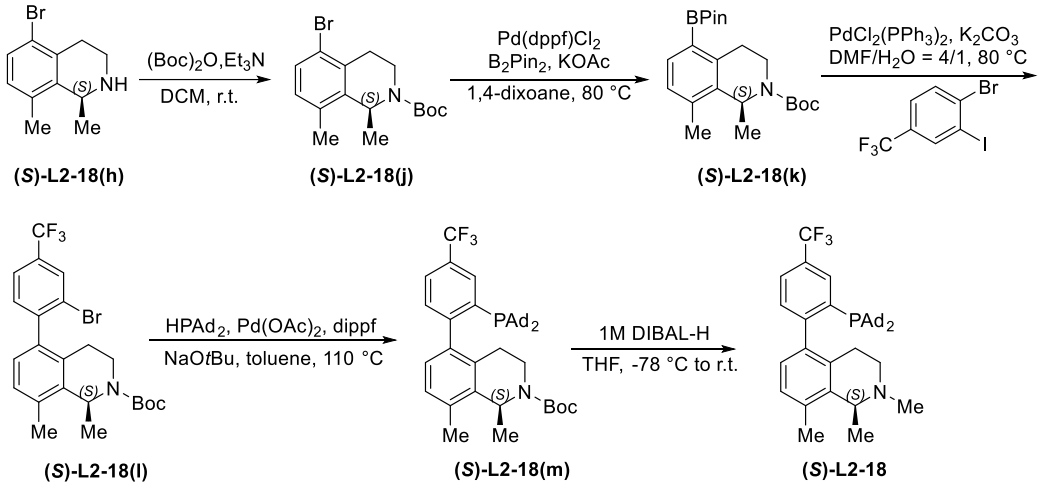
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.1 Hz, 1H), 6.85 (d, *J* = 8.1 Hz, 1H), 4.20 (q, *J* = 6.8 Hz, 1H), 3.27 (ddd, *J* = 13.3, 10.8, 5.5 Hz, 1H), 3.12 (ddd, *J* = 13.4, 7.0, 2.2 Hz, 1H), 2.77 (ddd, *J* = 17.6, 5.4, 2.2 Hz, 1H), 2.68 (ddd, *J* = 17.7, 10.9, 7.0 Hz, 1H), 2.23 (s, 3H), 1.38 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 141.94, 133.36, 133.29, 129.80, 129.32, 123.41, 77.25, 77.00, 76.75, 48.47, 37.18, 30.25, 20.43, 18.58; **HRMS (ESI-TOF)**: calculated for $[M+H]^+$ ($C_{11}H_{15}BrN$) requires *m/z* 240.0388, found *m/z* 240.0389; **99.5% *ee*** [determined by HPLC: Chiralcel® Chiral IC column, Hexane/^{i}PrOH/$HNEt_2$ = 97/3/0.1, 1.0 mL/min, λ = 225 nm; t_R(major) = 14.60 min, t_R(minor) = 12.10 min].

(*R*)-5-bromo-1,8-dimethyl-1,2,3,4-tetrahydroisoquinoline [(*R*)- L2-18(h)]

(*R*)- L2-18(h) was prepared using the same method as **(*S*)-L2-18(h)**. (1*S*, 2*S*)-TsDPEN was used in the asymmetric hydrogen transformation step. Dibenzoyl-*L*-tartaric acid was used in the recrystallization step.

99.7% *ee* [determined by HPLC: Chiralcel® Chiral IC column, Hexane/^{i}PrOH/$HNEt_2$ = 97/3/0.1, 1.0 mL/min, λ = 225 nm; t_R(major) = 11.88 min, t_R(minor) = 14.54 min].

Synthesis of (*S*)-L2-18



$(Boc)_2O$ (1.09 mL, 4.73 mmol) was added to a solution of **(*S*)-L2-18(h)** (1.08g, 4.5 mmol) and Et_3N (1.25 mL, 9 mmol) in 22.5 mL dichloromethane at 0 ℃, gas evolution was observed after adding $(Boc)_2O$. The reaction mixture was stirred overnight at room temperature. After removing the solvent under reduced pressure, the residue was purified by flash column chromatography (hexane/EtOAc = 20/1) to afford **(*S*)-L2-18(j)** (1.53 g, 100% yield) as a colorless oil.

$Pd(dppf)Cl_2•CH_2Cl_2$ (183.7 mg, 0.225 mmol), B_2Pin_2 (1.371 g, 5.4 mmol), KOAc (2.21g, 22.5 mmol), **(*S*)-L2-18(j)** (1.53 g, 4.5 mmol), and 22 mL dry 1,4-dioxane was added into a flamed dried Schlenk flask under nitrogen. The mixture was degassed by bubbling N_2 into the solution for 30 min and then heated to 80 ℃ for 24 h. Then the reaction mixture was cooled down to room temperature and filtrated through celite using DCM as eluent. The solvent of the filtrate was removed under reduced pressure, and the resulting

residue was purified by flash column chromatography (hexane/EtOAc = 20/1) to afford **(*S*)-L2-18(k)** (1.60 g, 92% yield) as a colorless oil, which solidified under high vacuum as a white solid.

$PdCl_2(PPh_3)_2$ (290.0 mg, 0.41 mmol), K_2CO_3 (2.28 g, 16.52 mmol), **(*S*)-L2-18(k)** (1.60 g, 4.13 mmol) were added into a Schlenk flask under nitrogen, followed by the addition of DMF (12 mL), H_2O (3 mL) and 1-bromo-2-iodobenzene (2.90 g, 8.26 mmol). The resulting mixture was degassed by bubbling N_2 for 30 min, and then heated to 80 ℃ for 24 h. The mixture was cooled down to room temperature and diluted with DCM. The organic layer was extracted three times with water, dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (hexane/EtOAc = 20/1) to afford **(*S*)-L2-18(l)** (1.47 g, 74% yield) as a colorless oil, which solidified under high vacuum as a white solid.

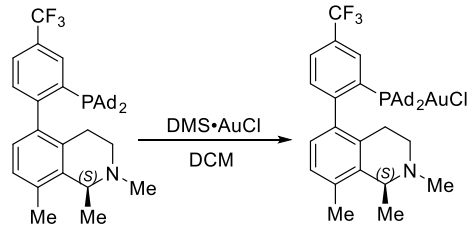
Under nitrogen atmosphere, **(*S*)-L2-18(l)** (1.47 g, 3.04 mmol), $Pd(OAc)_2$ (68.2 mg, 0.30 mmol),1,1'- bis(diisopropylphosphino)ferrocene (dippf, 152.6 mg, 0.36 mmol), NaO*t*Bu (876.4 mg, 9.12 mmol) and 15 mL dry toluene were added to a flamed dried Schlenk flask and the resulting suspension was stirred until apparently homogeneous (around 15 min). After adding di(1-adamantyl)phosphine (1.103 g, 3.65 mmol), the flask was heated at 110 ^oC in an oil bath for 24h, then cooled to room temperature, and filtrated through a pad of silica gel using DCM as eluent. The solvent of the filtrate was removed under reduced pressure, and the residue was purified by flash column chromatography (hexane only to hexane/EtOAc = 20/1) to afford **(*S*)-L2-18(m)** (1.61 g, 75% yield) as a colorless oil, which solidified under high vacuum as a white solid.

To a solution of **(*S*)-L2-18(m)** (1.61 g, 2.28 mmol) in dry THF (23 mL), DIBAL-H (1M in hexane, 46 mL, 46 mmol) was slowly added under nitrogen atmosphere at -78 ℃. After stirring at -78 ℃ for 2 h, the reaction mixture was slowly raised to room temperature and further stirring for 24 h. The reaction was diluted with ether, quenched carefully with water, and 15% *aq*. NaOH, dried over anhydrous $MgSO_4$. The reaction mixture was filtrated through celite to remove the insoluble solids. The solvent was removed under reduced pressure. The crude product was purified by recrystallization from DCM/MeOH to give **(*S*)-L2-18** (1.13 g, 70% yield) as a white solid.

^{1}H NMR (600 MHz, CD_2Cl_2) δ 8.17 (s, 1H), 8.14 (s, 1H), 7.59 (t, *J* = 8.2 Hz, 2H), 7.38 – 7.24 (m, 2H), 7.00 (dd, *J* = 7.6, 4.5 Hz, 2H), 6.86 (d, *J* = 7.6 Hz, 2H), 3.98 (q, *J* = 6.6 Hz, 1H), 3.89 (q, *J* = 6.6 Hz, 1H), 3.02 (td, *J* = 12.1, 8.0 Hz, 1H), 2.83 (td, *J* = 11.5, 4.5 Hz, 1H), 2.66 – 2.49 (m, 4H), 2.42 (s, 3H), 2.40 (s, 3H), 2.33 (s, 6H), 2.30 – 2.23 (m, 1H), 2.10 – 2.02 (m, 1H), 2.02 – 1.75 (m, 36H), 1.73 – 1.59 (m, 24H), 1.28 (d, *J* = 6.6 Hz, 3H), 1.20 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR (101 MHz, CD_2Cl_2)** δ 154.93, 154.84, 154.60, 154.51, 139.70, 139.64, 139.59, 139.50, 139.44, 138.64, 135.82, 135.80, 135.51, 135.49, 134.01, 133.74, 133.71, 133.68, 133.64, 133.50, 132.13, 132.07, 131.72, 131.66, 131.62, 131.28, 129.12, 129.09, 128.96, 128.92, 127.62, 127.60, 127.10, 127.03, 126.28, 125.11, 125.07, 125.03, 125.00, 124.90, 124.87, 124.83, 123.57, 56.33, 55.56, 45.64, 44.50, 42.81, 42.62, 42.52, 42.51, 42.49, 42.38, 42.29, 42.16, 38.49, 38.24, 38.19, 37.93, 37.80, 37.78, 37.54, 37.52, 37.17, 29.42, 29.40, 29.35, 29.34, 29.32, 29.27, 27.52, 26.26, 26.23, 19.12, 19.01, 18.07, 15.12. (As the coupling patterns could not be determined, all peaks were shown); **^{31}P NMR (162 MHz, CD_2Cl_2)** δ 23.12, 21.57; **^{19}F NMR (376 MHz, CD_2Cl_2)** δ -61.47, -

61.49. **HRMS (ESI-TOF)**: calculated for $[M+H]^+$ ($C_{39}H_{50}F_3NP$) requires *m/z* 620.3633, found *m/z* 620.3640.

Synthesis of (*S*)-L2-18AuCl



Chloro(dimethylsulfide)gold(I) (142 mg, 0.48 mmol) was added to a solution of **(*S*)-L2-18** (315 mg, 0.51 mmol) in 5 mL anhydrous DCM. The reaction mixture was stirred for 30 min at room temperature, and the solvent was evaporated off. The crude mixture was dissolved again in DCM and filtrated through a short pad of celite. The solvent was removed under the reduced pressure, and the resulting solid was recrystallized from DCM/pentane to afford **(*S*)-L2-18AuCl** (380.8 mg, 88% yield) as a white solid.

^{1}H NMR (600 MHz, CD_2Cl_2) δ 8.17 – 8.10 (m, 1H), 7.82 – 7.71 (m, 1H), 7.48 – 7.32 (m, 1H), 7.08 – 6.98 (m, 1H), 6.82 – 6.68 (m, 1H), 3.99 – 3.88 (m, 1H), 3.44 – 3.37 (m, 1H, minor), 3.04 – 2.84 (m, 1H), 2.69 – 2.59 (m, 1H, major), 2.54 – 2.30 (m, 7H), 2.22 – 1.92 (m, 19H), 1.74 – 1.60 (m, 12H), 1.34 – 1.25 (m, 3H); **^{13}C NMR (101 MHz, CD_2Cl_2)** δ 154.33, 154.19, 140.64, 140.47, 137.71, 137.65, 137.63, 137.58, 136.95, 136.41, 134.88, 134.81, 134.73, 134.66, 132.04, 132.00, 131.97, 131.93, 131.89, 131.84, 131.65, 131.33, 129.05, 128.98, 128.72, 128.65, 128.29, 128.27, 127.57, 127.48, 127.46, 127.43, 127.41, 127.37, 126.47, 126.18, 126.06, 125.77, 125.73, 123.01, 56.24, 55.90, 54.38, 54.11, 53.84, 53.57, 53.30, 45.53, 44.37, 43.66, 43.50, 43.44, 43.37, 43.14, 43.10, 43.07, 43.02, 42.99, 42.96, 42.45, 42.43, 42.42, 42.36, 42.34, 36.60, 36.58, 29.32, 29.27, 29.22, 29.17, 29.14,

29.08, 29.04, 27.72, 26.52, 19.59, 19.18, 18.19, 15.50, 14.57. (As the coupling patterns could not be determined, all peaks were shown); **^{31}P NMR (162 MHz, CD_2Cl_2)** δ 61.33, 61.12; **^{19}F NMR (376 MHz, CD_2Cl_2)** δ -61.88; **HRMS (ESI-TOF)**: calculated for $[M+H]^+$ ($C_{39}H_{50}AuClF_3NP$) requires *m/z* 852.2987, found *m/z* 852.2992.

2.5. References

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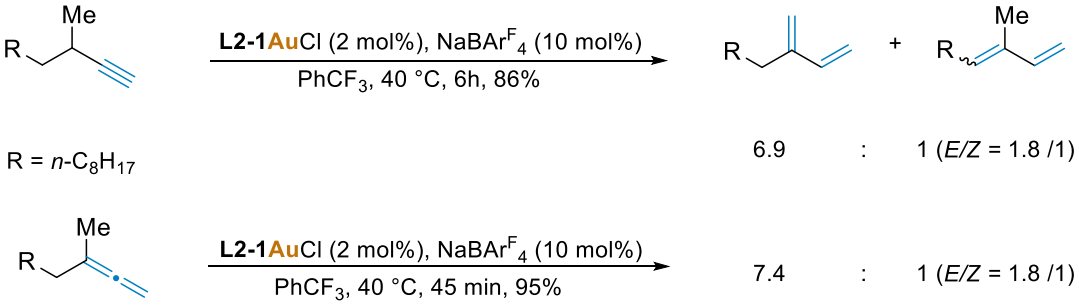
3. Asymmetric Cycloisomerization of Propargylic Alcohols into 2,5-Dihydrofuran

3.1. Introduction

As discussed in **Chapter 2.2.1**, internal alkynes could go through soft propargylic deprotonation promoted by gold-ligand cooperation to generate the allene intermediate **2-C**, which can be further isomerized to 1,3-diene via another proton migration process. However, allene intermediates were undetectable during the reaction process, suggesting allene isomerization is a facile transformation. As shown in Scheme 25, under the same reaction condition, allenes isomerization was much faster, i.e., 45 min, than alkynes isomerization, i.e., 6 h, which supports our assumption.

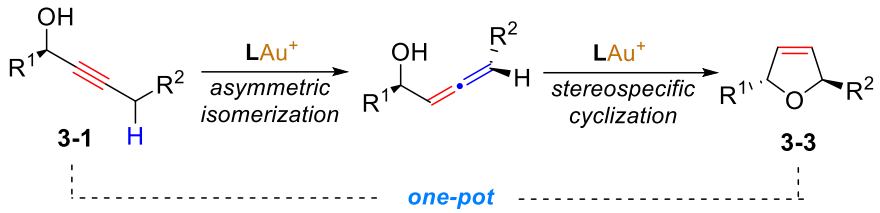
Scheme 25. Chemoselectivity Between Alkyne and Allene in the Process of Alkynes Isomerization



To expand our discovery beyond the scope of 1,3-diene formation, we envisioned that alternative reaction outcomes would emerge when the isomerization to 1,3-diene is impeded or disfavored. 5-*en*do-*trig* cyclization of allenyl alcohol [1-3] is a well-established facile transformation. Using the propargylic alcohol **3-1** as the substrate, we envisioned that cyclization of the allenol intermediate might outcompete the allene isomerization into diene to afford 2,5-dihydrofuran **3-3** as the final product (Scheme 26). Of note, with the

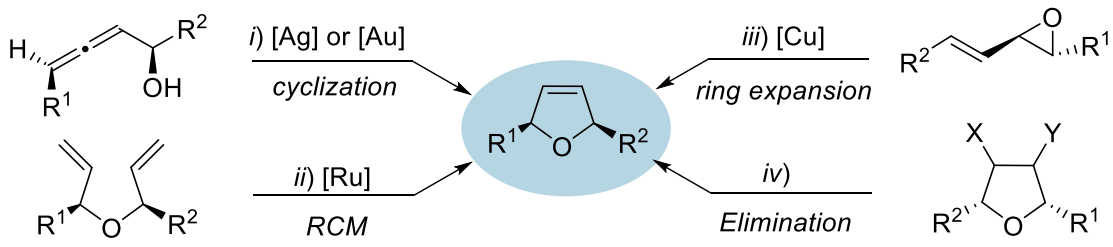
chiral version of the **L2-1** or **L2-2** as the ligand, chiral 2,5-dihydrofuran could be accessible via asymmetric isomerization of alkynes into allenes and stereospecific cyclization of allenols.

Scheme 26. Reaction Design for Asymmetric Cycloisomerization of Propargylic Alcohol



The typical approaches to the construction of chiral 2,5-disubstituted 2,5-dihydrofuran are shown in Scheme 27. The olefin ring-closing metathesis[4] (i.e., approaches ii) and the elimination[5] (i.e., approaches iv) do not feature an increase in stereochemical complexity as the two requisite chiral centers are preinstalled. The coin-metal catalyzed intramolecular cyclization of α-hydroxyallenes[6, 7] (i.e., approaches i) and stereoselective ring expansion of vinyl oxiranes [8] (i.e., approaches iv) also do not increase the stereochemical complexity because the new generated chiral elements are derived from existing chiral elements via stereoselective/stereospecific processes. An asymmetric approach starting from only one chiral element, as in the case of chiral propargylic alcohol, leads to enhanced stereochemical complexity and is inherently advantageous but has yet to be realized.

Scheme 27. Synthetic Approaches to Access Chiral 2,5-Disubstituted 2,5-Dihydrofuran

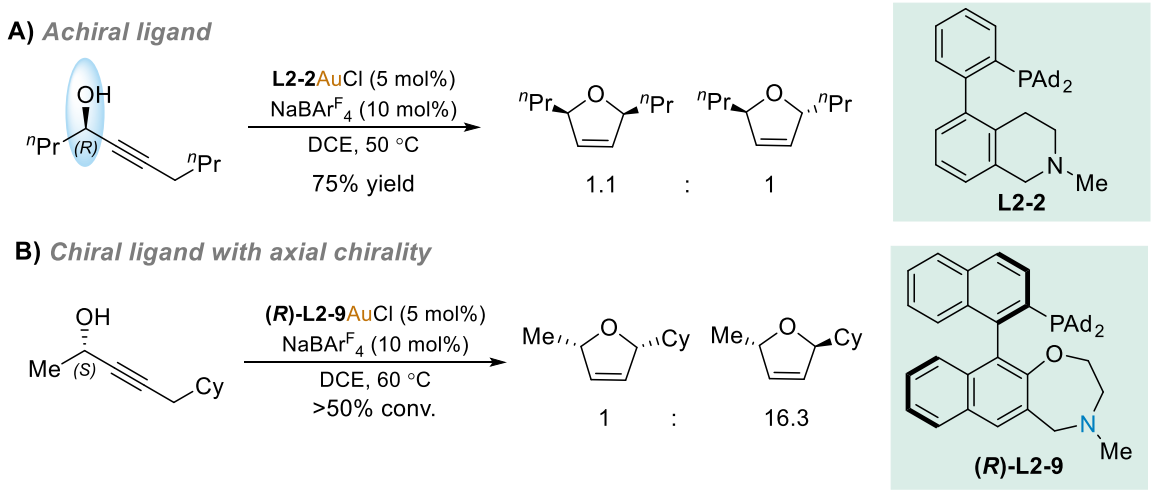


3.2. Reaction Conditions Optimization and Scope Study

3.2.1. Reaction Conditions Optimization

To validate our reaction design, the former member of our group, Dr. Wang, first examine the designed reaction under gold catalysis with achiral ligand **L2-2**. We chose chiral propargylic alcohols as the substrate because the pre-existing stereocenter permits expedient analysis of the stereoselectivity at the newly generated chiral center by examining the reaction diastereoselectivity. To our delight, 2,5-dihydrofuran was synthesized from (*R*)-dec-5-yn-4-ol in 75% yield and with *d.r* = 1.1/1 (Scheme 28A). Later, Dr. Wang synthesized the BINOL-type chiral bifunctional ligand (*R*)-**L2-9** and subjected the corresponding gold complex to similar reaction conditions (Scheme 28B) to afford chiral 2,5-dihydrofuran with a *trans/cis* ratio = 16.3 /1.

Scheme 28. Initial Result of Isomerization of Propargylic Alcohol

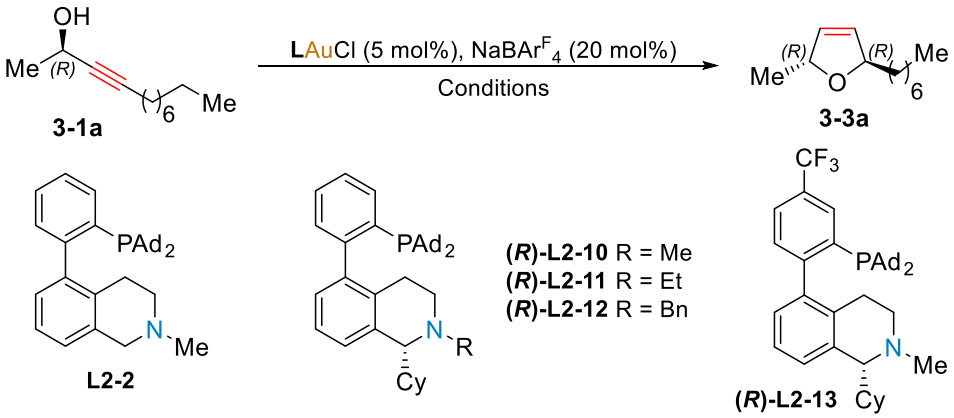


Although these results supported our assumption, the synthesis of chiral ligand (*R*)-**L2-9** suffered very poor yield in the PAd_2 installation step, as discussed in Chapter **2.3**. Thus, we decided to study this transformation using our newly designed chiral ligands [i.e. (*R*)-

L2-10 – (*R*)-**L2-13**] featuring a chiral center at the 1 position of the tetrahydroisoquinoline motif.

With the chiral ligands [i.e. (*R*)-**L2-10 –** (*R*)-**L2-13**] in hands, we set out to study the designed cycloisomerization by using (*R*)-dodec-3-yn-2-ol (**3-1a**, 99% ee) as the substrate (Table 1). Instead of the desired cycloisomerization, JohnPhos led only to the Meyer-Schuster rearrangement (entry 1). With the achiral **L2-2** as ligand, the desired 2,5-dihydrofuran **3-3a** was indeed formed in 79% yield but with little diastereoselectivity (entry 2). This result confirmed the essential role of the remote amino group in this reaction and revealed that the pre-existing stereocenter has little directing effect on the configuration of the newly generated stereocenter and likely the preceding allene chirality. To our delight, with (*R*)-**L2-10** featuring a bulky cyclohexyl group at its chiral center, the gold catalysis afforded **3-3a** in 70% yield and with a *trans/cis* ratio of 92/8 (entry 3). This amounts to >11:1 preference for the (*R*)-configuration at the new chiral center. Changing the ligand *N*-substituent from methyl in (*R*)-**L2-10** to bulkier ethyl in (*R*)-**L2-11** or benzyl in (*R*)-**L2-12** resulted in a significant decrease in conversion and, moreover, reaction yields (entries 4-5). The installation of an inductively electron-withdrawing CF_3 group on the C4 of (*R*)-**L2-10** delivered the ligand (*R*)-**L2-13**, which led to a better yield (76%) and a slightly improved diastereoselectivity (*trans/cis* = 93:7, entry 6). Further studies (entries 7-10) with (*R*)-**L2-13** as ligand revealed that a better yield (85%) could be achieved by running the gold catalysis at 80 ˚C and in a lower substrate initial concentration of 0.05 M (entry 10). A lower loading of $NaBAr^F_4$ or the addition of 3 Å MS led to a slightly lower yield (entries 11-12). It was also found that the solvent DCE was important for the optimal yield as $PhCF_3$, toluene, and PhF led to lower yields (entries 13-15).

Table 1. Asymmetric Cycloisomerization of Propargylic Alcohols Reaction Conditions Optimization. [a,b]



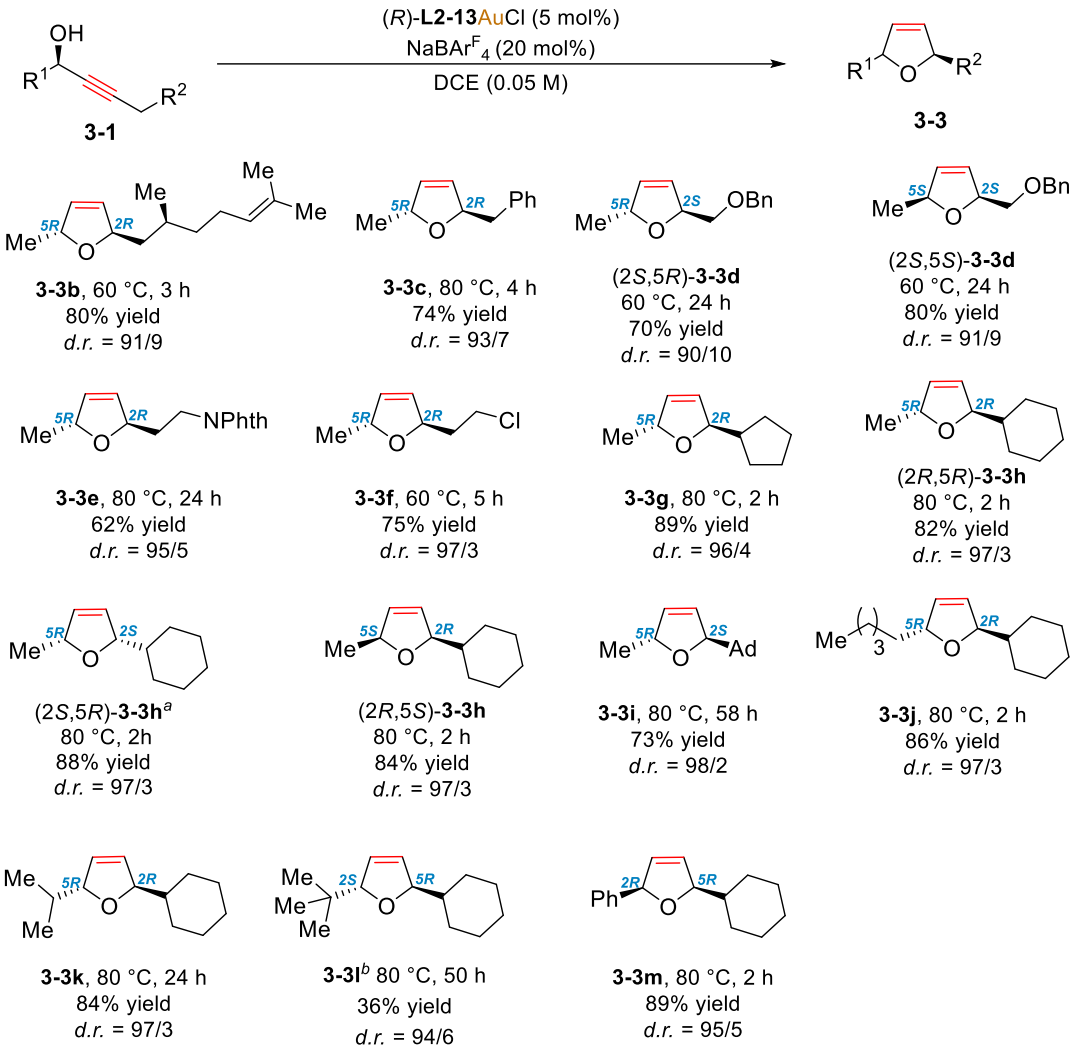
Entry	Ligand	Solvent	Temp/Time	Conv.	Yield	*d.r.*
1	JohnPhos	DCE (0.1 M)	60 °C/7 h	>99%	<1%	-
2	**L2-2**	DCE (0.1 M)	60 °C/4 h	>99%	79%	54:46
3	(*R*)-**L2-10**	DCE (0.1 M)	60 °C/7 h	>99%	70%	92:8
4	(*R*)-**L2-11**	DCE (0.1 M)	60 °C/7 h	48%	16%	89:11
5	(*R*)-**L2-12**	DCE (0.1 M)	60 °C/7 h	58%	3%	80:10
6	(*R*)-**L2-13**	DCE (0.1 M)	60 °C/7 h	>99%	76%	93:7
7	(*R*)-**L2-13**	DCE (0.1 M)	40 °C/18 h	>99%	48%	94:6
8	(*R*)-**L2-13**	DCE (0.1 M)	80 °C /2 h	>99%	83%	93:7
9	(*R*)-**L2-13**	DCE (0.25M)	80 °C /2 h	>99%	75%	93:7
10	(*R*)-**L2-13**	DCE (0.05 M)	80 °C /2 h	>99%	85%	93:7
11[c]	(*R*)-**L2-13**	DCE (0.05 M)	80 °C /2 h	>99%	79%	92:8
12[d]	(*R*)-**L2-13**	DCE (0.05 M)	80 °C /2 h	93%	69%	92:8
13	(*R*)-**L2-13**	Toluene (0.05 M)	80 °C /2 h	>99%	13%	91:9
14	(*R*)-**L2-13**	$PhCF_3$ (0.05 M)	80 °C /2 h	>99%	68%	93:7
15	(*R*)-**L2-13**	PhF (0.05 M)	80 °C /2 h	>99%	51%	93:7

[a] All the reactions were run in the 1-dram clean vials. The reaction scale is 0.05 mmol. [b] The NMR yields were determined by using 1,3,5-trimethoxybenzene as internal standard. [c] 10 mol% NaBAr$^F_4$. was used. [d] 5 mg 3 Å M.S was used.

3.2.2. Scope Study

With the optimized reaction conditions in hand, we set out to investigate the reaction scope (**Table 2**). Initially, a series of chiral secondary propargylic alcohols (**3-1**, R^1=alkyl or phenyl, R^2 = H) were examined. Various functional groups such as C-C double bond (**3-3b**), phenyl (**3-3c**), benzyloxy [(2*S*, 5*R*)- **3-3d**], phthalimide (**3-3e**), and chloro (**3-3f**) were all readily tolerated, and moderate to high yields and good diastereoselectivities were realized. Changing the R^2 group of **3-1** from linear chains to more steric hindered cyclopentyl (**3-3g**), cyclohexyl [(2*R*, 5*R*)-**3-3h**], and 1-adamantyl (**3-3i**) groups led to excellent diastereoselectivities without compromising the reaction yields. Switching the R^1 group from methyl to *n*-pentyl (**3-3j**), isopropyl (**3-3k**), or phenyl (**3-3m**) also resulted in excellent yield and diastereoselectivity. However, a *tert*-butyl group appeared detrimental and led to a much lower yield of **3-3l**, albeit the *trans/cis* selectivity remained excellent. Notably, the *cis*-counterpart of (2*S*, 5*R*)-**3-3d**, i.e., (2*S*, 5*S*)-**3-3d**, was readily accessed from the corresponding substrate enantiomer in a higher 80% yield and with a slightly improved *cis/trans* selectivity. Notably, (2*S*, 5*S*)-**3-3d** is a key intermediate employed in the total synthesis of (-)-varitriol.[9] A similar phenomenon was observed in the cases of (2*R*, 5*S*)-**3-3h** and (2*R*, 5*R*)-**3-3h**. Moreover, employing the ligand enantiomer, i.e., (*S*)-**L2-13**, (2*S*, 5*R*)-**3-3h** was isolated in 88% yield and with an identical 97/3 diastereomeric ratio. These results established that by using different combinations of **L2-13** and substrate enantiomers, all four stereoisomers of 2,5-disubstituted 2,5-dihydrofuran can be accessed with high to excellent levels of stereoselectivity.

Table 2. Asymmetric Cycloisomerization of Chiral Propargylic Alcohols

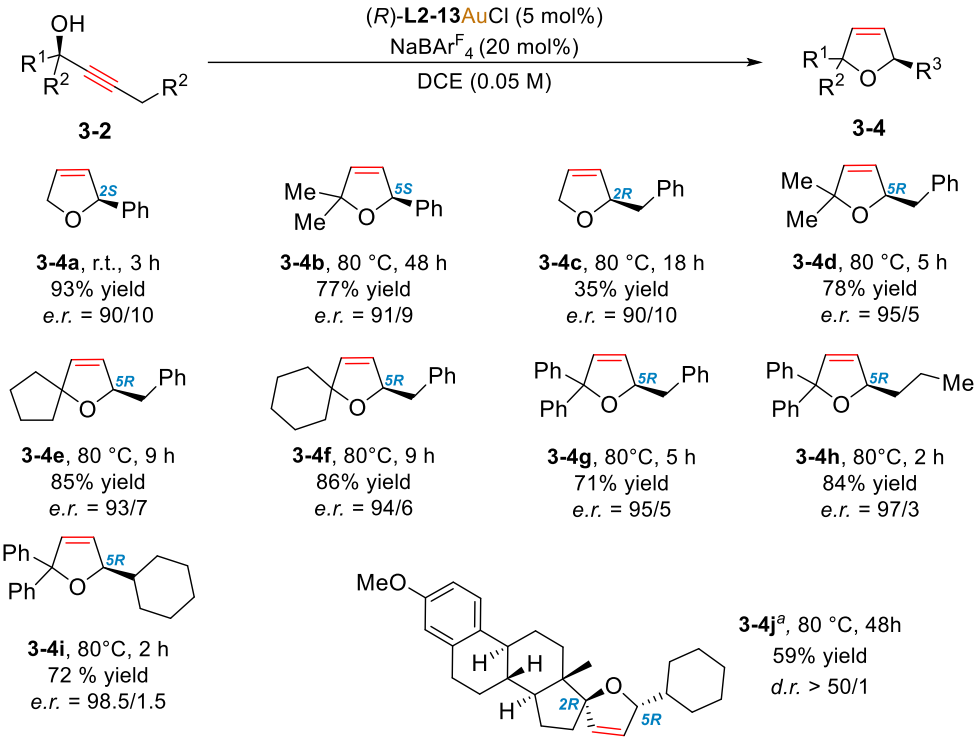


[a] [(*S*)-**L2-13**]AuCl used. [b] 10 mol% [(*R*)-**L2-13**]AuCl used.

We turned our attention next to achiral propargylic alcohol substrates **3-2** (Table 3). The enantioselective cycloisomerization occurred smoothly. In the cases of **3-4a** and **3-4b**, despite that chiral arylallenes are known to undergo rapid epimerization under gold catalysis,[10-12] products were still obtained with good enantiomeric ratios, comfirming the HO cyclization step is kinetically facile. While **3-4c** with a 2-benzyl group was formed in a low yield, its homologs derived from achiral tertiary propargylic alcohols such as **3-4d** - **3-4g** were all formed in good to excellent yields and with high enantiomeric ratios. The

tolerance of steric hindrance in these cases is notable. Outstanding asymmetric inductions by our chiral ligand were observed in the cases of **3-4h**, **3-4i,** and **3-4j** due mainly to increased steric bulk around the C-C triple bond. In the last case where the substrate was derived from estrone, the reaction was slow, likely due to steric hindrance, and required a higher catalyst loading and a longer reaction time. However, the cycloisomerization is exceptionally diastereoselective (>50:1).

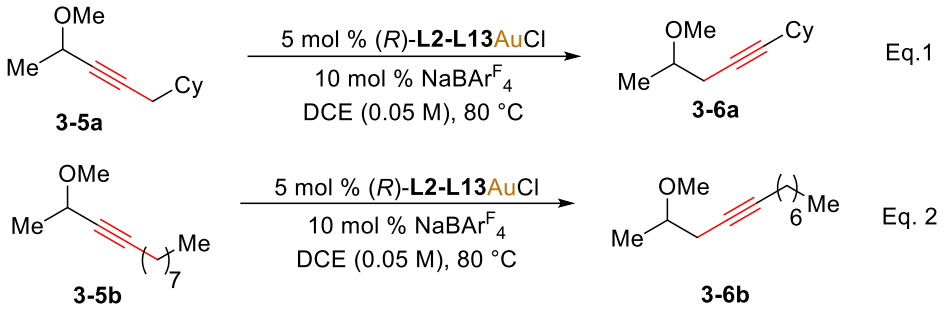
Table 3. Asymmetric Cycloisomerization of Achiral Propargylic Alcohols



[a] 10 mol% [(*R*)-**L2-13**]AuCl used.

Methyl propargyl ethers was used as substrates in control experiments.. As shown in Eq.1, subjecting **3-5a** to the gold catalysis, the reaction went through apparent 1,3-triple bond migration to afford **3-6a** as the major product (Eq.1), and the allene or the 1,3-diene was not observed during the transformation. In addition, the reaction was insensitive to steric hindrance as the substrate **3-5b** gave a similar outcome (Eq.2). These results

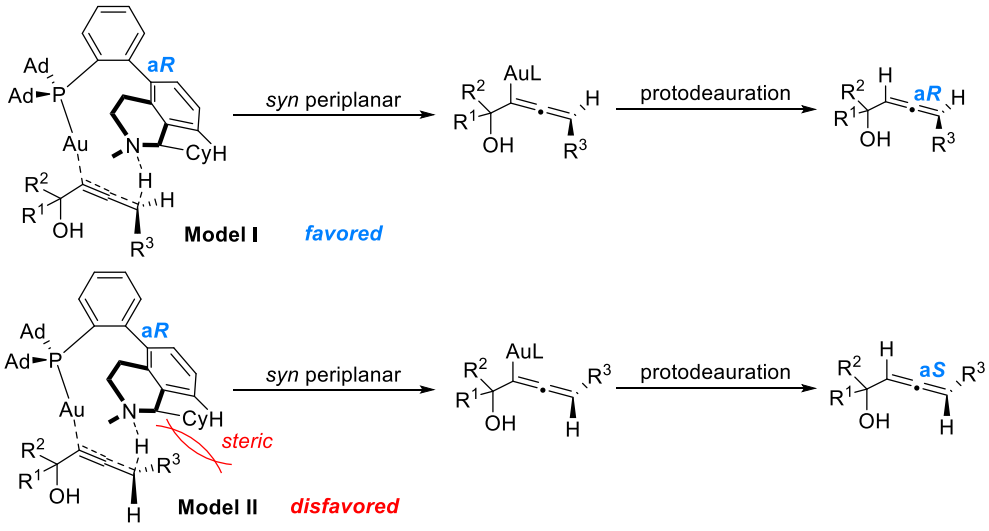
indicated the essential role of the *5-endo-dig* cyclization step in dictating the reaction outcome.



3.3. Proposed Mechanism

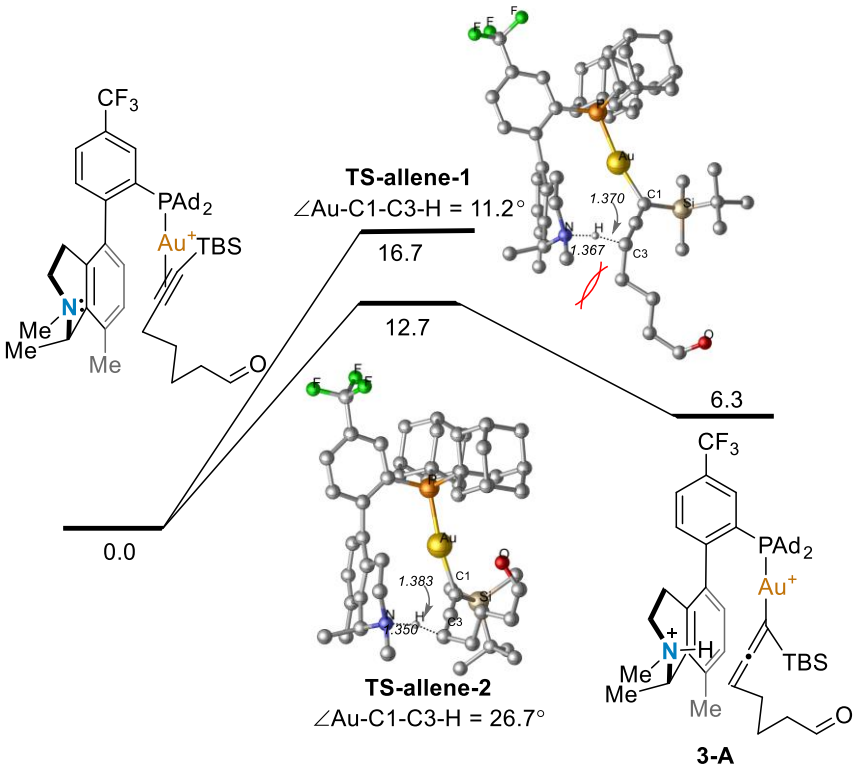
Previous DFT calculations[13] suggested the reaction should go through *syn*-periplanar deprotonation. As such, two competing models leading to opposing allene configurations can be constructed. As shown in Scheme 29, Model II experiences destabilizing steric interaction between the R^3 group and the ligand pendant arene ring, while Model I does not. Consequently, the deprotonation will favor the latter model. The predicted product is consistent with our experiment outcome, assuming that the subsequent protodeauration is stereoretentive, which is well documented.[14, 15]

Scheme 29. Reaction Models for Asymmetric Cycloisomerization of Alkynes



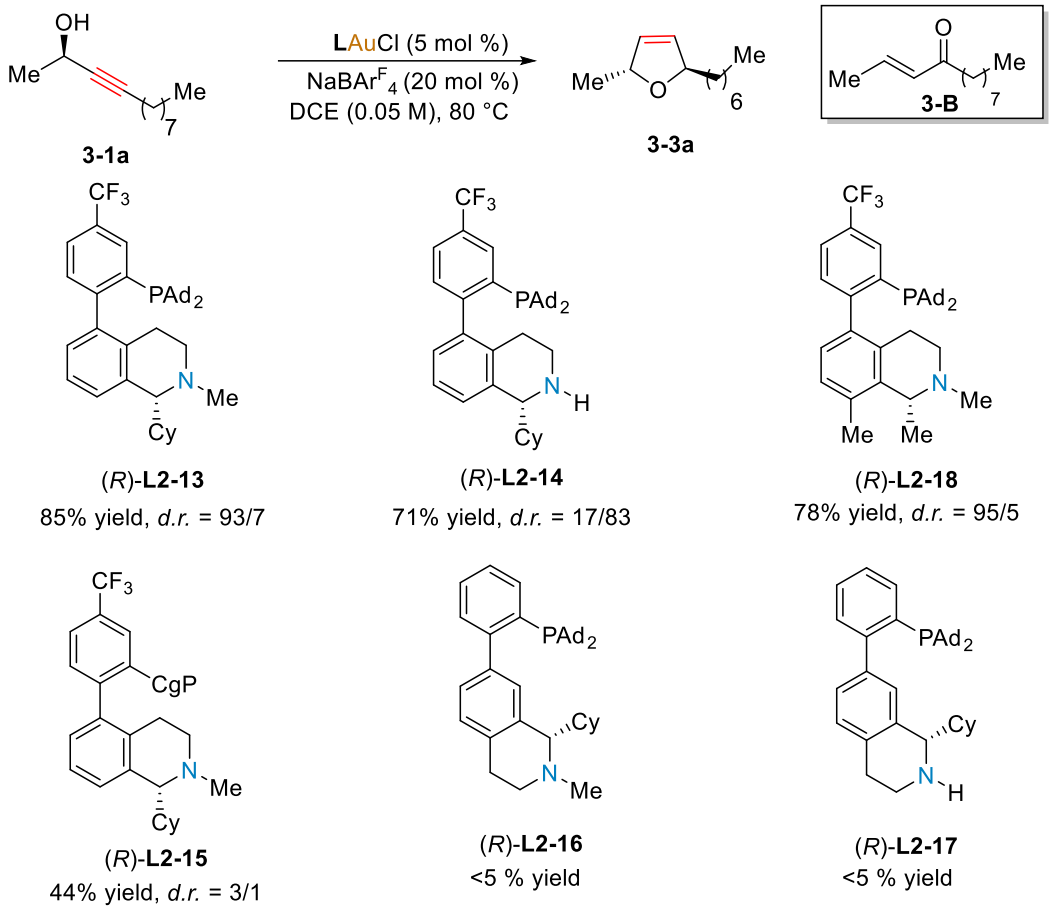
In **Chapter 2.3**, we discussed the intramolecular propargylation of aldehydes using (*S*)-**L2-18** as the ligand. A DFT calculation was performed to explain the stereochemistry outcome (Scheme 30). Although the ligands we used are different, the DFT calculation still provides valulabe insights into the *soft propargylic deprotonation* step. The deprotonation transition state **TS-allene-2** leading to the allenylgold intermediate **3-A** with an (a*R*)-allene is favored by 4.0 kcal/mol over **TS-allene-1**. This difference in activation energy can be largely attributed to the indicated steric congestion in the latter and is consistent with the observed high enantioselectivities. The deprotonation follows a *syn*-periplanar process with the dihedral angle of Au-C1-C3-H being 11.2º in **TS-allene-1** and 26.7º in **TS-allene-2**.

Scheme 30. DFT-Calculated Transition States for Soft Propargylic Deprotonation



3.4. Catalyst Reactivity Test and Extension to Other Substrates

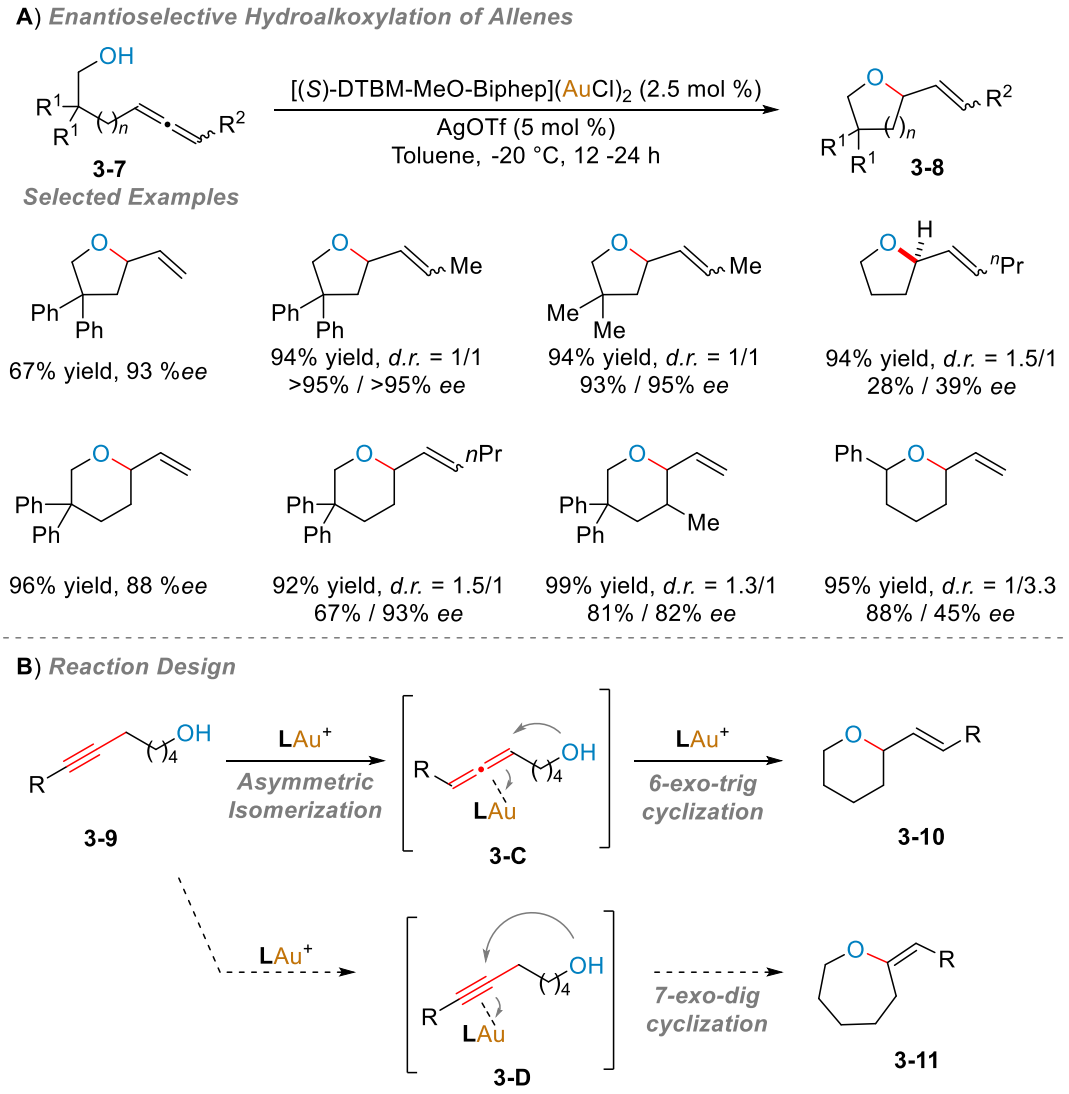
Scheme 31. Catalyst Reactivity Test



In **Chapter 2.3**, the synthesis of several chiral bifunctional ligands with central chirality was discussed. To test the reactivity of the corresponding gold complexes of these ligands, we set asymmetric cycloisomerization of chiral propargylic alcohol **3-1a** as the model reaction (**Scheme 31**). To our surprise, when the chiral ligand (*R*)-**L2-14** featuring a secondary amine was deployed as the ligand for the gold catalysis, 2,5-dihydrofuran **3-2a** was formed in 71% yield and with a *trans/cis* ratio of 17/83. Notably, the diastereoselective is reversed when replacing the methyl group [i.e., (*R*)-**L2-13**] on the basic ligand nitrogen with a hydrogen [i.e., (*R*)-**L2-14**], albeit the yield remains excellent. In line with the previous results, the trimethyl chiral ligand (*R*)-**L2-18** offered slightly

higher diastereoselectivity compared with **(*R*)-L2-13**. The chiral cage ligand (*R*)-**L2-15** led to moderate yield and poor enantioselectivity. Moving the basic ligand nitrogen to another position [i.e., (*R*)-**L2-16**, (*R*)-**L2-17**] afforded the enone **3-B** as the major product via the Meyer-Schuster arrangement. This result revealed that an appropriate position for ligand basic nitrogen is essential for the desired cooperative gold catalysis.

Scheme 32. Access Chiral Tetrahydropyran with Gold Catalysis



In 2006, Widenhoefer reported[16] the synthesis of chiral tetrahydrofurans or tetrahydropyrans via enantioselective hydroalkoxylation of allenes (Scheme 32A). The *Si*-

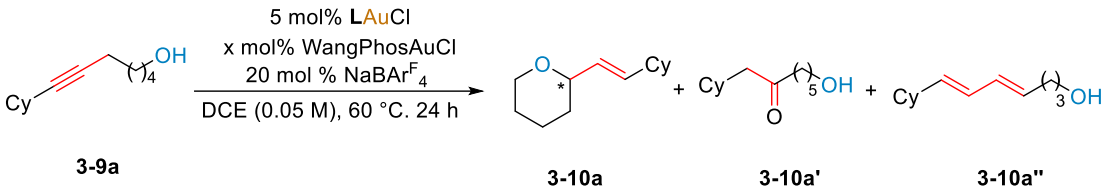
face of the allene is preferred for oxygen atom attack with chiral binuclear gold complex. The *E/Z* isomers were generated as a mixture with high enantioselectivities because the racemic allenol was used as the starting material. Notably, the Thorpe-Ingold effect plays a crucial role in the enantioselectivity since the unsubstituted allenol substrate formed tetrahydrofuran with less than 40% *ee*. Later, as discussed in Chapter 1, Toste[17] used the chiral counterion strategies to access the same type of substrates.

Our ligand design offers an expedited way of accessing chiral allenes, which could be harvested by a *5-endo-trig* cyclization reaction. As exemplified in Scheme 32B, *6-exo-trig* cyclization could be another reaction pathway to expand our reaction design further and offers access to enantiomerically enriched tetrahydropyrans **3-10**. The competing direct 7-*exo-dig* cyclization might have a higher energy barrier than then tandem isomerization/6-*exo-trig* cyclization and thus less favorable.

To begin with, we chose 6-cyclohexyl-5-hexyn-1-ol as the substrate to study the tandem isomerization/6-*exo-trig* cyclization (Table 4). To our delight, the desired chiral tetrahydropyran **3-10a** was formed in 32% yield and with -20% *ee* using **(*R*)-L2-13** as the ligand for gold catalysis. In addition, 20% 1,3-diene **3-10a''** was also observed in the product mixture, suggesting that the allene isomerization has a comparable reaction rate with *6-exo-trig* cyclization (entry 1). To speed up the cyclization and suppress the 1,3-diene formation, 0.1 mol% WangPhos was used to afford **3-10a** in 68% yield and with 55% *ee*. Although the amount of 1,3-diene **3-10a''** decreased from 20% to 2%, the hydrolysis product of *7-exo-dig* cyclization, i.e., **3-10a'**, emerged due to more facile alkyne hydroalkoxylation promoted by WangPhosAuCl (entry 2). Increasing the loading of WangPhosAuCl from 0.5 mol% to 10 mol% led to improvement in enantioselectivity and

a lower yield due to the formation of side product **3-10a'** (entry 3-4, 6-7). Changing the ligand from (*R*)-**L2-13** into (*R*)-**L2-18** offered a comparable result (entry 5). The lower the reaction temperature, i.e., 40 ˚C, gave a slight boost in enantioselective and a significant decrease in the reaction yield (entry 8). The higher reaction temperature was detrimental to the enantioselectivity (entry 9). More reaction condition screening is required to improve the enantioselectivity and suppress the formation of **3-10a'**.

Table 4. Reaction Conditions Optimization for 6-Cyclohexyl-5-Hexyn-1-ol



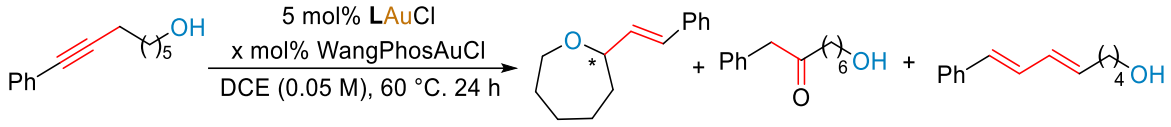
3-9a **3-10a** **3-10a'** **3-10a''**

Entry	Ligand	WangPhosAuCl Loading (mol %)	Conv.	**3-10a**	**3-10a'**	**3-10a''**	*ee*
1	(*R*)-**L2-13**	-	70%	32%	-	20%	-20%
2	(*R*)-**L2-13**	0.1	100%	68%	10%	2%	55%
3	(*R*)-**L2-13**	0.5	100%	69%	16%	-	67%
4	(*R*)-**L2-13**	1	100%	57%	36%	-	77%
5	(*R*)-**L2-18**	1	100%	52%	45%	-	78%
6	(*R*)-**L2-13**	5	100%	36%	57%	-	86%
7[a]	(*R*)-**L2-13**	10	100%	18%	80%	-	89%
8[b]	(*R*)-**L2-13**	5	100%	24%	50%	-	91%
9[c]	(*R*)-**L2-13**	5	100%	45%	50%	-	82%

[a] 40 mol % NaBAr$^F_4$; [b] 40 ˚C; [c] 80 ˚C

In addition to the *6-exo-trig* cyclization, we also studied the 7-*exo-trig* cyclizaiton using 7-phenyl-6-heptyn-1ol as the substrate (Table 5). To our disappointment, 7-*exo-trig* cyclization was sluggish even in the presence of 20 mol% WangPhosAuCl and could not outcompete with the isomerization of allene into 1,3-diene **3-10b''** (entry 1-3).

Table 5. Preliminary Studies on the Cycloisomerization of for 7-Phenyl-6-Heptyn-1-ol



3-9b **3-10b** **3-10b'** **3-10b"**

Entry	Ligand	WangPhosAuCl Loading	**3-10b**	**3-10b'**	**3-10b''**
1	(*R*)-**L2-13**	-	3%	-	71%
2	(*R*)-**L2-13**	1	5%	-	65%
3	(*R*)-**L2-13**	20	13%	-	27%

3.5. Conclusion

In conclusion, for the first time, a generally applicable asymmetric isomerization of alkynes to chiral allenes is realized via homogeneous gold catalysis enabled by a designed chiral bifunctional biphenyl-2-ylphosphine ligand. Instead of relying on a chiral biaryl axis to achieve asymmetry, this catalysis employs a more readily installed center chirality in the designed ligand. With chiral or nonchiral propargylic alcohols as substrates, chiral 2,5-dihydrofurans are directly formed in mostly good yields and importantly with good to excellent levels of stereoselectivity at the newly generated stereocenter. In addition, this transformation was deployed as the model reaction to exam the reactivity of other chiral

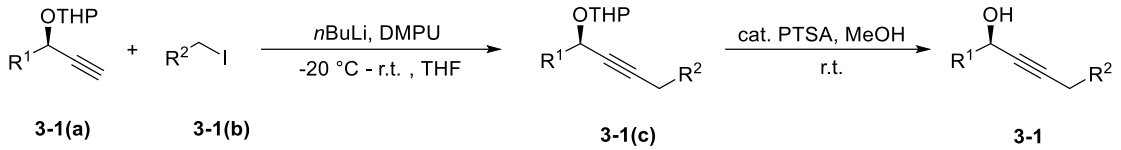
bifunctional ligands. Chemoselectivity and regioselectivity issues emerged when the reaction design was applied to 6-*exo-trig* and 7-*exo-trig* cyclization.

3.6. Experimental Section

General: Ethyl acetate (ACS grade), hexanes (ACS grade), and diethyl ether (ACS grade) were purchased from Fisher Scientific and used without further purification. Anhydrous dichloromethane (HPLC grade), 1,2-dichloroethane (HPLC grade) were purified by distillation over calcium hydride. Tetrahydrofuran and toluene were distilled over sodium/benzophenone. Commercially available reagents were used without further purification. (*R*)-3-butyn-2-ol (99.8% *ee*) and (*S*)-3-butyn-2-ol (99.8% *ee*) were purchased from Oakwood Chemicals. Reactions were monitored by thin-layer chromatography (TLC) using Silicycle precoated silica gel plates. Flash column chromatography was performed over Silicycle silica gel (230-400 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian 400 MHz, 500 MHz, and 600 MHz spectrometers using residue solvent peaks as internal standards ($CDCl_3$, ^{1}H: 7.26 ppm; ^{13}C: 77.00 ppm. CD_2Cl_2, ^{1}H: 5.32 ppm; ^{13}C: 53.84 ppm.). ^{31}P NMR spectra were recorded on an Agilent 400MHz spectrometer calibrated by phosphoric acid peak (H_3PO_4, ^{31}P: 0.00 ppm). ^{19}F NMR spectra were recorded on an Agilent 400MHz spectrometer calibrated by trifluoroacetic acid peak (CF_3COOH, ^{19}F: -76.55 ppm).

Preparation of Propargylic Alcohol

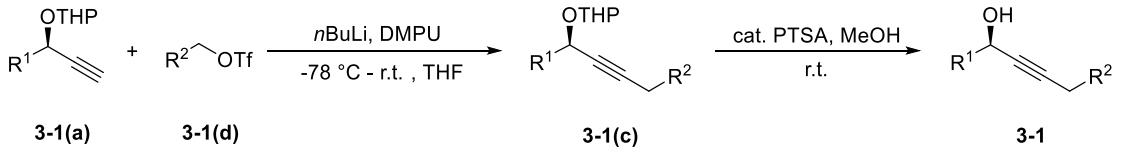
General Procedure A:



3-1(a) **3-1(b)** **3-1(c)** **3-1**

To a solution of the alkyne (**3-1(a)**, 3 mmol) in dry THF (6 mL), *n*-BuLi (2.5 M in hexane, 1.5 mL, 3.6 mmol) was added under nitrogen atmosphere at -20 ℃ (ice-salt bath) and stirred for 30 min. A mixture of alkyl iodide (**3-1(b)**, 6 mmol) and *N*, *N*′-Dimethylpropyleneurea (DMPU, 0.8 mL) were added to the resulting reaction mixture. The reaction mixture was slowly raised to room temperature and further stirred for 12 h. The reaction was quenched with *saq*. NH_4Cl (*aq*). The aqueous phase was extracted with Et_2O three times; the combined organic phase was washed with *saq.* NaCl(*aq*), dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography, resulting in an inseparable mixture of THP protected chiral propargylic alcohol **3-1(c)** and unreacted alkyne **3-1(a)**. This mixture was dissolved in MeOH (10 mL), followed by adding *p*-toluenesulfonic acid monohydrate (30 mg, 0.16 mmol), and stirred at room temperature until reaction completion. An excess amount of $NaHCO_3$ solid was added into the reaction mixture and stirring for 30 min. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography, resulting in the desire propargylic alcohol **3-1**.

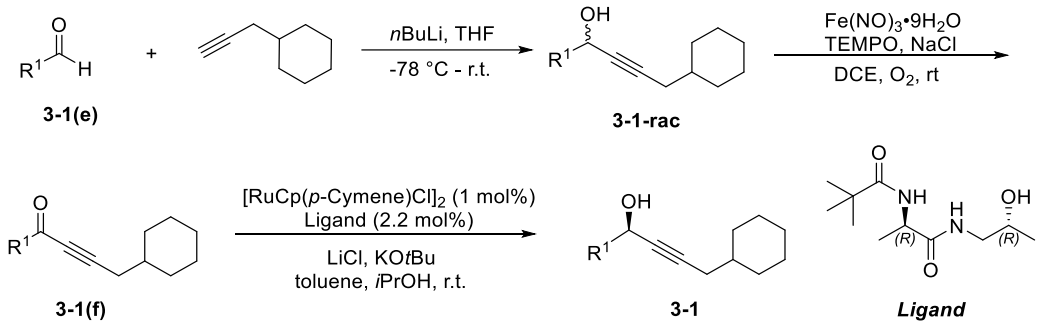
General Procedure B:



3-1(a) **3-1(d)** **3-1(c)** **3-1**

To a solution of the alkyne (**3-1(a)**, 3 mmol) in dry THF, *n*-BuLi (2.5 M in hexane, 1.5 mL, 3.6 mmol) was added under nitrogen atmosphere at -78 ℃ and stirred for 5 min. *N*, *N*′ -Dimethylpropyleneurea (DMPU, 0.8 mL) was added into the reaction mixture and further stirring for 30 min. Then the reaction mixture was raised to -20 ℃, followed by the addition of alkyl triflate (**3-1(d)**, 3.6 mmol). Then the mixture was slowly warm up to room temperature and further stirred for 12 h. The reaction was quenched with *saq*. NH_4Cl (*aq*). The aqueous phase was extracted with Et_2O three times; the combined organic phase was washed with *saq.* NaCl(*aq*), dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography to resulting THP protected chiral propargylic alcohol **3-1(c)**. This mixture was dissolved in MeOH (10 mL), followed by adding *p*-toluenesulfonic acid monohydrate (30 mg, 0.16 mmol), and stirred at room temperature until reaction completion. An excess amount of $NaHCO_3$ solid was added into the reaction mixture and stirring for 30 min. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography, resulting in the desire propargylic alcohols **3-1**.

General Procedure C:



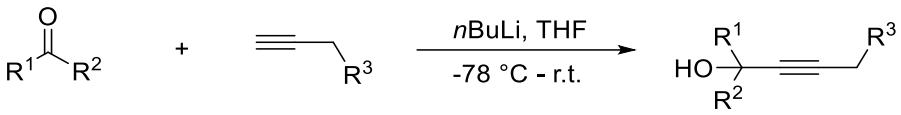
To a solution of 3-cyclohexyl-1-propyne (611.1 mg, 5 mmol) in dry THF, *n*-BuLi (2.5 M in hexane, 2.0 mL, 5 mmol) was added under nitrogen atmosphere at -78 ℃ and stirred for 30 min. Aldehyde [**3-1(*e*)**, 5 mmol] was added into the resulting reaction mixture and further stirring for 30 min at -78 ℃. The reaction mixture was slowly raised to room temperature and quench with *saq*. NH_4Cl (*aq*). The aqueous phase was extracted with Et_2O three times; the combined organic phase was washed with saq. NaCl(*aq*), dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography to resulting in the racemic propargylic alcohol **3-1-rac.**

Following literature procedure, [18] oxidation was performed in a round bottom flask equipped with a rubber septum, stirring bar, and oxygen balloon. Iron (III) nitrate nonahydrate (50.5 mg, 0.125 mmol), TEMPO (11.7 mg, 0.075 mmol), and sodium chloride (7.3 mg, 0.125 mmol) were dissolved in DCE (1.25 mL) and stirred under oxygen for 5 minutes. Then alcohol **3-1-rac** (2.5 mmol) was added, and the reaction was stirred for several dozen hours with monitoring by TLC. When maximum conversion seemed to be reached, the reaction mixture was diluted with diethyl ether, filtered through celite. The solvent was removed under reduced pressure, and the reside was purified by flash column chromatography to afford propargylic ketones **3-1(f)**.

Following literature procedure, [18] dichloro(p-cymene)ruthenium (II) dimer (12.2 mg, 1 mol %, 0.02 mmol) was evacuated for 15 min in a Schlenk flask equipped with a stirring bar and septa. The reaction vial was then filled with nitrogen, after which lithium chloride (0.2 mmol, 10 mol %, 0.532% w/w solution in IPA, 2 mL), pseudo-dipeptide ligand (0.044 mmol, 2.2 mol %, 0.682% w/w solution in IPA, 2 mL), ketone **3-1(f)** (2 mmol), and degassed toluene (14 mL) were added. The reaction mixture was then stirred

for 10 min, after which potassium *tert*-butoxide (0.2 mmol, 10 mol %, 1.4% w/w solution in IPA, 2 mL) was added, and stirring was continued at room temperature for several dozen hours with monitoring by TLC. When maximum conversion seemed to be reached, the reaction mixture was filtrated through a pad of celite using DCM as eluent. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography to afford chiral propargylic alcohol **3-1**.

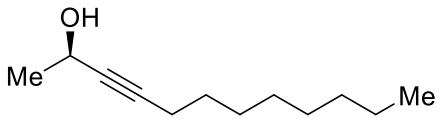
General Procedure D:



3-2(a) **3-2(b)** **3-2**

To a solution of alkyne [**3-2(a)**, 3 mmol] in dry THF, *n*-BuLi (2.5 M in hexane, 1.2 mL) was added under nitrogen atmosphere at -78 ℃ and stirred for 30 min. Ketone [**3-2(b)**, 3 mmol] was added into the resulting reaction mixture and further stirring for 30 min at -78 ℃. The reaction mixture was slowly raised to room temperature and quench with *saq*. NH_4Cl (*aq*). The aqueous phase was extracted with Et_2O three times; the combined organic phase was washed with saq. NaCl(*aq*), dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography, resulting in the desire propargylic alcohol **3-2**.

(*R*)-dodec-3-yn-2-ol (3-1a)

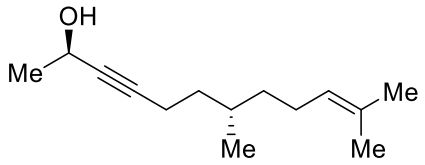


3-1a

Following general procedure A, THP protected (*R*)-3-butyl-2-ol (3 mmol, 462.6 mg) was reacted with 1-iodooctante (6 mmol, 1.44 g) to give **3-1a** (330.1 mg, 63 % overall yield) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.50 (qt, *J* = 6.5, 1.9 Hz, 1H), 2.18 (td, *J* = 7.2, 1.9 Hz, 2H), 1.48 (p, *J* = 7.2 Hz, 2H), 1.42 (d, *J* = 6.5 Hz, 3H), 1.39 – 1.21 (m, 10H), 0.87 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 84.73, 82.14, 58.57, 31.81, 29.15, 29.06, 28.83, 28.61, 24.72, 22.63, 18.61, 14.09; **HRMS (EI-TOF)**: calculated for $[M]^+$ ($C_{12}H_{22}O$) requires *m/z* 182.1671, found *m/z* 182.1666.

(2*R*,7*S*)-7,11-dimethyldodec-10-en-3-yn-2-ol (3-1b)

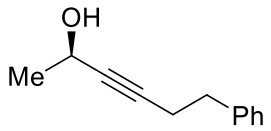


3-1b

Following general procedure A, THP protected (*R*)-3-butyl-2-ol (3 mmol, 462.6 mg) was reacted with (*S*)-8-iodo-2,6-dimethyloct-2-ene (6 mmol, 1.60 g) to give **3-1b** (449.3 mg, 72% overall yield) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.12 – 5.07 (m, 1H), 4.51 (qt, *J* = 6.6, 1.9 Hz, 1H), 2.27 – 2.13 (m, 2H), 2.06 – 1.90 (m, 2H), 1.69 – 1.67 (m, 3H), 1.61 (s, 3H), 1.58 – 1.48 (m, 2H), 1.42 (d, *J* = 6.5 Hz, 3H), 1.38 – 1.28 (m, 2H), 1.15 (m, *J* = 13.4, 9.4, 7.5, 6.0 Hz, 1H), 0.88 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 131.23, 124.72, 84.85, 82.09, 58.63, 36.65, 35.69, 31.65, 25.70, 25.40, 24.75, 19.09, 17.65, 16.36; **HRMS (EI-TOF)**: calculated for $[M]^+$ ($C_{14}H_{24}O$) requires *m/z* 208.1827, found *m/z* 208.1836.

(*R*)-6-phenylhex-3-yn-2-ol (3-1c)



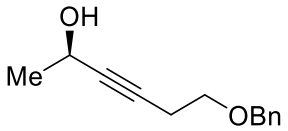
3-1c

To a solution of THP protected (*R*)-3-butyl-2-ol (3 mmol, 462.6 mg) in dry THF (6 mL), *n*-BuLi (2.5 M in hexane, 1.5 mL, 3.6 mmol) was added under nitrogen atmosphere at -78 ℃ and stirred for 30 min. The reaction mixture was warmed up to room temperature, followed by the addition of NaI (22.5 mg, 0.15 mmol). Then the mixture was cooled back to -78 ℃ and phenethyl bromide (610.7 mg, 3.3 mmol) was added to the reaction mixture. Then the mixture was slowly warmed up to room temperature and refluxed for 12 h. The reaction was quenched with *saq*. NH_4Cl (*aq*). The aqueous phase was extracted with Et_2O three times; the combined organic phase was washed with *saq*. NaCl(*aq*), dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (hexane/EtOAc = 20: 1) to resulting in an inseparable mixture of THP protected (*R*)-3-butyl-2-ol and THP protected (*R*)-6-phenylhex-3-yn-2-ol. This mixture was dissolved in MeOH (10 mL), followed by adding p-toluenesulfonic acid monohydrate (30 mg, 0.16 mmol), and stirred at room temperature until reaction completion. An excess amount of $NaHCO_3$ solid was added into the reaction mixture and stirring for 30 min. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (hexane /EtOAc = 10: 1) to give **3-1c** (63.7 mg, 12% overall yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 2H), 7.26 – 7.21 (m, 3H), 4.50 (qt, *J* = 6.5, 1.9 Hz, 1H), 2.83 (t, *J* = 7.6 Hz, 2H), 2.50 (td, *J* = 7.6, 1.9 Hz, 2H), 1.42 (d, *J* = 6.6

Hz, 3H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 140.55, 128.43, 128.32, 126.27, 83.84, 83.01, 58.51, 35.00, 24.61, 20.84; These data are in accordance with literature. [19]

(*R*)-6-(benzyloxy)hex-3-yn-2-ol [(*R*)-3-1d]

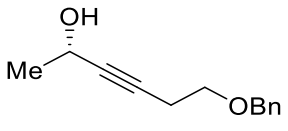


(*R*)-3-1d

Following general procedure A, THP protected (*R*)-3-butyl-2-ol (3 mmol, 462.9 mg) was reacted with 1-benzyloxy-2-iodoethane (6 mmol, 1.57 g) to give (*R*)-**3-1d** (386.1 mg, 63 % overall yield) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.33 (m, 4H), 7.32 – 7.27 (m, 1H), 4.55 (s, 2H), 4.50 (qt, *J* = 6.6, 2.0 Hz, 1H), 3.58 (t, *J* = 7.0 Hz, 2H), 2.52 (td, *J* = 7.0, 1.9 Hz, 2H), 1.42 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 137.98, 128.38, 127.68, 127.67, 83.31, 81.17, 72.90, 68.26, 58.44, 24.52, 20.05; These data are in accordance with literature. [20]

(*S*)-6-(benzyloxy)hex-3-yn-2-ol [(*S*)-3-1d]

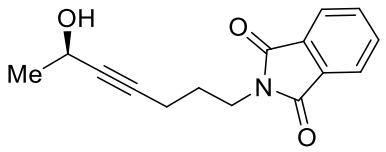


(*S*)-3-1d

Following general procedure A, THP protected (*S*)-3-butyl-2-ol (3 mmol, 462.9 mg) was reacted with 1-benzyloxy-2-iodoethane (6 mmol, 1.57 g) to give (*S*)-**3-1d** (313.9 mg, 51 % overall yield) as a colorless oil.

^{1}H NMR is identical with (*R*)-**3-1d.**

(*R*)-2-(6-hydroxyhept-4-yn-1-yl)isoindoline-1,3-dione (3-1e)

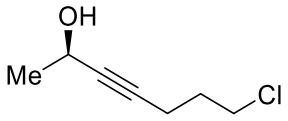


3-1e

To a solution of (*R*)-7-chlorohept-3-yn-2-ol (**3-1f**, 337.2 mg, 2.30 mmol) and phthalimide (406.0 mg, 2.76 mmol) in DMF (3 mL), potassium iodide (10.0 mg, 0.06 mmol) and potassium carbonate (560.0 mg, 4.06 mmol) was added and the reaction mixture was stirred at 60 ℃ for 8 h. The solution was diluted with DCM; the organic layer was washed three times with water and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (hexane/EtOAc = 2: 1) to afford **3-1e** (503.0 mg, 85% yield) as a white solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85 – 7.79 (m, 2H), 7.72 – 7.67 (m, 2H), 4.37 (qt, *J* = 6.6, 1.8 Hz, 1H), 3.78 (t, *J* = 7.0 Hz, 2H), 2.25 (td, *J* = 6.9, 1.9 Hz, 2H), 1.89 (p, *J* = 6.9 Hz, 2H), 1.33 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 168.38, 133.96, 132.01, 123.22, 83.28, 82.95, 58.33, 37.08, 27.07, 24.43, 16.32; **HRMS (EI-TOF)**: calculated for $[M-H_2O]^+$ ($C_{15}H_{13}NO_2$) requires *m/z* 239.0946, found *m/z* 239.0936.

(*R*)-7-chlorohept-3-yn-2-ol (3-1f)

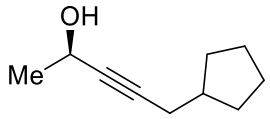


3-1f

Following general procedure B, THP protected (*R*)-3-butyl-2-ol (3 mmol, 462.9 mg) was reacted with 3-chloropropyl triflate (3.6 mmol, 815. 7 mg) to give **3-1f** (368.4 mg, 84 % overall yield) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.50 (qt, *J* = 6.5, 1.9 Hz, 1H), 3.63 (t, *J* = 6.3 Hz, 2H), 2.39 (td, *J* = 6.9, 2.0 Hz, 2H), 1.95 (p, *J* = 6.6 Hz, 2H), 1.86 (br s, 1H), 1.42 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 83.19, 82.49, 58.45, 43.61, 31.20, 24.63, 16.03; **HRMS (EI-TOF)**: calculated for $[M]^+$ ($C_7H_{11}ClO$) requires *m/z* 146.0498, found *m/z* 146.0492.

(*R*)-5-cyclopentylpent-3-yn-2-ol (3-1g)

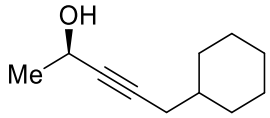


3-1g

Following general procedure B, THP protected (*R*)-3-butyl-2-ol (3 mmol, 462.9 mg) was reacted with cyclopentylmethyl triflate (3.6 mmol, 835.2 mg) to give **3-1g** (342.7 mg, 75 % overall yield) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.51 (qt, *J* = 6.5, 1.9 Hz, 1H), 2.19 (dd, *J* = 6.8, 2.0 Hz, 2H), 2.01 (hept, *J* = 7.5 Hz, 1H), 1.84 – 1.72 (m, 3H), 1.66 – 1.48 (m, 4H), 1.42 (d, *J* = 6.5 Hz, 3H), 1.33 – 1.18 (m, 2H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 84.14, 82.27, 58.60, 38.95, 31.93, 25.18, 24.78, 24.38; **HRMS (EI-TOF)**: calculated for $[M]^+$ ($C_{10}H_{16}O$) requires *m/z* 152.1201, found *m/z* 152.1199.

(*R*)-5-cyclohexylpent-3-yn-2-ol [(*R*)-3-1h]

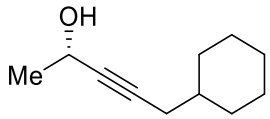


(*R*)-3-1h

Following general procedure B, THP protected (*R*)-3-butyl-2-ol (3 mmol, 462.9 mg) was reacted with cyclohexylmethyl triflate (3.6 mmol, 886.5 mg) to give (*R*)-**3-1h** (302.7 mg, 61 % overall yield) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.51 (qdt, *J* = 6.7, 5.0, 2.0 Hz, 1H), 2.08 (dd, *J* = 6.7, 2.0 Hz, 2H), 1.82 – 1.74 (m, 3H), 1.71 (dt, *J* = 13.0, 3.5 Hz, 2H), 1.68 – 1.61 (m, 1H), 1.48 – 1.40 (m, 1H), 1.42 (d, *J* = 6.5 Hz, 3H), 1.23 (qt, *J* = 12.7, 3.4 Hz, 2H), 1.13 (qt, *J* = 12.7, 3.4 Hz, 1H), 0.96 (qd, *J* = 12.6, 3.5 Hz, 2H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 83.53, 83.05, 58.61, 37.22, 32.64, 26.42, 26.22, 26.08, 24.78; **HRMS (EI-TOF)**: calculated for $[M]^+$ ($C_{11}H_{18}O$) requires *m/z* 166.1358, found *m/z* 166.1360.

(*S*)-5-cyclohexylpent-3-yn-2-ol [(*S*)-3-1h]

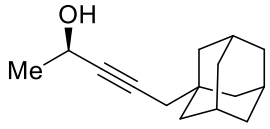


(*S*)-3-1h

Following general procedure B, THP protected (*S*)-3-butyl-2-ol (3 mmol, 462.9 mg) was reacted with cyclohexylmethyl triflate to give (*S*)-**3-1h** (408.2 mg, 82 % overall yield) as a colorless oil.

^{1}H NMR is identical with (*R*)-**3-1h.**

(*R*)-5-adamantan-1-yl)pent-3-yn-2-ol (3-1i)

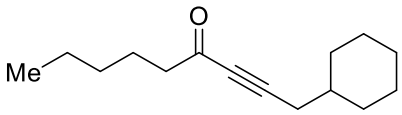


3-1i

Following general procedure B, THP protected (*R*)-3-butyl-2-ol (3 mmol, 462.9 mg) was reacted with 1-adamantanyl methyl triflate (3.6 mmol, 1.0739 g) to give **3-1i** (56 mg, 9% overall yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.54 (q, *J* = 6.7 Hz, 1H), 1.99 – 1.93 (m, 5H), 1.73 – 1.66 (m, 3H), 1.65 – 1.59 (m, 3H), 1.56 – 1.53 (m, 6H), 1.45 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 84.35, 81.88, 58.68, 41.97, 36.86, 33.85, 32.61, 28.61, 24.92; **HRMS (EI-TOF)**: calculated for $[M]^+$ ($C_{15}H_{22}O$) requires *m/z* 218.1671, found *m/z* 218.1673.

1-cyclohexylnon-2-yn-4-one [3-1j(k)]

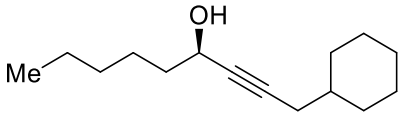


3-1j(k)

Following general procedure C, 1-cyclohexylnon-2-yn-4-ol (**3-1j-rac,** 556.4 mg, 2.5 mmol) was oxidized to give **3-1j(k)** (432.4 mg, 78% yield) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 2.51 (t, *J* = 7.5 Hz, 2H), 2.25 (d, *J* = 6.7 Hz, 2H), 1.85 – 1.76 (m, 2H), 1.72 (dt, *J* = 13.1, 3.5 Hz, 2H), 1.69 – 1.62 (m, 3H), 1.59 – 1.50 (m, 1H), 1.35 – 1.27 (m, 4H), 1.23 (tt, *J* = 12.8, 3.4 Hz, 2H), 1.14 (qt, *J* = 12.8, 3.4 Hz, 1H), 1.01 (qd, *J* = 12.5, 3.4 Hz, 2H), 0.89 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (151 MHz, $CDCl_3$)** δ 188.58, 93.34, 81.78, 45.51, 36.77, 32.67, 31.11, 26.65, 26.02, 25.96, 23.87, 22.36, 13.84; **HRMS (EI-TOF)**: calculated for $[M]^+$ ($C_{15}H_{24}O$) requires *m/z* 220.1827, found *m/z* 220.1834.

(*R*)-1-cyclohexylnon-2-yn-4-ol (3-1j)

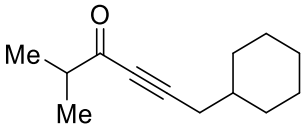


3-1j

Following general procedure C, 1-cyclohexylnon-2-yn-4-one [**3-1j(f),** 1.93 mmol] was asymmetrically reduced to give **3-1j** (429.1 mg, 73 % yield) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.35 (tt, *J* = 6.5, 2.0 Hz, 1H), 2.09 (dd, *J* = 6.7, 2.0 Hz, 2H), 1.81 – 1.61 (m, 8H), 1.49 – 1.38 (m, 3H), 1.36 – 1.28 (m, 4H), 1.23 (qt, *J* = 12.5, 3.2 Hz, 2H), 1.12 (qt, *J* = 12.7, 3.2 Hz, 1H), 0.97 (qd, *J* = 12.5, 3.4 Hz, 2H), 0.89 (t, *J* = 6.9 Hz, 3H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 84.29, 82.24, 62.79, 38.20, 37.28, 32.65, 31.46, 26.47, 26.25, 26.09, 24.88, 22.56, 13.96; **HRMS (EI-TOF)**: calculated for $[M]^+$ ($C_{15}H_{26}O$) requires *m/z* 222.1984, found *m/z* 220.1982; ***e.r.*** = 98.7/1.3 [determined by HPLC using corresponding benzyl ester: Chiralcel® Chiral IB column, Hexane/*i*PrOH = 1000/1, 1.0 mL/min, λ = 230 nm; t_R(major) = 6.24 min, t_R(minor) = 7.63 min].

6-cyclohexyl-2-methylhex-4-yn-3-one [3-1k(f)]



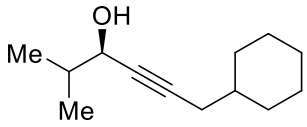
3-1k(f)

Following general procedure C, 6-cyclohexyl-2-methylhex-4-yn-3-ol (**3-1k-rac**, 5.91 mmol, 1.1481 g) was oxidized to give **3-1k(f)** (1.0372 g, 91% yield) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.60 (hept, *J* = 7.0 Hz, 1H), 2.26 (d, *J* = 6.6 Hz, 2H), 1.83 – 1.76 (m, 2H), 1.72 (dt, *J* = 12.9, 3.4 Hz, 2H), 1.68 – 1.61 (m, 1H), 1.60 – 1.50 (m, 1H), 1.24 (qt, *J* = 12.7, 3.2 Hz, 2H), 1.17 (d, *J* = 6.9 Hz, 6H), 1.14 (qt, *J* = 12.5, 3.4 Hz, 1H), 1.07 – 0.96 (m, 2H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 192.34, 94.19, 80.67, 42.98,

36.78, 32.66, 26.68, 26.03, 25.95, 17.99; **HRMS (EI-TOF)**: calculated for $[M]^+$ ($C_{13}H_{20}O$) requires *m/z* 192.1514, found *m/z* 192.1507.

(*R*)-6-cyclohexyl-2-methylhex-4-yn-3-ol (3-1k)

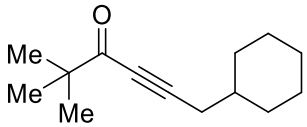


3-1k

Following general procedure C, 6-cyclohexyl-2-methylhex-4-yn-3-one [**3-1k(f)**, 5.12 mmol, 984.7 mg] was asymmetrically reduced to give **3-1k** (573.8 mg, 58% yield) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.16 (tt, *J* = 5.6, 2.0 Hz, 1H), 2.11 (dd, *J* = 6.6, 2.0 Hz, 2H), 1.87 – 1.81 (m, 1H), 1.81 – 1.75 (m, 2H), 1.74 – 1.68 (m, 3H), 1.67 – 1.62 (m, 1H), 1.50 – 1.39 (m, 1H), 1.24 (qt, *J* = 12.7, 3.4 Hz, 2H), 1.13 (qt, *J* = 12.8, 3.5 Hz, 1H), 1.01 – 0.95 (m, 1H), 0.99 (d, *J* = 6.7 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 85.03, 80.61, 68.16, 37.29, 34.67, 32.64, 26.49, 26.24, 26.09, 18.15, 17.42; **HRMS (EI-TOF)**: calculated for $[M\text{-}H_2O]^+$ ($C_{13}H_{20}$) requires *m/z* 176.1565, found *m/z* 192.1568; ***e.r.*** = 99.5/0.5 [determined by HPLC using corresponding benzyl ester: Chiralcel® Chiral IB column, Hexane/*i*PrOH = 1000/1, 1.0 mL/min, λ = 227 nm; t_R(major) = 5.81 min, t_R(minor) = 8.64 min].

6-cyclohexyl-2,2-dimethylhex-4-yn-3-one [3-1l(f)]

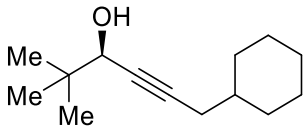


3-1l(f)

Following general procedure C, 6-cyclohexyl-2,2-dimethylhex-4-yn-3-ol (**3-1l-rac**, 5.76 mmol, 1.20 00g) was oxidized to give **3-1l(f)** (1.1884 g, 89% yield) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.27 (d, *J* = 6.5 Hz, 2H), 1.83 – 1.76 (m, 2H), 1.72 (dt, *J* = 12.9, 3.4 Hz, 2H), 1.68 – 1.61 (m, 1H), 1.60 – 1.50 (m, 1H), 1.24 (qt, *J* = 12.6, 3.3 Hz, 2H), 1.18 (s, 9H), 1.12 (dt, *J* = 12.5, 3.4 Hz, 1H), 1.03 (qd, *J* = 12.4, 3.3 Hz, 2H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 194.34, 94.68, 79.71, 44.54, 36.80, 32.66, 26.71, 26.06, 26.03, 25.95.**HRMS (EI-TOF)**: calculated for $[M]^+$ ($C_{14}H_{22}O$) requires *m/z* 206.1671, found *m/z* 206.1674.

(*R*)-6-cyclohexyl-2,2-dimethylhex-4-yn-3-ol (3-1l)



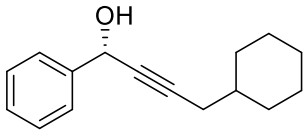
3-1l

Following general procedure C, 6-cyclohexyl-2-methylhex-4-yn-3-one [**3-1l(f),** 4.84 mmol, 999.3 mg] was asymmetrically reduced to give **3-1l** (46 mg, 5% yield) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.99 (dt, *J* = 6.0, 2.0 Hz, 1H), 2.11 (dd, *J* = 6.6, 2.1 Hz, 2H), 1.81 – 1.75 (m, 2H), 1.71 (dt, *J* = 13.3, 3.5 Hz, 2H), 1.67 (d, *J* = 6.0 Hz, 1H), 1.67 – 1.62 (m, 1H), 1.49 – 1.41 (m, 1H), 1.24 (qt, *J* = 12.7, 3.5 Hz, 2H), 1.12 (qt, *J* = 12.8, 3.5 Hz, 1H), 1.04 – 0.96 (m, 2H), 0.98 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 85.07, 80.60, 71.63, 37.32, 35.85, 32.66, 26.50, 26.24, 26.10, 25.29; **HRMS (EI-TOF)**: calculated for $[M]^+$ ($C_{14}H_{24}O$) requires *m/z* 208.1827, found *m/z* 208.1825; ***e.r.*** = 95.8/4.2 [determined by

HPLC using corresponding benzyl ester: Chiralcel® Chiral IB column, Hexane/*i*PrOH = 1000/1, 1.0 mL/min, λ = 227 nm; t_R(major) = 5.04 min, t_R(minor) = 5.56 min].

(*S*)-4-cyclohexyl-1-phenylbut-2-yn-1-ol (3-1m)

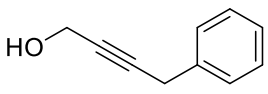


3-1m

Following general procedure B, THP protected (*R*)-1-phenylprop-2-yn-1-ol (3 mmol, 648.8 mg) was reacted with cyclohexylmethyl triflate (3.6 mmol, 886.5 mg) to give **3-1m** (136.8 mg, 20% overall yield) as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 – 7.53 (m, 2H), 7.41 – 7.36 (m, 2H), 7.34 – 7.30 (m, 1H), 5.49 – 5.42 (m, 1H), 2.22 (d, *J* = 5.4 Hz, 1H), 2.17 (dd, *J* = 6.7, 2.1 Hz, 2H), 1.85 – 1.79 (m, 2H), 1.76 – 1.69 (m, 2H), 1.69 – 1.63 (m, 1H), 1.56 – 1.44 (m, 1H), 1.25 (qt, *J* = 12.6, 3.2 Hz, 2H), 1.14 (qt, *J* = 12.7, 3.2 Hz, 1H), 1.01 (qd, *J* = 11.9, 2.8 Hz, 2H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 141.28, 128.48, 128.13, 126.62, 86.55, 80.77, 64.85, 37.23, 32.70, 26.60, 26.22, 26.07; **HRMS (EI-TOF)**: calculated for $[M]^+$ ($C_{16}H_{20}O$) requires *m/z* 228.1514, found *m/z* 228.1510; ***e.r.*** = 97.5/2.5 [determined by HPLC: Chiralcel® Chiral IB column, Hexane/*i*PrOH = 97/3, 1.0 mL/min, λ = 200 nm; t_R(major) = 21.18 min, t_R(minor) = 27.09 min].

4-phenylbut-2-yn-1-ol (3-2a)



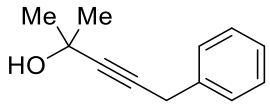
3-2a

3-Phenyl-1-propyne (10.0 mmol, 1.1615 g, 1.24 mL) was dissolved in anhydrous THF (8 mL) under argon atmosphere, and the mixture was cooled to -78 ºC. *n*-BuLi (2.5

M in hexanes, 10.5 mmol, 4.2 mL) was then added dropwise, and the mixture was left to warm to 0 ºC. Dry paraformaldehyde (25.0 mmol, 751.0 mg) was added in one portion, and the mixture was left to warm to ambient temperature. Then the mixture was warmed to 40 ºC for 40 minutes until it became a clear viscous solution. After that, *saq.*NH_4Cl was added, and the slurry was mixed for another 10 minutes until it became a clear two-phase mixture. Then the mixture was extracted twice with Et_2O and the combined organic layer dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (hexanes/EtOAc = 10: 1) to afford **3-2a** (821.5 mg, 56% yield) as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.31 (m, 4H), 7.26-7.21 (m, 1H), 4.32 (t, J= 2.2 Hz, 2H), 3.64 (t, J = 2.2 Hz, 2H); These data are in accordance with literature. [21]

2-methyl-5-phenylpent-3-yn-2-ol (3-2b)

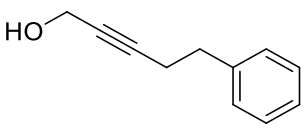


3-2b

Following general procedure D, 3-phenyl-1-propyne (3 mmol, 348.5 mg) was reacted with acetone (3 mmol, 174.2 mg). The crude product was purified as a yellow oil by flash chromatography (hexane/EtOAc = 10: 1), resulting in **3-2b** (439.0 mg, 84 % yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 – 7.29 (m, 4H), 7.25 – 7.21 (m, 1H), 3.62 (s, 2H), 1.55 (s, 6H); These data are in accordance with literature. [22]

5-phenylpent-2-yn-1-ol (3-2c)

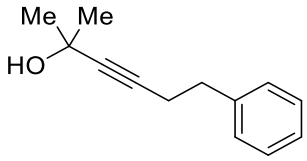


3-2c

Compound **3-2c** was prepared similarly with **3-2a**. 4-phenyl-1-butyne (3 mmol, 390.6 mg) was reacted with paraformaldehyde (7.5 mmol, 225.3 mg) to afford **3-2c** (379.7 mg, 79% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 2H), 7.25 – 7.19 (m, 3H), 4.24 (t, *J* = 2.1 Hz, 2H), 2.84 (t, *J* = 7.6 Hz, 2H), 2.52 (tt, *J* = 7.5, 2.2 Hz, 2H); These data are in accordance with literature.[23]

2-methyl-6-phenylhex-3-yn-2-ol (3-2d)

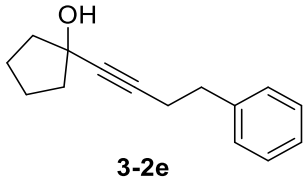


3-2d

Following general procedure D, 4-phenyl-1-butyne (3 mmol, 390.6 mg) was reacted with acetone (3 mmol, 174.2 mg). The crude product was purified as a yellow oil by flash chromatography (hexane/EtOAc = 10 : 1), resulting in **3-2d** (533.5 mg, 95% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 2H), 7.25 – 7.19 (m, 3H), 2.81 (t, *J* = 7.5 Hz, 2H), 2.47 (t, *J* = 7.5 Hz, 2H), 1.47 (s, 6H); These data are in accordance with literature. [24]

1-(4-phenylbut-1-yn-1-yl)cyclopentan-1-ol (3-2e)



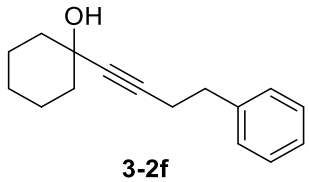
3-2e

Following general procedure D, 4-phenyl-1-butyne (3 mmol, 390.6 mg) was reacted with cyclopentanone (3 mmol, 252.4 mg). The crude product was purified as a

yellow oil by flash chromatography (hexane/EtOAc = 10: 1), resulting in **3-2e** (426.1 mg, 66% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 – 7.28 (m, 2H), 7.25 – 7.18 (m, 3H), 2.82 (t, *J* = 7.6 Hz, 2H), 2.50 (t, *J* = 7.6 Hz, 2H), 1.95 – 1.85 (m, 3H), 1.84 – 1.77 (m, 3H), 1.75 – 1.66 (m, 2H); **^{13}C NMR (151 MHz, $CDCl_3$)** δ 140.64, 128.46, 128.25, 126.21, 84.86, 82.74, 74.57, 42.41, 35.09, 23.32, 20.94; **HRMS (EI-TOF)**: calculated for $[M]^+$ ($C_{15}H_{18}O$) requires *m/z* 214.1358, found *m/z* 214.1362.

1-(4-phenylbut-1-yn-1-yl)cyclohexan-1-ol (3-2f)

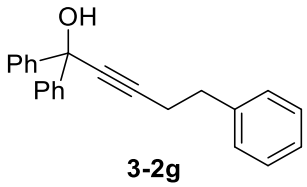


3-2f

Following general procedure D, 4-phenyl-1-butyne (3 mmol, 390.6 mg) was reacted with cyclohexanone (3 mmol, 294.5 mg). The crude product was purified as a yellow oil by flash chromatography (hexane/EtOAc = 10 : 1), resulting in **3-2f** (533.5 mg, 78% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 – 7.26 (m, 2H), 7.25 – 7.18 (m, 3H), 2.82 (t, *J* = 7.5 Hz, 2H), 2.51 (t, *J* = 7.5 Hz, 2H), 1.90 – 1.79 (m, 3H), 1.66 – 1.60 (m, 2H), 1.55 – 1.41 (m, 4H), 1.25 – 1.15 (m, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 140.60, 128.46, 128.26, 126.20, 84.66, 83.81, 68.74, 40.11, 35.11, 25.16, 23.29, 20.83; **HRMS (EI-TOF)**: calculated for $[M]^+$ ($C_{16}H_{20}O$) requires *m/z* 228.1514, found *m/z* 228.1508.

1,1,5-triphenylpent-2-yn-1-ol (3-2g)

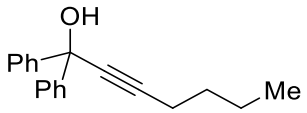


3-2g

Following general procedure D, 4-phenyl-1-butyne (3 mmol, 390.6 mg) was reacted with benzophenone (3 mmol, 546.7 mg). The crude product was purified as a yellow oil by flash chromatography (hexane/EtOAc = 20 : 1), resulting in **3-2g** (927.8 mg, 99% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 – 7.48 (m, 4H), 7.32 – 7.26 (m, 6H), 7.26 – 7.22 (m, 5H), 2.90 (t, *J* = 7.3 Hz, 2H), 2.67 (s, 1H), 2.66 (t, *J* = 7.3 Hz, 2H); **^{13}C NMR (151 MHz, $CDCl_3$)** δ 145.28, 140.42, 128.57, 128.40, 128.10, 127.45, 126.33, 125.97, 87.29, 83.87, 74.39, 34.74, 20.99; **HRMS (EI-TOF)**: calculated for $[M]^+$ ($C_{23}H_{20}O$) requires *m/z* 312.1514, found *m/z* 312.1505.

1,1-diphenylhept-2-yn-1-ol (3-2h)

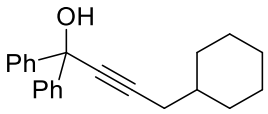


3-2h

Following general procedure D, 1-hexyne (3 mmol, 246.4 mmol) was reacted with benzophenone (3 mmol, 546.7 mg). The crude product was purified as a yellow oil by flash chromatography (hexane/EtOAc = 20: 1), resulting in **3-2h** (736.3 mg, 93% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.63 – 7.58 (m, 4H), 7.34 – 7.30 (m, 4H), 7.24 (d, *J* = 6.7 Hz, 2H), 2.35 (t, *J* = 7.1 Hz, 2H), 1.58 (p, *J* = 7.2 Hz, 2H), 1.46 (h, *J* = 7.3 Hz, 2H), 0.93 (t, *J* = 7.3 Hz, 3H); These data are in accordance with literature. [25]

4-cyclohexyl-1,1-diphenylbut-2-yn-1-ol (3-2i)

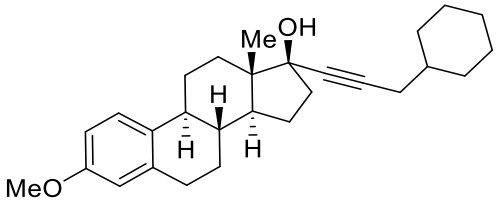


3-2i

Following general procedure D, 3-cyclohexyl-1-propyne (3 mmol, 366.6 mg) was reacted with benzophenone (3 mmol, 546.7 mg). The crude product was purified as a yellow oil by flash chromatography (hexane/EtOAc = 20 : 1), resulting in **3-2i** (384.6 mg, 42 % yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65 – 7.60 (m, 4H), 7.36 – 7.29 (m, 4H), 7.28 – 7.23 (m, 2H), 2.72 (s, 1H), 2.25 (d, *J* = 6.6 Hz, 2H), 1.88 – 1.83 (m, 2H), 1.74 (dt, *J* = 13.0, 3.5 Hz, 2H), 1.70 – 1.62 (m, 1H), 1.61 – 1.53 (m, 1H), 1.27 (qt, *J* = 12.7, 3.5 Hz, 2H), 1.15 (qt, *J* = 12.8, 3.5 Hz, 1H), 1.06 (qd, *J* = 12.4, 3.5 Hz, 2H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 145.56, 128.11, 127.43, 125.97, 87.21, 83.90, 74.52, 37.32, 32.77, 26.70, 26.24, 26.10. HRMS (EI-TOF): calculated for $[M]^+$ ($C_{22}H_{24}O$) requires *m/z* 304.1827, found *m/z* 304.1825.

(8*R*,9*S*,13*S*,14*S*,17*S*)-17-(3-cyclohexylprop-1-yn-1-yl)-3-methoxy-13-methyl 7,8,9,11,12,13, 14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-17-ol (3-2j)



3-2j

To an efficiently stirred solution of 3-cyclohexyl-1-propyne (4 mmol, 488.8 mg) in anhydrous THF (6 mL) at -78 ℃, *n*-BuLi (2.5 M in hexane, 1.2 mL, 3 mmol) was added under nitrogen atmosphere. After one hour of stirring at -78 ℃, a solution of estrone 3-

methyl ether (1 mmol, 284.4 mg) in THF (3 mL) was added in 30 min. The mixture was stirred for one hour at -78 ℃ and then allowed to warm to room temperature. The reaction was quenched with *saq*. NH_4Cl (*aq*) after stirring 12 h at room temperature. The aqueous phase was extracted with Et_2O three times; the combined organic phase was washed with saq. NaCl(*aq*), dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (hexane/EtOAc = 10: 1) to afford **3-2j** (350.7 mg, 86% yield) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.5 Hz, 1H), 6.77 (dd, *J* = 8.6, 2.9 Hz, 1H), 6.68 (d, *J* = 3.0 Hz, 1H), 3.82 (s, 3H), 2.98 – 2.85 (m, 2H), 2.46 – 2.38 (m, 1H), 2.35 – 2.29 (m, 1H), 2.28 – 2.21 (m, 2H), 2.20 (d, *J* = 6.6 Hz, 2H), 2.07 (td, *J* = 13.1, 12.6, 3.5 Hz, 1H), 2.03 – 1.89 (m, 2H), 1.90 – 1.82 (m, 2H), 1.82 – 1.73 (m, 4H), 1.73 – 1.66 (m, 1H), 1.59 – 1.37 (m, 5H), 1.35 – 1.04 (m, 5H), 0.93 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 157.17, 137.73, 132.44, 126.17, 113.56, 111.28, 84.89, 84.54, 79.75, 54.94, 49.26, 47.02, 43.56, 39.28, 38.99, 37.29, 32.70, 32.55, 29.69, 27.20, 26.43, 26.34, 26.16, 25.97, 22.62, 12.69; **HRMS (EI-TOF)**: calculated for $[M]^+$ ($C_{28}H_{38}O_2$) requires *m/z* 406.2872, found *m/z* 406.2875

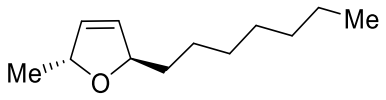
Asymmetric Isomerization of Propargylic Alcohols

General Procedure:

To a 6-dram vial were added sequentially 0.3 mmol propargylic alcohol, 5 mol % [(*R*)-**L2-13**]AuCl (13.6 mg), 20 mol% $NaBAr^F{}_4$ (53.2 mg) and 6 mL dry dichloroethane (DCE). The reaction was stirred at the indicated temperature and monitored by TLC. Upon

completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography to yield the desired product.

(2*R*,5*R*)-2-heptyl-5-methyl-2,5-dihydrofuran (3-3a)

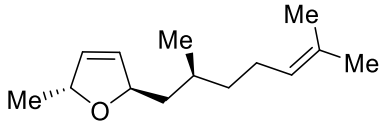


3-3a

Following the general procedure, (*R*)-dodec-3-yn-2-ol (**3-1a,** 0.3 mmol, 52.2 mg), 5 mol % [(*R*)-**L2-13**]AuCl (13.6 mg), 20 mol% $NaBAr^F_4$ (53.2 mg) and 6 mL dry dichloroethane were stirred at 80 ℃ for 3 h. The solvent was removed and the residue was purified by flash column chromatography (hexane/EtOAc = 40: 1) to afford **3-3a** (46.7 mg, 89% yield, *d.r.* = 93/7) as a colorless oil.

$[\alpha]^{20}_D$ = +166.6 (c 1.05, $CHCl_3$); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 5.79 – 5.71 (m, 2H), 4.97 – 4.88 (m, 1H), 4.88 – 4.82 (m, 1H), 1.56 – 1.46 (m, 2H), 1.41 – 1.19 (m, 13H), 0.86 (t, J = 7.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 131.17, 129.45, 85.46, 81.33, 36.14, 31.80, 29.72, 29.27, 25.33, 22.63, 21.82, 14.07; **HRMS (EI-TOF)**: calculated for $[M]^+$ ($C_{12}H_{22}O$) requires *m/z* 182.1671, found *m/z* 182.1663.

(2*R*,5*R*)-2-((*S*)-2,6-dimethylhept-5-en-1-yl)-5-methyl-2,5-dihydrofuran (3-3b)



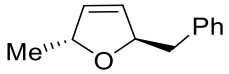
3-3b

Following the general procedure, (2*R*,7*S*)-7,11-dimethyldodec-10-en-3-yn-2-ol (**3-1b,** 0.3 mmol, 62.7 mg), 5 mol % [(*R*)-**L2-13**]AuCl (13.6 mg), 20 mol% $NaBAr^F_4$ (53.2 mg) and 6 mL dry dichloroethane were stirred at 60 ℃ for 9 h. The solvent was removed

and the residue was purified by flash column chromatography (hexane/EtOAc = 40: 1) to afford **3-3b** (50.2 mg, 80% yield, *d.r.* = 91/9) as a colorless oil.

$[\alpha]^{20}_D$ = -112.0 (c 1.09, $CHCl_3$); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 5.79 – 5.71 (m, 2H), 5.13 – 5.05 (m, 1H), 4.96 – 4.89 (m, 2H), 2.04 – 1.90 (m, 2H), 1.71 – 1.61 (m, 4H), 1.59 (s, 3H), 1.57 – 1.47 (m, 1H), 1.37 – 1.29 (m, 1H), 1.27 – 1.12 (m, 5H), 0.92 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 131.00, 130.93, 130.17, 124.83, 83.56, 80.93, 43.54, 37.81, 29.49, 25.68, 25.42, 21.78, 19.50, 17.59; **HRMS (EI-TOF)**: calculated for $[M]^+$ ($C_{14}H_{24}O$) requires *m/z* 208.1827, found *m/z* 208.1823.

(2*R*,5*R*)-2-benzyl-5-methyl-2,5-dihydrofuran (3-3c)

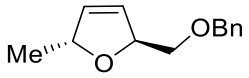


3-3c

Following the general procedure, (*R*)-6-phenylhex-3-yn-2-ol (**3-1c,** 0.3 mmol, 55.7 mg), 5 mol % [(*R*)-**L2-13**]AuCl (13.6 mg), 20 mol% $NaBAr^F_4$ (53.2 mg) and 6 mL dry dichloroethane were stirred at 80 ℃ for 4 h. The solvent was removed and the residue was purified by flash column chromatography (hexane/EtOAc = 40: 1) to afford **3-3c** (41.2 mg, 74% yield, *d.r.* = 93/7) as a colorless oil.

$[\alpha]^{20}_D$ = -102.8 (c 1.20, $CHCl_3$); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.32 – 7.27 (m, 2H), 7.25 – 7.20 (m, 3H), 5.79 – 5.73 (m, 2H), 5.14 – 5.08 (m, 1H), 4.93 – 4.87 (m, 1H), 2.94 (dd, *J* = 13.4, 5.8 Hz, 1H), 2.81 (dd, *J* = 13.4, 6.9 Hz, 1H), 1.24 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR (151 MHz, $CDCl_3$)** δ 138.01, 131.83, 129.45, 128.81, 128.15, 126.10, 86.21, 81.64, 42.74, 21.72; **HRMS (EI-TOF)**: calculated for $[M]^+$ ($C_{12}H_{14}O$) requires *m/z* 174.1045, found *m/z* 174.1048.

(2*S*,5*R*)-2-((benzyloxy)methyl)-5-methyl-2,5-dihydrofuran [(2*S*,5*R*)-3-3d]

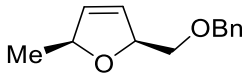


(2*S*,5*R*)-**3-3d**

Following the general procedure, (*R*)-6-(benzyloxy)hex-3-yn-2-ol [(*R*)-**3-1d,** 0.3 mmol, 61.2 mg], 5 mol % [(*R*)-**L2-13**]AuCl (13.6 mg), 20 mol% $NaBAr^F_4$ (53.2 mg) and 3 mL dry dichloroethane were stirred at 60 ℃ for 24 h. The solvent was removed and the residue was purified by flash column chromatography (hexane/EtOAc = 30: 1) to afford (2*S*,5*R*)-**3-3d** (42.9 mg, 70% yield, *d.r.* = 90/10) as a colorless oil.

$[\alpha]^{20}_D$ = -123.5 (c 1.09, $CHCl_3$); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.36 – 7.31 (m, 4H), 7.30 – 7.26 (m, 1H), 5.87 (dt, *J* = 6.0, 1.6 Hz, 1H), 5.77 (dt, *J* = 6.1, 1.7 Hz, 0H), 5.06 – 4.99 (m, 1H), 4.61 (d, *J* = 12.2 Hz, 1H), 4.56 (d, *J* = 12.2 Hz, 1H), 3.50 (dd, *J* = 4.9, 1.9 Hz, 2H), 1.27 (d, *J* = 6.1 Hz, 3H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 138.25, 133.05, 128.26, 127.58, 127.57, 127.47, 126.51, 84.77, 81.97, 73.33, 72.84, 21.65. These data are in accordance with literature. [8]

(2*S*,5*S*)-2-((benzyloxy)methyl)-5-methyl-2,5-dihydrofuran [(2*S*,5*S*)-3-3d]



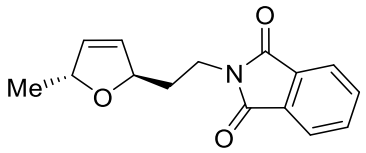
(2*S*,5*S*)-**3-3d**

Following the general procedure, (*S*)-6-(benzyloxy)hex-3-yn-2-ol [(*S*)-**3-1d,** 0.3 mmol, 60.6 mg], 5 mol % [(*R*)-**L2-13**]AuCl (13.6 mg), 20 mol% $NaBAr^F_4$ (53.2 mg) and 3 mL dry dichloroethane were stirred at 60 ℃ for 24 h. The solvent was removed and the residue was purified by flash column chromatography (hexane/EtOAc = 30: 1) to afford (2*S*,5*S*)-**3-3d** (48.5 mg, 80% yield, *d.r.* = 91/9) as a colorless oil.

$[\alpha]^{20}_D$ = -19.7 (c 1.10, $CHCl_3$); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.37 – 7.31 (m, 4H), 7.30 – 7.25 (m, 1H), 5.85 (d, *J* = 5.2 Hz, 1H), 5.78 (d, *J* = 6.1 Hz, 1H), 4.98 – 4.91 (m,

2H), 4.62 (d, *J* = 12.2 Hz, 1H), 4.58 (d, *J* = 12.3 Hz, 1H), 3.51 (dd, *J* = 4.9, 2.0 Hz, 2H), 1.29 (d, *J* = 6.1 Hz, 3H); **^{13}C NMR (151 MHz, $CDCl_3$)** δ 138.26, 132.84, 128.24, 127.55, 127.44, 126.81, 85.20, 82.25, 73.89, 73.28, 22.73; These data are in accordance with literature. [8]

2-(2-((2*R*,5*R*)-5-methyl-2,5-dihydrofuran-2-yl)ethyl)isoindoline-1,3-dione (3-3e)

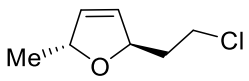


3-3e

Following the general procedure, (*R*)-2-(6-hydroxyhept-4-yn-1-yl)isoindoline-1,3-dione (**3-1e,** 0.3 mmol, 77.7 mg), 5 mol % [(*R*)-**L2-13**]AuCl (13.6 mg), 20 mol% $NaBAr^F_4$ (53.2 mg) and 6 mL dry dichloroethane were stirred at 80 ℃ for 24 h. The solvent was removed and the residue was purified by flash column chromatography (hexane/EtOAc = 10 : 1) to afford **3-3e** (48.0 mg, 62% yield, *d.r.* = 95/5) as a colorless oil.

[α]$^{20}_D$ = -135.9 (c 1.06, $CHCl_3$); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.80 (dd, *J* = 5.4, 3.0 Hz, 1H), 7.67 (dd, *J* = 5.5, 3.0 Hz, 1H), 5.78 (dt, *J* = 6.2, 1.5 Hz, 1H), 5.75 (dt, *J* = 6.1, 1.7 Hz, 1H), 4.98 – 4.89 (m, 2H), 3.82 (dt, *J* = 13.7, 7.7 Hz, 1H), 3.73 (dt, *J* = 14.0, 7.1 Hz, 1H), 1.90 (td, *J* = 7.3, 5.6 Hz, 2H), 1.19 (d, *J* = 6.2 Hz, 3H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 168.22, 133.74, 132.19, 132.14, 128.35, 123.04, 83.06, 81.66, 34.71, 34.17, 21.59; **HRMS (EI-TOF)**: calculated for $[M]^+$ ($C_{15}H_{15}NO_3$) requires *m/z* 257.1052, found *m/z* 257.1042.

(2*R*,5*R*)-2-(2-chloroethyl)-5-methyl-2,5-dihydrofuran (3-3f)

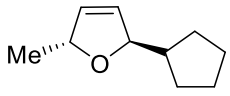


3-3f

Following the general procedure, (*R*)-7-chlorohept-3-yn-2-ol (**3-1f,** 0.3 mmol, 44.0 mg), 10 mol % [(*R*)-**L2-13**]AuCl (27.2 mg), 20 mol% $NaBAr^F_4$ (53.2 mg) and 3 mL dry dichloromethane were stirred at 60 ℃ for 5 h. The solvent was removed, and the residue was purified by flash column chromatography (pentane/Et_2O = 20: 1) to afford **3-3f** (33.2 mg, 75% yield, *d.r.* = 95/5) as a colorless oil. [Note: **3-3f** is very volatile, need to carefully remove the solvent]

$[\alpha]^{20}_D$ = -165.6 (c 1.08, $CHCl_3$); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 5.81 (dt, *J* = 6.1, 1.7 Hz, 1H), 5.76 (dt, *J* = 6.1, 1.8 Hz, 1H), 5.01 (dddt, *J* = 7.5, 5.7, 3.8, 1.8 Hz, 1H), 4.96 – 4.91 (m, 1H), 3.67 – 3.60 (m, 2H), 2.05 – 1.97 (m, 1H), 1.97 – 1.90 (m, 1H), 1.24 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 132.05, 128.42, 82.56, 81.61, 41.36, 38.92, 21.70; **HRMS (CI-TOF)**: calculate for $[M+H]^+$ ($C_7H_{12}ClO$) requires *m/z* 147.0577, found *m/z* 147.0561.

(2*R*,5*R*)-2-cyclopentyl-5-methyl-2,5-dihydrofuran (3-3g)



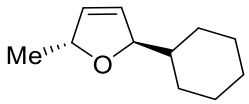
3-3g

Following the general procedure, (*R*)-5-cyclopentylpent-3-yn-2-ol (**3-1g,** 0.3 mmol, 45.7 mg), 5 mol % [(*R*)-**L2-13**]AuCl (13.6 mg), 20 mol% $NaBAr^F_4$ (53.2 mg) and 6 mL dry dichloroethane were stirred at 80 ℃ for 2 h. The solvent was removed and the residue was purified by flash column chromatography (hexnae/EtOAc = 40: 1) to afford **3-3g** (40.7 mg, 89% yield, *d.r.* = 96/4) as a colorless oil.

$[\alpha]^{20}_D$ = -192.0 (c 1.12, $CHCl_3$); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 5.78 (dt, *J* = 6.1, 1.7 Hz, 1H), 5.75 (dt, *J* = 6.3, 1.6 Hz, 1H), 4.97 – 4.89 (m, 1H), 4.76 – 4.71 (m, 1H), 1.97 (dq, *J* = 16.4, 8.1 Hz, 1H), 1.77 – 1.70 (m, 1H), 1.69 – 1.47 (m, 4H), 1.39 – 1.25 (m, 3H),

1.24 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR (151 MHz, $CDCl_3$)** δ 131.62, 128.69, 89.29, 81.63, 45.26, 28.80, 28.19, 25.72, 25.60, 21.93; **HRMS (EI-TOF)**: calculated for $[M]^+$ ($C_{10}H_{16}O$) requires *m/z* 152.1201, found *m/z* 152.1206.

(2*R*,5*R*)-2-cyclopentyl-5-methyl-2,5-dihydrofuran [(2*R*,5*R*)-3-3h]

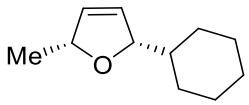


(2*R*,5*R*)-**3-3h**

Following the general procedure, (*R*)-5-cyclohexylpent-3-yn-2-ol [(*R*)-**3-1h,** 0.3 mmol, 49.9 mg], 5 mol % [(*R*)-**L2-13**]AuCl (13.6 mg), 20 mol% $NaBAr^F_4$ (53.2 mg) and 6 mL dry dichloroethane were stirred at 80 ℃ for 2 h. The solvent was removed and the residue was purified by flash column chromatography (hexnae/EtOAc = 40: 1) to afford (2*R*, 5*R*)-**3-3h** (40.8 mg, 82% yield, *d.r.* = 97/3) as a colorless oil.

$[\alpha]^{20}_D$ = -216.8 (c 1.02, $CHCl_3$); **^{1}H NMR (500 MHz, CD_2Cl_2)** δ 5.80 (dt, *J* = 6.2, 1.7 Hz, 1H), 5.76 (dt, *J* = 6.1, 1.7 Hz, 1H), 4.88 – 4.82 (m, 1H), 4.59 (tt, *J* = 5.5, 1.7 Hz, 1H), 1.79 – 1.58 (m, 6H), 1.45 – 1.36 (m, 1H), 1.19 (d, *J* = 6.4 Hz, 3H), 1.27 – 0.92 (m, 4H); **^{13}C NMR (126 MHz, CD_2Cl_2)** δ 132.27, 128.22, 90.35, 82.04, 44.06, 29.21, 28.91, 27.06, 26.68, 26.63, 22.19; **HRMS (EI-TOF)**: calculated for $[M]^+$ ($C_{11}H_{18}O$) requires *m/z* 166.1358, found *m/z* 166.1355.

(2*S*,5*R*)-2-cyclopentyl-5-methyl-2,5-dihydrofuran [(2*S*,5*R*)-3-3h]



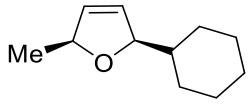
(2*S*,5*R*)-**3-3h**

Following the general procedure, (*R*)-5-cyclohexylpent-3-yn-2-ol [(*R*)-**3-1h,** 0.3 mmol, 49.9 mg], 5 mol % [(*S*)-**L2-13**]AuCl (13.6 mg), 20 mol% $NaBAr^F_4$ (53.2 mg) and 6 mL dry dichloroethane were stirred at 80 ℃ for 2 h. The solvent was removed and the

residue was purified by flash column chromatography (hexnae/EtOAc = 40: 1) to afford (2*S*, 5*R*)-**3-3h** (43.7 mg, 88% yield, *d.r.* = 97/3) as a colorless oil.

$[\alpha]^{20}_D$ = +30.8 (c 0.94, $CHCl_3$); **^{1}H NMR (500 MHz, CD_2Cl_2)** δ 5.78 – 5.74 (m, 2H), 4.86 – 4.77 (m, 1H), 4.54 – 4.48 (m, 1H), 1.81 – 1.57 (m, 6H), 1.42 – 1.34 (m, 1H), 1.28 – 1.15 (m, 2H), 1.21 (d, *J* = 6.4 Hz, 3H), 1.03 – 0.94 (m, 2H); **^{13}C NMR (126 MHz, CD_2Cl_2)** δ 132.19, 128.55, 90.91, 81.64, 43.88, 29.34, 29.30, 27.09, 26.69, 22.58; These data are in accordance with literature. [26]

(2*R*,5*S*)-2-cyclopentyl-5-methyl-2,5-dihydrofuran [(2*R*,5*S*)-3-3h]

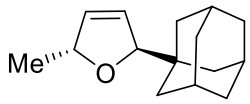


(2*R*,5*S*)-**3-3h**

Following the general procedure, (*S*)-5-cyclohexylpent-3-yn-2-ol [(*S*)-**3-1h,** 0.3 mmol, 49.4 mg], 5 mol % [(*R*)-**L2-13**]AuCl (13.6 mg), 20 mol% $NaBAr^F_4$ (53.2 mg) and 6 mL dry dichloroethane were stirred at 80 ℃ for 2 h. The solvent was removed, and the residue was purified by flash column chromatography (hexnae/EtOAc = 40: 1) to afford (2*R*, 5*S*)-**3-3h** (41.6 mg, 84% yield, *d.r.* = 97/3) as a colorless oil.

$[\alpha]^{20}_D$ = -31.2 (c 1.02, $CHCl_3$); ^{1}H and ^{13}C NMR are in accordance with **[(2*S*,5*R*)-3-3h].**

(2*S*,5*R*)-2-(adamantan-1-yl)-5-methyl-2,5-dihydrofuran (3-3i)



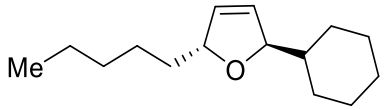
3-3i

Following the general procedure, (*R*)-5-adamantan-1-yl)pent-3-yn-2-ol (**3-1i,** 0.3 mmol, 65.3 mg), 10 mol % [(*R*)-**L2-13**]AuCl (27.2 mg), 20 mol% $NaBAr^F_4$ (53.2 mg) and

6 mL dry dichloroethane were stirred at 80 ℃ for 58 h. The solvent was removed and the residue was purified by flash column chromatography (hexnae/EtOAc = 40: 1) to afford **3-3i** (47.7 mg, 73% yield, *d.r.* = 98/2) as a colorless oil.

$[\alpha]^{20}_D$ = -189.7 (c 1.30, $CHCl_3$); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 5.81 (ddd, *J* = 6.2, 2.2, 1.4 Hz, 1H), 5.75 (dt, *J* = 6.2, 1.9 Hz, 1H), 4.88 – 4.82 (m, 1H), 4.37 (dt, *J* = 6.0, 1.9 Hz, 1H), 1.98 – 1.91 (m, 3H), 1.72 – 1.66 (m, 3H), 1.66 – 1.55 (m, 6H), 1.47 (dq, *J* = 12.1, 2.6 Hz, 3H), 1.23 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 132.42, 125.86, 94.31, 82.09, 38.19, 37.68, 37.22, 28.29, 22.00; **HRMS (EI-TOF)**: calculated for $[M]^+$ ($C_{15}H_{22}O$) requires *m/z* 218.1671, found *m/z* 218.1679.

(2*R*,5*R*)-2-cyclohexyl-5-pentyl-2,5-dihydrofuran (3-3j)



3-3j

Following the general procedure, (*R*)-1-cyclohexylnon-2-yn-4-ol (**3-1j,** 0.3 mmol, 66.7 mg), 5 mol % [(*R*)-**L2-13**]AuCl (13.6 mg), 20 mol% $NaBAr^F_4$ (53.2 mg) and 6 mL dry dichloroethane were stirred at 80 ℃ for 2 h. The solvent was removed and the residue was purified by flash column chromatography (hexnae/EtOAc = 40: 1) to afford **3-3j** (58.0 mg, 86% yield, *d.r.* = 96/4) as a colorless oil.

$[\alpha]^{20}_D$ = -154.2 (c 1.02, $CHCl_3$); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 5.79 (dt, *J* = 6.3, 1.8 Hz, 1H), 5.75 (dt, *J* = 6.2, 1.8 Hz, 1H), 4.77 (qt, *J* = 5.9, 1.8 Hz, 1H), 4.61 (tt, *J* = 5.6, 1.8 Hz, 1H), 1.79 – 1.69 (m, 3H), 1.68 – 1.60 (m, 2H), 1.57 – 1.41 (m, 3H), 1.38 – 1.09 (m, 9H), 1.07 – 0.95 (m, 2H), 0.87 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 130.34, 128.01, 90.13, 85.91, 43.55, 36.20, 32.01, 28.59, 28.49, 26.55, 26.19, 26.14, 24.85,

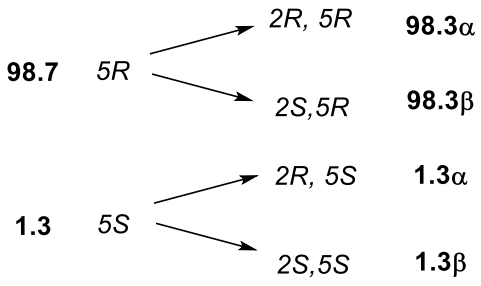
22.63, 14.04; **HRMS (EI-TOF)**: calculated for $[M]^+$ ($C_{15}H_{26}O$) requires *m/z* 222.1984, found *m/z* 222.1984.

Calculation for actual *d.r.*:

Starting material *e.r.* = 98.7 / 1.3

Observed *d.r.* = 96/4

Based on previous results, we assumed that the preexisting stereocenter would not affect the formation of a new stereocenter. α (percentage for the major stereoisomer), β (percentage for the minor stereoisomer)



$$\alpha + \beta = 1$$

$$\frac{(2R,5R) + (2S,5S)}{(2S,5R) + (2R,5S)} = oberserved\ d.r.$$

Based on these:

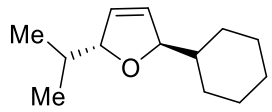
$$\begin{cases} \alpha + \beta = 1 \\ \dfrac{98.7\alpha + 1.3\beta}{98.7\beta + 1.3\alpha} = \dfrac{96}{4} \end{cases}$$

Solved it:

$$\begin{cases} \alpha = 0.972 \\ \beta = 0.028 \end{cases}$$

Thus, actual *d.r.* = 97/3

(2*R*,5*R*)-2-cyclohexyl-5-isopropyl-2,5-dihydrofuran (3-3k)



3-3k

Following the general procedure, (*R*)-6-cyclohexyl-2-methylhex-4-yn-3-ol (**3-1k,** 0.3 mmol, 60.0 mg), 5 mol % [(*R*)-**L2-13**]AuCl (13.6 mg), 20 mol % $NaBAr^F{}_4$ (53.2 mg) and 6 mL dry dichloroethane were stirred at 80 ℃ for 24 h. The solvent was removed and the residue was purified by flash column chromatography (hexnae/EtOAc = 40: 1) to afford **3-3k** (50.6 mg, 84% yield, *d.r.* = 97/3) as a colorless oil.

$[\alpha]^{20}_D$ = -216.1 (c 1.10, $CHCl_3$); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 5.81 (d, *J* = 6.4 Hz, 1H), 5.77 (d, *J* = 6.4 Hz, 1H), 4.65 – 4.56 (m, 2H), 1.83 – 1.69 (m, 4H), 1.68 – 1.61 (m, 2H), 1.47 (tdt, *J* = 11.7, 4.6, 3.2 Hz, 1H), 1.27 – 1.08 (m, 3H), 1.05 – 0.93 (m, 2H), 0.89 (d, *J* = 6.9 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR (151 MHz, $CDCl_3$)** δ 128.94, 128.25, 91.05, 90.61, 43.62, 33.45, 28.71, 28.39, 26.59, 26.24, 26.15, 18.07, 17.63; **HRMS (EI-TOF)**: calculated for $[M]^+$ ($C_{13}H_{22}O$) requires *m/z* 194.1671, found *m/z* 194.1675.

Calculation for actual *d.r.*:

Starting material *e.r.* = 99.5 / 0.5

Observed *d.r.* = 97/3

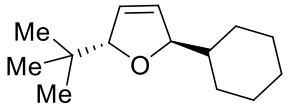
$$\begin{cases} \alpha + \beta = 1 \\ \dfrac{99.5\alpha + 0.5\beta}{99.5\beta + 0.5\alpha} = \dfrac{97}{3} \end{cases}$$

Solved it:

$$\begin{cases} \alpha = 0.975 \\ \beta = 0.025 \end{cases}$$

Thus, actual *d.r.* = 97/3

(2*S*,5*R*)-2-(tert-butyl)-5-cyclohexyl-2,5-dihydrofuran (3-3l)



3-3l

Following the general procedure, (*R*)-6-cyclohexyl-2,2-dimethylhex-4-yn-3-ol (**3-1l,** 0.15 mmol, 31.2 mg), 10 mol % [(*R*)-**L2-13**]AuCl (13.6 mg), 20 mol% $NaBAr^F_4$ (26.6 mg) and 3 mL dry dichloroethane were stirred at 80 ℃ for 50 h. The solvent was removed and the residue was purified by flash column chromatography (hexnae/EtOAc = 40: 1) to afford **3-3l** (11.2 mg, 36% yield, *d.r.* = 90/10) as a colorless oil.

$[\alpha]^{20}_D$ = -219.5 (c 0.46, $CHCl_3$); **^{1}H NMR (500 MHz, $CDCl_3$)** δ 5.83 (ddd, *J* = 6.3, 2.1, 1.4 Hz, 1H), 5.80 (ddd, *J* = 6.3, 2.3, 1.4 Hz, 1H), 4.60 (dddd, *J* = 5.1, 3.6, 2.8, 1.6 Hz, 1H), 4.43 (ddd, *J* = 6.2, 2.2, 1.4 Hz, 1H), 1.80 – 1.62 (m, 5H), 1.50 (tdt, *J* = 11.8, 5.1, 3.2 Hz, 1H), 1.27 – 1.09 (m, 3H), 1.04 – 0.92 (m, 2H), 0.87 (s, 9H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 129.18, 128.04, 94.45, 90.89, 43.61, 35.73, 28.93, 28.13, 26.65, 26.32, 26.12, 25.60; **HRMS (EI-TOF)**: calculated for $[M]^+$ ($C_{14}H_{24}O$) requires *m/z* 208.1827, found *m/z* 208.1832.

Calculation for actual *d.r.*:

Starting material *e.r.* = 95.8 / 4.2

Observed *d.r.* = 90/10

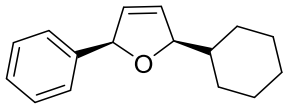
$$\begin{cases} \alpha + \beta = 1 \\ \dfrac{95.8\alpha + 4.2\beta}{95.8\beta + 4.2\alpha} = \dfrac{90}{10} \end{cases}$$

Solved it:

$$\begin{cases} \alpha = 0.937 \\ \beta = 0.063 \end{cases}$$

Thus, actual *d.r.* = 94/6

(2*R*,5*R*)-2-cyclohexyl-5-phenyl-2,5-dihydrofuran (3-3m)



3-3m

Following the general procedure, (*S*)-4-cyclohexyl-1-phenylbut-2-yn-1-ol (**3-1m**, 0.3 mmol, 69.8 mg), 5 mol % [(*R*)-**L2-13**]AuCl (13.6 mg), 20 mol% $NaBAr^F_4$ (53.2 mg) and 6 mL dry dichloroethane were stirred at 80 ℃ for 2 h. The solvent was removed and the residue was purified by flash column chromatography (hexnae/EtOAc = 40 : 1) to afford **3-3m** (62.4 mg, 89% yield, *d.r.* = 93/7) as a colorless oil.

$[\alpha]^{20}_D$ = +65.6 (c 1.03, $CHCl_3$); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.37 – 7.30 (m, 4H), 7.30 – 7.25 (m, 1H), 5.99 (ddd, *J* = 6.1, 2.5, 1.4 Hz, 1H), 5.88 (ddd, *J* = 6.1, 2.5, 1.5 Hz, 1H), 5.73 – 5.71 (m, 1H), 4.66 – 4.61 (m, 1H), 1.96 – 1.89 (m, 1H), 1.78 – 1.70 (m, 3H), 1.67 (dddd, *J* = 11.0, 5.0, 3.3, 1.6 Hz, 1H), 1.53 (dddd, *J* = 15.1, 11.7, 6.8, 3.4 Hz, 1H), 1.24 (qt, *J* = 12.9, 3.5 Hz, 2H), 1.15 (qt, *J* = 12.7, 3.2 Hz, 1H), 1.11 – 1.00 (m, 2H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 141.90, 130.35, 129.29, 128.34, 127.66, 126.84, 91.01, 87.11, 43.54, 29.33, 28.91, 26.49, 26.03; **HRMS (EI-TOF)**: calculated for $[M]^+$ ($C_{16}H_{20}O$) requires *m/z* 228.1514, found *m/z* 228. 1507.

Calculation for actual *d.r.*:

Starting material *e.r.* = 97.5 / 2.5

Observed *d.r.* = 93/7

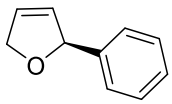
$$\begin{cases} \alpha + \beta = 1 \\ \dfrac{97.5\alpha + 2.5\beta}{97.5\beta + 2.5\,\alpha} = \dfrac{93}{7} \end{cases}$$

Solved it:

$$\begin{cases} \alpha = 0.953 \\ \beta = 0.047 \end{cases}$$

Thus, actual *d.r.* = 95/5

(*S*)-2-phenyl-2,5-dihydrofuran (3-4a)

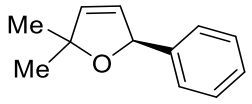


3-4a

Following the general procedure, 4-phenylbut-2-yn-1-ol (**3-2a**, 0.3 mmol, 45.1 mg), 5 mol % [(*R*)-**L2-13**]AuCl (13.6 mg), 20 mol% $NaBAr^F{}_4$ (53.2 mg) and 6 mL dry dichloroethane were stirred at room temperature for 3 h. The solvent was removed and the residue was purified by flash column chromatography (hexnae/EtOAc = 40: 1) to afford **3-4a** (42.1 mg, 93% yield) as a colorless oil.

$[\alpha]^{20}_D$ = -176.77 (c 1.04, $CHCl_3$); **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.39 – 7.27 (m, 5H), 6.05 (ddt, *J* = 5.9, 2.3, 1.6 Hz, 1H), 5.91 (dtd, *J* = 6.3, 2.5, 1.6 Hz, 1H), 5.81 (ddt, *J* = 6.0, 3.9, 2.0 Hz, 1H), 4.89 (dddd, *J* = 12.8, 6.1, 2.4, 1.7 Hz, 1H), 4.79 (dddd, *J* = 12.8, 4.1, 2.5, 1.6 Hz, 1H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 141.99, 129.92, 128.44, 127.75, 126.58, 126.34, 87.85, 75.76; ***e.r.*** = 90/10 [determined by HPLC: Chiralcel® Chiral IB column, Hexane/*i*PrOH = 1000/1, 1.0 mL/min, λ = 200 nm; t_R(major) = 14.18 min, t_R(minor) = 12.18 min]; These data are in accordance with literature. [27]

(*S*)-2,2-dimethyl-5-phenyl-2,5-dihydrofuran (3-4b)

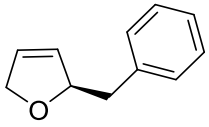


3-4b

Following the general procedure, 2-methyl-5-phenylpent-3-yn-2-ol (**3-2b**, 0.3 mmol, 52.3 mg), 5 mol % [(*R*)-**L2-13**]AuCl (13.6 mg), 20 mol% $NaBAr^F_4$ (53.2 mg) and 6 mL dry dichloroethane were stirred at 30 ℃ for 48 h. The solvent was removed and the residue was purified by flash column chromatography (hexnae/EtOAc = 40: 1) to afford **3-4b** (42.0 mg, 77% yield) as a colorless oil.

$[\alpha]^{20}_D$ = -117.5 (c 1.27, $CHCl_3$); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.35 (d, *J* = 5.3 Hz, 4H), 7.30 – 7.26 (m, 1H), 5.89 (dd, *J* = 5.9, 2.5 Hz, 1H), 5.81 (dd, *J* = 2.5, 1.5 Hz, 1H), 5.75 (dd, *J* = 5.9, 1.5 Hz, 1H), 1.47 (s, 3H), 1.41 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 141.94, 135.66, 128.38, 128.19, 127.62, 126.59, 88.08, 86.83, 28.79, 27.82; **HRMS (EI-TOF)**: calculated for $[M]^+$ ($C_{12}H_{14}O$) requires *m/z* 174.1045, found *m/z* 174.1043; ***e.r.*** = 91/9 [determined by HPLC: Chiralcel® Chiral IB column, Hexane/*i*PrOH = 1000/1, 1.0 mL/min, λ = 200 nm; t_R(major) = 11.55 min, t_R(minor) = 7.67 min]; These data are in accordance with literature. [28]

(*R*)-2-benzyl-2,5-dihydrofuran (3-4c)



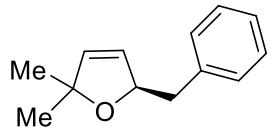
3-4c

Following the general procedure, 5-phenylpent-2-yn-1-ol (**3-2c**, 0.3 mmol, 47.6 mg), 5 mol % [(*R*)-**L2-13**]AuCl (13.6 mg), 20 mol% $NaBAr^F_4$ (53.2 mg) and 6 mL dry dichloroethane were stirred at 80 ℃ for 18 h. The solvent was removed and the residue

was purified by flash column chromatography (hexnae/EtOAc = 40 : 1) to afford **3-4c** (16.8 mg, 35% yield) as a colorless oil.

$[\alpha]^{20}_D$ = -105.4 (c 0.08, $CHCl_3$); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.31 – 7.27 (m, 2H), 7.24 – 7.19 (m, 3H), 5.87 (dq, *J* = 6.3, 1.8 Hz, 1H), 5.77 (dtd, *J* = 6.3, 2.5, 1.4 Hz, 1H), 5.08 – 5.02 (m, 1H), 4.66 – 4.57 (m, 2H), 2.91 (dd, *J* = 13.5, 6.1 Hz, 1H), 2.83 (dd, *J* = 13.5, 6.5 Hz, 1H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 138.05, 129.41, 129.20, 128.21, 126.86, 126.17, 86.84, 75.19, 42.68; ***e.r.*** = 90/10 [determined by HPLC: Chiralcel® Chiral IB column, Hexane/*i*PrOH = 1000/1, 1.0 mL/min, λ = 200 nm; t_R(major) = 13.23 min, t_R(minor) = 11.03 min]. These data are in accordance with literature. [27]

(*R*)-5-benzyl-2,2-dimethyl-2,5-dihydrofuran (3-4d)



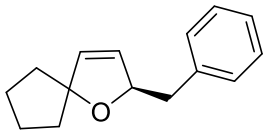
3-4d

Following the general procedure, 2-methyl-6-phenylhex-3-yn-2-ol (**3-2d**, 0.3 mmol, 56.7 mg), 5 mol % [(*R*)-**L2-13**]AuCl (13.6 mg), 20 mol% $NaBAr^F_4$ (53.2 mg) and 6 mL dry dichloroethane were stirred at 80 ℃ for 5 h. The solvent was removed and the residue was purified by flash column chromatography (hexnae/EtOAc = 40 : 1) to afford **3-4d** (43.9 mg, 78% yield) as a colorless oil.

$[\alpha]^{20}_D$ = -92.9 (c 1.06, $CHCl_3$); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.31 – 7.27 (m, 2H), 7.23 – 7.19 (m, 3H), 5.73 (dd, *J* = 6.0, 2.2 Hz, 1H), 5.65 (dd, *J* = 6.0, 1.4 Hz, 1H), 5.06 – 5.02 (m, 1H), 2.99 (dd, *J* = 13.3, 5.7 Hz, 1H), 2.78 (dd, *J* = 13.3, 7.2 Hz, 1H), 1.29 (s, 3H), 1.26 (s, 3H); **^{13}C NMR (151 MHz, $CDCl_3$)** δ 137.98, 135.70, 129.59, 128.11, 127.44, 126.13, 87.60, 85.86, 43.78, 29.06, 27.97; **HRMS (EI-TOF)**: calculated for $[M]^+$

($C_{13}H_{16}O$) requires *m/z* 188.1201, found *m/z* 188.1206; ***e.r.*** = 95/5 [determined by HPLC: Chiralcel® Chiral IB column, Hexane/*i*PrOH = 1000/1, 1.0 mL/min, λ = 200 nm; t_R(major) = 13.25 min, t_R(minor) = 9.53 min].

(*R*)-2-benzyl-1-oxaspiro[4.4]non-3-ene (3-4e)

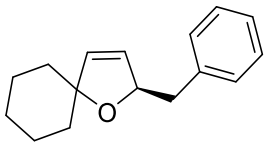


3-4e

Following the general procedure, 1-(4-phenylbut-1-yn-1-yl)cyclopentan-1-ol (**3-2e**, 0.3 mmol, 65.9 mg), 5 mol % [(*R*)-**L2-13**]AuCl (13.6 mg), 20 mol% $NaBAr^F_4$ (53.2 mg) and 6 mL dry dichloroethane were stirred at 80 ℃ for 9 h. The solvent was removed and the residue was purified by flash column chromatography (hexnae/EtOAc = 40: 1) to afford **3-4e** (56.2 mg, 85% yield) as a colorless oil.

$[\alpha]^{20}_D$ = -99.7 (c 0.94, $CHCl_3$); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.31 – 7.27 (m, 2H), 7.23 – 7.19 (m, 3H), 5.73 (dd, *J* = 6.0, 2.1 Hz, 1H), 5.70 (dd, *J* = 6.0, 1.3 Hz, 1H), 4.99 (ddt, *J* = 7.4, 5.6, 1.7 Hz, 1H), 2.99 (dd, *J* = 13.2, 5.6 Hz, 1H), 2.74 (dd, *J* = 13.2, 7.4 Hz, 1H), 1.90 – 1.74 (m, 3H), 1.71 – 1.59 (m, 5H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 137.99, 133.62, 129.57, 128.10, 127.95, 126.10, 97.81, 85.71, 43.76, 39.86, 38.59, 24.53, 24.37; **HRMS (EI-TOF)**: calculated for $[M]^+$ ($C_{15}H_{18}O$) requires *m/z* 214.1358, found *m/z* 214.1357; ***e.r.*** = 93/7 [determined by HPLC: Chiralcel® Chiral IB column, Hexane/*i*PrOH = 1000/1, 1.0 mL/min, λ = 200 nm; t_R(major) = 14.71 min, t_R(minor) = 9.59 min].

(*R*)-2-benzyl-1-oxaspiro[4.5]dec-3-ene (3-4f)

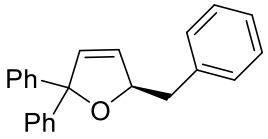


3-4f

Following the general procedure, 1-(4-phenylbut-1-yn-1-yl)cyclohexan-1-ol (**3-2f**, 0.3 mmol, 69.0 mg), 5 mol % [(*R*)-**L2-13**]AuCl (13.6 mg), 20 mol% $NaBAr^F{}_4$ (53.2 mg) and 6 mL dry dichloroethane were stirred at 80 ℃ for 9 h. The solvent was removed and the residue was purified by flash column chromatography (hexnae/EtOAc = 40: 1) to afford **3-4f** (59.5 mg, 86% yield) as a colorless oil.

$[\alpha]^{20}_D$ = -87.4 (c 1.12, $CHCl_3$); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.32 – 7.27 (m, 2H), 7.24 – 7.19 (m, 3H), 5.87 (dd, *J* = 6.2, 2.2 Hz, 1H), 5.70 (dd, *J* = 6.1, 1.4 Hz, 1H), 5.02 (ddt, *J* = 7.4, 5.6, 1.8 Hz, 1H), 3.01 (dd, *J* = 13.3, 5.6 Hz, 1H), 2.76 (dd, *J* = 13.3, 7.3 Hz, 1H), 1.76 – 1.68 (m, 2H), 1.62 – 1.36 (m, 8H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 138.10, 134.13, 129.61, 128.06, 128.01, 126.07, 89.64, 85.42, 38.67, 37.47, 25.43, 23.46, 23.36; **HRMS (CI-TOF)**: calculated for $[M+H]^+$ ($C_{16}H_{21}O$) requires *m/z* 229.1592, found *m/z* 229.1582; ***e.r.*** = 94/6 [determined by HPLC: Chiralcel® Chiral IB column, Hexane/*i*PrOH = 1000/1, 1.0 mL/min, λ = 200 nm; t_R(major) = 15.30 min, t_R(minor) = 13.13 min].

(*R*)-5-benzyl-2,2-diphenyl-2,5-dihydrofuran (3-4g)



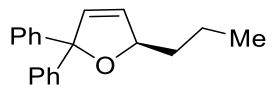
3-4g

Following the general procedure, 1,1,5-triphenylpent-2-yn-1-ol (**3-2g**, 0.3 mmol, 94.6 mg), 5 mol % [(*R*)-**L2-13**]AuCl (13.6 mg), 20 mol% $NaBAr^F{}_4$ (53.2 mg) and 6 mL dry dichloroethane were stirred at 80 ℃ for 5 h. The solvent was removed and the residue

was purified by flash column chromatography (hexnae/Et_2O = 50 : 1) to afford **3-4g** (67.3 mg, 71% yield) as a yellow oil.

$[\alpha]^{20}_D$ = -59.3 (c 1.07, $CHCl_3$); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.39 – 7.19 (m, 15H), 6.33 (dd, *J* = 6.0, 2.3 Hz, 1H), 5.96 (dd, *J* = 6.0, 1.4 Hz, 1H), 5.27 – 5.22 (m, 1H), 3.16 (dd, *J* = 13.3, 6.0 Hz, 1H), 2.85 (dd, *J* = 13.4, 7.6 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 145.60, 145.31, 137.82, 133.04, 129.43, 129.24, 128.30, 128.10, 128.03, 127.04, 127.01, 126.58, 126.28, 126.24, 94.58, 87.05, 42.81; **HRMS (EI-TOF)**: calculated for $[M]^+$ ($C_{23}H_{20}O$) requires *m/z* 312.1514, found *m/z* 312.1513; ***e.r.*** = 95/5 [determined by HPLC: Chiralcel® Chiral IB column, Hexane/*i*PrOH = 1000/1, 1.0 mL/min, λ = 200 nm; t_R(major) = 23.49 min, t_R(minor) = 25.52 min].

(*R*)-2,2-diphenyl-5-propyl-2,5-dihydrofuran (3-4h)



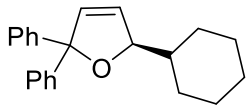
3-4h

Following the general procedure, 1,1-diphenylhept-2-yn-1-ol (**3-2h**, 0.3 mmol, 79.2 mg), 5 mol % [(*R*)-**L2-13**]AuCl (13.6 mg), 20 mol% $NaBAr^F_4$ (53.2 mg) and 6 mL dry dichloroethane were stirred at 80 ℃ for 2 h. The solvent was removed and the residue was purified by flash column chromatography (hexnae/Et_2O = 50: 1) to afford **3-4h** (66.9 mg, 84% yield) as a yellow oil.

$[\alpha]^{20}_D$ = -74.4 (c 1.05, $CHCl_3$); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.40 – 7.32 (m, 8H), 7.28 – 7.24 (m, 2H), 6.32 (dd, *J* = 6.0, 2.3 Hz, 1H), 6.00 (dd, *J* = 6.0, 1.4 Hz, 1H), 5.03 (tt, *J* = 6.3, 1.8 Hz, 1H), 1.75 – 1.68 (m, 1H), 1.66 – 1.59 (m, 1H), 1.56 – 1.49 (m, 1H), 1.49 – 1.41 (m, 1H), 0.97 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 145.86, 145.55, 132.55, 129.97, 128.08, 127.99, 126.96, 126.90, 126.50, 126.32, 94.01, 85.88, 38.14,

18.87, 14.19; **HRMS (EI-TOF)**: calculated for $[M]^+$ ($C_{19}H_{20}O$) requires *m/z* 264.1514, found *m/z* 264.1508; ***e.r.*** = 97/3 [determined by HPLC: Chiralcel® Chiral IA column, Hexane/*i*PrOH = 1000/1, 1.0 mL/min, λ = 200 nm; t_R(major) = 11.04 min, t_R(minor) = 10.24 min].

(*R*)-5-cyclohexyl-2,2-diphenyl-2,5-dihydrofuran (3-4i)

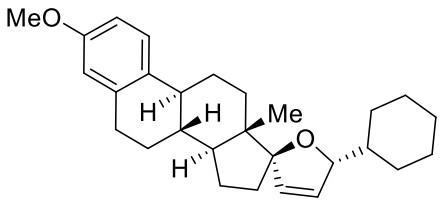


3-4i

Following the general procedure, 4-cyclohexyl-1,1-diphenylbut-2-yn-1-ol (**3-2i**, 0.3 mmol, 92.1 mg), 5 mol % [(*R*)-**L2-13**]AuCl (13.6 mg), 20 mol% $NaBAr^F{}_4$ (53.2 mg) and 6 mL dry dichloroethane were stirred at 80 ℃ for 2 h. The solvent was removed and the residue was purified by flash column chromatography (hexnae/Et_2O = 50: 1) to afford **3-4i** (66 mg, 72% yield) as a yellow oil.

$[\alpha]^{20}_D$ = -113.4 (c 1.12, $CHCl_3$); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.40 – 7.38 (m, 2H), 7.36 – 7.30 (m, 6H), 7.28 – 7.23 (m, 2H), 6.36 (dd, *J* = 6.0, 2.4 Hz, 1H), 6.03 (dd, *J* = 6.0, 1.4 Hz, 1H), 4.78 (ddd, *J* = 6.3, 2.4, 1.4 Hz, 1H), 2.01 – 1.93 (m, 1H), 1.80 – 1.72 (m, 2H), 1.71 – 1.66 (m, 2H), 1.61 – 1.55 (m, 1H), 1.32 – 1.11 (m, 3H), 1.11 – 1.00 (m, 2H); **^{13}C NMR (151 MHz, $CDCl_3$)** δ 145.77, 145.67, 133.03, 128.46, 128.06, 127.97, 126.88, 126.87, 126.64, 126.21, 93.72, 90.62, 43.00, 29.45, 28.79, 26.53, 26.09, 26.01; **HRMS (EI-TOF)**: calculated for $[M]^+$ ($C_{22}H_{24}O$) requires *m/z* 304.1827, found *m/z* 304.1836. ***e.r.*** = 98.5/1.5 [determined by HPLC: Chiralcel® Chiral IA column, Hexane/*i*PrOH = 1000/1, 1.0 mL/min, λ = 220 nm; t_R(major) = 26.64 min, t_R(minor) = 25.14 min].

(5'*R*,8*R*,9*S*,13*S*,14*S*,17*R*)-5'-cyclohexyl-3-methoxy-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-5'H-spiro[cyclopenta[a]phenanthrene-17,2'-furan] (3-4j)



3-4j

Following the general procedure, (8*R*,9*S*,13*S*,14*S*,17*S*)-17-(3-cyclohexylprop-1-yn-1-yl)-3-methoxy-13-methyl 7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthre -n-17-ol (**3-2j**, 0.3 mmol, 122.0 mg), 10 mol % [(*R*)-**L2-13**]AuCl (27.2 mg), 20 mol% $NaBAr^F{}_4$ (53.2 mg) and 6 mL dry dichloroethane were stirred at 80 ℃ for 48 h. The solvent was removed and the residue was purified by flash column chromatography (hexnae/EtOAc = 30 : 1) to afford **3-4j** (72.2 mg, 59% yield, *d.r.* >50/1) as a white solid.

$[\alpha]^{20}_D$ = +6.4 (c 1.12, $CHCl_3$); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.22 (dd, *J* = 8.7, 1.0 Hz, 1H), 6.73 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.65 (d, *J* = 2.8 Hz, 1H), 5.88 (dd, *J* = 6.1, 2.2 Hz, 1H), 5.80 (dd, *J* = 6.1, 1.5 Hz, 1H), 4.44 (dt, *J* = 7.6, 1.8 Hz, 1H), 3.79 (s, 3H), 2.93 – 2.82 (m, 2H), 2.29 (dtd, *J* = 12.8, 4.1, 2.5 Hz, 1H), 2.16 (td, *J* = 11.2, 4.2 Hz, 1H), 2.10 – 2.04 (m, 1H), 2.01 – 1.95 (m, 1H), 1.93 (ddt, *J* = 12.6, 5.8, 2.6 Hz, 1H), 1.81 – 1.66 (m, 6H), 1.60 – 1.13 (m, 11H), 1.08 – 0.96 (m, 2H), 0.94 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 157.33, 137.97, 132.75, 132.67, 126.31, 126.21, 113.68, 111.41, 100.14, 89.15, 55.14, 50.44, 45.48, 44.69, 43.90, 39.26, 35.92, 33.57, 29.88, 29.71, 28.87, 27.25, 26.56, 26.35, 26.08, 26.00, 23.02, 13.82; **HRMS (EI-TOF)**: calculated for $[M]^+$ ($C_{28}H_{38}O_2$) requires *m/z* 406.2872, found *m/z* 406.2868.

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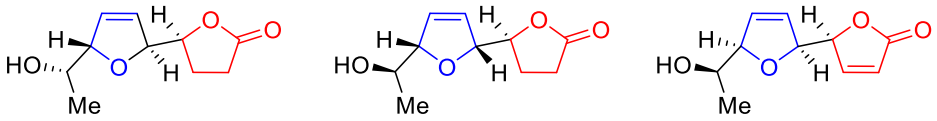
4. Total Synthesis of Diplobifuranylone B and Nominal Diplobifuranylone A

4.1. Introduction and Retrosynthetic Analysis

Diplobifuranylone B (**4-2**),[1] isolated from *Diplodia Corticola* in 2006, is a fungus pathogen of the cork oak. Compounds of its family include diplobifuranylone A (**4-1**)[1] and diplobifuranylone C (**4-3**) as additional members.[2] The absolute configurations of these compounds were not determined until 2017 by electronic and vibrational circular dichroism (ECD and VCD) and optical rotatory dispersion (ORD) studies.[3] In ***Chapter 3***, we demonstrated that highly diastereoselective or enantioselective asymmetric isomerization of propargylic alcohols with the help of newly designed bifunctional ligand **(*R*)-L2-13**. To illustrate the synthetic potential of this methodology in a challenging setting of natural product synthesis, we embarked on a 10-steps synthesis of this natural product. Notably, diplobifuranylone B as well as the other members of the diplobifuranylone family has not been previously synthesized.

Figure 10. Diplobifuranylones Produced by *Diplodia Corticola*



Diplobifuranylone A
4-1

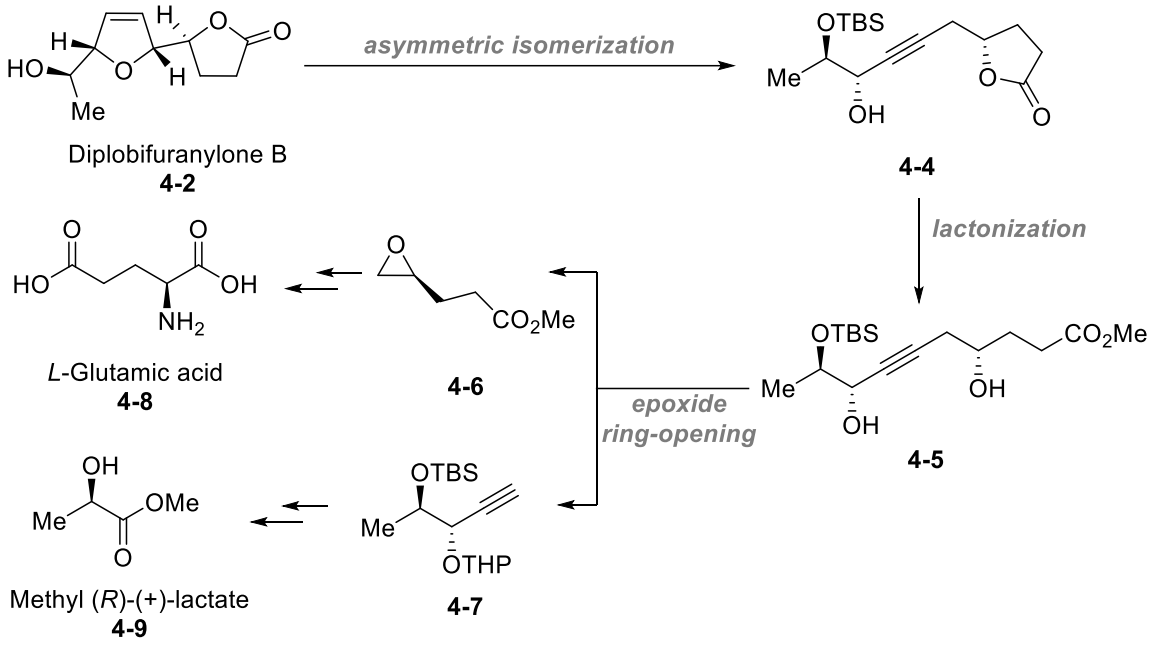
Diplobifuranylone B
4-2

Diplobifuranylone C
4-3

Our retrosynthetic analysis of diplobifuranylone B (**4-2**) is shown in Scheme 33. The critical transformation is constructing the *cis*-2,5-dihydrofuran ring by the gold-catalyzed asymmetric isomerization/cyclization of the lactone **4-4** at the final stage. The lactone **4-4** could be easily accessed through lactonization of the dihydroxy ester **4-5**,

which could be synthesized from the epoxide **4-6** and the alkyne **4-7** via the epoxide ring-opening reaction. The epoxide **4-6** and the alkyne **4-7** are readily prepared from commercially available *L*-glutamic acid (**4-8**) and methyl (*R*)-(+)-lactate (**4-9**) via the known literature procedures.[4]

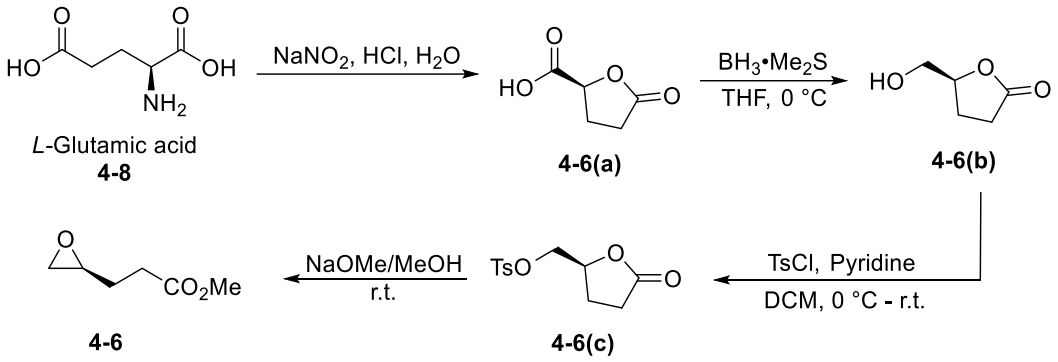
Scheme 33. Retrosynthetic Analysis of Diplobifuranylone B



4.2. Total Synthesis of Diplobifuranylone B

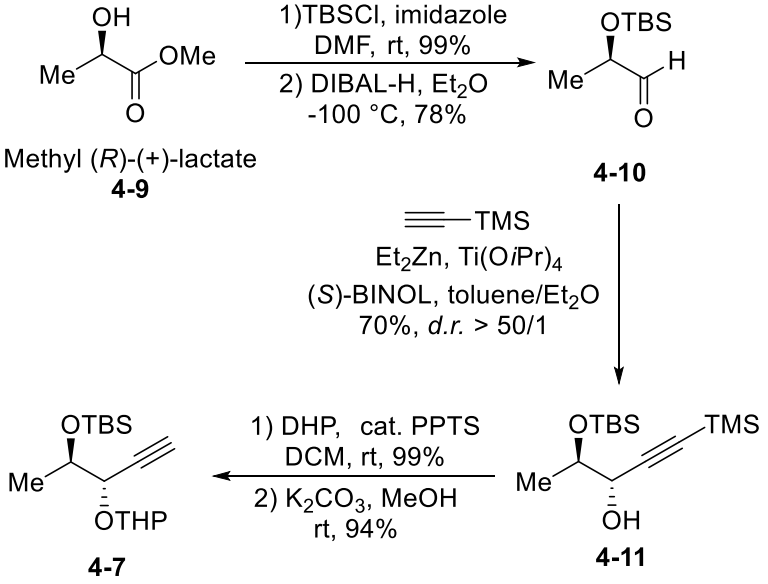
We commenced the synthesis with the preparation of the two fragments **4-6** and **4-7**. **4-6** was prepared from *L*-glutamic acid (**4-8**) by following a reported four-step sequence (Scheme 34).[4] *L*-Glutamic acid (**4-8**) was deamination by *in-situ* generated nitrous acid to afford lactone **4-6(a)**, followed by the reduction of the carboxylic acid into alcohol **4-6(b)** by borane-methyl sulfide (BH_3-Me_2S). The 4-step synthesis was finished by tosylation of **4-6(b)**, followed by treatment with sodium methoxide to give the epoxides **4-6.**

Scheme 34. Preparation of the Chiral Epoxide 4-6



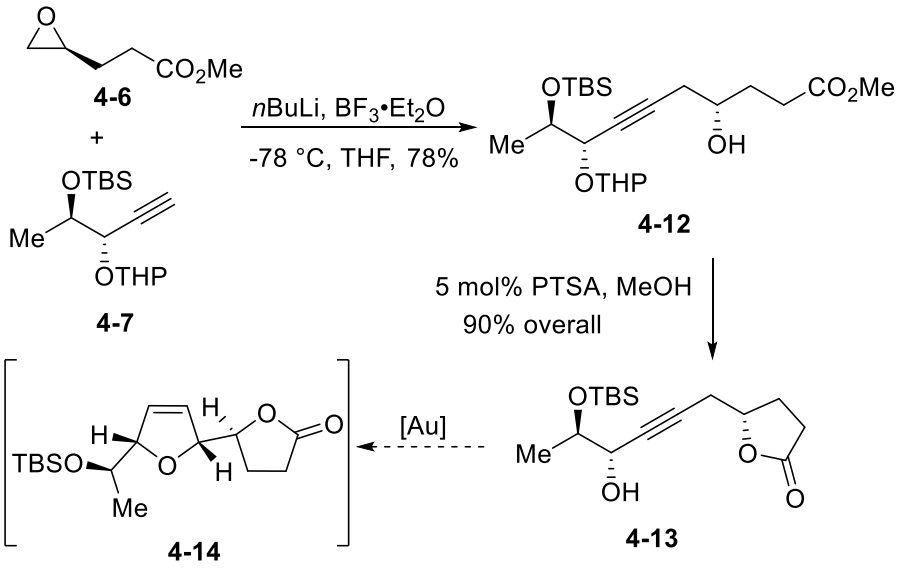
4-7 was synthesized from methyl (*R*)-(+)-lactate (**4-9**) in five steps. The synthetic sequence began with a TBS group protection of **4-9**, followed by a DIBAL-H reduction. The α-siloxypropanal **4-10** was isolated in 78% overall yield. An asymmetric nucleophilic addition to **4-10** by ethynyltrimethylsilane was achieved in the presence of a stoichiometric Ti(O*i*Pr)$_4$-BINOL complex[5] to afford the propargylic alcohol **4-11** in 70% isolated yield and *d.r.* >50:1 upon careful column separation. THP protection of **4-11** followed by selective removal of the TMS group gave the desired terminal alkyne **4-7** in a combined 94% yield.

Scheme 35. Preparation of the Alkyne 4-7.



With these two chiral fragments in hand, we carried out the planned end game. As shown in Scheme 36, the BF_3-mediated ring opening[6] of the chiral epoxide **4-6** by deprotonated **4-7** delivered the γ-hydroxy ester **4-12** with the requisite carbon skeleton of the natural product. Removal of the THP group and lactonization were achieved in one step to give the lactone **4-13** in 90% overall yield. However, when **4-13** was subjected to the asymmetric gold catalysis to construct the 2,5-dihydrofuran ring, the reaction was sluggish, with most of the starting material **4-13** remained after 12 h; moreover, no desired product **4-14** was found in the reaction mixture.

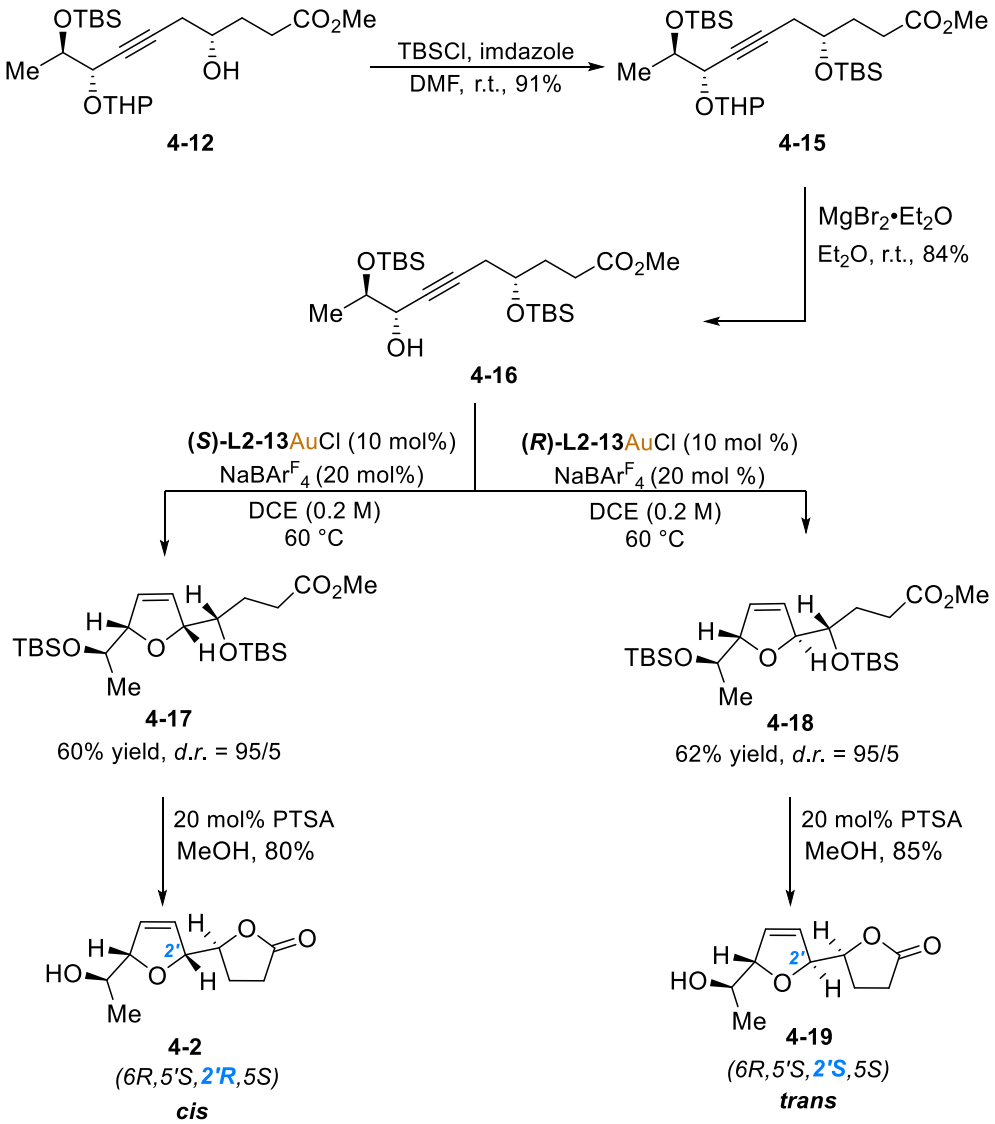
Scheme 36. Initial Attempt on the Total Synthesis of Diplobifuranylone B



We speculated that the strong electron-withdrawing nature of the lactone motif might affect the gold-catalyzed isomerization of alkyne to allene and hence decided to modify the synthesis sequence to have the 2,5-dihydrofuran ring installed before the lactonization step. To this end, we converted the γ-hydroxy esters **4-12** to the desired propargylic alcohol **4-16** in 76% combined yield through a two-step sequence, i.e., TBS protection of the free hydroxyl group to avoid potential gold-catalyzed 5-*endo-trig* cyclization and subsequent

selective deprotection of the THP group in the presence of magnesium bromide (Scheme 37).[7]

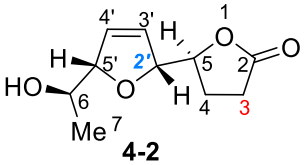
Scheme 37. Revised Route of Total Synthesis of Nominal Diplobifuranylone B



To our delight, subjecting **4-16** to our asymmetric gold catalysis with (*S*)-**L2-13** as the ligand afforded smoothly the 2,5-dihydrofuran product **4-17** in 60% yield and with a diastereomeric ratio of 95/5. One-pot removal of both TBS groups of **4-17** and lactonization in the presence of PTSA/MeOH completed the synthesis of the nominal diplobifuranylone B (**4-2**) in 80% yield. The absolute stereochemistry of C2' is assigned based on our previous

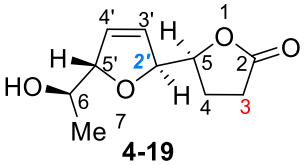
report on chiral 2,5-dihydrofuran synthesis.[8] To our surprise, there are obvious discrepancies between the ^{1}H NMR (**Table 6**) and ^{13}C NMR (Table 7) as well as the optical rotation {$[\alpha]^{20}D$ = +24.7 (c = 1.06, $CHCl_3$); lit. $[\alpha]^{20}D$ = -90.7 (c = 0.55, $CHCl_3$)}of our synthetic compound (**4-2**) and what were reported.[1]

Table 6. ^{1}H NMR Comparison for Diplobifuranylone B



4-2

(6R,5'S,2'R,5S)



4-19

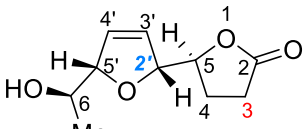
(6R,5'S,2'S,5S)

	4-2	**4-19**	Literature[1]
5	4.53 (dt, *J* = 7.3, 5.8 Hz, 1H)	4.54 (ddd, *J* = 8.0, 5.3, 2.8 Hz, 1H)	4.55 (ddd, *J* = 8.0, 5.3, 2.8, 1H)
4	2.39 – 2.31 (m, 1H) 2.19 – 2.11 (m, 1H)	2.34 – 2.27 (m, 1H) 2.26 – 2.18 (m, 1H)	2.29 (m, 1H) 2.22 (m, 1H)
3	2.61 – 2.49 (m, 2H)	2.66 (ddd, *J* = 17.7, 10.1, 7.0, 1H) 2.47 (ddd, *J* = 17.7, 10.3, 6.4, 1H)	2.66 (ddd, *J* = 16.7, 10.1, 7.0, 1H) 2.45 (ddd, *J* = 16.7, 10.3, 6.4, 1H)
2'	4.85 – 4.81 (m, 1H)	4.97 (dtd, *J* = 6.1, 2.5, 1.7 Hz)	4.97 (m, 1H)
3'	5.96 (dt, *J* = 6.3, 1.8 Hz, 1H)	5.90 (dt, *J* = 6.3, 2.0 Hz, 1H)	5.92 (br,d, *J* = 9.3 Hz, 1H)
4'	6.07 (dt, *J* = 6.6, 1.7 Hz, 1H)	6.01 (dt, *J* = 6.3, 2.0 Hz, 1H)	6.01(br,d, *J* = 9.3 Hz, 1H)
5'	4.74 – 4.71 (m, 1H)	4.79 (dddd, *J* = 5.9, 3.7, 2.3, 1.5 Hz, 1H)	4.79 (m, 1H)
6	3.89 (dq, *J* = 6.5, 3.8 Hz)	3.90 (dq, *J* = 6.5, 3.4 Hz)	3.90 (dq, *J* = 6.6, 3.4 Hz, 1H)
7	1.22 (d, *J* = 6.5 Hz)	1.17 (d, *J* = 6.5 Hz)	1.18 (d, *J* = 6.6 Hz, 1H)
OH	-	1.64, br, s	1.85, br,s

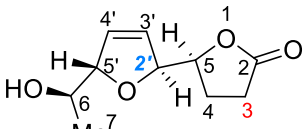
Our asymmetric gold catalysis permits easy access to the C2'-epimer of **4-2**, i.e., the *trans*-2,5-dihydrofuran **4-19** (Scheme 37) by simply employing the ligand enantiomer, i.e., (*R*)-**L2-19**, in the conversion of **4-16**. Indeed, by following the same two-step endgame, compound **4-19** was synthesized with comparable diastereoselectivity and

efficiency to **4-2**. Much to our delight, the spectroscopic data including ^{1}H NMR, ^{13}C NMR, ^{1}H spin decouple, COSY, HMQC, and HMBC, and the HR-MS measurement of **4-19** match those reported for diplobifuranylone B well except one surprising outlier in the ^{13}C data. The ^{13}C chemical shifts of **4-2**, **4-19**, and the parent γ-lactone[1] and those reported in the isolation paper are listed in Table 7 for comparison.

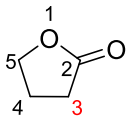
Table 7. ^{13}C NMR Comparison for Diplobifuranylone B



4-2
(6R,5'S,2'R,2S)



4-19
(6R,5'S,2'S,2S)



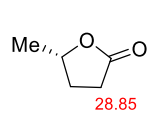
4-20

	4-2	**4-19**	**4-20**	**Lit.**	**Δ[(4-2)-Lit.]**[a]	**Δ[(4-19)-Lit.]**[a]
5	81.04	80.12	68.49	80.1	+0.94	+0.02
4	23.54	23.75	22.06	23.7	-0.16	+0.05
3	**27.74**	**27.97**	**27.70**	**22.9**	**+4.84**	**+5.07**
2	176.39	177.24	177.81	177.2	-0.85	+0.04
2’	87.11	87.97	-	87.9	-0.79	+0.07
3’	129.50	128.79	-	128.7	+0.80	+0.09
4’	127.20	127.33	-	127.3	-0.10	+0.03
5’	91.00	91.01	-	90.9	+0.10	+0.11
6	69.08	69.09	-	69.1	-0.02	-0.01
7	18.92	17.94	-	17.9	+1.02	+0.04

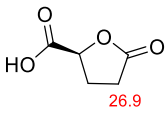
[a] Calculated with the accuracy of the literature data extended to 0.01 ppm.

All the ^{13}C chemical shifts of **4-19** are within 0.11 ppm difference from the literature data, which were reported with accuracy down to the 0.1 ppm level, and hence can be considered identical except that of the lactone C3. For this outlier, the reported value is 22.9 ppm, but our measured value is 27.9 ppm, which is identical to that of the parent γ-lactone.[9] In addition, the chemical shift of the lactone C3 of diplobifuranylone A[1] is 28.2 ppm. We also performed a relatively comprehensive literature search (Figure 11) of γ-lactones possessing only one substituent at C5, as in the case of diplobifuranylone B, and found that the chemical shifts of the lactone C3 range from 26.9 ppm to 29.5 ppm.[10] In no example, the ^{13}C signal could shift to as high a field as 22.9 ppm. Unfortunately, we could not obtain the original ^{1}H and ^{13}C spectra of diplobifuranylone B. Considering that all the other ^{13}C chemical shifts are essentially identical between the reported data and those of **4-19**, we feel confident to conclude that the reported C3 ^{13}C chemical shift is a typo and should be 27.9 ppm.

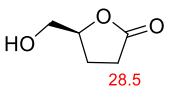
Figure 11. The Chemical Shifts of the C3 of γ-lactones Possessing Only One Substituent at C5

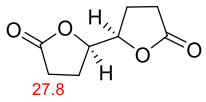


Synth. Commun. **48**, 2801-2808

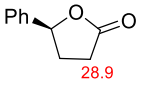


J. Org. Chem. **75**, 2820-2835

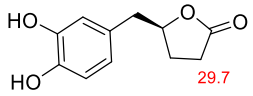




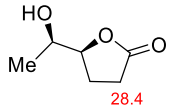
Tetrahedron, **65**, 396-399



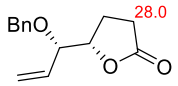
Angew. Chem. Int. Ed. **57**, 1386-1389.



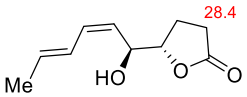
Synthesis, **9**, 1512-1520

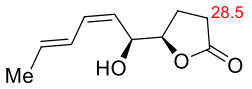


Tetrahedron, **55**,1043-1056

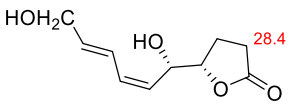


Tetrahedron, **67**, 9358-9367

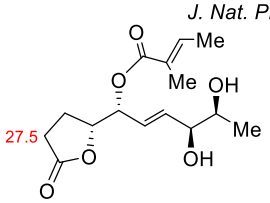




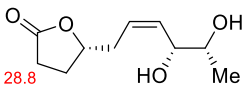
J. Nat. Prod. **62**, 253-256



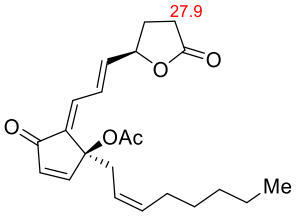
J. Agric. Food Chem. **64**, 217-225



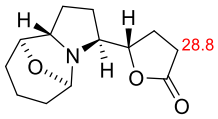
Eur. J. Org. Chem. **31**, 6891-6899



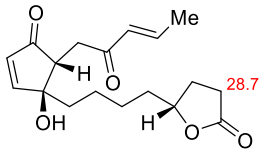
Org. Lett. **12**, 5752-5755



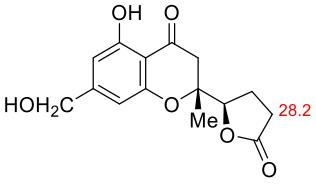
Org. Biomol. Chem. **13**, 4051-4058



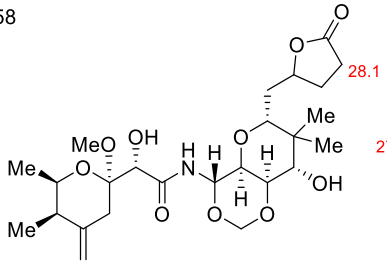
Synlett, **5**, 779-782



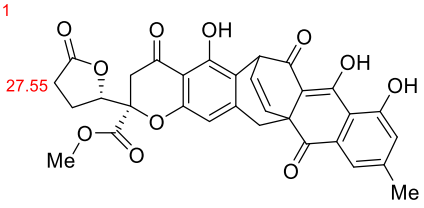
J. Nat. Prod. **71**, 701-705



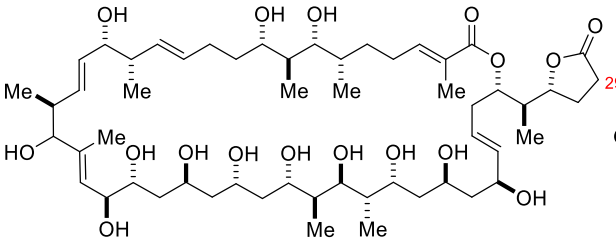
J. Nat. Prod. **69**, 980-982



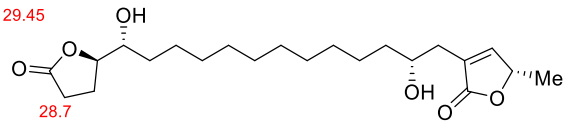
J. Org. Chem. **57**, 3828-3832



J. Am. Chem. Soc. **115**, 8558-8564



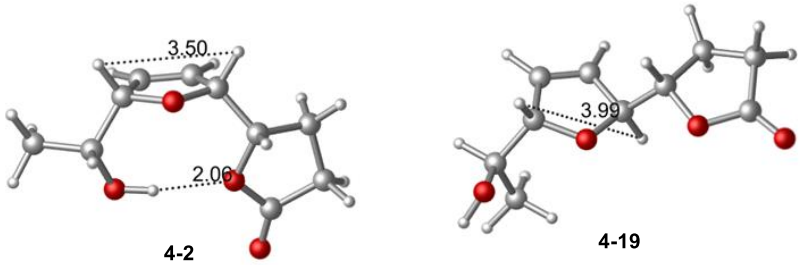
Angew. Chem. Int. Ed. **46**, 545-548.



J. Nat. Prod. **66**, 279–281

To understand the misassignment of the natural product's 2,5-dihydrofuran stereochemistry, we carefully examined the original reports.[1,3] It was based on the NOESY, ROESY, and double decoupling experiments. Our DFT calculations reveal the distances between H-2' and H-5' in the optimized structures of the *cis* (**4-2**) and the *trans* (**4-19**) isomers at the B3LYP//cc-pVDZ level are 3.50 Å and 3.99 Å, respectively. With both measurements less than 4 Å, the observed NOE might not be a reliable indicator of a *cis* configuration.

Figure 12. DFT Calculation for the *cis* (4-2) and *trans* (4-19) Isomers.



at the B3LYP 4-5 level of theory with cc-pVDZ basis set.

The double coupling experiment revealed that the long-distance coupling constant between H-2' and H-5' is 5.5 Hz, which was suggested to corroborate the *cis* stereochemistry. However, this large long-range coupling constant is characteristic of *trans*-2,5-dihydrofurans.[11] Typically, the *J* values of *trans*-2,5-dihydrofurans are > 5 Hz, while those of *cis*-2,5-dihydrofurans are <4 Hz. Some of the examples we found in the literature are listed in Figure 13.[12-16] Our decoupling experiments reveal that the coupling constants between H-2' and H-5' are 3.8 Hz and 5.8 Hz for **4-2** and **4-19**, respectively, which is consistent with our stereochemistry assignments. A related case is furanomycin (**4-30**, **Figure *14***). The relative stereochemistry of its featured 2,5-dihydrofuran ring was initially assigned incorrectly as *cis* in **4-31** based on the coupling constant of 5.7 Hz

between H-2 and H-5.[17] However, it was later determined to be *trans* upon its total synthesis[12] and X-ray diffraction studies.[18]

Figure 13. The Long-Range Coupling Constant Between H-2 and H-5 ($J_{2,5}$) in the 2,5-Dihydrofuran Systems

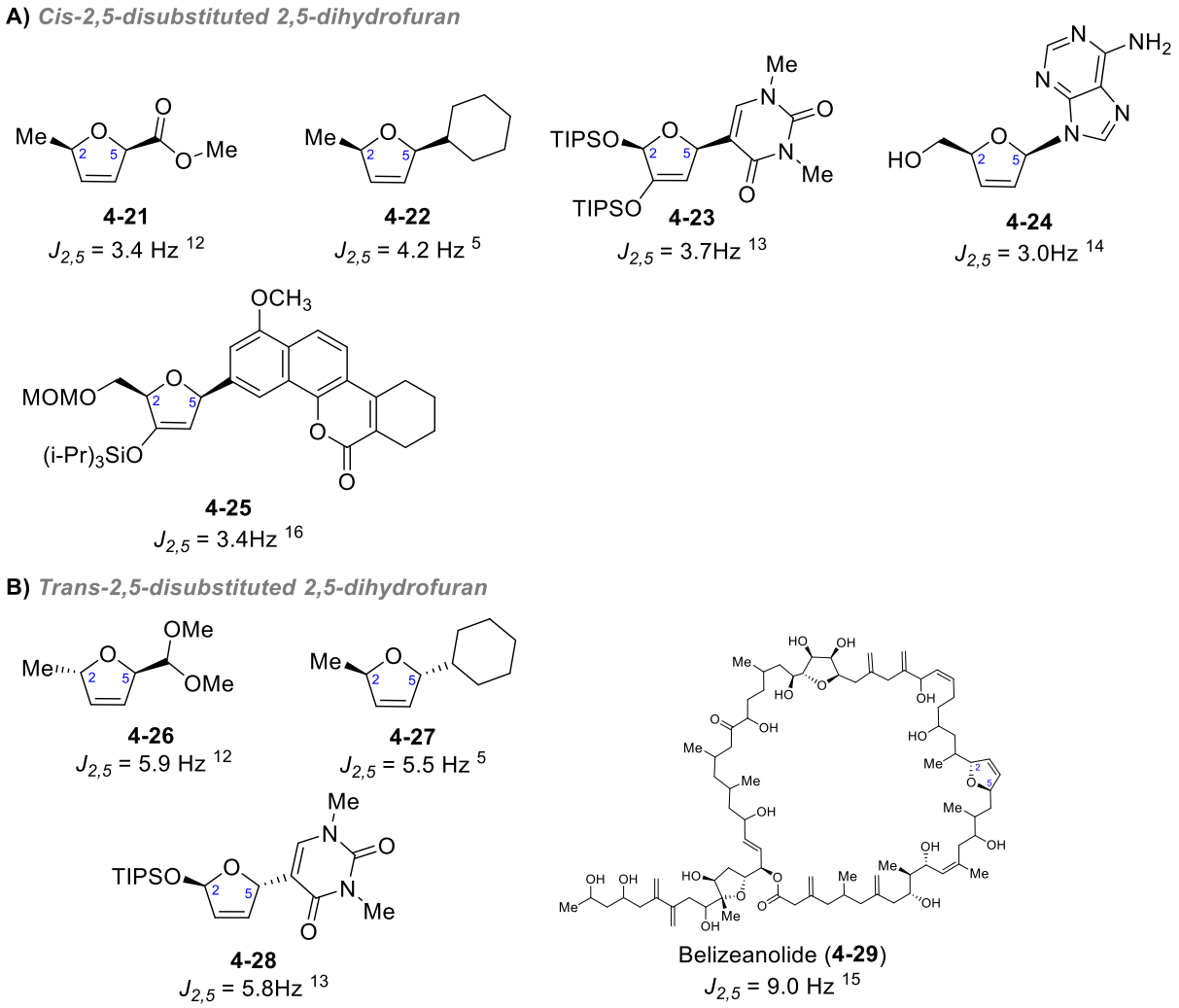
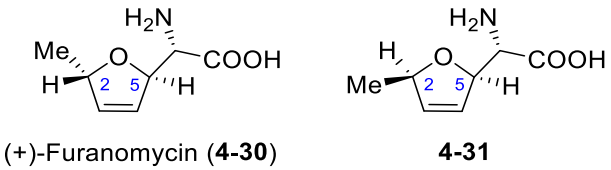
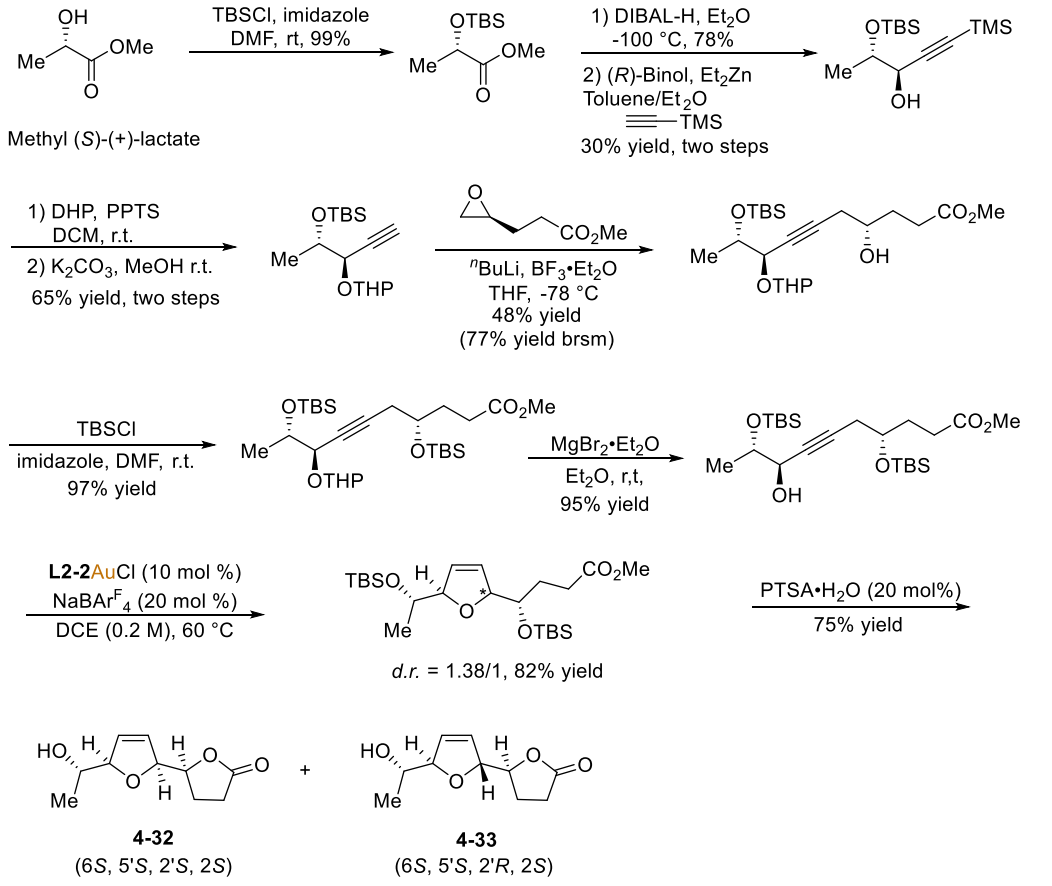


Figure 14. Structure of (+)-Furanomycin and its Initially Misassigned *cis*-Structure 31.



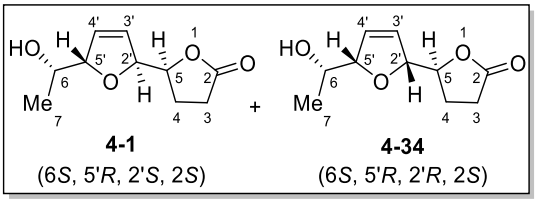
4.3. Total Synthesis of Nominal Diplobifuranylone A

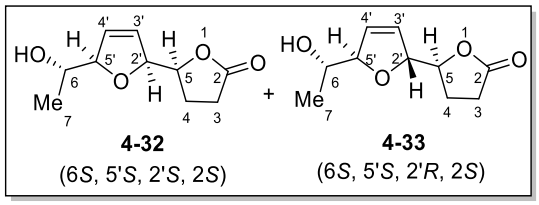
Scheme 38. Synthesis of Nominal Diplobifuranylone A and its Stereoisomers



With the established route in hand and with doubts on the structural assignments of the other diplobifuranylones, we decided to take on the total synthesis of diplobifuranylone A. As shown in Scheme 38, using methyl (*S*)-(+)-lactate as the starting material, we followed the same synthetic sequence as that for diplobifuranylone B to access nominal diplobifuranylone A **4-1** and its stereoisomers **4-32**, **4-33,** and **4-34**. (*R*)-BINOL and its enantiomer were used in asymmetric alkyne addition step to give *trans*-diol and *cis*-diol, respectively. To simplify the synthetic route and test the stereo assignment of diplobifuranylone A more efficiently, achiral ligand **L2-2** was used to access two stereoisomers in one step. Thus, in the end, we obtained a mixture of **4-1** and **4-34** as well as a mixture of **4-32** and **4-33**.

Table 8. ^{13}C NMR Comparison for Diplobifuranylone A





	4-1 +4-34 (mixture)		4-32+4-33 (mixture)		Lit.
5	79.99	81.27	79.81	81.38	80.1
4	23.64	23.69	22.42	24.15	23.2
3	27.97	27.83	28.10	28.21	28.2
2	TBD	TBD	TBD	TBD	177.4
2'	**87.48**	**87.11**	**87.30**	**87.50**	**75.6**
3'	129.89	129.96	129.16	129.30	132.4
4'	127.03	127.58	127.59	127.31	126.1
5'	**91.43**	**91.44**	**91.11**	**91.17**	**69.1**

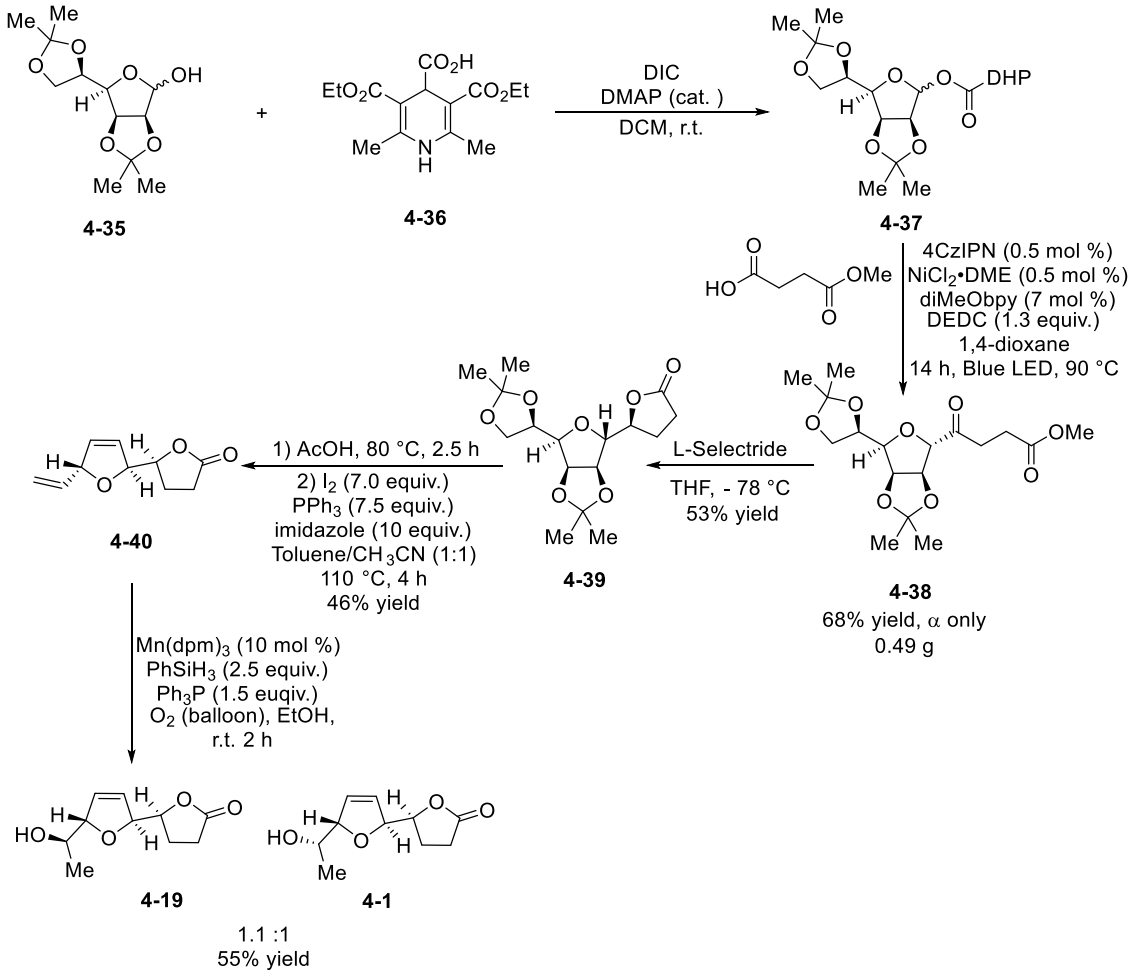
6	**70.16**	**70.29**	**69.16**	**69.29**	**75.4**
7	18.54	18.63	17.87	19.22	18.4

Next, we collected the ^{13}C NMR of a mixture of **4-1** and **4-34** in 2/1 ratio and a mixture of **4-32** and **4-33** in 1/1 ratio and compared with the reported literature value of Diplobifuranylone A (Table 8). To our surprise, the reported literature value cannot match with any stereoisomers. In addition, there are significant discrepancies for C2', C5', and C6', suggesting stereochemistry reassignment and structure revision are required.

Of note, two years after publishing our results, Dr. Diao[19] reported a concise synthetic route to access mixture of diplobifuranylone B (**4-19**) and the nominal diplobifuranylone A (**4-1)** with the longest linear sequence being 6 steps and in 7 total steps (Scheme 39). To begin with, glycosyl DHP carboxylate ester **4-37** was synthesized by coupling between D-mannofuranose **4-35** and carboxylic acid **4-36**. Under the photoredox-nickel dual catalytic condition, glycosyl radical was formed via anomeric C-O bond homolysis of glycosyl DHP carboxylate esters **4-37** and CO_2 evaluation. With diethyl decarbonate (DEDC) as an activator for the carboxylic acid, the glycosyl radical reacted with monomethyl succinate to afford C-acyl furanoside **4-38** as a single α-anomer in 68% yield. Reduction of the carbonyl group by L-selectride and lactonization led to compound **4-39** in 53% yield. Acid-catalyzed deprotection of acetal group and diol elimination gave access to 2,5-dihydrofuran **4-40** in 46% yield, followed by Mukaiyama hydration to give diplobifuranylone B (**4-19**) and the nominal diplobifuranylone A (**4-1**) in 55% yield and *d.r.* 1.1/1. As expected, diplobifuranylone B (**4-19**) and the nominal diplobifuranylone A **(4-1**) matched our spectrum. Dr. Diao also noticed the discrepancy between the spectroscopic data of **4-1** and

that of diplobifuranylone A and suggested the original structural assignment requires reconsideration.

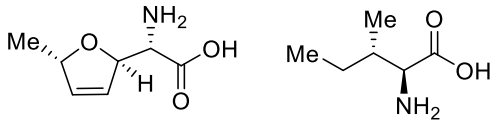
Scheme 39. Total Synthesis of Diplobifuranylone B via C-acylation of Furanosides



4.4. An Unsuccessful Trial of Furanomycin Synthesis

Furanomycin (**4-30**) is an isoleucine analog isolated by Katagiri from *Streptomyces* L-803 in 1967 (Figure 15).[20] The first total synthesis of furanomycin (**4-30**) was finished by Joullié in 1980.[21] This work also corrected the stereochemistry misassignment in the initial report, as we discussed in ***Chapter 4.2***.

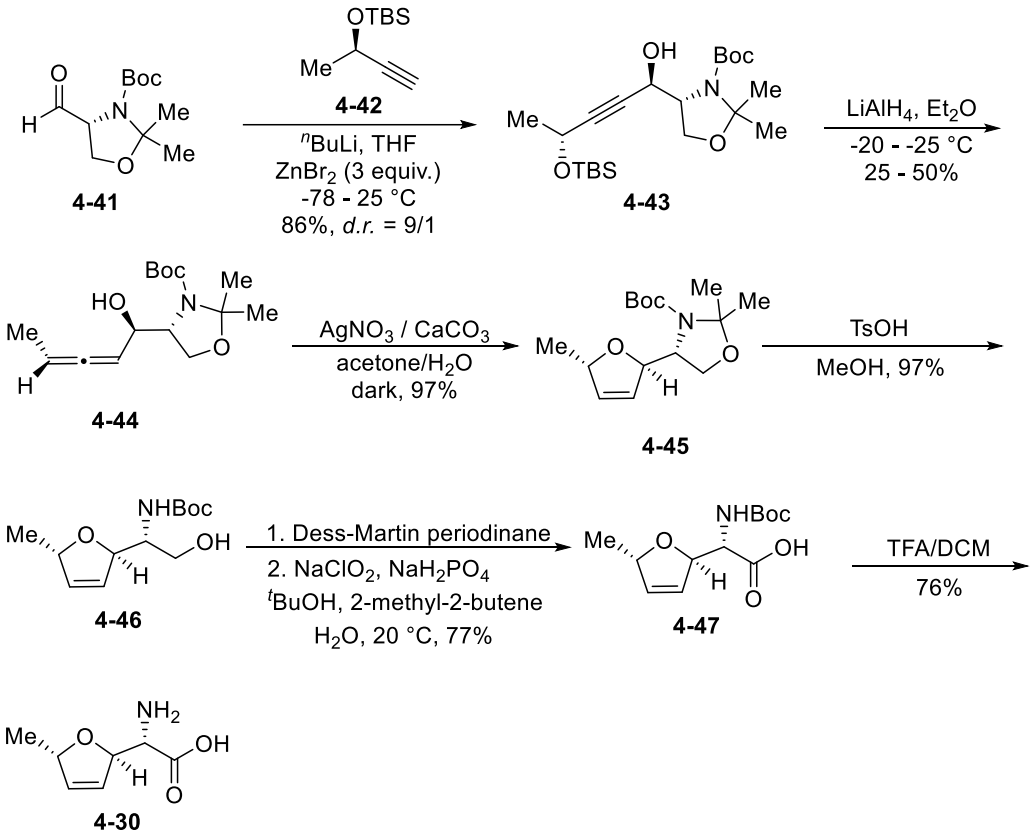
Figure 15. Structure of Furanomycin and Isoleucine



4-30 isoleucine

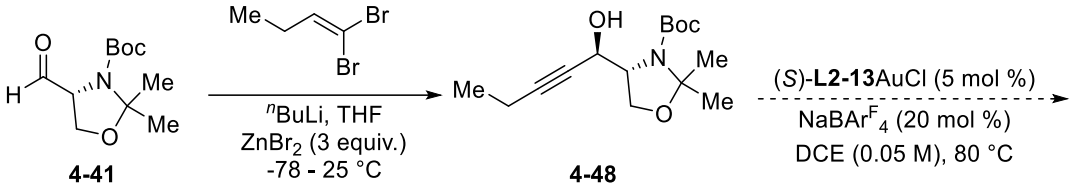
In 2000, Standaert reported a seven-step synthesis of (+)-furanomycin (**4-30**) in 12% overall yield (Scheme 40).[22] To begin with, TBS protection of commercially available (*R*)-3-butyn-2-ol led to the formation of the silyl propargylic ether **4-42,** followed by lithiation by ^{n}BuLi and nucleophilic addition to the Garner's aldehyde **4-41** to afford a 9/1 mixture of diastereomers, from which the major isomer **4-43** could be isolated in 77% yield. The hydroxyl-directed reduction promoted by $LiAH_4$ affored the allenic alcohol **4-44** in 25-50% yield. Intramolecular cyclization of the allenic alcohol **4-44** with $AgNO_3$ and deprotection of acetonide with TsOH led to *N*-Boc furanomycinol **4-46** in 94% yield. Stepwise oxidation of alcohol with the Dess-Martin reagent and the Pinnick oxidation gave *N*-Boc furanomycin in 77% yield. The synthesis is finished by deprotection of the Boc group with TFA, affording furanomycin **4-30** in 76% yield.

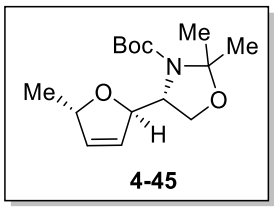
Scheme 40. Total Synthesis of Furanomycin



Inspired by this work, we envisioned that the synthesis of 2,5-dihydrofuran intermediate **4-45** could be shortened from four steps into two steps via asymmetric isomerization of propargylic alcohol (Scheme 41). Propargylic alcohol **4-48** was obtained via nucleophilic addition between Garner's aldehyde **4-41** and *in-situ* generated lithium acetylide. However, we cannot observe any desired product **4-45** when we subjected **4-48** into our optimized condition for asymmetric isomerization of propargylic alcohol. Instead, furan and pyrrole were found in the reaction mixture, suggesting the reaction went through deprotection of the acetonide and 5-endo-*dig* cyclization.

Scheme 41. An Unsuccessful Attempt to Synthesize Furanomycin





4.5. Conclusion

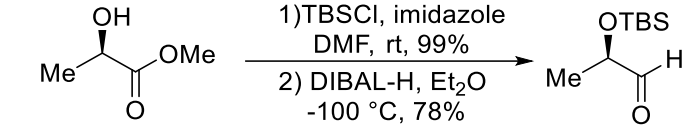
In conclusion, the asymmetric total synthesis of diplobifuranylone B was accomplished in 10 steps for the longest linear sequence and 14 total steps from the commercially available methyl (*R*)-(+)-lactate and *L*-glutamic acid. The overall yield was 15.8%. The key 2,5-dihydrofuran moiety of the natural product is constructed via a recently published asymmetric gold catalysis. This work allows the revision of the structure of diplobifuranylone B, in which the relative stereochemistry of its 2,5-dihydrofuran moiety is established as *trans* instead of the originally assigned *cis*. Using the same strategy, we synthesized nominal diplobifuranylone A and its three stereoisomers and found that the structure revision of diplobifuranylone A is required because of the discrepancy in NMR spectra.

4.6. Experimental Section

General Information: Ethyl acetate (ACS grade), hexanes (ACS grade), and diethyl ether (ACS grade) were purchased from Fisher Scientific and used without further purification. Anhydrous dichloromethane (HPLC grade), 1,2-dichloroethane (HPLC

grade) were purified by distillation over calcium hydride. Tetrahydrofuran, toluene, and o-xylene were distilled over sodium/benzophenone. Commercially available reagents were used without further purification. Reactions were monitored by thin-layer chromatography (TLC) using Silicycle precoated silica gel plates. Flash column chromatography was performed over Silicycle silica gel (230-400 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian 400 MHz, 500 MHz, and 600 MHz spectrometers using residue solvent peaks as internal standards ($CDCl_3$, ^{1}H: 7.26 ppm; ^{13}C: 77.00 ppm).

(R)-2-((tert-butyldimethylsilyl)oxy)propanal (**4-10**).



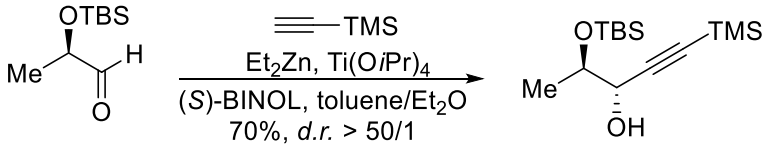
Methyl (*R*)-(+)-lactate
4-9

4-10

Aldehyde (**4-10**) was synthesized from Methyl (*R*)-(+)-lactate (**4-9**) according to literature procedure. [23] 78% yield, colorless oil;

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.61 (d, *J* = 1.3 Hz, 1H), 4.09 (qd, *J* = 6.8, 1.3 Hz, 1H), 1.28 (d, *J* = 6.8 Hz, 3H), 0.92 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{1}H NMR is in accordance with literature. [23]

(3S,4R)-4-((tert-butyldimethylsilyl)oxy)-1-(trimethylsilyl)pent-1-yn-3-ol (**4-11**).



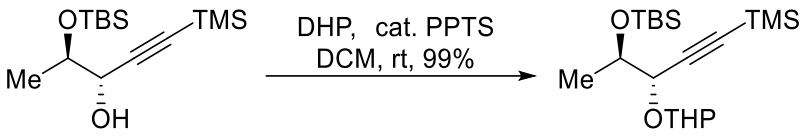
4-10

4-11

According to a modified literature procedure, [24] propargylic alcohol (**4-11**) was synthesized from aldehyde (**4-10**). Under N_2 protection, TMS acetylene (5.54 mL, 40 mmol) and 14 mL toluene were added into a Schlenk flask. 1.5 M Et_2Zn in toluene (26.7 mL, 40 mmol) was added to the solution carefully. The mixture was heated to reflux for 1 h, during which time a large amount of white precipitate formed in the reaction flask. The mixture was cooled to room temperature, and (*S*)-BINOL (1.14 g, 4 mmol), Et_2O (80 mL), and Ti(O*i*Pr)$_4$ (2.96 mL, 10 mmol) were added. After stirring for 1 h, aldehyde **4-9** (1.88 g, 10 mmol) was added, and the mixture was stirred overnight. 1.0 M tartaric acid was slowly added into the reaction mixture to quench the reaction and further stirring for 30 min. The mixture was partitioned in a separatory funnel, and the aqueous portion was extracted three times with Et_2O. The combined organic extracts were washed with brine and dried over $MgSO_4$. Filtration and concentration, followed by flash column chromatography on silica gel (hexane/Et_2O = 100/1 to hexane/Et_2O = 10:1 gradient), resulting in propargylic alcohol **4-11** (2.03 g, 70% yield, *d.r* > 50 :1) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.23 (dd, *J* = 5.1, 3.8 Hz, 1H), 3.91 (qd, *J* = 6.2, 3.9 Hz, 1H), 2.34 (d, *J* = 5.4 Hz, 1H), 1.22 (d, *J* = 6.2 Hz, 3H), 0.90 (s, 9H), 0.17 (s, 9H), 0.10 (s, 3H) , 0.09 (s, 3H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 103.7, 90.8, 71.0, 67.5, 25.8, 18.2, 18.0, -0.2, -4.4, -4.8. These data are in accordance with literature. [24]

***Tert-butyldimethyl(((2R,3S)-3-((tetrahydro-2H-pyran-2-yl)oxy)-5-(trimethylsilyl)pent-4-yn-2-yl)oxy)silane* [4-11(a)].**

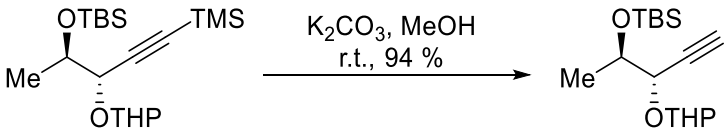


4-11 **4-11(a)**

Propargylic alcohol (**4-11**) (631.5 mg, 2.2 mmol) was dissolved in 10 mL DCM. 3,4-dihydro-2H-pyran (0.3 mL, 3.3 mmol) and pyridinium *p*-toluenesulfonate (28 mg, 0.11 mmol) were added to this solution and stirring overnight. After the reaction was completed, sodium bicarbonate solid was added into the reaction mixture and stirred for 30 min. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel (hexane/Et_2O = 50:1), resulting in compound **4-11(a)** (805.6 mg, 99% yield, *d.r.* = 1/1) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.03 (t, *J* = 3.1 Hz, 1H), 4.85 (t, *J* = 3.2 Hz, 1H), 4.15 (d, *J* = 5.9 Hz, 1H), 4.13 (d, *J* = 5.1 Hz, 1H), 4.07 – 4.01 (m, 1H), 3.94 – 3.90 (m, 2H), 3.92 – 3.87 (m, 1H), 3.83 – 3.76 (m, 2H), 1.97 – 1.46 (m, 12H), 1.24 (d, *J* = 6.1 Hz, 3H), 1.21 (d, *J* = 6.2 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.15 (s, 9H), 0.15 (s, 9H), 0.10 – 0.06 (m, 12H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 104.4, 103.2, 99.4, 94.6, 90.7, 89.8, 72.9, 71.3, 70.4, 61.9, 61.6, 30.2, 30.2, 25.8, 25.8, 25.52, 25.51, 20.4, 19.1, 18.9, 18.8, 18.1, 18.0, -0.08, -0.11, -4.51, -4.53, -4.7.

***Tert-butyldimethyl(((2R,3S)-3-((tetrahydro-2H-pyran-2-yl)oxy)pent-4-yn-2-yl)oxy) silane* (4-7).**

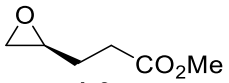


4-11(a) **4-7**

Compound **4-11(a)** (0.80g, 2.2 mmol) was dissolved in 10 mL MeOH, followed by adding K_2CO_3 (450 mg, 3.3 mmol) into this reaction mixture. The solution was stirred at room temperature for 1 h. 30 mL Et_2O was added into this reaction mixture, and then solid was removed via filtration through a silica gel pad (Et_2O as eluent). The solvent was removed under reduced pressure to afford terminal alkyne (**4-7**) (612.1 mg, 94% yield) as a colorless liquid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.02 (t, *J* = 3.3 Hz, 1H), 4.84 (t, *J* = 3.4 Hz, 1H), 4.21 (t, *J* = 4.5 Hz, 1H), 4.21 (t, *J* = 4.6 Hz, 1H), 4.02 (ddd, *J* = 11.4, 9.5, 3.1 Hz, 1H), 3.98 – 3.94 (m, 1H), 3.94 – 3.90 (m, 1H), 3.82 (ddd, *J* = 11.0, 9.7, 2.9 Hz, 1H), 3.57 – 3.49 (m, 2H), 2.41 (d, *J* = 2.2 Hz, 1H), 2.33 (d, *J* = 2.1 Hz, 1H), 1.91 – 1.48 (m, 12H), 1.26 (d, *J* = 6.2 Hz, 3H), 1.23 (d, *J* = 6.2 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.09 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 99.7, 94.8, 82.2, 81.1, 74.1, 73.4, 72.0, 71.3, 70.3, 69.9, 62.2, 61.7, 30.2, 30.2, 25.8, 25.8, 25.5, 25.4, 20.2, 20.0, 18.9, 18.7, 18.2, 18.0, -4.55, -4.59, -4.59, -4.8.

Methyl (*S*)-3-(oxiran-2-yl)propanoate (**4-6**).

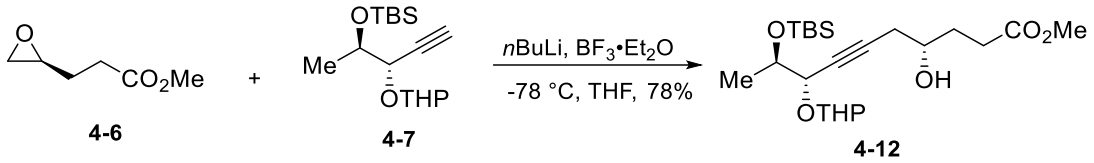


4-6

Epoxide (**4-6**) was synthesized from *L*-glutamic acid (**4-8**) according to literature procedure. [6] 20% overall yield, colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.63 (s, 3H), 2.95 – 2.90 (m, 1H), 2.72 – 2.69 (m, 1H), 2.46 – 2.43 (m, 1H), 2.43 – 2.38 (m, 2H), 1.96 – 1.87 (m, 1H), 1.76 – 1.67 (m, 1H). ^{1}H NMR is in accordance with literature. [6]

Methyl (4*S*,8*S*,9*R*)-9-((tert-butyldimethylsilyl)oxy)-4-hydroxy-8-((tetrahydro-2H-pyran-2-yl)oxy)dec-6-ynoate (4-12).

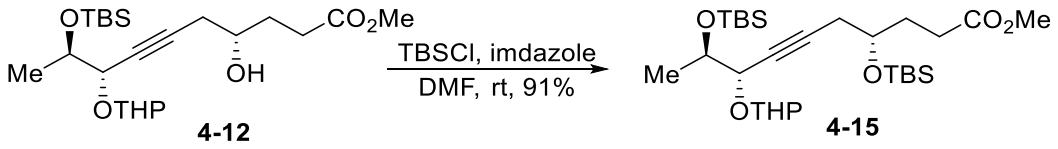


Compound **4-12** was synthesized according to a modified literature procedure. [6] Under nitrogen at -78 ℃, terminal alkyne (**4-7**) (2.09 g, 7.0 mmol) was dissolved in dry THF (5 mL), then *n*-BuLi (2.5 M in hexane, 2.8 mL, 7.0 mmol) was added. After 5 min, $BF_3{\cdot}Et_2O$ (0.86 mL, 7.0 mmol) was added, and 30 min later, epoxide (**4-6**) (650.7 mg, 5.0 mmol) was added. The reaction media was stirred at -78 ℃ for 3 h, then quenched with *sat.* $NaHCO_3$ (*aq*). The aqueous layer was extracted with Et_2O three times. The combined organic layers were washed with brine, dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 20:1 to hexane/EtOAc = 10: 1 to hexane/EtOAc = 1:1) to afford compound **4-12** (1.68 g, 78% yield) as a colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.97 (t, *J* = 3.2 Hz, 1H), 4.80 (t, *J* = 3.5 Hz, 1H), 4.19 (dt, *J* = 3.8, 1.8 Hz, 1H), 4.13 (dt, *J* = 4.1, 2.0 Hz, 1H), 4.02 – 3.92 (m, 2H), 3.88 (td, *J* = 6.2, 4.3 Hz, 2H), 3.79 – 3.70 (m, 2H), 3.66 (s, 6H), 3.53 – 3.46 (m, 2H), 2.53 – 2.26 (m, 8H), 1.96 – 1.44 (m, 16H), 1.20 (d, *J* = 6.5 Hz, 3H), 1.19 (d, *J* = 6.5 Hz, 3H), 0.87 (s, 9H), 0.87 (s, 9H), 0.07 – 0.04 (m, 12H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 174.1, 174.1, 99.7, 94.8, 82.5, 82.0, 81.6, 80.1, 73.1, 71.2, 70.7, 70.3, 69.2, 69.2, 62.3, 61.8, 51.6, 51.6, 31.1, 31.0, 30.5, 30.38, 30.36, 30.2, 27.97, 27.93, 25.76, 25.72, 25.42, 25.33, 20.32, 19.18, 19.12,

19.01, 18.1, 18.0, -4.56, -4.67, -4.75, -4.75; **HRMS (ESI-TOF)** *m/z* : $[M+Na]^+$ calculated for $C_{22}H_{40}O_6SiNa$ 451.2492; Found 451.2494.

***Methyl (4S,8S,9R)-4,9-bis((tert-butyldimethylsilyl)oxy)-8-((tetrahydro-2H-pyran-2-yl)oxy)dec-6-ynoate* (4-15).**

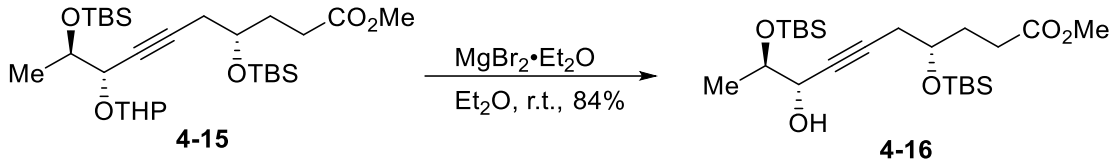


TBSCl (370.8 mg, 2.46 mmol) was added into a solution of **4-12** (878.9 mg, 2.05 mmol) and imidazole (279.1 mg, 4.10 mmol) in DMF (10 mL) at room temperature and stirred for 24 h. The reaction was quench by adding *sat*. $NaHCO_3$ (*aq*) into the mixture. The aqueous phase was extracted with Et_2O four times. The combined organic layer was washed with brine, dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 20:1), afforded compound **4-15** (1.01 g, 91% yield) as a colorless liquid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.99 (t, *J* = 3.3 Hz, 1H), 4.85 (t, *J* = 3.4 Hz, 1H), 4.23 (dt, *J* = 4.1, 2.1 Hz, 1H), 4.19 (dt, *J* = 4.9, 1.9 Hz, 1H), 4.00 (ddd, *J* = 11.4, 9.5, 3.0 Hz, 1H), 3.89 (dqd, *J* = 12.4, 6.2, 4.4 Hz, 2H), 3.85 – 3.79 (m, 3H), 3.65 (s, 6H), 3.49 (dqd, *J* = 12.0, 4.1, 1.5 Hz, 2H), 2.44 – 2.29 (m, 8H), 2.03 – 1.95 (m, 2H), 1.89 – 1.77 (m, 4H), 1.75 – 1.45 (m, 10H), 1.22 (d, *J* = 6.2 Hz, 3H), 1.20 (d, *J* = 6.2 Hz, 3H), 0.89 – 0.85 (m, 36H), 0.09 – 0.03 (m, 24H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 174.0, 173.9, 99.4, 94.7, 82.6, 82.1, 79.2, 72.1, 71.7, 70.6, 70.2, 69.9, 69.8, 62.1, 61.6, 51.4, 31.4, 31.3, 30.26, 30.23, 29.62, 29.62, 27.63, 27.57, 25.80, 25.75, 25.72, 25.52, 25.46, 20.1, 19.02, 18.99, 18.5, 18.1,

18.00, 17.96, -4.56, -4.57, -4.65, -4.80, -4.88, -4.89; **HRMS (ESI-TOF)** *m/z* : $[M+Na]^+$ calculated for $C_{28}H_{54}O_6Si_2Na$ 565.3357; Found 565.3362

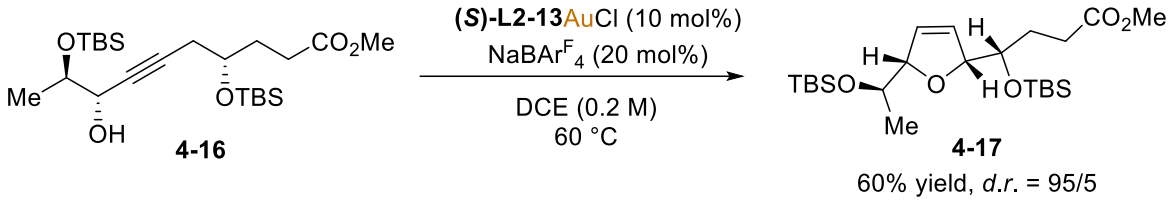
***Methyl (4S,8S,9R)-4,9-bis((tert-butyldimethylsilyl)oxy)-8-hydroxydec-6-ynoate* (4-16)**



$MgBr_2 \cdot Et_2O$ (1.44 g, 5.57 mmol) was added into a solution of **4-15** (859.8 mg, 1.58 mmol) in Et_2O, and the reaction mixture was stirred at room temperature until reaction completion. The solvent was removed, and the residue was purified by flash column chromatography (hexane/EtOAc = 20: 1 to hexane/EtOAc = 10: 1) to give **4-16** (609.3 mg, 84% yield) as a colorless oil.

$[\alpha]^{20}_D$ = -22.7 (*c* = 1.19, $CHCl_3$); **^{1}H NMR (500 MHz, $CDCl_3$)** δ 4.27 – 4.22 (m, 1H), 3.89 (qd, *J* = 6.2, 3.6 Hz, 1H), 3.84 (tt, *J* = 7.6, 4.3 Hz, 1H), 3.66 (s, 3H), 2.44 – 2.29 (m, 5H), 2.00 (dddd, *J* = 13.8, 9.1, 6.7, 3.9 Hz, 1H), 1.82 (dddd, *J* = 13.7, 8.9, 7.4, 6.1 Hz, 1H), 1.21 (d, *J* = 6.2 Hz, 3H), 0.89 (s, 9H), 0.87 (s, 9H), 0.08 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 174.0, 83.0, 80.0, 71.2, 69.8, 67.1, 51.5, 31.4, 29.6, 27.5, 25.8, 18.0, 18.0, -4.47, -4.55, -4.84, -4.86; **HRMS (ESI-TOF)** *m/z* : $[M+Na]^+$ calculated for $C_{23}H_{46}O_5Si_2Na$ 481.2781; Found 481.2796.

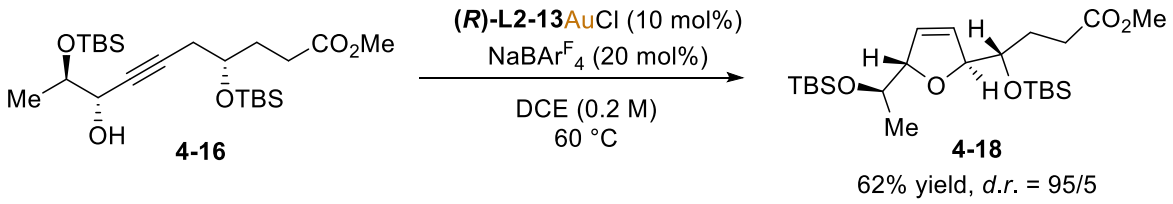
***Methyl (S)-4-((tert-butyldimethylsilyl)oxy)-4-((2R,5S)-5-((R)-1-((tert-butyldimethyl-silyl) oxy)ethyl)-2,5-dihydrofuran-2-yl)butanoate* (4-17)**



To a 2-dram vial were added sequentially **4-16** (68.0 mg, 0.15 mmol), 10 mol % **(*S*)-L2-13**AuCl (13.2 mg), 20 mol% $NaBAr^F_4$ (26.4 mg) and 0.75 mL dry dichloroethane (DCE). The reaction was stirred at 60 ℃ for 50 h. Upon completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/Et_2O = 20 : 1) to yield **4-17** (40.8 mg, 60% yield, *d.r.* = 95/5) as a colorless oil.

$[\alpha]^{20}_D$ = -13.7 (c = 1.11, $CHCl_3$); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 5.99 – 5.96 (m, 1H), 5.95 – 5.92 (m, 1H), 4.58 – 4.52 (m, 1H), 4.47 – 4.37 (m, 1H), 3.66 (s, 3H), 3.48 (qd, *J* = 4.3, 2.0 Hz, 2H), 2.47 (t, *J* = 8.0 Hz, 2H), 2.02 – 1.84 (m, 2H), 1.20 (d, *J* = 6.0Hz, 3H), 0.89 (s, 9H), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 174.3, 129.6, 129.5, 91.2, 88.2, 74.6, 72.4, 51.5, 29.3, 28.5, 25.8, 21.1, 18.04, 18.03, -4.23, -4.24, -4.5, -4.7; **HRMS (ESI-TOF)** *m/z*: $[M+Na]^+$ calculated for $C_{23}H_{46}O_5Si_2Na$ 481.2781; Found 481.2770.

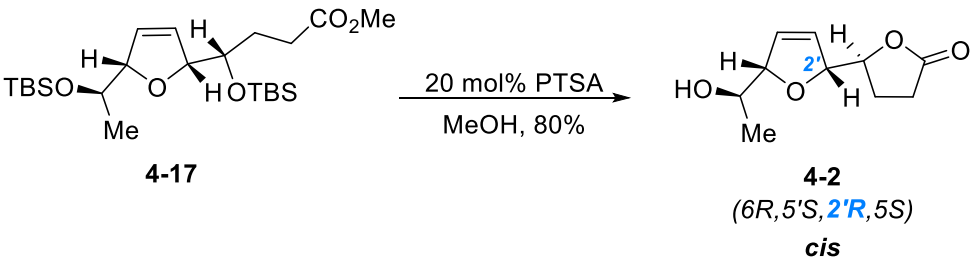
***Methyl (S)-4-((tert-butyldimethylsilyl)oxy)-4-((2S,5S)-5-((R)-1-((tert-butyldimethyl-silyl)oxy)ethyl)-2,5-dihydrofuran-2-yl)butanoate* (4-18).**



To a 2-dram vial were added sequentially **4-16** (68.0 mg, 0.15 mmol), 10 mol % **(*R*)-L2-13**AuCl (13.2 mg), 20 mol% $NaBAr^F_4$ (26.4 mg) and 0.75 mL dry dichloroethane (DCE). The reaction was stirred at 60 ℃ for 50 h. Upon completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/Et_2O = 20 : 1) to yield **4-18** (40.8 mg, 62% yield, *d.r.* = 95/5) as a colorless oil.

$[\alpha]^{20}_D$ = -124.0 (c = 1.08, $CHCl_3$); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 5.96 (dt, *J* = 6.3, 1.8 Hz, 1H), 5.85 (dt, *J* = 6.3, 1.8 Hz, 1H), 4.76 (tt, *J* = 5.2, 1.8 Hz, 1H), 4.55 (tt, *J* = 6.0, 1.8 Hz, 1H), 3.73 – 3.65 (m, 2H), 3.65 (s, 3H), 2.46 (ddd, *J* = 15.8, 10.2, 5.4 Hz, 1H), 2.30 (ddd, *J* = 16.1, 10.0, 6.1 Hz, 1H), 1.79 (tdt, *J* = 9.9, 6.1, 3.4 Hz, 1H), 1.64 – 1.54 (m, 1H), 1.15 (d, *J* = 6.2 Hz, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 174.2, 129.5, 127.6, 90.9, 89.4, 73.5, 71.3, 51.5, 30.5, 27.3, 25.9, 25.8, 20.3, 18.11, 18.07, -4.32, -4.43, -4.84, -4.88; **HRMS (ESI-TOF)** *m/z* : $[M+Na]^+$ calculated for $C_{23}H_{46}O_5Si_2Na$ 481.2781; Found 481.2786.

***(S)-5-((2R,5S)-5-((R)-1-hydroxyethyl)-2,5-dihydrofuran-2-yl)dihydrofuran-2(3H)-one* (4-2).**



4-17 → **4-2**

(6R,5'S,2'R,5S)

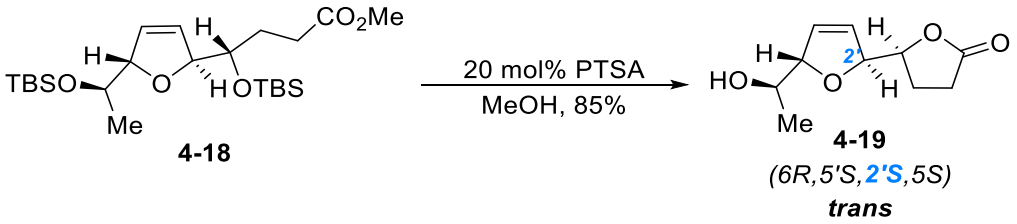
cis

p-Toluenesulfonic acid monohydrate (1.0 mg, 0.0055 mmol) was added into a solution of **4-17** (12.5 mg, 0.03 mmol) in MeOH (0.3 mL). The mixture was stirred at room

temperature until starting material **4-17** had been consumed. The solvent was removed under reduced pressure, and the residue was dissolved in DCM and stirred for 1 h. Then the solvent was removed again, and the residue was purified by flash column chromatography (hexane/EtOAc = 1/2) to yield **4-2** (4.5 mg, 83% yield) as a colorless oil.

$[\alpha]^{20}_D$ = +24.7 (c = 1.06, $CHCl_3$); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 6.07 (dt, *J* = 6.6, 1.7 Hz, 1H), 5.96 (dt, *J* = 6.3, 1.8 Hz, 1H), 4.85 – 4.81 (m, 1H), 4.74 – 4.71 (m, 1H), 4.53 (dt, *J* = 7.3, 5.8 Hz, 1H), 3.89 (dq, J = 6.5, 3.8 Hz, 1H), 2.61 – 2.49 (m, 2H), 2.39 – 2.31 (m, 1H), 2.19 – 2.11 (m, 1H), 1.22 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 176.4, 129.5, 127.2, 91.0, 87.1, 81.0, 69.1, 27.7, 23.5, 18.9; **HRMS (ESI-TOF)** *m/z:* $[M+Na]^+$ calculated for $C_{10}H_{14}O_4Na$ 221.0790; Found 221.0789; *J*(H_2'-H_5') = 3.8 Hz.

***(S)-5-((2S,5S)-5-((R)-1-hydroxyethyl)-2,5-dihydrofuran-2-yl)dihydrofuran-2(3H)-one* (4-19).**



p-Toluenesulfonic acid monohydrate (2.0 mg, 0.01 mmol) was added into a solution of **4-18** (22.4 mg, 0.05 mmol) in MeOH (0.5 mL). The mixture was stirred at room temperature until starting material **4-18** had been consumed. The solvent was removed under reduced pressure, and the residue was dissolved in DCM and stirred for 1 h. Then the solvent was removed again, and the residue was purified by flash column

chromatography (hexane/EtOAc = 1/2) to yield diplobifuranylone B (**4-19**) (7.0 mg, 73% yield) as a colorless oil.

$[\alpha]^{20}_D$ = -132.4 (c = 0.55, $CHCl_3$); Literature[1] : **$[\alpha]^{20}_D$** = -90.7 (c = 0.55, $CHCl_3$); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 6.01 (dt, *J* = 6.3, 2.0 Hz, 1H), 5.90 (dt, *J* = 6.3, 2.0 Hz, 1H), 4.97 (dtd, *J* = 6.1, 2.5, 1.7 Hz, 1H), 4.79 (dddd, *J* = 5.9, 3.7, 2.3, 1.5 Hz, 1H), 4.54 (ddd, *J* = 8.0, 5.3, 2.8 Hz, 1H), 3.90 (dq, *J* = 6.5, 3.4 Hz, 1H), 2.66 (ddd, *J* = 17.7, 10.1, 7.0, 1H), 2.47 (ddd, *J* = 17.7, 10.3, 6.4, 1H), 2.34 – 2.27 (m, 1H), 1.64 (br, s, 1H), 1.17 (d, *J* = 6.5 Hz); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 177.2, 128.8, 127.3, 91.0, 88.0, 80.1, 69.1, 28.0, 23.8, 17.9; **HRMS (ESI-TOF)** *m/z*: $[M+Na]^+$ calculated for $C_{10}H_{14}O_4Na$ 221.0790; Found 221.0785; ***J*(H$_2$'-H$_5$')** = 5.8 Hz, ***J*(H$_2$-H$_2$')** = 2.8 Hz; Literature[1]: ***J*(H$_2$'-H$_5$')** = 5.5 Hz; ***J*(H$_2$-H$_2$')** = 2.8 Hz.

4.7. Reference

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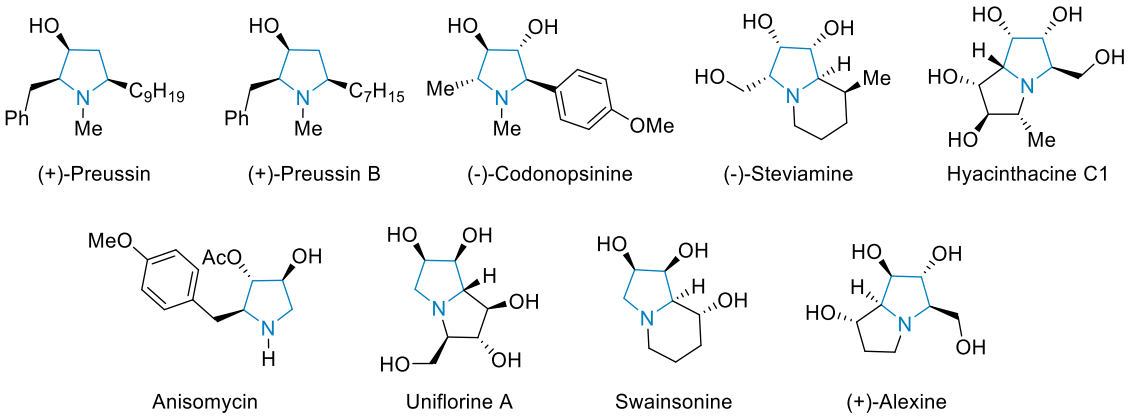
5. Asymmetric Cycloisomerization of Propargylic Sulfonamides into Pyrrolines

5.1. Introduction and Reaction Design

As exemplified in Scheme 42, pyrrolidines are structural motifs prevalent in natural alkaloid natural products prossessing various bioactivities. For example, (+)-preussin is known as a novel antifungal agent,[1] (-)-codonopsinine displayed antibiotic as well as hypotensive activities,[2] (-)-steviamine showed relatively moderate glycoside inhibitory activity,[3] and anisomycin is a potent protein inhibitor in eukaryotic organisms.[4]

Scheme 42. Pyrrolidine Motif in Alkaloid Natural Products



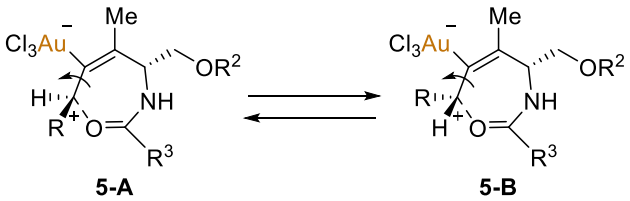
In 2004, Krause reported the first examples of gold(III)-catalyzed intramolecular hydroamination of allenes.[5] Using $AuCl_3$ as the catalyst, cyclization of α-aminoallenes (*d.r.* >99/1) led to corresponding 3-pyrrolines in moderate to high yields. Various *N*-protecting groups were tested. Short reaction time, i.e., 30 min, and high-level of chirality transfer, were reported with mesyl (Ms) or tosyl (Ts) as the protecting group. Although the unprotected aminoallene also gave excellent-level chirality transfer, a much longer reaction time, i.e., 5 days, was required. The diminished reactivity could be attributed to the

deactivation of gold catalyst by amino group. Notably, very poor chiral transfer was observed when Boc or Ac was used as the protecting group. The proposed mechanism for allene epimerization is shown in Scheme 43; zwitterionic complex **5-A** could isomerize into zwitterionic complex **5-B** via single bond rotation. The lone pair electron on the carbonyl oxygen can stabilize these two complexes and thereby facilitate their equilibration.

Table 9. Gold-Catalyzed Cycloisomerization of α-Aminoallenes

PG	Time	Yield (%)	*d.r.*
Ms	30 min	77	94/6
Ts	30 min	93	95/5
Ac	30 min	80	70/30
Boc	30 min	69	46/54
H	5 days	74	>99/1

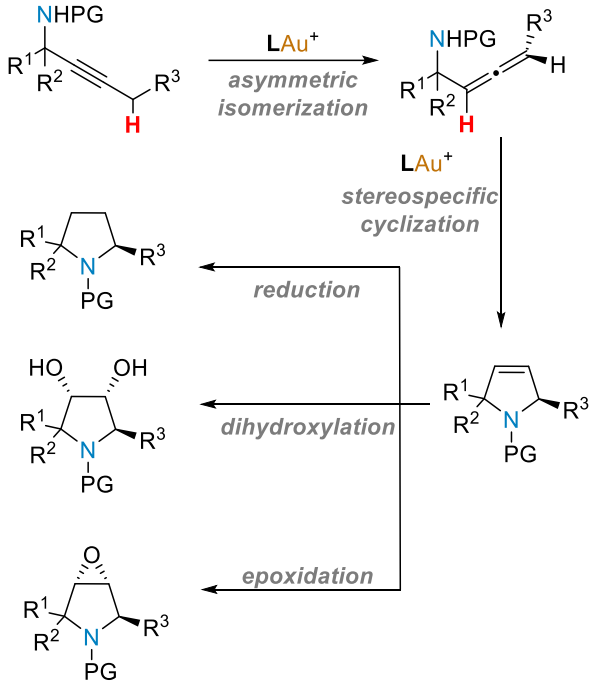
Scheme 43. Proposed Mechanism for Allene Epimerization



As discussed in ***Chapter 3***, using chiral bifunctional ligand (*R*)-**L2-13**, propargylic alcohol could be readily converted into chiral 2,5-dihydrofuran with high diastereoselectivity or enantioselectivity via a chiral allenol intermediate. We envisioned that this approach could be further extended to the synthesis of chiral 3-pyrrolines if

propargylic sulfonamides were to be employed (Scheme 44). Although the mechanisms of these two reactions are similar, the larger sulfonamide moiety and the coordination between gold and nitrogen may hinder the desired gold catalysis. This chemistry, if successfully implemented, would provide expedient synthesis of chiral 3-pyrrolines and, upon manipulation, i.e., reduction/dihydroxylation/epoxidation, chiral pyrrolidines from readily accessible propargylic sulfonamides.[6]

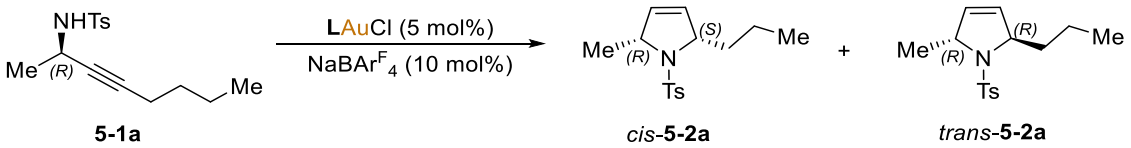
Scheme 44. Reaction Design for Asymmetric Cycloisomerization of Propargylic Sulfonamides



5.2. Reaction Condition Optimization and Scope Study

5.2.1. Reaction Condition Optimization

Table 10. Reaction Condition Optimization for Asymmetric Cycloisomerization of Propargylic Sulfonamide [a]



5-1a *cis*-**5-2a** *trans*-**5-2a**

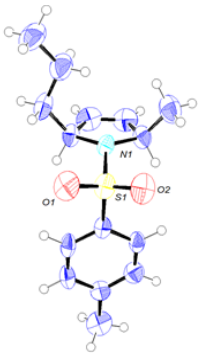
Entry	Ligand	Solvent	Temp/Time	Conv.	Yields [b]	*d.r.*
1	**JohnPhos**	$PhCF_3$/0.5M	95 ˚C/48 h	7%	2%	-
2 [c]	**JohnPhos**	$PhCF_3$/0.5M	95 ˚C/48 h	4%	<2%	-
3	**L2-2**	$PhCF_3$/0.5M	95 ˚C/48 h	>99%	92%	3/1
4	(*S*)-**L2-13**	$PhCF_3$/0.5M	95 ˚C/48 h	>99%	97%	96/4
5	(*S*)-**L2-13**	$PhCF_3$/0.5M	80 ˚C/48 h	5%	4%	-
6	(*S*)-**L2-13**	PhCl/0.5M	95 ˚C/48 h	>99%	98%	96/4
7	(*S*)-**L2-13**	PhMe/0.5M	95 ˚C/48 h	>99%	96%	97/3
8	(*S*)-**L2-13**	Neat	95 ˚C/24 h	>99%	35%	97/3
9	(*S*)-**L2-13**	PhMe/0.5M	110 ˚C/14 h	>99%	96% [d]	97/3
10	(*S*)-**L2-13**	PhCl/0.5M	120˚C/7 h	>99%	98%	95/5
11	(*R*)-**L2-18**	PhMe/0.2 M	110 ˚C/72 h	>99%	81%	9/91
12	(*R*)-**L2-13**	PhMe/0.2M	110 ˚C/72 h	>99%	89% [e]	8/92

[a] Conditions: **5-1a** (0.05 mmol), 5 mol% LAuCl and 10 mol% NaBAr$^F_4$. [b] NMR yield was determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as the internal reference. [c] 5 mol% *N, N*-Diisopropylethylamine (DIPEA) was added. [d] 93% isolated yield. [e] 91% isolated yield.

At the outset, we chose (*R*)-4-methyl-*N*-(oct-3-yn-2-yl)benzenesulfonamide (**5-1a**) as the model substrate for the designed reaction. As shown in Table 10, JohnPhos led to little

conversion (entry 1) as expected, and the addition of catalytic DIPEA did not improve the reaction (entry 2). When the achiral tertiary amine-functionalized ligand **L2-2** was employed, the gold catalysis resulted in the desired 3-pyrroline **5-2a** as a diastereomeric mixture in 92% yield (entry 3). Compared to the 2,5-dihydrofuran chemistry[7] where the reaction was completed in 2 h at 80℃, the higher required temperature (i.e., 95℃) and much longer reaction time (i.e., 48 h) reflects the challenge posed by the sterically bulky toluenesulfonamide moiety. In the product mixture, *cis*-**5-2a** was favored by a 3/1 ratio over its *trans* counterpart, revealing a moderate level of innate diastereoselectivity. In contrast to the lack of reactivity in entry 1, this result confirmed the role of the ligand remote amino group in enabling this reaction. To our delight, when the chiral ligand (*S*)-**L2-13** was employed, the reaction went smoothly to afford **5-2a** in 97% yield and with an outstanding *cis*/*trans* ratio of 96/4 (entry 4). The absolute stereochemistry of *cis*-**5-2a** was confirmed by an X-ray diffraction study.

Figure 16. X-ray Diffraction of *cis*-*5*-*2a*.



cis-**5-2a**
CCDC 2052076

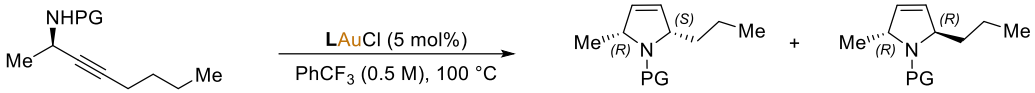
This excellent result is consistent with the 'matched' nature of asymmetric induction between the inherent *cis*-preference and the chiral ligand-induced (*S*)-configuration at the nascent chiral center. When the temperature was lower to 80 ˚C, the reaction became sluggish, and low conversion was observed (entry 5). It was found that the solvent toluene

was optimal for the reaction (entry 7), as $PhCF_3$ and chlorobenzene led to slightly lower diastereoselectivities (entry 4, 6). The reaction carried out under neat conditions gave significantly lower yields (entry 8). After increasing the reaction temperature to 110 ˚C, the reaction time was shortened to 14 h without compromising reaction yield and diastereoselectivity (entry 9). Further increasing reaction temperature to 120 ˚C and using chlorobenzene as the solvent led to a faster reaction, but lower diastereoselectivity (i.e., 95/5, entry 10). In the preparative scale, *cis*-**5-2a** was isolated in 93% yield by following the conditions in entry 9. With the ligand enantiomer, i.e., (*R*)-**L2-13**, employed in the gold catalysis, the ligand-induced asymmetry mismatches the inherent *cis* preference. As such, the observed diastereomeric ratio (i.e., 92/8, entry 12) was expectedly lower than that achieved with (*S*)-**L2-13** (see entry 9), but the ligand induction remained dominant, and *trans*-**5-2a** was the major diastereomer. Likely the consequence of the 'mismatch', the reaction was sluggish, needing 72 h to complete. The reaction gave slightly lower yields and diastereoselectivities with (*R*)-**L2-18** as the ligand (entry 11). Nevertheless, the ability to access the disfavored *trans*-isomer as the predominant product is valuable in synthesis. By performing this reaction on a preparative scale, *trans*-**5-2a** was isolated in 91% yield (entry 12).

Next, different *N*-protecting groups were tested (Table 11). A mesylate behaved similarly to tosyl group (entries 1-3). By using the achiral ligand L2-2, the *cis*-3-pyrroline product is preferred over its *trans*-counterpart by a ratio of 3.8/1. In the "matching" scenario, i.e., using (*S*)-**L2-13**, we observed high diastereoselectivity while the "mismatching" scenario, i.e., using (*R*)-**L2-13,** gave moderate diastereoselectivity of the opposing sense was detected. No reaction was observed with a triflyl group (entries 4-6).

This highly electron-withdrawing group increased the acidity of the hydrogen on the sulfonamide significantly. Thus, the lack of reactivity could be attributed to the deactivation of the gold catalyst via protonation of ligand nitrogen. On the other hand, the diethylphosphoryl group led to lower conversions and/or yields (entry 7-9). The diastereoselectivity was not determined. Even a lower conversation was observed using the achiral ligand **L2-2** with the 4-nitrobenzenesulfonyl group (4-Ns) as the protecting group (entry 10). Although a good yield was obtained with the *tert*-butylsulfonyl (Bus) group, ^{1}H NMR did not allow the determination of the diastereoselectivity. Consequently, we decided to use the tosyl (Ts) group for the substrate scope study. One additional benefit of using Ts group is that most of the Ts-protected substrates are solid, making purification via recrystallization possible.

Table 11. Effect of *N*-Protecting Groups on the Cycloisoermization of Propargylic Amide

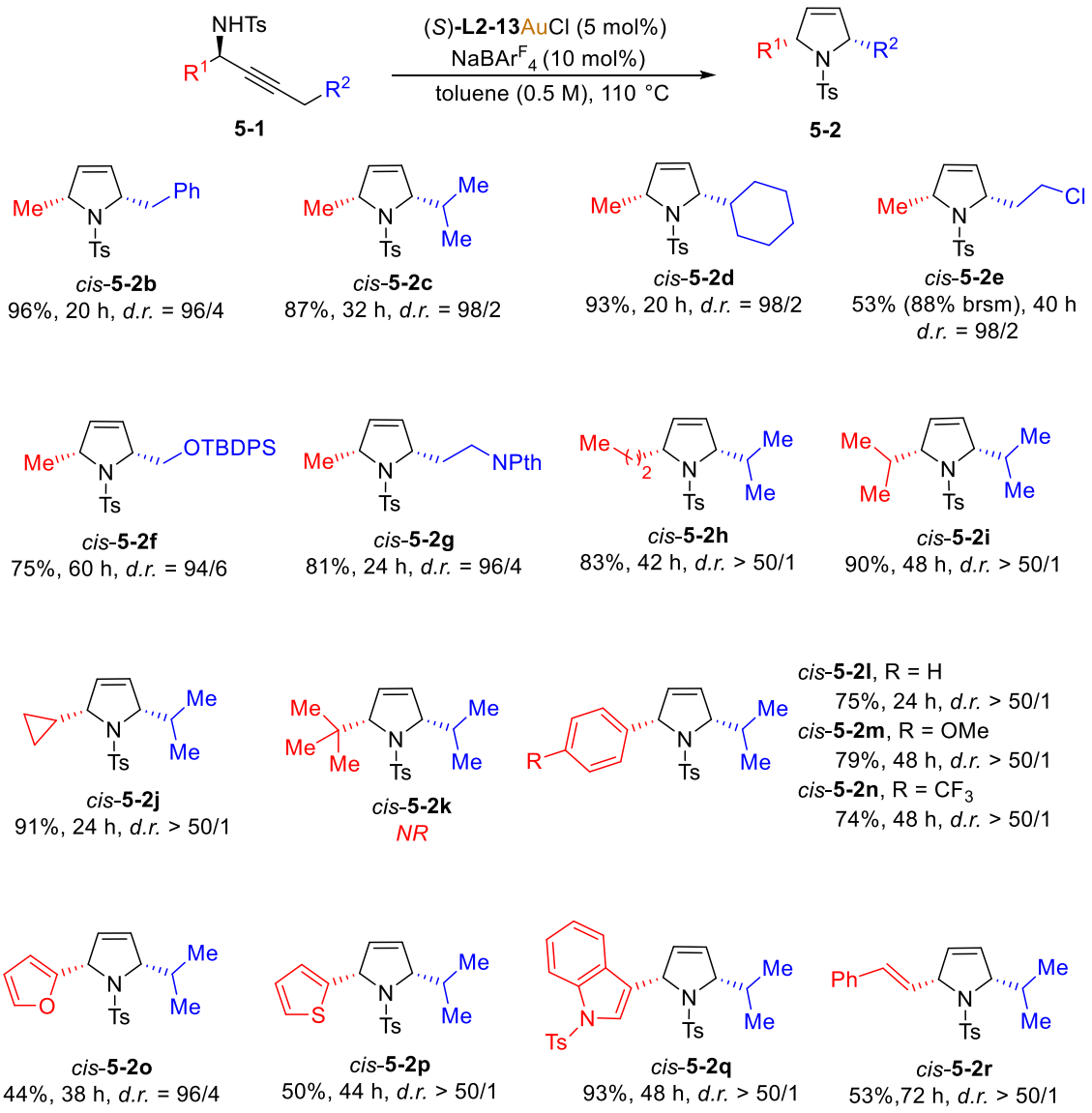


Entry	PG	Ligand	Conv.	Yields	*d.r.*
1		**L2-2**	>99%	95%	3.8/1
2	Ms	(*S*)-**L2-13**	>99%	94%	20/1
3		(*R*)-**L2-13**	>99%	76%	1/5
4		**L2-2**	<5%	-	-
5	Tf	(*S*)-**L2-13**	<5%	-	-
6		(*R*)-**L2-13**	<5%	-	-
7		**L2-2**	>99%	82%	ND
8	-P(O)(OPh)$_2$	(*S*)-**L2-13**	36%	31%	ND
9		(*R*)-**L2-13**	54%	43%	ND
10	*p*-Ns	**L2-2**	21%	19%	ND
12	Bus	**L2-2**	92%	85%	ND

5.2.2. Reaction Scope Study

With the optimized reaction conditions (Table 10, entries 9 and 11) in hand, we set out to explore the reaction scope. The synthesis of chiral *cis*-3-pyrrolines was first studied (Scheme 45). For the R^2 group in the chiral propargylic amide substrate **5-1**, a benzyl group was allowed, affording the *cis*-3-pyrrolines *cis*-**5-2b** in 96% yield and 96/4 diastereoselectivity. More steric demanding groups such as isopropyl and cyclohexyl lead to even higher *cis*-selectivities of the products (e.g., *cis*-**5-2c** and *cis*-**5-2d**) while maintaining excellent reaction efficiency. Several functionalized R^2 groups were tolerated. An incomplete conversion was observed in the presence of a primary chloride in the case of **5-2e**. We attribute it to the deactivation of the gold catalyst by leached chloride. The yield based on conversion (88%), however, remains excellent. In addition, a silyl ether (**5-2f**) and a phthalimide (**5-2g**) groups were allowed.

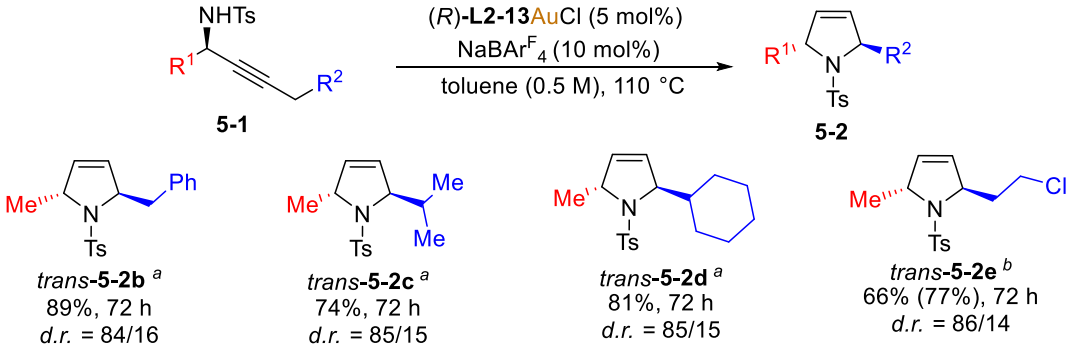
Scheme 45. Reaction Scope of Propargylic Sulfonamides for the Formation of *cis*-3-Pyrrolines



We then varied the propargylic R^1 group while fixing R^2 as isopropyl (Scheme 45). Alkyl groups including *n*-propyl (**5-2h**), isopropyl (**5-2i**), and cyclopropyl (**5-2j**) reacted uneventfully to deliver the desired *cis*-3-pyrroline products in good yields and with >50/1 diastereomeric ratios. However, a *tert*-butyl group proved to be too bulky to permit any detectable conversion even at 130 ˚C using chlorobenzene as the solvent (**5-2k**). A phenyl group and its electronically modified variants were readily tolerated, and the *cis*-pyrroline

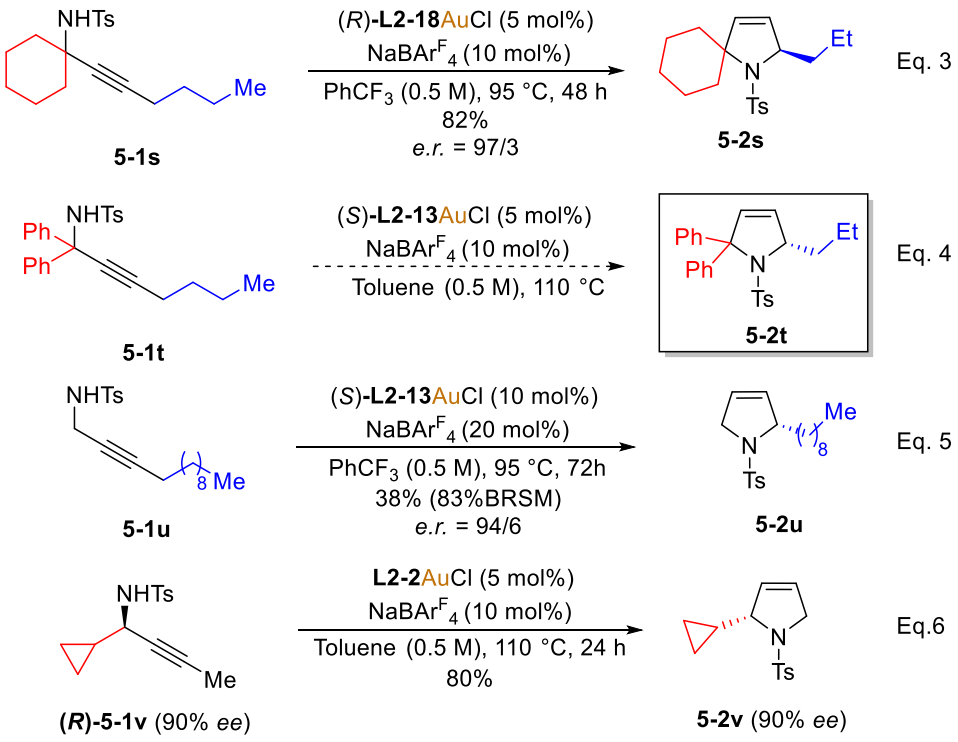
products (**5-2l**) -(**5-2n**) were formed in 74 - 79% yields and with >50/1 diastereoselectivity. Electron-rich heteroaryl groups including 2-furyl (**5-2o**), 2-thienyl (**5-2p**), *N*-tosylindol-3-yl (**5-2q**) were accommodated, and the preference for the *cis*-products remained excellent. The yields of **5-2o** and **5-2p** were moderate, which is likely due to side reactions related to their electron-rich arene moiety. A similar phenomenon was observed in the formation of the *cis*-pyrroline **5-2r** featuring a *β*-styryl as the R^1 group.

Scheme 46. Reaction Scope of Propargylic Sulfonamides for the Formation of *trans*-3-Pyrrolines



[a] A second batch of (*R*)-**L2-13**AuCl (5 mol%) and $NaBAr^F_4$ (10 mol%) were added after 24 h. [b] 10 mol% (*R*)-**L2-13**AuCl and 20 mol% $NaBAr^F_4$ were used.

We then examined several representative cases of forming disfavored *trans*-3-pyrrolines besides *trans*-**5-2a**. As shown in Scheme 46, **5-2b**, **5-2c**, **5-2d**, and **5-2e** were formed in synthetically useful *trans*/*cis* ratios of around 5-6/1 and in mostly good to excellent yields. A second batch of catalysts was added to consume all the substrates in the first three cases. In the formation of the chlorinated 3-pyrroline **5-2e**, the reaction similarly did not proceed to completion even with 10 mol % catalyst loading.



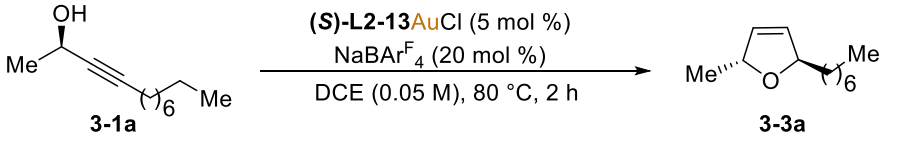
Lastly, we subjected achiral propargylic tosylamides to the reaction. As shown in Eq. 3, the reaction worked well in the case of **5-1s**, where the propargylic substituents are part of a cyclohexane ring, and an enantiomeric ratio of 97/3 of the product **5-2s** was achieved by using (*R*)-**L2-18** as the ligand performed better and was used, and running the reaction in $PhCF_3$ and at 95 °C. When the propargyl substituents are phenyl groups, the desired **5-2t** was not formed, probably due to steric hindrance (Eq. 4). In the absence of any propargylic substituent, the conversion of the propargylic tosylamide **5-1u** to the mono-substituted chiral 3-pyrroline product **5-2u** was slow, leading to only 38% yield (83% brsm) after 72 h even with the catalyst loading doubled, although the enantioselectivity (i.e., 94/6) was good (Eq. 5). To establish a complementary and yet more efficient access to this class of chiral monosubstituted 3-prolines, we subjected the chiral tosylamide substrate (*R*)-**5-1v** (90% *ee*) to the gold catalysis (Eq. 6). As no new stereocenter was generated in the product

5-2v, the achiral ligand **L2-2** was employed. The reaction was efficient, and full retention of the propargylic chiral center was observed.

5.3. Mechanistic Study

As shown in Scheme 47, we studied the effect of adding the propargylic sulfonamide **5-1a** to the asymmetric isomerization reaction discussed in ***Chapter 3***. Without propargylic sulfonamide **5-1a**, the reaction went smoothly to afford chiral 2,5-dihydrofuran **3-3a** in 85% yield and with *d.r.* = 93/7. However, the conversion and yield decreased significantly when 10 mol% **5-1a** was added into the reaction mixture. Less than 5% conversion was observed with 50 mol % **5-1a**. These results suggest that the propargylic sulfonamide is detrimental to the reaction, probably due to the deactivation of the gold catalyst by basic nitrogen. This is consistent with the high-temperature requirement for the asymmetric cycloisomerization of propargylic sulfonamides.

Scheme 47. Asymmetric Isomerization of Propargylic Alcohol in the Presence of Propargylic Sulfonamide

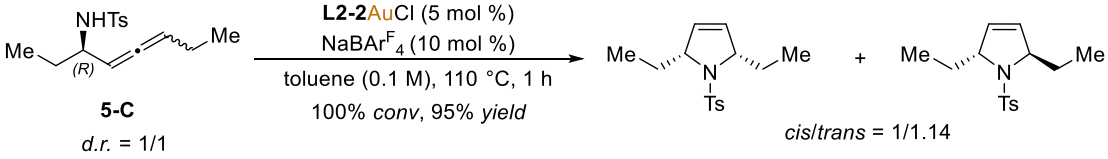


A. no additive	> 99% conv. 85% yield, d.r. = 93/7
B. adding 10 mol % **5-1a**	43% conv. 18% yield, *d.r.* = 93/7
C. adding 50 mol % **5-1a**	<5% conv.

As discussed in **Chapter 5.2**, The *cis* isomer was favored over its *trans*-counterpart by a 3/1 ratio when achiral ligand **L2-2** served as the ligand for the isomerization of **5-1a**. The stereo-preference of this reaction could come from the isomerization of propargylic sulfonamide into allenic sulfonamide or cyclization of allenic sulfonamide. To rule out the

latter possibility, we prepared the allenic sulfonamide **5-C** with a *d.r.* ratio of 1/1 from the corresponding chiral propargylic sulfonamide. Subjecting **5-C** to the gold catalysis using achiral ligand **L2-2** led to the formation of 3-pyrroline in 95% yield and with a *cis/trans* ratio of 1/1.14. In addition, in contrast to the fourteen-hour reaction time for cycloisomerization of the propargylic sulfonamide, cyclization of **5-C** only took one hour to complete. These results indicate that the inherent stereo-preference is the result of the diastereoselective alkyne isomerization, which is also the rate-determining step.

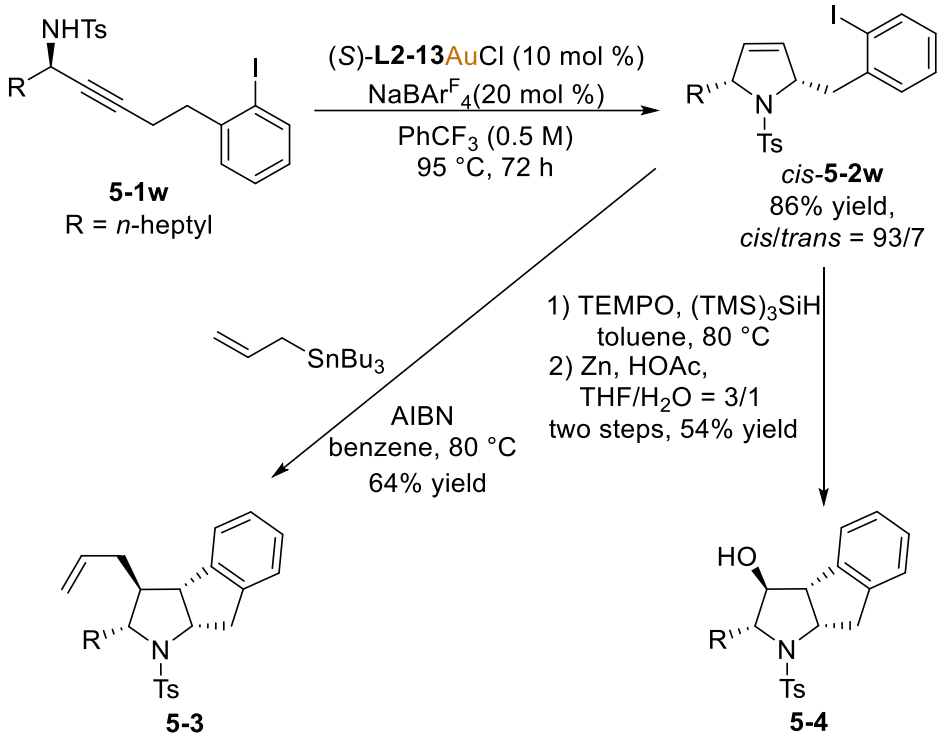
Scheme 48. Cyclization of Allenic Sulfonamide



5.4. Synthetic Application

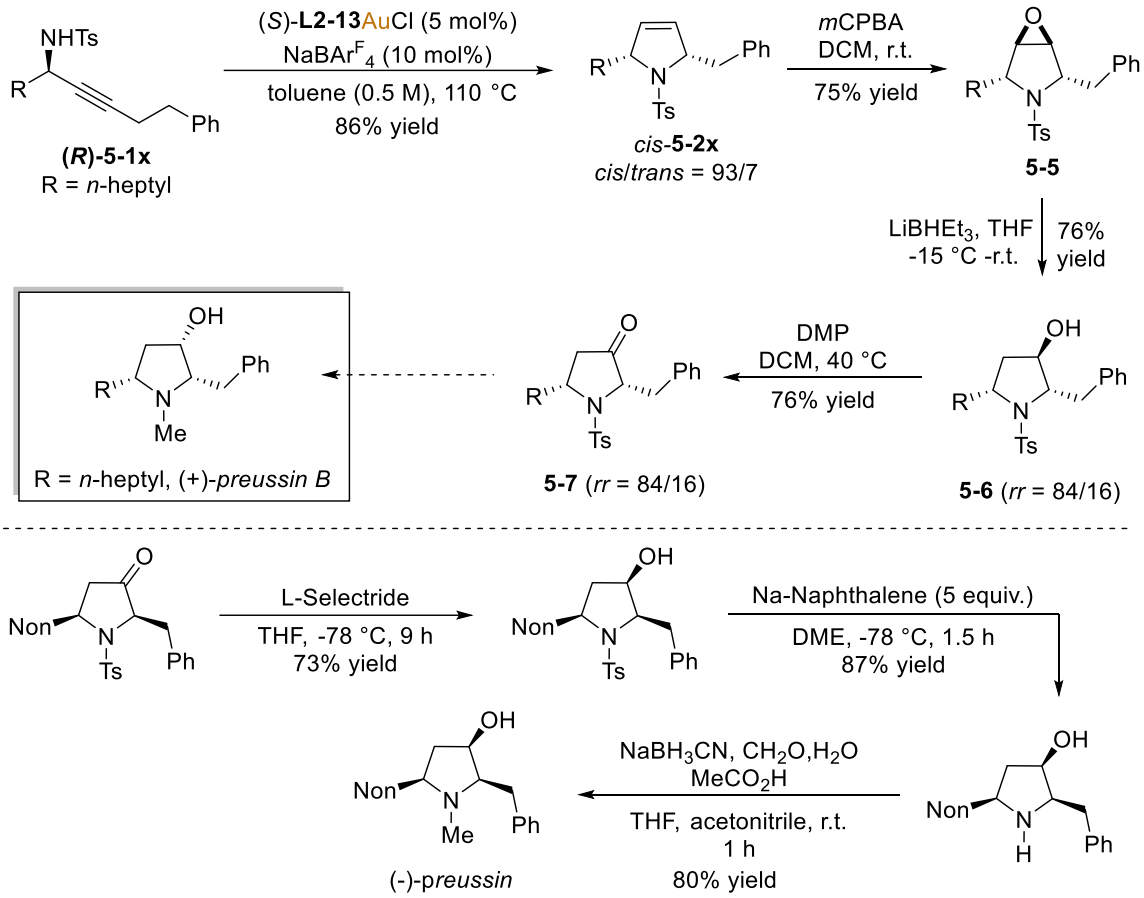
To probe the synthetic utility of this asymmetric gold catalysis, we employed the propargylic amide substrate **5-1w** featuring an iodinated phenyl group for further transformation. As shown in Scheme 49, its gold catalysis smoothly afforded **5-2w** in 86% yield as a diastereomeric mixture with a *cis*/*trans* ratio of 93/7. Subjecting *cis*-**5-2w** to radical reaction conditions and two different radical trapping strategies led to synthesizing the chiral tricyclic allylated pyrroline **5-3** and its alcohol counterpart **5-4** in moderate yields and as single stereoisomers.

Scheme 49. Functionalization via Radical Cyclization



This gold catalysis could also enable a formal synthesis of (+)-preussin B.[8-10] As shown in Scheme 50, the iodine-less version of *cis*-**5-2w**, i.e., *cis*-**5-2x**, was synthesized in a similar efficiency from (*R*)-**5-1x**. It then underwent diastereoselective epoxidation and regioselective reductive ring opening by super hydride to afford the 3-hydroxypyrrolidine **5-6** in a combined 57% yield. Dess-Martin oxidation of **5-6** arrived at the pyrrolidinone **5-7**. The homolog of **5-7** with R being *n*-nonyl instead of *n*-heptyl serves as an intermediate[11, 12] for the total synthesis of (+)-preussin B in three steps (Scheme 50). Although the conversion of **5-7** to (+)-preussin B is not known, it is reasonable to assume the same 3-step sequence in the synthesis of (+)-preussin, i.e., reduction of the carbonyl group, deprotonation of tosylate, and reductive amination, could be uneventfully followed to convert **5-7** to (+)-preussin B. As such, our sequence could provide a formal synthesis of the natural product.

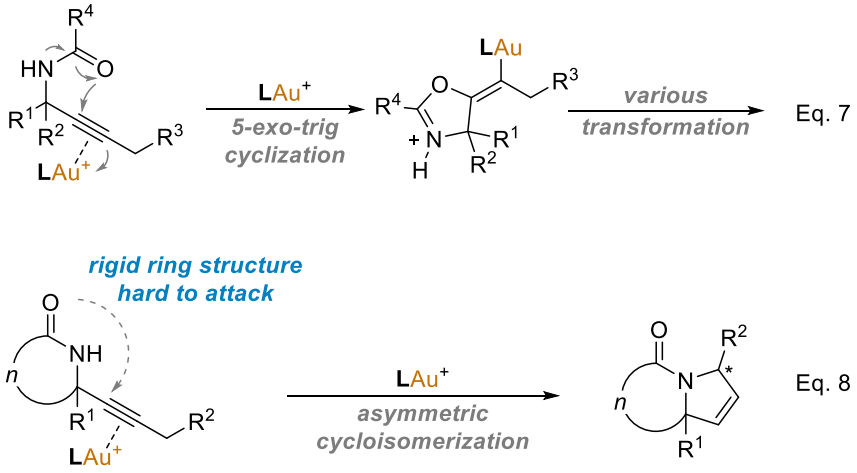
Scheme 50. Access to an Advanced Intermediate for the Synthesis of (+)-Preussin B



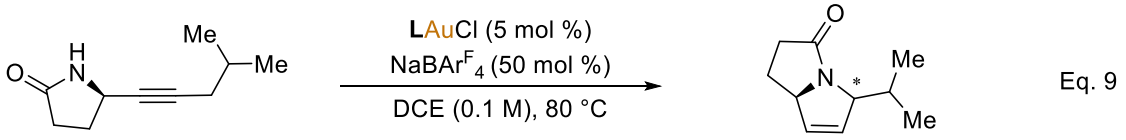
5.5. Extension to Other Substrates

As discussed in **Chapter 5.2**, various sulfonyl protecting group was screened for reaction condition optimization. However, using the acyl group as the protecting group for asymmetric cycloisomerization remained to be challenging. As shown in Eq. 7, a competitive carbonyl 5-*exo*-dig cyclization could happen when *N*-propargylcarboxamides were used as the substrate.[13, 14] In addition, the carbonyl group could stabilize the zwitterion structure **5-A** and **5-B** and facilitate the epimerization of chiral allene intermediate, resulting in very poor chirality transfer and low enantioselectivity. We envisioned that tethering the amide to a ring, i.e., lactam, would slow down the *5-exo-dig* cyclization and

the epimerization because the rigid ring system makes *5-exo-dig* cyclization energetically disfavor. (Eq. 8) Additionally, lactam has less stereo bulk compared with sulfonamide. Thus, it was thought that the inherent stereo preference toward the *cis* isomer could be minimized, and hence the synthesis of *trans*-3-pyrroline could be stereo-selective and facile.

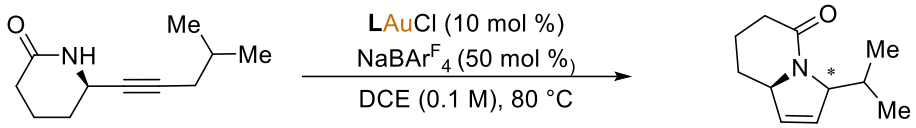


With these considerations in mind, we set out to examine the *N*-propargylic pyrrolidone and piperidinone. As exemplified in Eq. 9, asymmetric cycloisomerization of *N*-propargylic pyrrolidone **5-8a** by using the achiral catalyst **L2-2** turned out to be sluggish at 80 ºC, affording chiral 3-pyrroline **5-9a** with 35% conversion and in 27% yield with a *d.r.* ratio 4/1. The "matching" and "mismatching" situation persisted. The "matching" scenario, i.e., using (*R*)-**L2-13** as the ligand, afforded a *d.r.* ratio of 11/1, and the "mismatching" scenario, i.e., using (*S*)-**L2-13** as the ligand, offered a *d.r.* ratio of 1/2.43. A similar situation was observed in the *N*-propargylic piperidinone **5-8b** (Eq. 10). An excellent diastereoselectivity, i.e., *d.r.* >50/1, was observed with (*R*)-**L2-13** as the ligand, but the usage of (*S*)-**L2-13** ligand led to a poor diastereoselectivity.



5-8a **5-9a** Eq. 9

L2-2: 35% conv., 27% yield, d.r. = 4/1
(*S*)-**L2-13**: 32% conv., 20% yield, *d.r.* = 1/2.43
(*R*)-**L2-13**: 29% conv., 21% yield, *d.r.* = 11/1



5-8b **5-9b** Eq.10

L2-2: 33% conv., 26% yield, d.r. = 4.73/1
(*S*)-**L2-13**: 25% conv., 13% yield, *d.r.* = 1.1/1
(*R*)-**L2-13**: 24% conv., 21% yield, *d.r.* > 50/1

5.6. Conclusion

In conclusion, we have developed gold-catalyzed asymmetric access to chiral 3-pyrrolines from readily available propargylic tosylamides. 2,5-*cis*-3-Pyrrolines are synthesized in excellent selectivities over their *trans*-counterparts due to the 'matched' scenario. With the ligand enantiomer, this cooperative catalysis overcomes 'mismatching' and delivers disfavored 2,5-*trans*-3-pyrrolines in >5/1 diastereoselectivities. Mechanistic studies indicate that propargylic sulfonamide is detrimental to the reaction, probably due to the deactivation of the gold catalyst by basic nitrogen. The diastereoselective alkyne isomerization step is the rate-determining step and the origin of the inherent stereo-preference. Chiral tricyclic pyrrolines can be easily accessed via radical cyclization of 2,5-*cis*-3-Pyrrolines. In addition, a synthesis of advanced intermediate for (+)-preussin B was performed to further demonstrate the synthetic potential. The substrate scope could be extended to *N*-propargylic pyrrolidone and piperidinone, but the inherent stereo-preference problem persists.

5.7. Experimental Section

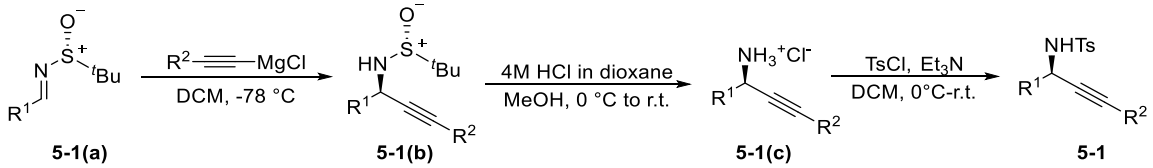
General Information

Ethyl acetate (ACS grade), hexanes (ACS grade), dichloromethane (ACS grade) were purchased from Fisher Scientific and used without further purification. ACS grade 1,2-dichloroethane was purchased from Acros Organics and used directly. Commercially available reagents were used without further purification. Reactions were monitored by thin-layer chromatography (TLC) using Silicycle precoated silica gel plates. Flash column chromatography was performed over Silicycle silica gel (230-400 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 400 MHz, 500 MHz and 600 MHz spectrometers using residue solvent peaks as internal standards ($CDCl_3$, ^{1}H: 7.26 ppm; ^{13}C: 77.00 ppm. CD_2Cl_2, ^{1}H: 5.32 ppm; ^{13}C: 53.84 ppm) (multiplicity: s = singlet, d = doublet, t = triplet, q = quadruplet, quint = quintuplet, sext = sextuplet, sept = septuplet, oct = octuplet, non = nonuplet, m = multiplet).^{31}P NMR spectra were recorded on an Agilent 400MHz spectrometer calibrated by phosphoric acid peak (H_3PO_4, ^{31}P: 0.00 ppm). ^{19}F NMR spectra were recorded on an Agilent 400MHz spectrometer calibrated by trifluoroacetic acid peak (CF_3COOH, ^{19}F: -76.55 ppm). Mass spectra were recorded with Waters micro mass ZQ detector using the electrospray method.

Synthesis of Propargylic Sulfonamide

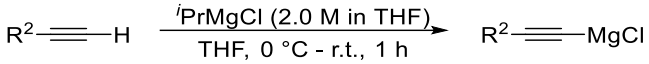
N-Sulfinyl imines **5-1(a)** were synthesized from the condensation[15, 16] of aldehyde/ketone with chiral *tert*-butylsulfinamide.

General Procedure A:



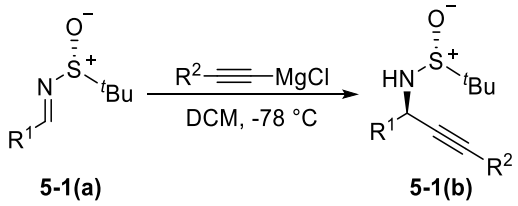
Compound **5-1(a)** was synthesized according to a modified literature procedure. [17]

Preparation of Alkynyl Grignard Reagents



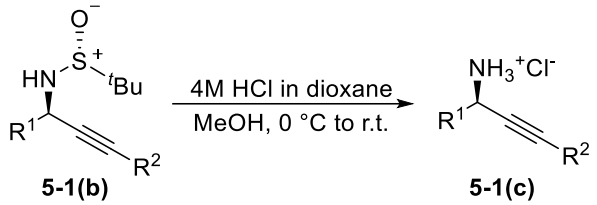
To a solution of terminal alkynes (22 mmol, 2.2 equiv.) in THF (3 mL) at 0 ℃, 2 M *iPr*MgCl in THF (10 mL, 20 mmol, 2.0 equiv.) was added slowly, and gas evolution was observed during the process. The resulting solution was allowed to warm to room temperature and stirred for 60 min to afford the alkynyl Grignard solution.

*Preparation of Compound **5-1(b)***



The freshly prepared alkynyl Grignard solution was slowly added into a solution of *N*-sulfinyl imine **5-1(a)** (10 mmol, 1.0 equiv.) in CH_2Cl_2 (40 mL) via cannula at -78 ℃ under argon protection. The resulting solution was stirred at -78 ˚C for 2 h, then gradually warmed to room temperature and stirred overnight. The reaction was quenched by saturated NH_4Cl solution, followed by extraction with EtOAc three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and the combined organic layer was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography eluting with EtOAc/hexane to separate the diastereomers.

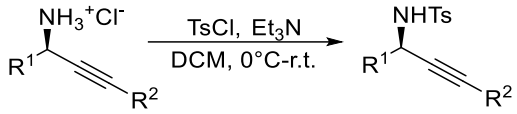
*Preparation of Compound **5-1(c)***



5-1(b) **5-1(c)**

4M HCl solution in dioxane (4 mmol, 1 mL, 4.0 equiv.) was added into a solution of **5-1(b)** (1 mmol) in MeOH (5 mL). The reaction mixture was stirred at room temperature for 30 min. The solvent was removed under reduced pressure to afford crude product **5-1(c)**, which was directly used in the next step without further purification.

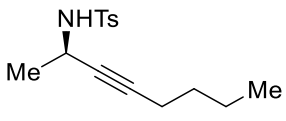
*Synthesis of Compound **5-1***



5-1(c) **5-1**

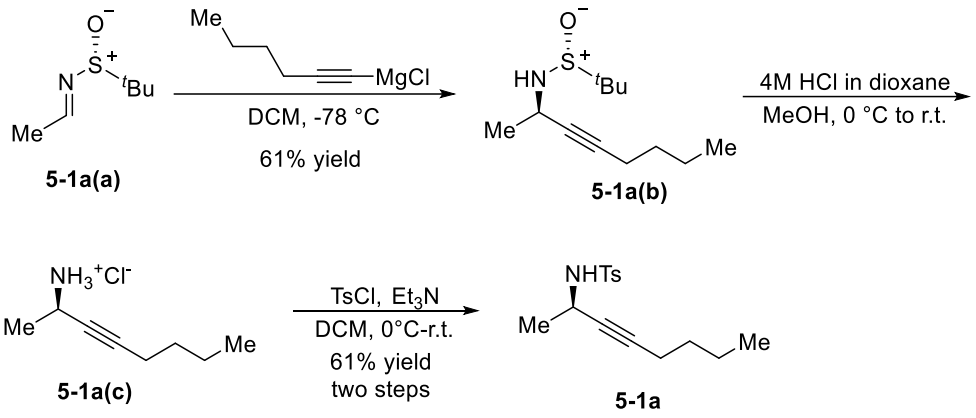
Crude product **5-1(c)** (1 mmol) was dissolved in 5 mL CH_2Cl_2 at 0 ℃, followed by the addition of Et_3N (0.42 mL, 3 mmol, 3 equiv.) and TsCl (229 mg, 1.2 mmol, 1.2 equiv.). The resulting mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with *saturated* NH_4Cl solution, and extracted by CH_2Cl_2 three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography eluting with EtOAc/hexane to afford a light-yellow solid. The product was further purified by recrystallization from hexane to afford a white needle compound **5-1**.

(*R*)-4-Methyl-*N*-(oct-3-yn-2-yl)benzenesulfonamide (5-1a)



5-1a

Compound **5-1a** was synthesized according to General Procedure A.



To a solution of 1-hexyne (4.36 mL, 38 mmol, 2.2 equiv.) in THF (5 mL) at 0 ℃, 2M ^{i}PrMgCl in THF (17.3 mL, 34.5 mmol, 2.0 equiv.) was added slowly. The resulting solution was allowed to warm to room temperature and stirred for 60 min to afford the 1-hexynyl magnesium chloride solution.

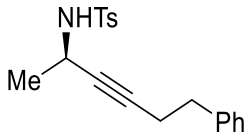
The freshly prepared 1-hexynyl magnesium chloride solution was slowly added into a solution of *N*-sulfinyl imine **5-1a(a)** (2.53 g, 17.2 mmol, 1.0 equiv.) in CH_2Cl_2 (70 mL) via cannula at -78 ℃ under argon protection. The resulting solution was stirred at -78 ˚C for 2 h, then gradually warmed to room temperature and stirred overnight. The reaction was quenched by saturated NH_4Cl solution, followed by extraction with EtOAc three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and the combined organic layer was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 3/1–2/1) to afford **5-1a(b)** (2.41 g, 10.5 mmol, 61% yield) as a colorless oil.

4M HCl solution in dioxane (4 mmol, 1 mL, 4.0 equiv.) was added into a solution of **5-1a(b)** (229.5 mg, 1 mmol) in MeOH (5 mL). The reaction mixture was stirred at room temperature for 30 min. The solvent was removed under reduced pressure to afford crude

product **5-1a(c)**, which was directly used in the next step without further purification. Crude product **5-1a(c)** was dissolved in 5 mL CH_2Cl_2 at 0 ℃, followed by the addition of Et_3N (0.42 mL, 3 mmol, 3 equiv.) and TsCl (229 mg, 1.2 mmol, 1.2 equiv.). The resulting mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with *saturated* NH_4Cl solution and extracted by CH_2Cl_2 three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 10/1) to afford a light-yellow solid. The product was further purified by recrystallization from hexane to afford **5-1a** (170.2 mg, 0.61 mmol) as a white needle.

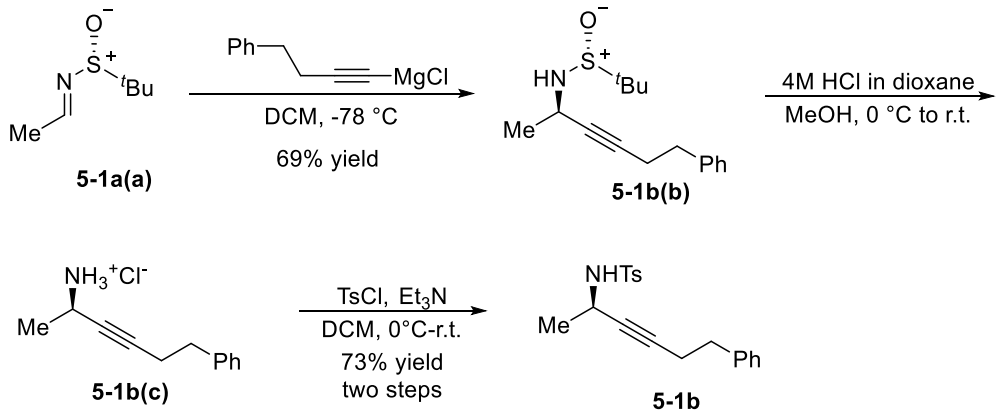
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 4.52 (d, *J* = 8.9 Hz, 1H), 4.15 (dqt, *J* = 8.9, 6.9, 2.1 Hz, 1H), 2.42 (s, 3H), 1.92 – 1.86 (m, 2H), 1.37 (d, *J* = 6.9 Hz, 3H), 1.28 – 1.19 (m, 4H), 0.88 – 0.81 (m, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 143.2, 137.6, 129.4, 127.4, 84.3, 79.1, 41.7, 30.4, 24.0, 21.8, 21.5, 18.0, 13.5. **HRMS (ESI)** *m/z:* $[M+Na]^+$ calcd for $C_{15}H_{21}NO_2SNa$ 302.1191; Found *m/z* 302.1198. **99.8% *ee***; HPLC (IC, Hexane/*i*PrOH = 90/10, flow rate = 1.0 mL/min, λ = 202 nm) t_R= 19.13 min (major), t_R= 15.55 min (minor).

(*R*)-4-Methyl-*N*-(6-phenylhex-3-yn-2-yl)benzenesulfonamide (5-1b)



5-1b

Compound **5-1b** was synthesized according to General Procedure A.



To a solution of 4-phenyl-1-butyne (1.55 mL, 11 mmol, 2.2 equiv.) in THF (1.5 mL) at 0 ℃, 2M ^{i}PrMgCl in THF (5 mL, 10 mmol, 2.0 equiv.) was added slowly. The resulting solution was allowed to warm to room temperature and stirred for 60 min to afford the 4-phenyl-1-butynyl magnesium chloride solution.

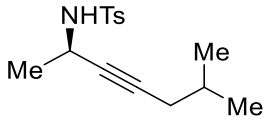
The freshly prepared 4-phenyl-1-butynyl magnesium chloride solution was slowly added into a solution of *N*-sulfinyl imine **5-1a(a)** (736.2 mg, 5 mmol, 1.0 equiv.) in CH_2Cl_2 (20 mL) via cannula at -78 ℃ under argon protection. The resulting solution was stirred at -78 ˚C for 2 h, then gradually warmed to room temperature and stirred overnight. The reaction was quenched by saturated NH_4Cl solution, followed by extraction with EtOAc three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and the combined organic layer was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 3/1–2/1) to afford **5-1b(b)** (951 mg, 3.43 mmol, 69% yield) as a colorless oil.

4M HCl solution in dioxane (13.6 mmol, 3.4 mL, 4.0 equiv.) was added into a solution of **5-1b(b)** (951 mg, 3.43 mmol) in MeOH (17 mL). The reaction mixture was stirred at room temperature for 30 min. The solvent was removed under reduced pressure to afford crude product **5-1b(c)**, which was directly used in the next step without further purification.

Crude product **5-1b(c)** was dissolved in 15 mL CH_2Cl_2 at 0 °C, followed by the addition of Et_3N (2.41 mL, 17 mmol, 5 equiv.) and TsCl (785 mg, 4.11 mmol, 1.2 equiv.). The resulting mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with *saturated* NH_4Cl solution and extracted by CH_2Cl_2 three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 10/1) to afford a light-yellow solid. The product was further purified by recrystallization from hexane to afford **5-1b** (821.5 mg, 2.51 mmol, 74% yield) as a white needle.

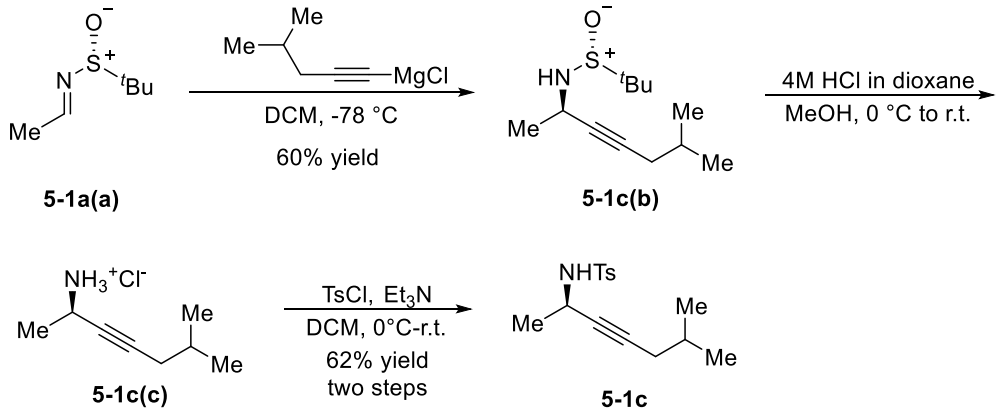
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.32 – 7.24 (m, 4H), 7.24 – 7.18 (m, 1H), 7.10 (d, *J* = 8.4 Hz, 2H), 4.59 (d, *J* = 8.6 Hz, 1H), 4.14 (ddt, *J* = 8.8, 6.8, 2.0 Hz, 1H), 2.56 (t, *J* = 7.6 Hz, 2H), 2.40 (s, 3H), 2.17 (tt, *J* = 7.6, 1.8 Hz, 2H), 1.36 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 143.3, 140.4, 137.4, 129.4, 128.3, 128.3, 127.4, 126.3, 83.5, 79.9, 41.6, 34.7, 23.7, 21.5, 20.6. **HRMS (ESI)** *m/z:* $[M+Na]^+$ calcd for $C_{19}H_{21}NO_2SNa$ 350.1191; Found *m/z* 350.1184.

(*R*)-4-Methyl-*N*-(6-methylhept-3-yn-2-yl)benzenesulfonamide (5-1c)



5-1c

Compound **5-1c** was synthesized according to General Procedure A.



To a solution of 4-methyl-1-pentyne (1.29 mL, 11 mmol, 2.2 equiv.) in THF (1.5 mL) at 0 ℃, 2M *iPr*MgCl in THF (5 mL, 10 mmol, 2.0 equiv.) was added slowly. The resulting solution was allowed to warm to room temperature and stirred for 60 min to afford the 4-methyl-1-pentynyl magnesium chloride solution.

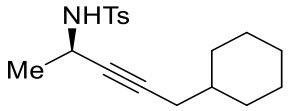
The freshly prepared 4-methyl-1-pentynyl magnesium chloride solution was slowly added into a solution of *N*-sulfinyl imine **5-1a(a)** (736.2 mg, 5 mmol, 1.0 equiv.) in CH_2Cl_2 (20 mL) via cannula at -78 ℃ under argon protection. The resulting solution was stirred at -78 ˚C for 2 h, then gradually warmed to room temperature and stirred overnight. The reaction was quenched by saturated NH_4Cl solution, followed by extraction with EtOAc three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and the combined organic layer was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 3/1) to afford **5-1c(b)** (687.4 mg, 3.00 mmol, 60% yield) as a colorless oil.

4M HCl solution in dioxane (12.0 mmol, 3.0 mL, 4.0 equiv.) was added into a solution of **5-1c(b)** (687.4 mg, 3.00 mmol) in MeOH (15 mL). The reaction mixture was stirred at room temperature for 30 min. The solvent was removed under reduced pressure to afford crude product **5-1c(c)**, which was directly used in the next step without further purification.

Crude product **5-1c(c)** was dissolved in 15 mL CH_2Cl_2 at 0 ℃, followed by the addition of Et_3N (2.11 mL, 15 mmol, 5 equiv.) and TsCl (686.3 mg, 3.60 mmol, 1.2 equiv.). The resulting mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with *saturated* NH_4Cl solution and extracted by CH_2Cl_2 three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 10/1) to afford a light-yellow solid. The product was further purified by recrystallization from hexane to afford **5-1c** (520.2 mg, 1.86 mmol, 62% yield) as a white needle.

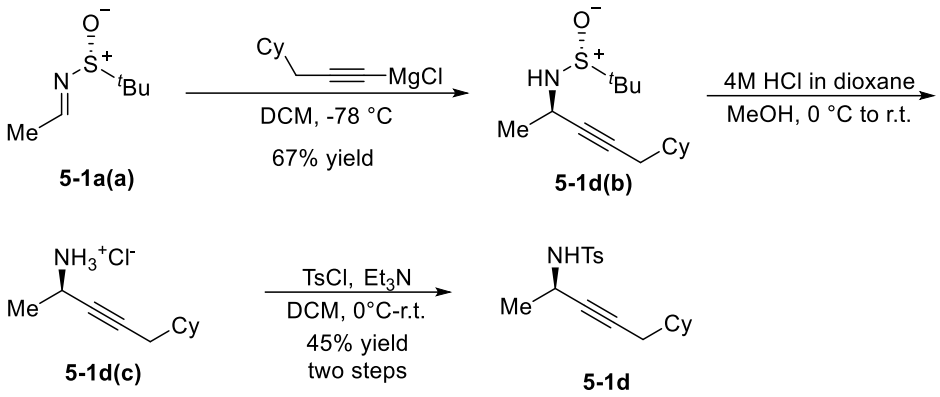
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 4.61 (d, *J* = 8.7 Hz, 1H), 4.16 (dqt, *J* = 8.9, 6.9, 2.1 Hz, 1H), 2.41 (s, 3H), 1.78 (dd, *J* = 6.6, 2.1 Hz, 2H), 1.54 (non, *J* = 6.7 Hz, 1H), 1.38 (d, *J* = 6.9 Hz, 3H), 0.80 (d, *J* = 6.7 Hz, 6H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 143.2, 137.5, 129.4, 127.4, 83.2, 80.0, 41.7, 27.7, 27.5, 24.0, 21.8, 21.5. **HRMS (ESI)** *m/z:* $[M+Na]^+$ calcd for $C_{15}H_{21}NO_2SNa$ 302.1191; Found *m/z* 350.1192.

(*R*)-*N*-(5-cyclohexylpent-3-yn-2-yl)-4-Methylbenzenesulfonamide (5-1d)



5-1d

Compound **5-1d** was synthesized according to General Procedure A.



To a solution of 3-cyclohexyl-1-propyne (1.60 mL, 11 mmol, 2.2 equiv.) in THF (1.5 mL) at 0 ℃, 2M *iPr*MgCl in THF (5 mL, 10 mmol, 2.0 equiv.) was added slowly. The resulting solution was allowed to warm to room temperature and stirred for 60 min to afford the 3-cyclohexyl-1-propynyl magnesium chloride solution.

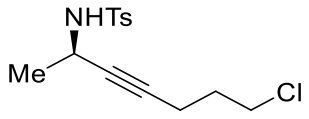
The freshly prepared 3-cyclohexyl-1-propynyl magnesium chloride solution was slowly added into a solution of *N*-sulfinyl imine **5-1a(a)** (736.2 mg, 5 mmol, 1.0 equiv.) in CH_2Cl_2 (20 mL) via cannula at -78 ℃ under argon protection. The resulting solution was stirred at -78 ˚C for 2 h, then gradually warmed to room temperature and stirred overnight. The reaction was quenched by saturated NH_4Cl solution, followed by extraction with EtOAc three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and the combined organic layer was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 3/1) to afford **5-1d(b)** (904.1 mg, 3.36 mmol, 67% yield) as a colorless oil.

4M HCl solution in dioxane (11.2 mmol, 2.8 mL, 4.0 equiv.) was added into a solution of **5-1d(b)** (754.5 mg, 2.80 mmol) in MeOH (14 mL). The reaction mixture was stirred at room temperature for 30 min. The solvent was removed under reduced pressure to afford crude product **5-1d(c)**, which was directly used in the next step without further purification.

Crude product **5-1d(c)** was dissolved in 15 mL CH_2Cl_2 at 0 ℃, followed by the addition of Et_3N (1.20 mL, 8.6 mmol, 3 equiv.) and TsCl (640.5 mg, 3.36 mmol, 1.2 equiv.). The resulting mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with *saturated* NH_4Cl solution and extracted by CH_2Cl_2 three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 10/1) to afford a light-yellow solid. The product was further purified by recrystallization from hexane to afford **5-1d** (399.0 mg, 1.25 mmol, 45% yield) as a white needle.

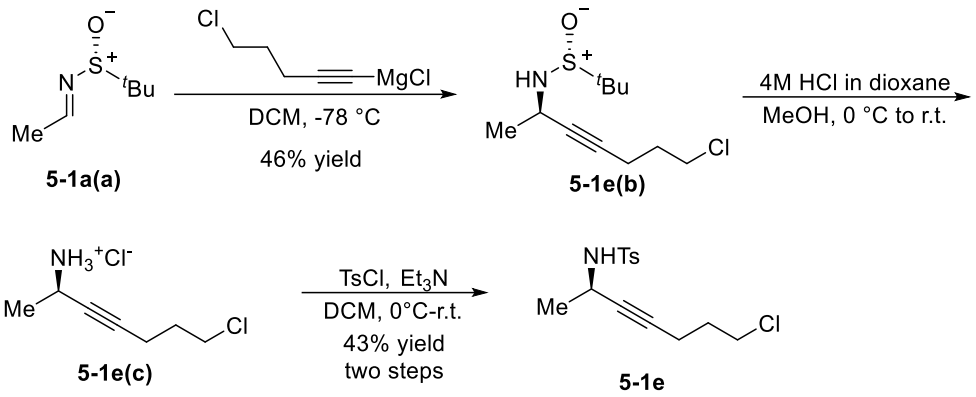
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 4.58 (d, *J* = 8.6 Hz, 1H), 4.16 (dqt, *J* = 8.9, 6.9, 2.1 Hz, 1H), 2.42 (s, 3H), 1.78 (dd, *J* = 6.7, 2.1 Hz, 2H), 1.70 – 1.56 (m, 5H), 1.38 (d, *J* = 6.9 Hz, 3H), 1.23 – 1.12 (m, 3H), 1.06 (qt, *J* = 12.8, 3.4 Hz, 1H), 0.79 (qd, *J* = 12.5, 3.3 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 143.2, 137.5, 129.4, 127.4, 83.2, 79.9, 41.7, 36.9, 32.5, 26.2, 26.1, 26.0, 24.0, 21.5. **HRMS (ESI)** *m/z:* $[M+Na]^+$ calcd for $C_{18}H_{25}NO_2SNa$) 342.1504; Found *m/z* 342.1508. **99.3% *ee;*** HPLC (IC, Hexane/iPrOH = 90/10, flow rate = 1.0 mL/min, λ = 205 nm) t_R = 23.57 min (major), t_R = 18.45 min (minor)

(*R*)-*N*-(7-chlorohept-3-yn-2-yl)-4-Methylbenzenesulfonamide (5-1e)



5-1e

Compound **5-1e** was synthesized according to General Procedure A.



To a solution of 5-chloro-1-pentyne (1.16 mL, 11 mmol, 2.2 equiv.) in THF (1.5 mL) at 0 ℃, 2M *iPr*MgCl in THF (5 mL, 10 mmol, 2.0 equiv.) was added slowly. The resulting solution was allowed to warm to room temperature and stirred for 60 min to afford the 5-chloro-1-pentynyl magnesium chloride solution.

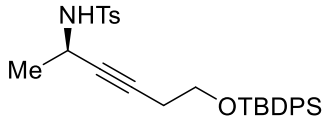
The freshly prepared 5-chloro-1-pentynyl magnesium chloride solution was slowly added into a solution of *N*-sulfinyl imine **5-1a(a)** (736.2 mg, 5 mmol, 1.0 equiv.) in CH_2Cl_2 (20 mL) via cannula at -78 ℃ under argon protection. The resulting solution was stirred at -78 ˚C for 2 h, then gradually warmed to room temperature and stirred overnight. The reaction was quenched by saturated NH_4Cl solution, followed by extraction with EtOAc three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and the combined organic layer was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 3/1) to afford **5-1e(b)** (580.7 mg, 2.32 mmol, 46% yield) as a colorless oil.

4M HCl solution in dioxane (9.2 mmol, 2.3 mL, 4.0 equiv.) was added into a solution of **5-1e(b)** (580.7 mg, 2.32 mmol) in MeOH (12 mL). The reaction mixture was stirred at room temperature for 30 min. The solvent was removed under reduced pressure to afford crude product **5-1e(c)**, which was directly used in the next step without further purification.

Crude product **5-1e(c)** was dissolved in 15 mL CH_2Cl_2 at 0 ℃, followed by the addition of Et_3N (1.62 mL, 11.6 mmol, 5 equiv.) and TsCl (442.0 mg, 2.32 mmol, 1.0 equiv.). The resulting mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with *saturated* NH_4Cl solution and extracted by CH_2Cl_2 three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 10/1) to afford a light-yellow solid. The product was further purified by recrystallization from hexane to afford **5-1e** (294.7 mg, 0.99 mmol, 43% yield) as a white needle.

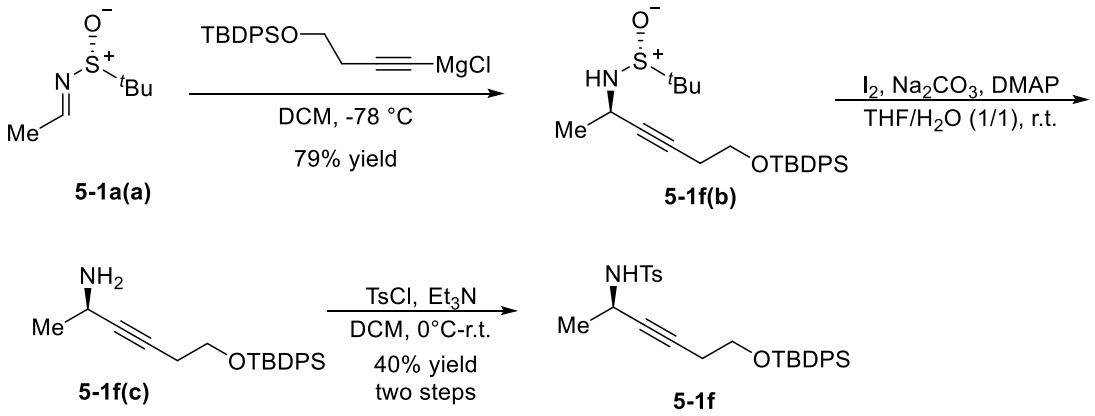
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 4.75 (d, *J* = 8.7 Hz, 1H), 4.15 (dqt, *J* = 8.8, 6.8, 2.1 Hz, 1H), 3.41 (t, *J* = 6.4 Hz, 2H), 2.42 (s, 3H), 2.08 (td, *J* = 6.9, 2.1 Hz, 2H), 1.69 (p, *J* = 6.6 Hz, 2H), 1.37 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 143.4, 137.5, 129.5, 127.4, 82.2, 80.2, 43.4, 41.5, 31.0, 23.7, 21.5, 15.8. **HRMS (ESI)** *m/z:* $[M+Na]^+$ calcd for $C_{14}H_{18}ClNO_2SNa$ 322.0645; Found *m/z* 322.0644.

(*R*)-*N*-(6-((tert-butyldiphenylsilyl)oxy)hex-3-yn-2-yl)-4-Methylbenzenesufonamide (5-1f)



5-1f

Compound **5-1f** was synthesized according to General Procedure A and a modified literature procedure. [18]



To a solution of *tert*-butyl(3-butynyloxy)diphenylsilane (3.39 g, 11 mmol, 2.2 equiv.) in THF (1.5 mL) at 0 ℃, 2M *iPr*MgCl in THF (5 mL, 10 mmol, 2.0 equiv.) was added slowly. The resulting solution was allowed to warm to room temperature and stirred for 60 min to afford the alkynyl magnesium chloride solution.

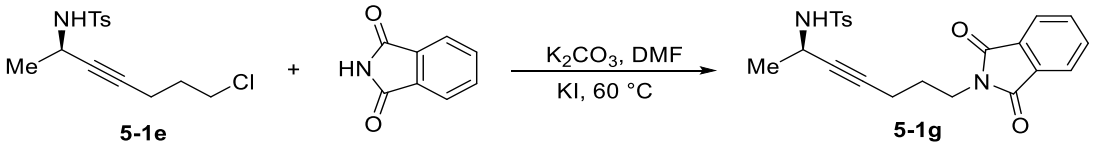
The freshly prepared alkynyl magnesium chloride solution was slowly added into a solution of *N*-sulfinyl imine **5-1a(a)** (736.2 mg, 5 mmol, 1.0 equiv.) in CH_2Cl_2 (20 mL) via cannula at -78 ℃ under argon protection. The resulting solution was stirred at -78 ˚C for 2 h, then gradually warmed to room temperature and stirred overnight. The reaction was quenched by saturated NH_4Cl solution, followed by extraction with EtOAc three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and the combined organic layer was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 3/1) to afford **5-1f(b)** (1.8075 mg, 3.97 mmol, 79% yield) as a colorless oil.

To a solution of **5-1f(b)** (1.5659 g, 3.1 mmol) in THF/H_2O (1:1, 60 mL) was added Na_2CO_3 (996 mg, 3.9 mmol) and DMAP (75.7 mg, 0.62 mmol). The reaction mixture was stirred for 5 min at room temperature before the addition of I_2 (1.9670 g, 7.75 mmol) under an argon atmosphere. The resulting mixture was then stirred at room temperature under

argon for 24 h. After consuming starting materials, the reaction was quenched by water and aqueous sodium thiosulphate at room temperature. The mixture was extracted with ethyl acetate three times. The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. Crude product **5-1f(c)** was dissolved in 18 mL CH_2Cl_2 at 0 ℃, followed by the addition of Et_3N (2.50 mL, 17.9 mmol, 5.8 equiv.) and TsCl (686.3 mg, 2.32 mmol, 1.16 equiv.). The resulting mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with *saturated* NH_4Cl solution and extracted by CH_2Cl_2 three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 10/1) to afford a light-yellow solid. The product was further purified by recrystallization from hexane to afford **5-1f** as a yellow oil (628.2 mg, 1.24 mmol, 40% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.3 Hz, 2H), 7.64 (dt, *J* = 8.1, 1.4 Hz, 4H), 7.46 – 7.43 (m, 2H), 7.41 – 7.38 (m, 4H), 7.19 (d, *J* = 8.0 Hz, 2H), 4.46 (d, *J* = 8.7 Hz, 1H), 4.12 (ddt, *J* = 8.8, 6.9, 2.0 Hz, 1H), 3.53 (t, *J* = 7.0 Hz, 2H), 2.33 (s, 3H), 2.16 (td, *J* = 7.0, 2.0, 2H), 1.35 (d, *J* = 6.9 Hz, 3H), 1.03 (s, 9H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 143.3, 137.3, 135.5, 133.4, 129.7, 129.3, 127.7, 127.4, 81.2, 80.1, 62.0, 41.6, 26.7, 23.7, 22.5, 21.4, 19.2. **HRMS (ESI)** *m/z:* $[M+Na]^+$ calcd for $C_{29}H_{35}NO_3SSiNa$ 528.2004; Found *m/z* 528.1998.

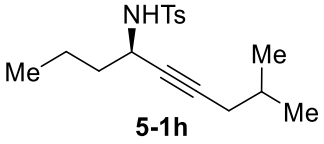
(*R*)-*N*-(7-(1,3-dioxoisoindolin-2-yl)hept-3-yn-2-yl)-4-Methylbenzenesulfonamide (5-1g)



To a solution of **5-1e** (600 mg, 2 mmol) in DMF (10 mL), K_2CO_3 (1.11 g, 8 mmol), KI (33.2 mg, 0.2 mmol) and phthalimide (588.5 mg, 4 mmol) were added. The resulting mixture was heated to 60 °C using an oil bath for 12 h. After completion, the reaction was quenched by adding water at room temperature. The mixture was extracted with ethyl acetate three times and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting oil was purified by column chromatography (hexane/EtOAc = 2/1) to afford **5-1g** (546.7 mg, 67%) as a white solid.

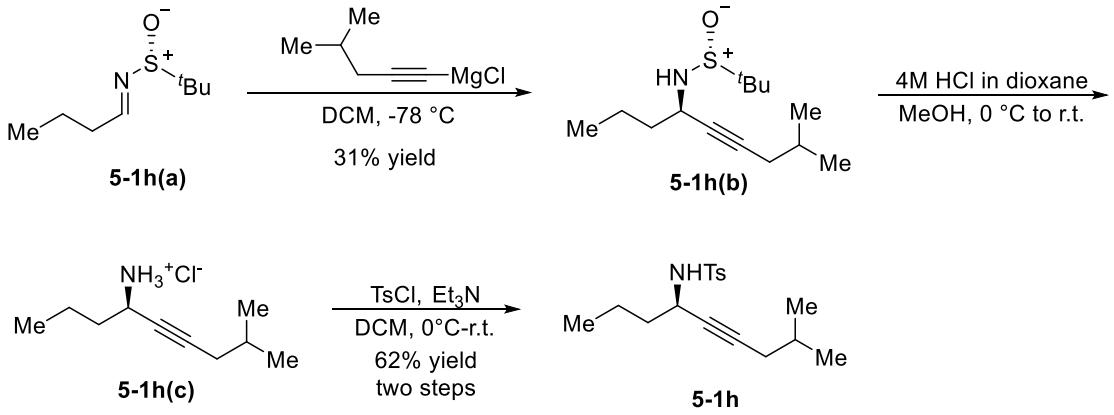
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.97 – 7.78 (m, 2H), 7.82 – 7.64 (m, 4H), 7.44 – 7.22 (m, 2H), 4.77 (d, *J* = 8.8 Hz, 1H), 4.08 – 3.98 (m, 1H), 3.72 – 3.41 (m, 2H), 2.39 (s, 3H), 2.03 – 1.83 (m, 2H), 1.77 – 1.58 (m, 2H), 1.31 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 168.3, 143.2, 137.4, 134.1, 132.0, 129.4, 127.4, 123.2, 82.7, 80.2, 41.6, 36.8, 26.7, 23.8, 21.4, 16.0. **HRMS (ESI)** *m/z:* $[M+Na]^+$ calcd for $C_{22}H_{22}N_2O_4SNa$) 433.1198; Found *m/z* 433.1192.

(*R*)-4-Methyl-*N*-(8-methylnon-5-yn-4-yl)benzenesulfonamide (5-1h)



5-1h

Compound **5-1h** was synthesized according to General Procedure A.



To a solution of 4-methyl-1-pentyne (1.29 mL, 11 mmol, 2.2 equiv.) in THF (1.5 mL) at 0 ℃, 2M *iPr*MgCl in THF (5 mL, 10 mmol, 2.0 equiv.) was added slowly. The resulting solution was allowed to warm to room temperature and stirred for 60 min to afford the 4-methyl-1-pentynyl magnesium chloride solution.

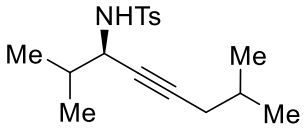
The freshly prepared 4-methyl-1-pentynyl magnesium chloride solution was slowly added into a solution of *N*-sulfinyl imine **5-1h(a)** (876.0 mg, 5 mmol, 1.0 equiv.) in CH_2Cl_2 (20 mL) via cannula at -78 ℃ under argon protection. The resulting solution was stirred at -78 ˚C for 2 h, then gradually warmed to room temperature and stirred overnight. The reaction was quenched by saturated NH_4Cl solution, followed by extraction with EtOAc three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and the combined organic layer was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 4/1) to afford **5-1h(b)** (401.1 mg, 1.56 mmol, 31% yield) as a colorless oil.

4M HCl solution in dioxane (6.4 mmol, 1.6 mL, 4.0 equiv.) was added into a solution of **5-1h(b)** (401.1 mg, 1.56 mmol) in MeOH (8 mL). The reaction mixture was stirred at room temperature for 30 min. The solvent was removed under reduced pressure to afford crude product **5-1h(c)**, which was directly used in the next step without further purification. Crude product **5-1h(c)** was dissolved in 7 mL CH_2Cl_2 at 0 ℃, followed by the addition of Et_3N (1.09 mL, 7.8 mmol, 5 equiv.) and TsCl (297.4 mg, 1.56 mmol, 1.0 equiv.). The resulting mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with *saturated* NH_4Cl solution and extracted by CH_2Cl_2 three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel flash column

chromatography (hexane/EtOAc = 10/1) to afford a light-yellow solid. The product was further purified by recrystallization from hexane to afford **5-1h** (200.8 mg, 0.65 mmol, 42% yield) as a white needle.

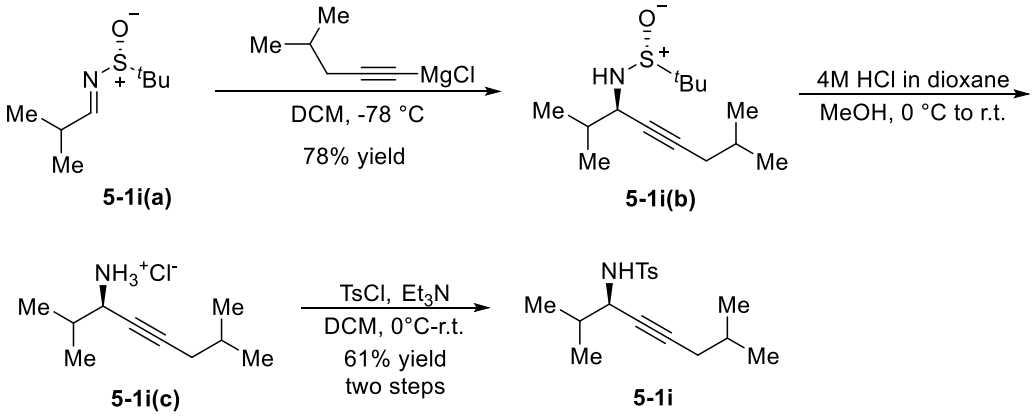
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 7.9 Hz, 2H), 4.47 (d, *J* = 9.1 Hz, 1H), 4.09 – 3.99 (m, 1H), 2.41 (s, 3H), 1.78 (dd, *J* = 6.5, 2.1 Hz, 2H), 1.68 – 1.49 (m, 3H), 1.44 (h, *J* = 7.4 Hz, 2H), 0.90 (t, *J* = 7.3 Hz, 3H), 0.79 (d, *J* = 6.7 Hz, 6H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 143.2, 137.5, 129.4, 127.4, 83.8, 79.0, 45.8, 39.2, 27.7, 27.5, 21.8, 21.5, 18.7, 13.4. **HRMS (ESI)** *m/z:* $[M+Na]^+$ calcd for $C_{17}H_{25}NO_2SNa$ 330.1504; Found *m/z* 330.1506.

(*R*)-*N*-(2,7-dimethyloct-4-yn-3-yl)-4-Methylbenzenesulfonamide (5-1i)



5-1i

Compound **5-1i** was synthesized according to General Procedure A.



5-1i(a) **5-1i(b)** **5-1i(c)** **5-1i**

To a solution of 4-methyl-1-pentyne (1.29 mL, 11 mmol, 2.2 equiv.) in THF (1.5 mL) at 0 °C, 2M *iPr*MgCl in THF (5 mL, 10 mmol, 2.0 equiv.) was added slowly. The resulting

solution was allowed to warm to room temperature and stirred for 60 min to afford the 4-methyl-1-pentynyl magnesium chloride solution.

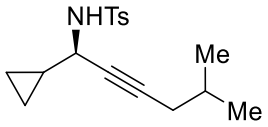
The freshly prepared 4-methyl-1-pentynyl magnesium chloride solution was slowly added into a solution of *N*-sulfinyl imine **5-1i(a)** (876.0 mg, 5 mmol, 1.0 equiv.) in CH_2Cl_2 (20 mL) via cannula at -78 ℃ under argon protection. The resulting solution was stirred at -78 ˚C for 2 h, then gradually warmed to room temperature and stirred overnight. The reaction was quenched by saturated NH_4Cl solution, followed by extraction with EtOAc three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and the combined organic layer was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 3/1) to afford **5-1i(b)** (1.0013 g, 3.89 mmol, 78% yield) as a colorless oil.

4M HCl solution in dioxane (15.6 mmol, 3.9 mL, 4.0 equiv.) was added into a solution of **5-1i(b)** (1.0013 g, 3.89 mmol) in MeOH (19 mL). The reaction mixture was stirred at room temperature for 30 min. The solvent was removed under reduced pressure to afford crude product **5-1i(c)**, which was directly used in the next step without further purification. Crude product **5-1i(c)** was dissolved in 20 mL CH_2Cl_2 at 0 ℃, followed by the addition of Et_3N (2.73 mL, 19.5 mmol, 5 equiv.) and TsCl (741.6 mg, 3.89 mmol, 1.0 equiv.). The resulting mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with *saturated* NH_4Cl solution and extracted by CH_2Cl_2 three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 10/1) to afford a light-yellow solid. The product was

further purified by recrystallization from hexane to afford **5-1i** (724.7 mg, 2.36 mmol, 61% yield) as a white needle.

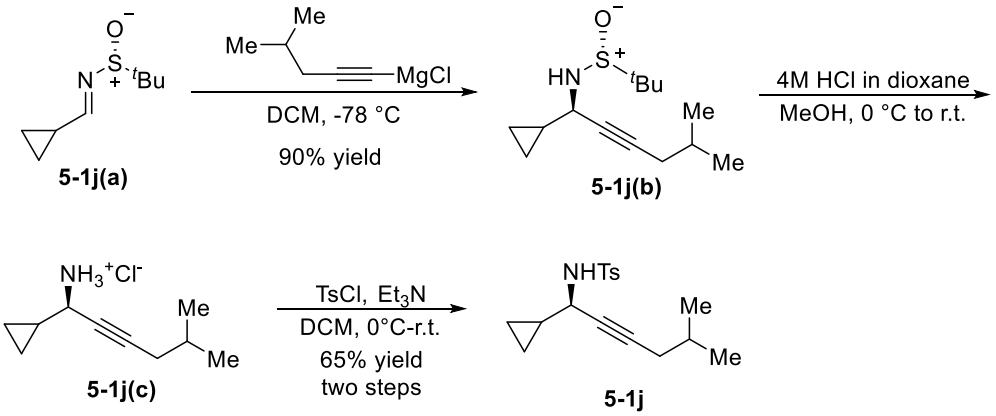
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.1 Hz, 2H), 7.28 (d, *J* = 7.9 Hz, 2H), 4.52 (d, *J* = 9.4 Hz, 1H), 3.95 – 3.81 (m, 1H), 2.41 (s, 3H), 1.91 – 1.83 (m, 1H), 1.78 (dd, *J* = 6.4, 2.2 Hz, 2H), 1.54 (non, *J* = 6.6 Hz, 1H), 0.95 (d, *J* = 6.7 Hz, 6H), 0.80 (d, *J* = 6.7 Hz, 6H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 143.2, 137.5, 129.4, 127.4, 84.6, 77.4, 51.9, 33.9, 27.7, 27.5, 21.8, 21.5, 18.7, 17.5. **HRMS (ESI)** *m/z:* $[M+Na]^+$ calcd for $C_{17}H_{25}NO_2SNa$ 330.1504; Found *m/z* 330.1508.

(*R*)-*N*-(1-cyclopropyl-5-methylhex-2-yn-1-yl)-4-Methylbenzenesulfonamide (5-1j)



5-1j

Compound **5-1j** was synthesized according to General Procedure A.



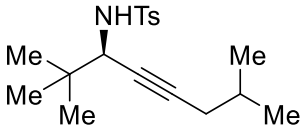
To a solution of 4-methyl-1-pentyne (1.29 mL, 11 mmol, 2.2 equiv.) in THF (1.5 mL) at 0 ℃, 2M *iPr*MgCl in THF (5 mL, 10 mmol, 2.0 equiv.) was added slowly. The resulting solution was allowed to warm to room temperature and stirred for 60 min to afford the 4-methyl-1-pentynyl magnesium chloride solution.

The freshly prepared 4-methyl-1-pentynyl magnesium chloride solution was slowly added into a solution of *N*-sulfinyl imine **5-1j(a)** (866.3 mg, 5 mmol, 1.0 equiv.) in CH_2Cl_2 (20 mL) via cannula at -78 ℃ under argon protection. The resulting solution was stirred at -78 ˚C for 2 h, then gradually warmed to room temperature and stirred overnight. The reaction was quenched by saturated NH_4Cl solution, followed by extraction with EtOAc three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and the combined organic layer was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 3/1) to afford **5-1j(b)** (1.1424 g, 4.47 mmol, 90% yield) as a colorless oil.

4M HCl solution in dioxane (18.0 mmol, 4.5 mL, 4.0 equiv.) was added into a solution of **5-1j(b)** (1.1424 g, 4.47 mmol) in MeOH (22 mL). The reaction mixture was stirred at room temperature for 30 min. The solvent was removed under reduced pressure to afford crude product **5-1j(c)**, which was directly used in the next step without further purification. Crude product **5-1j(c)** was dissolved in 20 mL CH_2Cl_2 at 0 ℃, followed by the addition of Et_3N (3.1 mL, 22.3 mmol, 5 equiv.) and TsCl (852.2 mg, 4.47 mmol, 1.0 equiv.). The resulting mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with *saturated* NH_4Cl solution and extracted by CH_2Cl_2 three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 10/1) to afford a light-yellow solid. The product was further purified by recrystallization from hexane to afford **5-1j** (882.9 mg, 2.89 mmol, 65% yield) as a white needle.

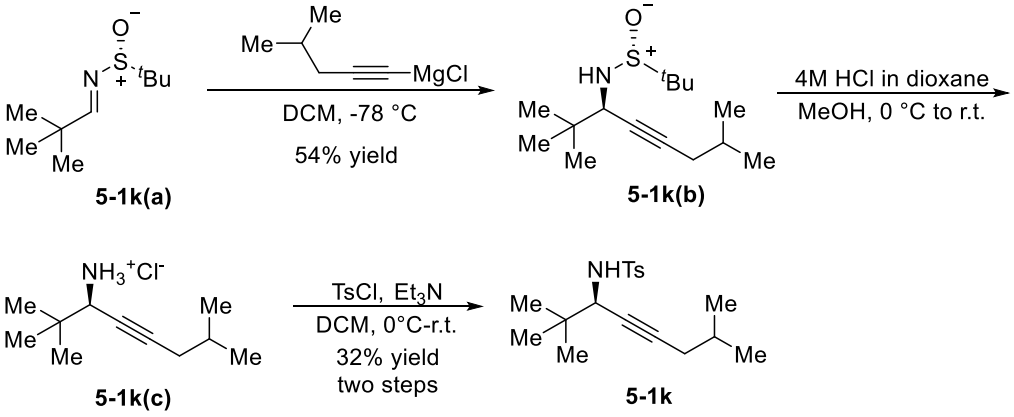
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 7.9 Hz, 2H), 4.71 (d, *J* = 8.8 Hz, 1H), 4.20 – 4.13 (m, 1H), 2.41 (s, 3H), 1.76 (dt, *J* = 6.3, 2.0 Hz, 2H), 1.54 (non, *J* = 6.6 Hz, 1H), 1.17 – 1.07 (m, 1H), 0.79 (d, *J* = 6.6 Hz, 6H) 0.50 – 0.35 (m, 4H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 143.1, 137.7, 129.4, 127.3, 84.4, 76.0, 49.0, 27.6, 27.5, 21.8, 21.5, 15.7, 2.9, 1.4. **HRMS (ESI)** *m/z:* $[M+Na]^+$ calcd for $C_{17}H_{23}NO_2SNa$ 328.1347; Found *m/z* 328.1352.

(*R*)-4-Methyl-N-(2,2,7-trimethyloct-4-yn-3-yl)benzenesulfonamide (5-1k)



1k

Compound **5-1k** was synthesized according to General Procedure A.



To a solution of 4-methyl-1-pentyne (1.94 mL, 16.5 mmol, 3.3 equiv.) in THF (2.5 mL) at 0 °C, 2M *iPr*MgCl in THF (7.5 mL, 15 mmol, 3.0 equiv.) was added slowly. The resulting solution was allowed to warm to room temperature and stirred for 60 min to afford the 4-methyl-1-pentynyl magnesium chloride solution.

The freshly prepared 4-methyl-1-pentynyl magnesium chloride solution was slowly added into a solution of *N*-sulfinyl imine **5-1k(a)** (946.5 mg, 5 mmol, 1.0 equiv.) in CH_2Cl_2

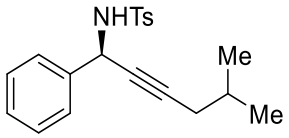
(20 mL) via cannula at -78 ℃ under argon protection. The resulting solution was stirred at -78 ˚C for 2 h, then gradually warmed to room temperature and stirred overnight. The reaction was quenched by saturated NH_4Cl solution, followed by extraction with EtOAc three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and the combined organic layer was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 3/1) to afford **5-1k(b)** (725.7 mg, 2.68 mmol, 54% yield) as a colorless oil.

4M HCl solution in dioxane (11.2 mmol, 2.8 mL, 4.0 equiv.) was added into a solution of **5-1k(b)** (725.7 mg, 2.68 mmol) in MeOH (15 mL). The reaction mixture was stirred at room temperature for 30 min. The solvent was removed under reduced pressure to afford crude product **5-1k(c)**, which was directly used in the next step without further purification. Crude product **5-1k(c)** was dissolved in 14 mL CH_2Cl_2 at 0 ℃, followed by the addition of Et_3N (1.97 mL, 13.4 mmol, 5 equiv.) and TsCl (613.1 mg, 3.89 mmol, 1.2 equiv.). The resulting mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with *saturated* NH_4Cl solution and extracted by CH_2Cl_2 three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 10/1) to afford a light-yellow solid. The product was further purified by recrystallization from hexane to afford **5-1k** (272.0 mg, 0.85 mmol, 32% yield) as a white needle.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 4.38 (d, *J* = 10.2 Hz, 1H), 3.70 (dt, *J* = 10.3, 2.1 Hz, 1H), 2.41 (s, 3H), 1.74 (dd, *J* = 6.5, 2.1 Hz, 2H), 1.52 (non, *J* = 6.7 Hz, 1H), 0.97 (s, 9H), 0.78 (d, *J* = 6.7 Hz, 6H). **^{13}C NMR (101**

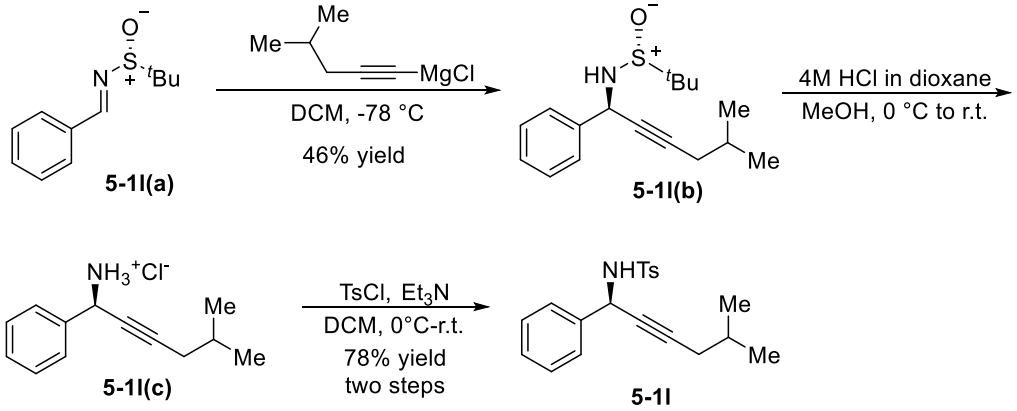
MHz, $CDCl_3$) δ 143.1, 137.4, 129.4, 127.5, 84.5, 77.8, 55.8, 35.6, 27.7, 27.5, 25.9, 21.82, 21.80, 21.5. **HRMS (ESI)** *m/z:* $[M+Na]^+$ calcd for $C_{18}H_{27}NO_2SNa$ 344.1660; Found *m/z* 344.1652.

(*R*)-4-Methyl-*N*-(5-methyl-1-phenylhex-2-yn-1-yl)benzenesulfonamide (5-1l)



5-1l

Compound **5-1l** was synthesized according to General Procedure A.



To a solution of 4-methyl-1-pentyne (1.94 mL, 16.5 mmol, 3.3 equiv.) in THF (2.5 mL) at 0 ℃, 2M *iPr*MgCl in THF (7.5 mL, 15 mmol, 3.0 equiv.) was added slowly. The resulting solution was allowed to warm to room temperature and stirred for 60 min to afford the 4-methyl-1-pentynyl magnesium chloride solution.

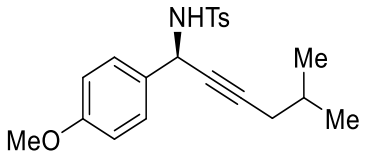
The freshly prepared 4-methyl-1-pentynyl magnesium chloride solution was slowly added into a solution of *N*-sulfinyl imine **5-1l(a)** (1.0465 g, 5 mmol, 1.0 equiv.) in CH_2Cl_2 (25 mL) via cannula at -78 ℃ under argon protection. The resulting solution was stirred at -78 ˚C for 2 h, then gradually warmed to room temperature and stirred overnight. The reaction was quenched by saturated NH_4Cl solution, followed by extraction with EtOAc

three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and the combined organic layer was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 3/1) to afford **5-1l(b)** (708.6 mg, 2.30 mmol, 46% yield) as a colorless oil.

4M HCl solution in dioxane (9.2 mmol, 2.30 mL, 4.0 equiv.) was added into a solution of **5-1l(b)** (708.6 mg, 2.30 mmol) in MeOH (12 mL). The reaction mixture was stirred at room temperature for 30 min. The solvent was removed under reduced pressure to afford crude product **5-1l(c)**, which was directly used in the next step without further purification. Crude product **5-1l(c)** was dissolved in 12 mL CH_2Cl_2 at 0 ℃, followed by the addition of Et_3N (1.62 mL, 11.5 mmol, 5 equiv.) and TsCl (526.2 mg, 2.76 mmol, 1.2 equiv.). The resulting mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with *saturated* NH_4Cl solution and extracted by CH_2Cl_2 three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 10/1) to afford a light-yellow solid. The product was further purified by recrystallization from hexane to afford **5-1l** (615.9 mg, 1.8 mmol, 78% yield) as a white needle.

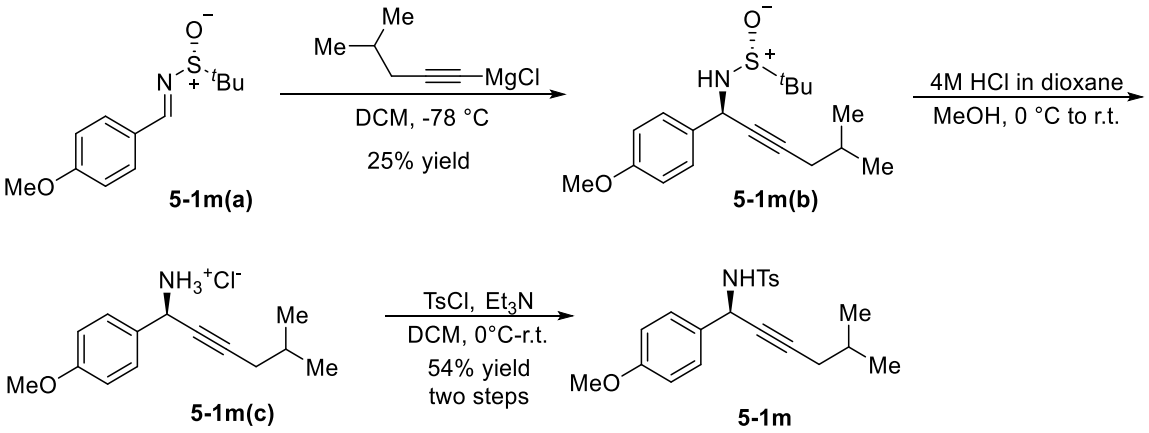
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.2 Hz, 2H), 7.47 (d, *J* = 7.2 Hz, 2H), 7.37 – 7.23 (m, 5H), 5.31 (dt, *J* = 8.9, 2.2 Hz, 1H), 4.83 (d, *J* = 8.8 Hz, 1H), 2.42 (s, 3H), 1.87 (dd, *J* = 6.6, 2.1 Hz, 2H), 1.67 – 1.54 (m, 1H), 0.84 (d, *J* = 6.7 Hz, 6H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 143.3, 138.2, 137.5, 129.4, 128.5, 128.2, 127.4, 127.2, 86.4, 77.5, 49.4, 27.72, 27.70, 21.9, 21.5. **HRMS (ESI)** *m/z:* $[M+Na]^+$ calcd for $C_{20}H_{23}NO_2SNa$ 364.1347; Found *m/z* 364.1353.

(*R*)-*N*-(1-(4-methoxyphenyl)-5-methylhex-2-yn-1-yl)-4-Methylbenzenesulfonamide (5-1m)



5-1m

Compound **5-1m** was synthesized according to General Procedure A.



To a solution of 4-methyl-1-pentyne (1.29 mL, 11 mmol, 2.2 equiv.) in THF (1.5 mL) at 0 ℃, 2M *iPr*MgCl in THF (5.0 mL, 10 mmol, 2.0 equiv.) was added slowly. The resulting solution was allowed to warm to room temperature and stirred for 60 min to afford the 4-methyl-1-pentynyl magnesium chloride solution.

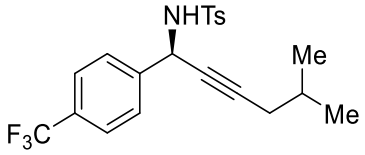
The freshly prepared 4-methyl-1-pentynyl magnesium chloride solution was slowly added into a solution of *N*-sulfinyl imine **5-1m(a)** (1.1965 mg, 5 mmol, 1.0 equiv.) in CH_2Cl_2 (20 mL) via cannula at -78 ℃ under argon protection. The resulting solution was stirred at -78 ˚C for 2 h, then gradually warmed to room temperature and stirred overnight. The reaction was quenched by saturated NH_4Cl solution, followed by extraction with EtOAc three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and the combined organic layer was concentrated under reduced pressure. The residue was

purified by silica gel flash column chromatography (hexane/EtOAc = 3/1) to afford **5-1m(b)** (405.4 mg, 1.26 mmol, 25% yield) as a colorless oil.

4M HCl solution in dioxane (5.2 mmol, 1.3 mL, 4.0 equiv.) was added into a solution of **5-1m(b)** (405.4 mg, 1.26 mmol) in MeOH (7 mL). The reaction mixture was stirred at room temperature for 30 min. The solvent was removed under reduced pressure to afford crude product **5-1m(c)**, which was directly used in the next step without further purification. Crude product **5-1m(c)** was dissolved in 7 mL CH_2Cl_2 at 0 °C, followed by the addition of Et_3N (0.92 mL, 6.30 mmol, 5 equiv.) and TsCl (240.2 mg, 1.26 mmol, 1.2 equiv.). The resulting mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with *saturated* NH_4Cl solution and extracted by CH_2Cl_2 three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 10/1) to afford a light-yellow solid. The product was further purified by recrystallization from hexane to afford **5-1m** (253.0 mg, 0.68 mmol, 54% yield) as a white needle.

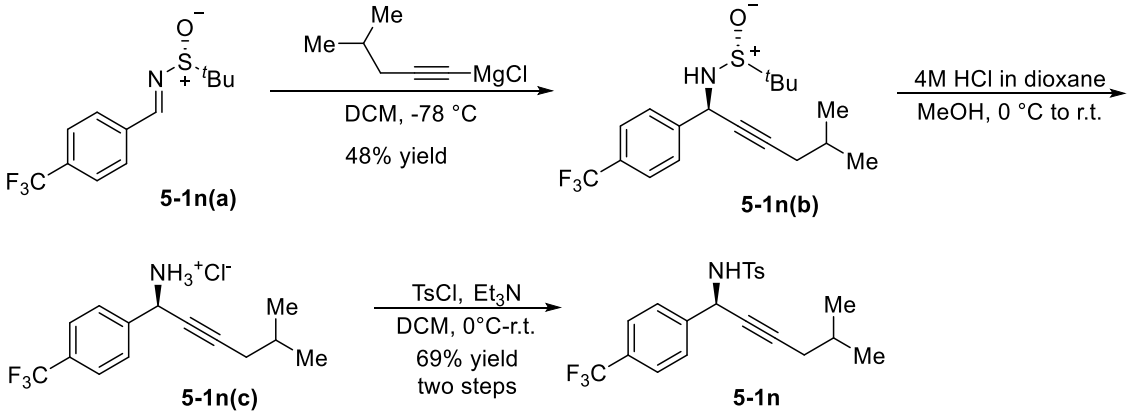
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 6.83 (d, *J* = 8.4 Hz, 2H), 5.30 – 5.23 (m, 1H), 4.76 (d, *J* = 8.7 Hz, 1H), 3.79 (s, 3H), 2.42 (s, 3H), 1.87 (dd, *J* = 6.7, 2.2 Hz, 2H), 1.65 – 1.55 (m, 1H), 0.84 (d, *J* = 6.7 Hz, 6H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 159.5, 143.2, 137.6, 130.3, 129.4, 128.5, 127.4, 113.8, 86.2, 76.8, 55.3, 49.0, 27.74, 27.72, 21.9, 21.5. **HRMS (ESI)** *m/z:* $[M+Na]^+$ calcd for $C_{21}H_{25}NO_3SNa$ 394.1453; Found *m/z* 394.1459.

(*R*)-4-Methyl-*N*-(5-methyl-1-(4-(trifluoromethyl)phenyl)hex-2-yn-1-yl)benzene-sulfonamide (5-1n)



5-1n

Compound **5-1n** was synthesized according to General Procedure A.



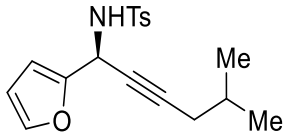
To a solution of 4-methyl-1-pentyne (1.94 mL, 16.5 mmol, 3.3 equiv.) in THF (2.5 mL) at 0 ℃, 2M *iPr*MgCl in THF (7.5 mL, 15 mmol, 3.0 equiv.) was added slowly. The resulting solution was allowed to warm to room temperature and stirred for 60 min to afford the 4-methyl-1-pentynyl magnesium chloride solution.

The freshly prepared 4-methyl-1-pentynyl magnesium chloride solution was slowly added into a solution of *N*-sulfinyl imine **5-1n(a)** (1.3865 mg, 5 mmol, 1.0 equiv.) in CH_2Cl_2 (25 mL) via cannula at -78 ℃ under argon protection. The resulting solution was stirred at -78 ˚C for 2 h, then gradually warmed to room temperature and stirred overnight. The reaction was quenched by saturated NH_4Cl solution, followed by extraction with EtOAc three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and the combined organic layer was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 3/1) to afford **5-1n(b)** (861.5 mg, 2.40 mmol, 48% yield) as a colorless oil.

4M HCl solution in dioxane (9.6 mmol, 2.4 mL, 4.0 equiv.) was added into a solution of **5-1n(b)** (861.5 mg, 2.40 mmol) in MeOH (12 mL). The reaction mixture was stirred at room temperature for 30 min. The solvent was removed under reduced pressure to afford crude product **5-1n(c)**, which was directly used in the next step without further purification. Crude product **5-1n(c)** was dissolved in 12 mL CH_2Cl_2 at 0 ℃, followed by the addition of Et_3N (1.69 mL, 12.0 mmol, 5 equiv.) and TsCl (549.1 mg, 2.76 mmol, 1.2 equiv.). The resulting mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with *saturated* NH_4Cl solution and extracted by CH_2Cl_2 three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 10/1) to afford a light-yellow solid. The product was further purified by recrystallization from hexane to afford **5-1n** (677.7 mg, 1.66 mmol, 69% yield) as a white needle.

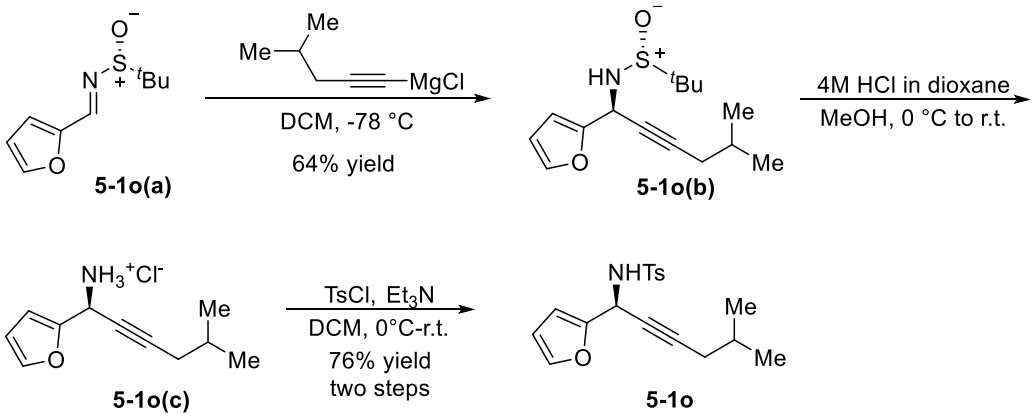
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.58 (d, *J* = 8.2 Hz, 2H), 7.54 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 8.2 Hz, 2H), 5.34 (dt, *J* = 8.8, 2.2 Hz, 1H), 5.00 (d, *J* = 8.7 Hz, 1H), 2.41 (s, 3H), 1.90 (dd, *J* = 6.5, 2.2 Hz, 2H), 1.67 – 1.57 (m, 1H), 0.84 (d, *J* = 6.7 Hz, 6H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 143.5, 142.2 (q, *J* = 1.5 Hz), 137.2, 130.3 (q, *J* = 32.4 Hz), 129.5, 127.6, 127.3, 125.4 (q, *J* = 3.8 Hz), 123.9 (q, *J* = 272.1 Hz), 87.1, 76.8, 49.1, 27.6, 27.6, 21.8, 21.4. **^{19}F NMR (376 MHz, $CDCl_3$)** δ -63.49. **HRMS (ESI)** *m/z:* $[M+Na]^+$ calcd for $C_{21}H_{22}F_3NO_2SNa$ 432.1221; Found *m/z* 432.1227.

(*S*)-*N*-(1-(furan-2-yl)-5-methylhex-2-yn-1-yl)-4-Methylbenzenesulfonamide (5-1o)



5-1o

Compound **5-1o** was synthesized according to General Procedure A.



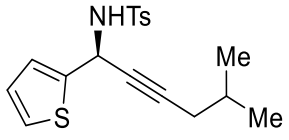
To a solution of 4-methyl-1-pentyne (1.94 mL, 16.5 mmol, 3.3 equiv.) in THF (2.5 mL) at 0 ℃, 2M *iPr*MgCl in THF (7.5 mL, 15 mmol, 3.0 equiv.) was added slowly. The resulting solution was allowed to warm to room temperature and stirred for 60 min to afford the 4-methyl-1-pentynyl magnesium chloride solution.

The freshly prepared 4-methyl-1-pentynyl magnesium chloride solution was slowly added into a solution of *N*-sulfinyl imine **5-1o(a)** (996.4 mg, 5 mmol, 1.0 equiv.) in CH_2Cl_2 (20 mL) via cannula at -78 ℃ under argon protection. The resulting solution was stirred at -78 ˚C for 2 h, then gradually warmed to room temperature and stirred overnight. The reaction was quenched by saturated NH_4Cl solution, followed by extraction with EtOAc three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and the combined organic layer was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 3/1) to afford **5-1o(b)** (895.2 mg, 3.18 mmol, 64% yield) as a colorless oil.

4M HCl solution in dioxane (12.8 mmol, 3.2 mL, 4.0 equiv.) was added into a solution of **5-1o(c)** (895.2 mg, 3.18 mmol) in MeOH (15 mL). The reaction mixture was stirred at room temperature for 30 min. The solvent was removed under reduced pressure to afford crude product **5-1o(c)**, which was directly used in the next step without further purification. Crude product **5-1o(c)** was dissolved in 16 mL CH_2Cl_2 at 0 ℃, followed by the addition of Et_3N (2.23 mL, 15.9 mmol, 5 equiv.) and TsCl (727.0 mg, 3.81 mmol, 1.2 equiv.). The resulting mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with *saturated* NH_4Cl solution and extracted by CH_2Cl_2 three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 5/1) to afford a light-yellow solid. The product was further purified by recrystallization from hexane to afford **5-1o** (803.6 mg, 2.42 mmol, 76% yield) as a white needle.

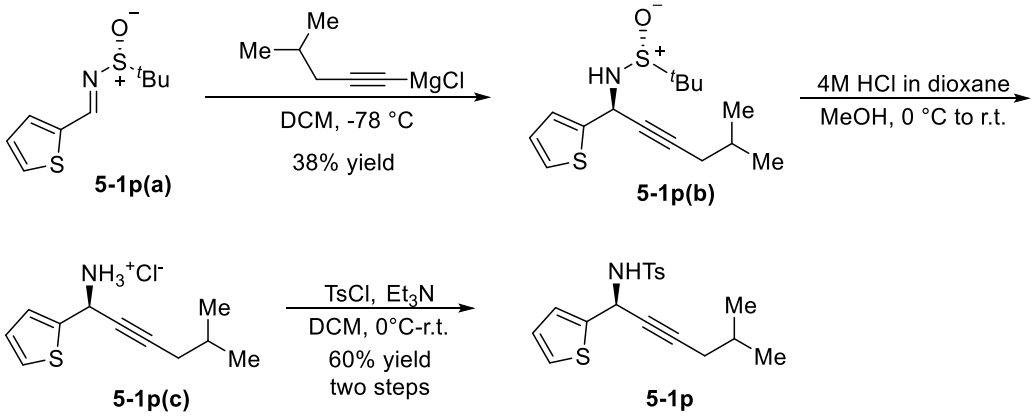
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 1.8 Hz, 1H), 7.27 (d, *J* = 8.3 Hz, 2H), 6.29 (d, *J* = 3.2 Hz, 1H), 6.25 (dd, *J* = 3.3, 1.9 Hz, 1H), 5.35 (dt, *J* = 8.7, 2.2 Hz, 1H), 4.89 (d, *J* = 8.7 Hz, 1H), 2.41 (s, 3H), 1.89 (dd, *J* = 6.5, 2.2 Hz, 2H), 1.63 (non, *J* = 6.7 Hz, 1H), 0.85 (d, *J* = 6.7 Hz, 6H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 150.3, 143.3, 142.9, 137.4, 129.4, 127.3, 110.3, 108.0, 85.3, 75.5, 43.7, 27.7, 27.6, 21.9, 21.5. **HRMS (ESI)** *m/z:* $[M+Na]^+$ calcd for $C_{18}H_{21}NO_3SNa$ 354.1140; Found *m/z* 354.1151.

(*S*)-4-Methyl-*N*-(5-methyl-1-(thiophen-2-yl)hex-2-yn-1-yl)benzenesulfonamide (5-1p)



5-1p

Compound **5-1p** was synthesized according to General Procedure A.



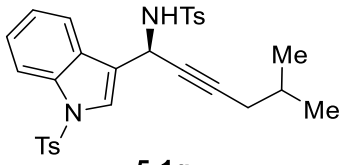
To a solution of 4-methyl-1-pentyne (1.29 mL, 11 mmol, 4.4 equiv.) in THF (1.5 mL) at 0 ℃, 2M *iPr*MgCl in THF (5.0 mL, 10 mmol, 4.0 equiv.) was added slowly. The resulting solution was allowed to warm to room temperature and stirred for 60 min to afford the 4-methyl-1-pentynyl magnesium chloride solution.

The freshly prepared 4-methyl-1-pentynyl magnesium chloride solution was slowly added into a solution of *N*-sulfinyl imine **5-1p(a)** (538 mg, 2.5 mmol, 1.0 equiv.) in CH_2Cl_2 (25 mL) via cannula at -78 ℃ under argon protection. The resulting solution was stirred at -78 ˚C for 2 h, then gradually warmed to room temperature and stirred overnight. The reaction was quenched by saturated NH_4Cl solution, followed by extraction with EtOAc three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and the combined organic layer was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 3/1) to afford **5-1p(b)** (280.5 mg, 0.94 mmol, 38% yield) as a colorless oil.

4M HCl solution in dioxane (3.76 mmol, 0.94 mL, 4.0 equiv.) was added into a solution of **5-1p(b)** (280.5 mg, 0.94 mmol) in MeOH (5 mL). The reaction mixture was stirred at room temperature for 30 min. The solvent was removed under reduced pressure to afford crude product **5-1p(c)**, which was directly used in the next step without further purification. Crude product **5-1p(c)** was dissolved in 5 mL CH_2Cl_2 at 0 ℃, followed by the addition of Et_3N (0.70 mL, 4.70 mmol, 5 equiv.) and TsCl (229.0 mg, 1.20 mmol, 1.2 equiv.). The resulting mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with *saturated* NH_4Cl solution and extracted by CH_2Cl_2 three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 5/1) to afford a light-yellow solid. The product was further purified by recrystallization from hexane to afford **5-1p** (196.2 mg, 0.56 mmol, 60% yield) as a white needle.

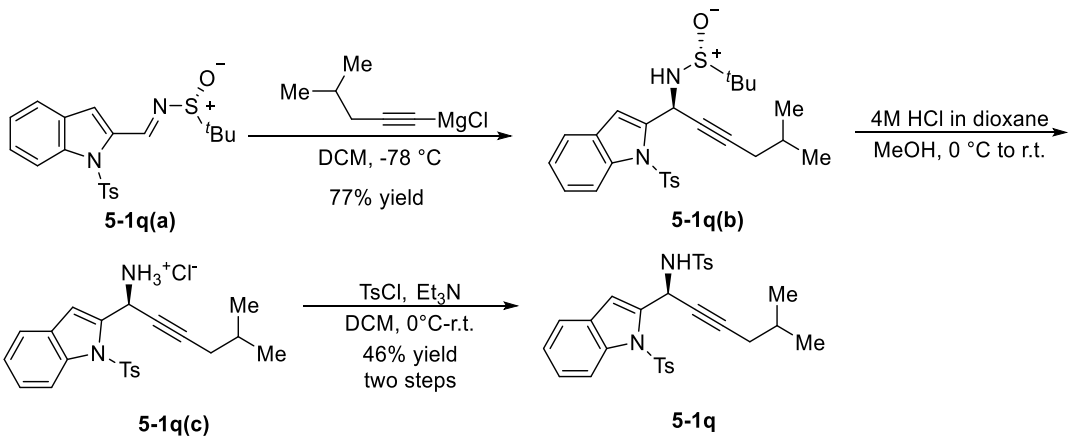
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.3 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.15 (dd, *J* = 5.1, 1.3 Hz, 1H), 7.01 (dt, *J* = 3.6, 1.2 Hz, 1H), 6.84 (dd, *J* = 5.1, 3.6 Hz, 1H), 5.44 (dtd, *J* = 9.0, 2.1, 1.1 Hz, 1H), 4.83 (d, *J* = 9.0 Hz, 1H), 2.36 (s, 3H), 1.81 (dt, *J* = 6.4, 2.0 Hz, 2H), 1.56 (non, *J* = 6.6 Hz, 1H), 0.79 (d, *J* = 6.7 Hz, 6H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 143.4, 142.5, 137.4, 129.5, 127.4, 126.8, 126.1, 126.0, 85.7, 77.4, 45.4, 27.7, 27.6, 21.9, 21.5. **HRMS (ESI)** *m/z:* $[M+Na]^+$ calcd for $C_{18}H_{21}NO_2S_2Na$ 370.0912; Found *m/z* 370.0917.

(*S*)-4-Methyl-*N*-(5-methyl-1-(1-tosyl-1H-indol-3-yl)hex-2-yn-1-yl)benzene-sulfonamide (5-1q)



5-1q

Compound **5-1q** was synthesized according to General Procedure A.



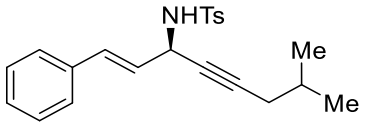
To a solution of 4-methyl-1-pentyne (1.94 mL, 16.5 mmol, 3.3 equiv.) in THF (2.5 mL) at 0 ℃, 2M *iPr*MgCl in THF (7.5 mL, 15 mmol, 3.0 equiv.) was added slowly. The resulting solution was allowed to warm to room temperature and stirred for 60 min to afford the 4-methyl-1-pentynyl magnesium chloride solution.

The freshly prepared 4-methyl-1-pentynyl magnesium chloride solution was slowly added into a solution of *N*-sulfinyl imine **5-1q(a)** (2.0126 g, 5.0 mmol, 1.0 equiv.) in CH_2Cl_2 (25 mL) via cannula at -78 ℃ under argon protection. The resulting solution was stirred at -78 ˚C for 2 h, then gradually warmed to room temperature and stirred overnight. The reaction was quenched by saturated NH_4Cl solution, followed by extraction with EtOAc three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and the combined organic layer was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 1/1) to afford **5-1q(b)** (1.8803 g, 3.87 mmol, 77% yield) as a colorless oil.

4M HCl solution in dioxane (16 mmol, 4.0 mL, 4.0 equiv.) was added into a solution of **5-1q(b)** (1.8803 g, 3.87 mmol) in MeOH (20 mL). The reaction mixture was stirred at room temperature for 30 min. The solvent was removed under reduced pressure to afford crude product **5-1q(c)**, which was directly used in the next step without further purification. Crude product **5-1q(c)** was dissolved in 20 mL CH_2Cl_2 at 0 ℃, followed by the addition of Et_3N (2.72 mL, 19.35 mmol, 5 equiv.) and TsCl (885 mg, 4.64 mmol, 1.2 equiv.). The resulting mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with *saturated* NH_4Cl solution and extracted by CH_2Cl_2 three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 5/1) to afford a light-yellow solid. The product was further purified by recrystallization from hexane to afford **5-1q** (947.8 mg, 1.77 mmol, 46% yield) as a white needle.

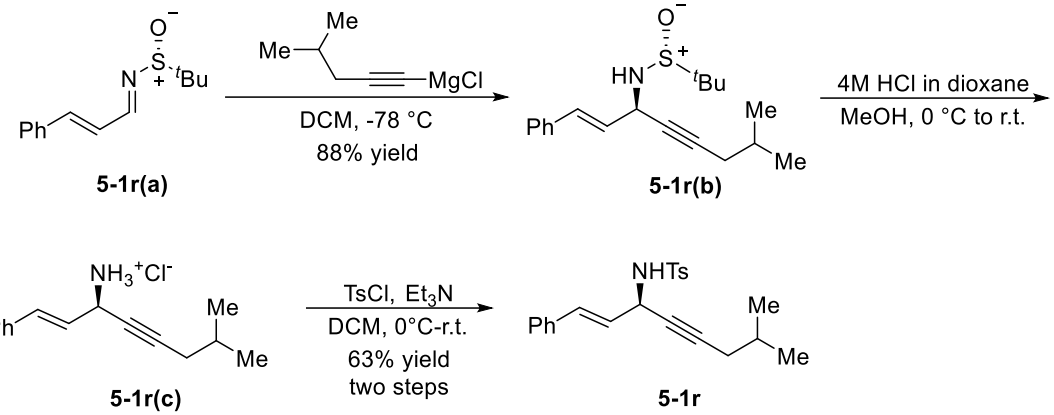
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.4 Hz, 1H), 7.78 – 7.71 (m, 5H), 7.57 (s, 1H), 7.33 – 7.29 (m, 1H), 7.25 – 7.20 (m, 5H), 5.53 – 5.47 (m, 1H), 4.65 (d, *J* = 9.1 Hz, 1H), 2.41 (s, 3H), 2.35 (s, 3H), 1.89 – 1.84 (m, 2H), 1.56 (non, *J* = 6.6 Hz, 1H), 0.84 (d, *J* = 6.7 Hz, 6H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 145.1, 143.4, 137.2, 135.4, 135.0, 129.9, 129.4, 128.0, 127.4, 126.8, 125.03, 124.95, 123.4, 120.5, 120.0, 113.4, 85.4, 76.5, 42.6, 27.67, 27.62, 21.91, 21.89, 21.54, 21.47. **HRMS (ESI)** *m/z:* $[M+Na]^+$ calcd for $C_{29}H_{30}N_2O_4S_2Na$ 557.1545; Found *m/z* 557.1559.

(*R*,*E*)-4-Methyl-*N*-(7-methyl-1-phenyloct-1-en-4-yn-3-yl)benzenesulfonamide (5-1r)



5-1r

Compound **5-1r** was synthesized according to General Procedure A.



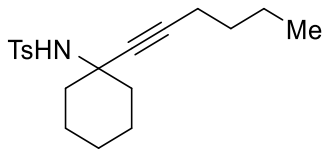
To a solution of 4-methyl-1-pentyne (1.94 mL, 16.5 mmol, 3.3 equiv.) in THF (2.5 mL) at 0 ℃, 2M *iPr*MgCl in THF (7.5 mL, 15 mmol, 3.0 equiv.) was added slowly. The resulting solution was allowed to warm to room temperature and stirred for 60 min to afford the 4-methyl-1-pentynyl magnesium chloride solution.

The freshly prepared 4-methyl-1-pentynyl magnesium chloride solution was slowly added into a solution of *N*-sulfinyl imine **5-1r(a)** (1.1767 g, 5.0 mmol, 1.0 equiv.) in CH_2Cl_2 (20 mL) via cannula at -78 ℃ under argon protection. The resulting solution was stirred at -78 ˚C for 2 h, then gradually warmed to room temperature and stirred overnight. The reaction was quenched by saturated NH_4Cl solution, followed by extraction with EtOAc three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and the combined organic layer was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 3/1) to afford **5-1r(b)** (1.4027 g, 4.42 mmol, 88% yield) as a colorless oil.

4M HCl solution in dioxane (17.6 mmol, 4.4 mL, 4.0 equiv.) was added into a solution of **5-1r(b)** (1.4027 g, 4.42 mmol) in MeOH (22 mL). The reaction mixture was stirred at room temperature for 30 min. The solvent was removed under reduced pressure to afford crude product **5-1r(b)**, which was directly used in the next step without further purification. Crude product **5-1r(c)** was dissolved in 20 mL CH_2Cl_2 at 0 ℃, followed by the addition of Et_3N (3.1 mL, 22.1 mmol, 5 equiv.) and TsCl (885 mg, 5.30 mmol, 1.2 equiv.). The resulting mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with *saturated* NH_4Cl solution and extracted by CH_2Cl_2 three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 8/1) to afford a light-yellow solid. The product was further purified by recrystallization from hexane to afford **5-1r** (842.7 mg, 2.77 mmol, 63% yield) as a white needle.

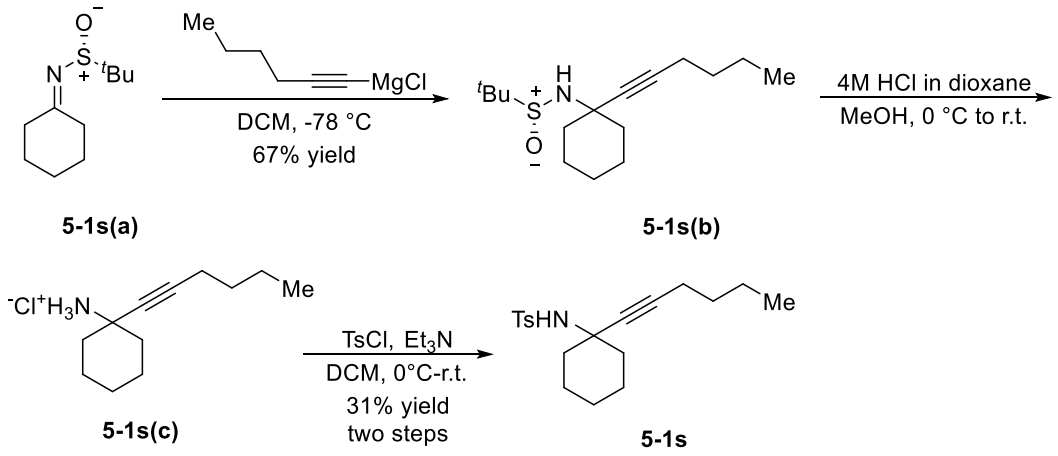
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.3 Hz, 2H), 7.31 – 7.17 (m, 7H), 6.69 (dd, *J* = 15.7, 1.7 Hz, 1H), 6.04 (dd, *J* = 15.7, 5.3 Hz, 1H), 4.90 – 4.83 (m, 1H), 4.64 (d, *J* = 8.8 Hz, 1H), 2.37 (s, 3H), 1.86 (dd, *J* = 6.9, 2.1 Hz, 2H), 1.60 (non, *J* = 6.7 Hz, 1H), 0.84 (d, *J* = 6.7 Hz, 4H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 143.4, 137.6, 135.8, 132.4, 129.5, 128.5, 128.1, 127.4, 126.7, 126.0, 86.4, 76.5, 47.6, 27.71, 27.69, 21.9, 21.5. **HRMS (ESI)** *m/z:* $[M+Na]^+$ calcd for $C_{22}H_{25}NO_2SNa$ 390.1504; Found *m/z* 390.1503.

***N*-(1-(hex-1-yn-1-yl)cyclohexyl)-4-Methylbenzenesulfonamide (5-1s)**



5-1s

Compound **5-1s** was synthesized according to General Procedure A.



To a solution of 1-hexyne (0.61 mL, 5.28 mmol, 2.2 equiv.) in THF (1.0 mL) at 0 ℃, 2M *iPr*MgCl in THF (2.4 mL, 4.8 mmol, 2.0 equiv.) was added slowly. The resulting solution was allowed to warm to room temperature and stirred for 60 min to afford the 1-hexynyl magnesium chloride solution.

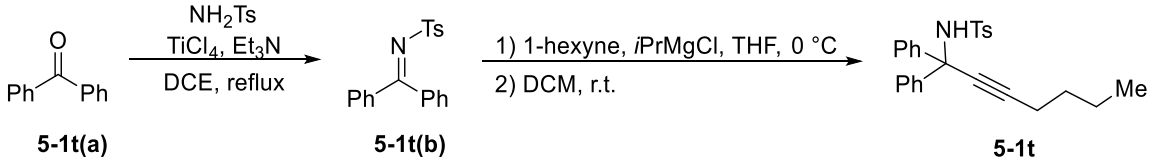
The freshly prepared 1-hexynyl magnesium chloride solution was slowly added into a solution of *N*-sulfinyl imine **5-1s(a)** (483.2 mg, 2.4 mmol, 1.0 equiv.) in CH_2Cl_2 (10 mL) via cannula at -78 ℃ under argon protection. The resulting solution was stirred at -78 ˚C for 2 h, then gradually warmed to room temperature and stirred overnight. The reaction was quenched by saturated NH_4Cl solution, followed by extraction with EtOAc three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and the combined organic layer was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 3/1) to afford **5-1s(b)** (453.6 mg, 1.60 mmol, 67% yield) as a colorless oil.

4M HCl solution in dioxane (6.4 mmol, 1.6 mL, 4.0 equiv.) was added into a solution of **5-1s(b)** (453.6 mg, 1.6 mmol) in MeOH (8 mL). The reaction mixture was stirred at room temperature for 30 min. The solvent was removed under reduced pressure to afford

crude product **5-1s(c)**, which was directly used in the next step without further purification. Crude product **5-1s(c)** was dissolved in 10 mL CH_2Cl_2 at 0 ℃, followed by the addition of Et_3N (1.1 mL, 8 mmol, 5 equiv.) and TsCl (336.0 mg, 1.92 mmol, 1.2 equiv.). The resulting mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with *saturated* NH_4Cl solution and extracted by CH_2Cl_2 three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 20/1 – hexane/EtOAc = 10/1) to afford **5-1s** (168.3 mg, 0.50 mmol, 31% yield) as a light-yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 4.80 (s, 1H), 2.40 (s, 3H), 2.02 – 1.89 (m, 2H), 1.81 (t, *J* = 6.9 Hz, 2H), 1.67 – 1.56 (m, 4H), 1.56 – 1.48 (m, 3H), 1.28 – 1.13 (m, 5H), 0.84 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 142.6, 139.5, 129.0, 127.6, 86.5, 79.8, 54.7, 39.3, 30.5, 25.0, 22.54, 21.9, 21.4, 18.2, 13.5. **HRMS (ESI)** *m/z:* $[M+Na]^+$ calcd for $C_{19}H_{27}NO_2SNa$ 356.1660; Found *m/z* 356.1659.

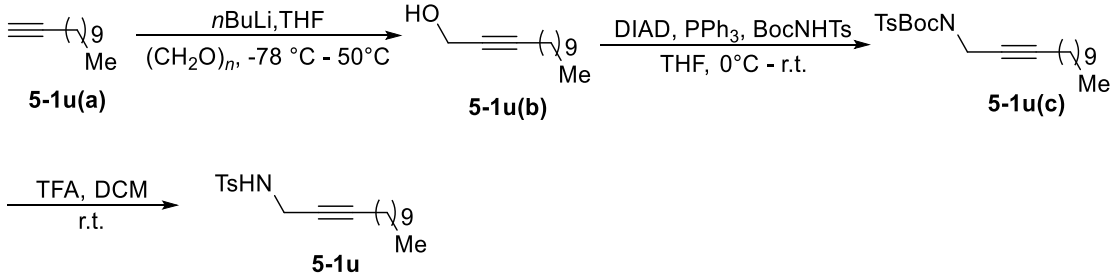
***N*-(1,1-diphenylhept-2-yn-1-yl)-4-Methylbenzenesulfonamide (5-1t)**



Compound **5-1t** was synthesized according to a literature procedure.[19] White solid, 52% yield (two steps overall). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.63 (d, *J* = 8.0 Hz, 2H), 7.56 – 7.44 (m, 4H), 7.34 – 7.15 (m, 8H), 5.35 (s, 1H), 2.42 (s, 3H), 2.05 (t, *J* = 6.8 Hz, 2H), 1.43 – 1.27 (m, 4H), 0.88 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 143.1, 142.6, 139.1, 128.9, 128.1, 127.7, 127.4, 127.0, 90.0, 79.2, 63.1, 30.3, 22.0, 21.4, 18.5,

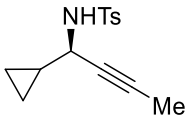
13.6. **HRMS (ESI)** *m/z:* $[M+Na]^+$ calcd for $C_{26}H_{27}NO_2SNa$ 417.1762; Found *m/z* 417.1755.

4-Methyl-N-(tridec-2-yn-1-yl)benzenesulfonamide (5-1u)



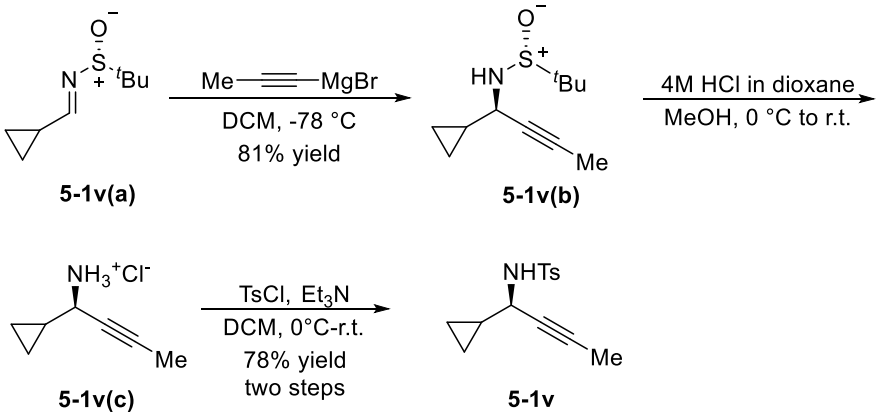
Compound **5-1u** was synthesized according to a literature procedure.[20] White solid, 65% yield (three steps overall). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 7.8 Hz, 2H), 4.52 (t, *J* = 6.0 Hz, 1H), 3.80 (dt, *J* = 6.0, 2.3 Hz, 2H), 2.42 (s, 3H), 1.94 (tt, *J* = 7.1, 2.2 Hz, 2H), 1.35 – 1.16 (m, 16H), 0.88 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 143.5, 136.9, 129.6, 127.4, 85.6, 74.0, 33.5, 31.9, 29.6, 29.5, 29.3, 29.1, 28.8, 28.3, 22.7, 21.5, 18.5, 14.1. **HRMS (ESI)** *m/z:* $[M+Na]^+$ calcd for $C_{20}H_{31}NO_2SNa$ 372.1973; Found *m/z* 372.1958.

(*R*)-*N*-(1-cyclopropylbut-2-yn-1-yl)-4-Methylbenzenesulfonamide (5-1v)



5-1v

Compound **5-1v** was synthesized according to General Procedure A.



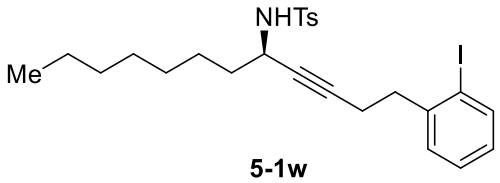
The 1-propynylmagnesium bromide solution (20 mL, 10 mmol, 0.5 M in THF) was slowly added into a solution of *N*-sulfinyl imine **5-1v(a)** (866.3 g, 5.0 mmol, 1.0 equiv.) in CH_2Cl_2 (25 mL) via cannula at -78 ℃ under argon protection. The resulting solution was stirred at -78 ˚C for 2 h, then gradually warmed to room temperature and stirred overnight. The reaction was quenched by saturated NH_4Cl solution, followed by extraction with EtOAc three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and the combined organic layer was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 3/1) to afford **5-1v(b)** (868.2 mg, 4.07 mmol, 81% yield) as a colorless oil (diastereomers are inseparable using the column chromatography, causing relatively low *ee* value for **5-1v**).

4M HCl solution in dioxane (16.0 mmol, 4.0 mL, 4.0 equiv.) was added into a solution of **5-1v(b)** (868.2 g, 4.07 mmol) in MeOH (20 mL). The reaction mixture was stirred at room temperature for 30 min. The solvent was removed under reduced pressure to afford crude product **5-1v(c)**, which was directly used in the next step without further purification. Crude product **5-1v(c)** was dissolved in 20 mL CH_2Cl_2 at 0 ℃, followed by the addition of Et_3N (2.81 mL, 20.3 mmol, 5 equiv.) and TsCl (931 mg, 4.88 mmol, 1.2 equiv.). The resulting mixture was allowed to warm to room temperature and stirred overnight. The

reaction was quenched with *saturated* NH_4Cl solution and extracted by CH_2Cl_2 three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 5/1) to afford a light-yellow solid. The product was further purified by recrystallization from hexane to afford **5-1v** (838.7 mg, 3.19 mmol, 78% yield) as a white needle.

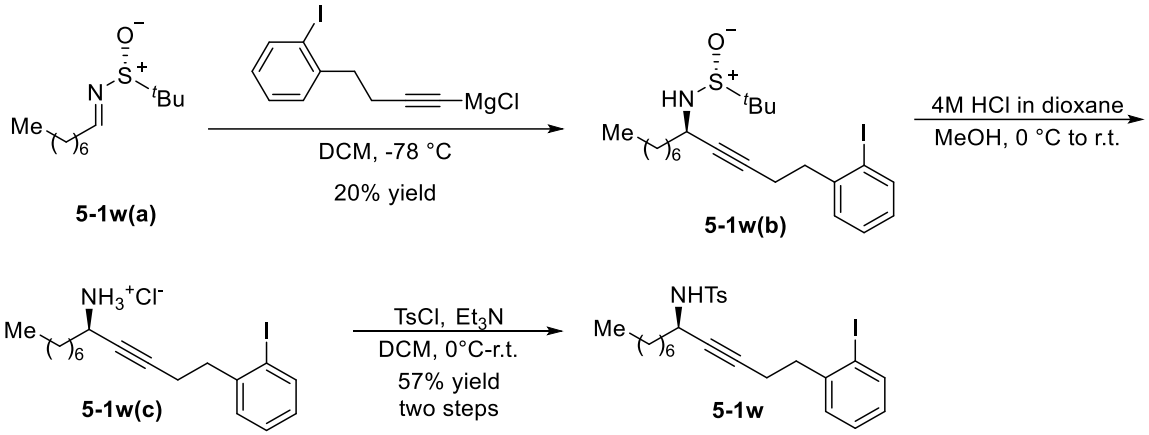
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 4.70 (d, *J* = 8.8 Hz, 1H), 4.04 (ddq, *J* = 8.3, 6.3, 2.2 Hz, 1H), 2.41 (s, 3H), 1.50 (d, *J* = 2.3 Hz, 3H), 1.11 – 1.05 (m, 1H), 0.46 – 0.40 (m, 2H), 0.40 – 0.34 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 143.2, 137.6, 129.3, 127.4, 81.0, 74.5, 49.1, 21.5, 15.7, 3.2, 3.0, 1.6. **HRMS (ESI)** *m/z:* $[M+Na]^+$ calcd for $C_{14}H_{17}NO_2SNa$ 286.0878; Found *m/z* 286.0878. **90% *ee***; HPLC(IC, Hexane/iPrOH = 90/10, flow rate = 1.0 mL/min, λ = 200 nm) t_R= 32.15 min (major), t_R= 29.18 min (minor)]

(*R*)-4-Methyl-*N*-(1-phenyldodec-3-yn-5-yl)benzenesulfonamide (5-1w)



5-1w

Compound **5-1w** was synthesized according to General Procedure A.



To a solution of 4-(2-iodo-1-phenyl)-1-butyne (5.63 g, 22 mmol, 2.2 equiv.) in THF (3.0 mL) at 0 ℃, 2M *iPr*MgCl in THF (10.0 mL, 20 mmol, 2.0 equiv.) was added slowly. The resulting solution was allowed to warm to room temperature and stirred for 60 min to afford the 4-(2-iodo-1-phenyl)-1-butynyl magnesium chloride solution.

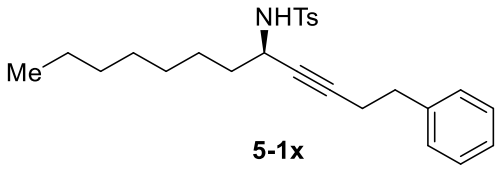
The freshly prepared 4-(2-iodo-1-phenyl)-1-butynyl magnesium chloride solution was slowly added into a solution of *N*-sulfinyl imine **5-1w(a)** (2.31 g, 10 mmol, 1.0 equiv.) in CH_2Cl_2 (50 mL) via cannula at -78 ℃ under argon protection. The resulting solution was stirred at -78 ˚C for 2 h, then gradually warmed to room temperature and stirred overnight. The reaction was quenched by saturated NH_4Cl solution, followed by extraction with EtOAc three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and the combined organic layer was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 3/1–2/1) to afford **5-1w(b)** (996.5 mg, 2.04 mmol, 20% yield) as a colorless oil.

2M HCl solution in Et_2O (8 mmol, 4.0 mL, 4.0 equiv.) was added into a solution of **5-1w(b)** (996.5 mg, 2.04 mmol) in MeOH (10 mL). The reaction mixture was stirred at room temperature for 30 min. The solvent was removed under reduced pressure to afford crude product **5-1w(c)**, which was directly used in the next step without further purification.

Crude product **5-1w(c)** was dissolved in 10 mL CH_2Cl_2 at 0 ℃, followed by the addition of Et_3N (1.42 mL, 10.0 mmol, 5 equiv.) and TsCl (467 mg, 2.44 mmol, 1.0 equiv.). The resulting mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with *saturated* NH_4Cl solution and extracted by CH_2Cl_2 three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 10/1) to afford a light-yellow solid. The product was further purified by recrystallization from hexane to afford **5-1w** (631.7 mg, 1.18 mmol, 58% yield) as a white needle.

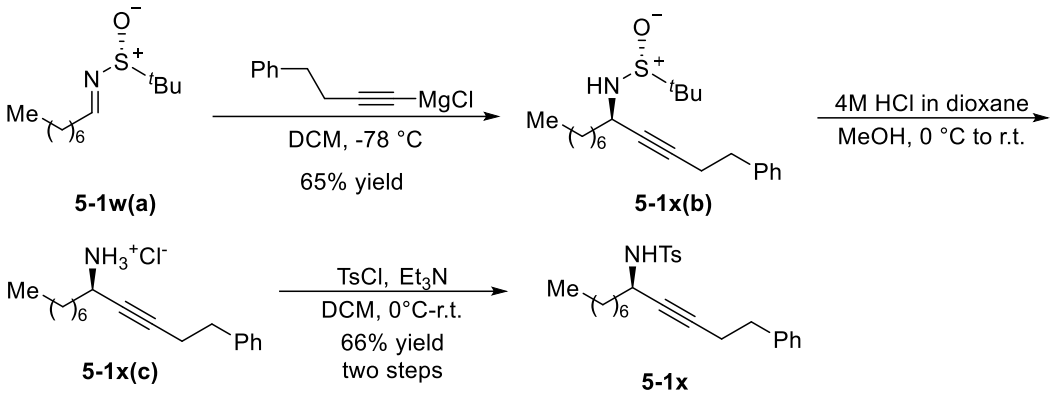
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.26 (ddt, *J* = 5.2, 3.6, 2.1 Hz, 3H), 7.12 (dd, *J* = 7.6, 1.7 Hz, 1H), 6.91 (td, *J* = 7.6, 1.7 Hz, 1H), 4.45 (d, *J* = 9.1 Hz, 1H), 4.00 (dtt, *J* = 9.0, 6.8, 2.1 Hz, 1H), 2.67 (t, *J* = 7.4 Hz, 2H), 2.41 (s, 3H), 2.19 (tt, *J* = 7.5, 2.1 Hz, 2H), 1.63 – 1.54 (m, 2H), 1.41 – 1.14 (m, 10H), 0.88 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 143.2, 142.7, 139.5, 137.5, 129.8, 129.4, 128.3, 128.2, 127.4, 100.3, 83.4, 79.4, 46.0, 39.4, 36.9, 31.7, 29.1, 28.9, 25.3, 22.6, 21.6, 19.0, 14.1. **HRMS (ESI)** *m/z:* $[M+Na]^+$ calcd for $C_{25}H_{32}INO_2SNa$ 560.1096; Found *m/z* 560.1080.

(*R*)-4-Methyl-*N*-(1-phenyldodec-3-yn-5-yl)benzenesulfonamide (5-1x)



5-1x

Compound **5-1x** was synthesized according to General Procedure A.



To a solution of 4-phenyl-1-butyne (3.1 mL, 22 mmol, 2.2 equiv.) in THF (3.0 mL) at 0 ℃, 2M *iPr*MgCl in THF (10.0 mL, 20 mmol, 2.0 equiv.) was added slowly. The resulting solution was allowed to warm to room temperature and stirred for 60 min to afford the 4-phenyl-1-butynyl magnesium chloride solution.

The freshly prepared 4-phenyl-1-butynyl magnesium chloride solution was slowly added into a solution of *N*-sulfinyl imine **5-1w(a)** (2.31 g, 10 mmol, 1.0 equiv.) in CH_2Cl_2 (50 mL) via cannula at -78 ℃ under argon protection. The resulting solution was stirred at -78 ˚C for 2 h, then gradually warmed to room temperature and stirred overnight. The reaction was quenched by saturated NH_4Cl solution, followed by extraction with EtOAc three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and the combined organic layer was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 3/1–2/1) to afford **5-1x(b)** (2.36 g, 6.53 mmol, 65% yield) as a colorless oil.

4M HCl solution in dioxane (26.0 mmol, 6.5 mL, 4.0 equiv.) was added into a solution of **5-1x(b)** (2.36 g, 6.53 mmol) in MeOH (30 mL). The reaction mixture was stirred at room temperature for 30 min. The solvent was removed under reduced pressure to afford crude product **5-1x(c)**, which was directly used in the next step without further purification. Crude product **5-1x(c)** was dissolved in 32 mL CH_2Cl_2 at 0 ℃, followed by the addition of

Et_3N (4.56 mL, 32.7 mmol, 5 equiv.) and TsCl (1.24 g, 6.5 mmol, 1.0 equiv.). The resulting mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with *saturated* NH_4Cl solution and extracted by CH_2Cl_2 three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 7/1) to afford a light-yellow solid. The product was further purified by recrystallization from hexane to afford **5-1x** (1.76 g, 4.28 mmol, 66% yield) as a white needle.

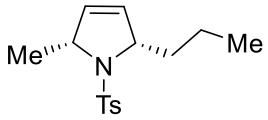
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.0 Hz, 2H), 7.31 – 7.23 (m, 4H), 7.23 – 7.17 (m, 1H), 7.09 (d, *J* = 7.4 Hz, 2H), 4.55 (d, *J* = 9.0 Hz, 1H), 4.00 (dt, *J* = 9.0, 6.6 Hz, 1H), 2.55 (t, *J* = 7.5 Hz, 2H), 2.40 (s, 3H), 2.17 (tt, *J* = 7.6, 2.0 Hz, 2H), 1.65 – 1.51 (m, 2H), 1.42 – 1.12 (m, 10H), 0.88 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 143.1, 140.4, 137.6, 129.3, 128.30, 128.28, 127.4, 126.3, 84.1, 79.1, 46.0, 36.9, 34.7, 31.7, 29.0, 28.9, 25.3, 22.6, 21.5, 20.5, 14.0. **HRMS (ESI)** *m/z:* $[M+Na]^+$ calcd for $C_{25}H_{33}NO_2SNa$ 434.2130; Found *m/z* 434.2129.

Synthesis of Compound 5-2

General Procedure B:

To a 1-dram vial were added sequentially 0.2 mmol sulfonamide **5-1**, 5 mol % (*S*)-**L2-13**AuCl (9.2 mg), 10 mol% $NaBAr^F_4$ (17.6 mg) and 0.4 mL dry toluene. The reaction was stirred at the indicated temperature using a heating block and monitored by TLC. Upon completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography to afford the desired product.

(2*R*,5*S*)-2-Methyl-5-propyl-1-tosyl-2,5-dihydro-1H-pyrrole (*cis*-5-2a)

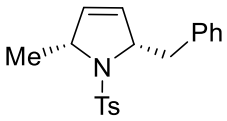


cis-**5-2a**

Following the general procedure B, **5-1a** (0.2 mmol, 56.7 mg), 5 mol % **(*S*)-L2-13**AuCl (9.2 mg), 10 mol% $NaBAr^F_4$ (17.6 mg) and 0.4 mL dry toluene were stirred at 110 ℃ for 14 h. The solvent was removed, and the residue was purified by flash column chromatography (hexane/EtOAc = 15: 1) to afford *cis*-**5-2a** as a white solid (52.7 mg, 93% yield, *d.r.* = 97/3). Crystal was obtained via slow evaporation of a solution of *cis*-**5-2a** in DCM/hexane (1/1) at room temperature.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 5.52 (dt, *J* = 6.2, 1.7 Hz, 1H), 5.49 (dt, *J* = 6.2, 1.8 Hz, 1H), 4.43 – 4.38 (m, 1H), 4.38 – 4.33 (m, 1H), 2.40 (s, 3H), 1.86 – 1.75 (m, 1H), 1.71 – 1.59 (m, 1H), 1.50 – 1.39 (m, 1H), 1.38 (d, *J* = 6.4 Hz, 3H), 1.37 – 1.23 (m, 1H), 0.94 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 143.2, 134.8, 130.3, 129.5, 128.3, 127.4, 67.8, 63.5, 39.7, 23.6, 21.4, 18.3, 14.0. These data are consistent with the literature. [21]

(2*S*,5*R*)-2-Benzyl-5-methyl-1-tosyl-2,5-dihydro-1H-pyrrole (*cis*-5-2b)



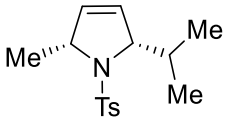
cis-**5-2b**

Following the general procedure B, **5-1b** (0.2 mmol, 65.2 mg), 5 mol % **(*S*)-L2-13**AuCl (9.2 mg), 10 mol% $NaBAr^F_4$ (17.6 mg) and 0.4 mL dry toluene were stirred at 110 ℃ for 20 h. The solvent was removed, and the residue was purified by flash column

chromatography (hexane/EtOAc = 15: 1) to afford *cis*-**5-2b** as a white solid (62.5 mg, 96% yield, *d.r.* = 96/4).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.33 – 7.27 (m, 4H), 7.25 – 7.19 (m, 3H), 5.47 – 5.38 (m, 2H), 4.61 – 4.55 (m, 1H), 4.38 – 4.32 (m, 1H), 3.25 (dd, *J* = 13.2, 3.3 Hz, 1H), 2.94 (dd, *J* = 13.1, 8.5 Hz, 1H), 2.41 (s, 3H), 1.04 (d, *J* = 6.5 Hz, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 143.3, 137.1, 134.7, 130.9, 130.2, 129.6, 128.0, 127.5, 127.4, 126.4, 69.0, 63.8, 43.9, 23.2, 21.4. **HRMS (ESI)** *m/z:* $[M+Na]^+$ calcd for $C_{19}H_{21}NO_2SNa$ 350.1191; Found *m/z* 350.1184.

(2*S*,5*R*)-2-Isopropyl-5-methyl-1-tosyl-2,5-dihydro-1H-pyrrole (*cis*-5-2c)

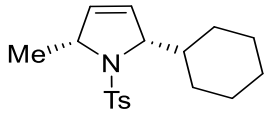


cis-**5-2c**

Following the general procedure B, **5-1c** (0.2 mmol, 55.9 mg), 5 mol % **(*S*)-L2-13**AuCl (9.2 mg), 10 mol% $NaBAr^F_4$ (17.6 mg) and 0.4 mL dry toluene were stirred at 110 ℃ for 32 h. The solvent was removed, and the residue was purified by flash column chromatography (hexane/EtOAc = 15: 1) to afford *cis*-**5-2c** as a white solid (48.5 mg, 87% yield, *d.r.* = 98/2).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 5.51 (dt, *J* = 6.2, 1.8 Hz, 1H), 5.46 (dt, *J* = 6.3, 1.7 Hz, 1H), 4.41 – 4.35 (m, 1H), 4.29 – 4.25 (m, 1H), 2.40 (s, 3H), 2.21 – 2.11 (m, 1H), 1.38 (d, *J* = 6.5 Hz, 3H), 0.96 (d, *J* = 7.1 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 143.2, 134.6, 131.2, 129.6, 127.5, 124.9, 73.6, 63.8, 32.6, 22.9, 21.4, 19.6, 16.6. **HRMS (ESI)** *m/z:* $[M+Na]^+$ calcd for $C_{15}H_{21}NO_2SNa$ 302.1191; Found *m/z* 302.1194.

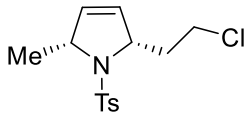
(2*S*,5*R*)-2-Cyclohexyl-5-methyl-1-tosyl-2,5-dihydro-1H-pyrrole (*cis*-5-2d)



cis-**5-2d**

Following the general procedure B, **5-1d** (0.2 mmol, 63.9 mg), 5 mol % **(*S*)-L2-13**AuCl (9.2 mg), 10 mol% $NaBAr^F_4$ (17.6 mg) and 0.4 mL dry toluene were stirred at 110 ℃ for 20 h. The solvent was removed, and the residue was purified by flash column chromatography (hexane/EtOAc = 15: 1) to afford *cis*-**5-2d** as a white solid (58.6 mg, 93% yield, *d.r.* = 98/2). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.68 (d, *J* = 8.2 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 5.53 – 5.41 (m, 2H), 4.42 – 4.34 (m, 1H), 4.28 – 4.23 (m, 1H), 2.39 (s, 3H), 1.85 – 1.72 (m, 5H), 1.70 – 1.63 (m, 1H), 1.36 (d, *J* = 6.5 Hz, 3H), 1.32 – 1.19 (m, 2H), 1.07 (qt, *J* = 13.0, 3.6 Hz, 1H), 0.97 (qd, *J* = 13.1, 3.8 Hz, 1H), 0.80 (qd, *J* = 12.7, 3.4 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 143.2, 134.4, 130.7, 129.5, 127.5, 125.8, 73.0, 63.5, 42.6, 30.3, 27.4, 26.5, 26.4, 25.9, 22.8, 21.5. **HRMS (ESI)** *m/z:* $[M+Na]^+$ calcd for $C_{18}H_{25}NO_2SNa$ 342.1504; Found *m/z* 350.1513.

(2*S*,5*R*)-2-(2-chloroethyl)-5-Methyl-1-tosyl-2,5-dihydro-1H-pyrrole (*cis*-5-2e)

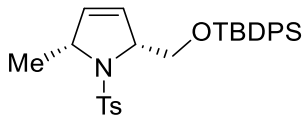


cis-**5-2e**

Following the general procedure B, **5-1e** (0.2 mmol, 60.0 mg), 5 mol % **(*S*)-L2-13**AuCl (9.2 mg), 10 mol% $NaBAr^F_4$ (17.6 mg) and 0.4 mL dry toluene were stirred at 110 ℃ for 40 h. The solvent was removed, and the residue was purified by flash column chromatography (hexane/EtOAc = 15: 1 to hexane/EtOAc = 10/1) to afford *cis*-**5-2e** as a white solid (31.8 mg, 53% yield, 88% yield based on recovery S.M., *d.r.* = 98/2) and recovery starting material **5-1e** (23.7mg). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.70 (d, *J* = 8.2

Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 5.58 – 5.49 (m, 2H), 4.54 – 4.47 (m, 1H), 4.45 – 4.37 (m, 1H), 3.76 (dt, *J* = 11.0, 6.9 Hz, 1H), 3.61 (dt, *J* = 11.0, 7.1 Hz, 1H), 2.41 (s, 3H), 2.24 – 2.12 (m, 2H), 1.39 (d, *J* = 6.5 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 143.6, 134.1, 131.2, 129.7, 127.52, 127.50, 65.6, 63.8, 41.2, 40.1, 23.8, 21.5. **HRMS (ESI)** *m/z:* $[M+Na]^+$ calcd for $C_{14}H_{18}ClNO_2SNa$ 322.0645; Found *m/z* 322.0648.

(2*R*,5*R*)-2-(((tert-butyldiphenylsilyl)oxy)methyl)-5-Methyl-1-tosyl-2,5-dihydro-1H-pyrrole (*cis*-5-2f)

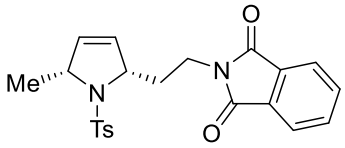


cis-**5-2f**

Following the general procedure B, **5-1f** (0.2 mmol, 60.0 mg), 5 mol % **(*S*)-L2-13**AuCl (9.2 mg), 10 mol% $NaBAr^F_4$ (17.6 mg) and 0.4 mL dry toluene were stirred at 110 ℃ for 60 h. The solvent was removed, and the residue was purified by flash column chromatography (hexane/EtOAc = 10: 1) to afford *cis*-**5-2f** as a white solid (76.5 mg, 75% yield, *d.r.* = 94 / 6).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 – 7.58 (m, 6H), 7.48 – 7.37 (m, 6H), 7.29 – 7.23 (m, 2H), 5.75 – 5.70 (m, 1H), 5.62 – 5.53 (m, 1H), 4.46 – 4.40 (m, 1H), 4.38 – 4.33 (m, 1H), 4.06 (dd, *J* = 9.9, 4.1 Hz, 1H), 3.68 (dd, *J* = 9.9, 7.6 Hz, 1H), 2.40 (s, 3H), 1.37 (d, *J* = 6.5 Hz, 3H), 1.08 (s, 9H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 143.3, 135.62, 135.58, 134.5, 133.4, 133.2, 131.4, 129.7, 129.63, 129.59, 127.7, 127.6, 127.4, 127.1, 68.4, 68.2, 63.9, 26.9, 23.7, 21.5, 19.2. **HRMS (ESI)** *m/z:* $[M+Na]^+$ calcd for $C_{29}H_{35}NO_3SSiNa$ 528.2004; Found *m/z* 528.1990.

2-(2-((2*S*,5*R*)-5-methyl-1-tosyl-2,5-dihydro-1H-pyrrol-2-yl)ethyl)Isoindoline-1,3-dione (*cis*-5-2g)

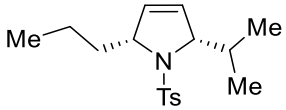


cis-**5-2g**

Following the general procedure B, **5-1g** (0.15 mmol, 61.6 mg), 5 mol % **(*S*)-L2-13**AuCl (6.6 mg), 10 mol% $NaBAr^F_4$ (13.2 mg) and 0.3 mL dry toluene were stirred at 110 ℃ for 24 h. The solvent was removed, and the residue was purified by flash column chromatography (hexane/EtOAc = 4:1) to afford *cis*-**5-2g** as a white solid (49.6 mg, 81% yield, *d.r.* = 96 / 4).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 – 7.82 (m, 2H), 7.74 – 7.70 (m, 2H), 7.70 – 7.65 (m, 2H), 7.28 – 7.23 (m, 3H), 5.61 (dt, *J* = 6.3, 1.9 Hz, 1H), 5.56 (dt, *J* = 6.1, 1.9 Hz, 1H), 4.49 – 4.41 (m, 2H), 3.87 – 3.77 (m, 2H), 2.40 (s, 3H), 2.20 – 2.13 (m, 1H), 2.07 – 1.98 (m, 1H), 1.39 (d, *J* = 6.5 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 168.2, 143.4, 134.6, 133.9, 132.1, 131.4, 129.6, 127.6, 127.5, 123.2, 65.8, 63.7, 36.0, 34.8, 23.6, 21.5. **HRMS (ESI)** *m/z:* $[M+Na]^+$ calcd for $C_{22}H_{22}N_2O_4SNa$ 433.1198; Found *m/z* 433.1187.

(2*S*,5*R*)-2-Isopropyl-5-propyl-1-tosyl-2,5-dihydro-1H-pyrrole (*cis*-5-2h)

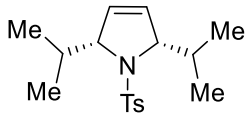


cis-**5-2h**

Following the general procedure B, **5-1h** (0.2 mmol, 62.0 mg), 5 mol % **(*S*)-L2-13**AuCl (9.2 mg), 10 mol% $NaBAr^F_4$ (17.6 mg) and 0.4 mL dry toluene were stirred at 110 ℃ for 42 h. The solvent was removed, and the residue was purified by flash column chromatography (hexane/EtOAc = 15:1) to afford *cis*-**5-2h** as a white solid (51.0 mg, 83% yield, *d.r.* > 50/1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.1 Hz, 2H), 7.27 (d, *J* = 8.1 Hz, 2H), 5.64 – 5.59 (m, 1H), 5.52 – 5.48 (m, 1H), 4.24 – 4.19 (m, 2H), 2.39 (s, 3H), 2.12 – 2.02 (m, 1H), 1.96 – 1.88 (m, 1H), 1.56 – 1.46 (m, 1H), 1.44 – 1.34 (m, 2H), 0.98 (d, *J* = 7.0 Hz, 3H), 0.94 (t, *J* = 7.3 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 143.2, 134.6, 129.6, 129.5, 127.6, 125.9, 73.5, 68.1, 39.9, 33.2, 21.4, 19.8, 19.4, 17.0, 14.0. **HRMS (ESI)** *m/z:* $[M+Na]^+$ calcd for $C_{17}H_{25}NO_2SNa$ 330.1504; Found *m/z* 330.1497.

(2*R*,5*S*)-2,5-Diisopropyl-1-tosyl-2,5-dihydro-1H-pyrrole (*cis*-5-2i)

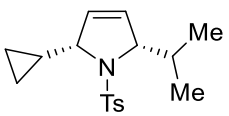


cis-**5-2i**

Following the general procedure B, **5-1i** (0.2 mmol, 62.2 mg), 5 mol % **(*S*)-L2-13**AuCl (9.2 mg), 10 mol% $NaBAr^F_4$ (17.6 mg) and 0.4 mL dry toluene were stirred at 110 ℃ for 48 h. The solvent was removed, and the residue was purified by flash column chromatography (hexane/EtOAc = 15:1) to afford *cis*-**5-2i** as a white solid (56.3 mg, 90% yield, *d.r.* > 50/1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 7.9 Hz, 2H), 5.60 – 5.58 (m, 2H), 4.06 – 4.04 (m, 1H), 4.04 – 4.03 (m, 1H), 2.39 (s, 3H), 1.87 (oct, *J* = 6.9 Hz, 2H), 1.07 (d, *J* = 7.0 Hz, 6H), 0.90 (d, *J* = 6.8 Hz, 6H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 143.2, 134.4, 129.4, 128.0, 127.9, 74.0, 34.3, 21.5, 20.5, 18.4. **HRMS (ESI)** *m/z:* $[M+Na]^+$ calcd for $C_{17}H_{25}NO_2SNa$ 330.1504; Found *m/z* 330.1511.

(2*R*,5*S*)-2-Cyclopropyl-5-isopropyl-1-tosyl-2,5-dihydro-1H-pyrrole (*cis*-5-2j)

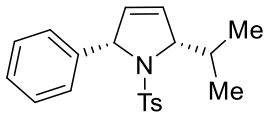


cis-**5-2j**

Following the general procedure B, **5-1j** (0.2 mmol, 61.1 mg), 5 mol % **(*S*)-L2-13**AuCl (9.2 mg), 10 mol% $NaBAr^F_4$ (17.6 mg) and 0.4 mL dry toluene were stirred at 110 ℃ for 24 h. The solvent was removed, and the residue was purified by flash column chromatography (hexane/EtOAc = 15:1) to afford *cis*-**5-2j** as a white solid (56.3 mg, 91% yield, *d.r.* > 50/1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 2H), 5.54 (dt, *J* = 6.4, 1.9 Hz, 1H), 5.51 (dt, *J* = 6.3, 2.0 Hz, 1H), 4.29 (dq, *J* = 5.4, 1.9 Hz, 1H), 3.82 (dq, *J* = 7.9, 1.9 Hz, 1H), 2.39 (s, 3H), 2.17 – 2.06 (m, 1H), 1.08 – 1.00 (m, 1H), 0.99 (d, *J* = 7.0 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.65 – 0.58 (m, 1H), 0.60 – 0.53 (m, 1H), 0.53 – 0.45 (m, 1H), 0.29 – 0.20 (m, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 143.1, 135.1, 129.5, 129.0, 127.5, 126.3, 73.8, 72.2, 33.1, 21.5, 19.8, 17.0, 16.8, 4.3, 2.6. **HRMS (ESI)** *m/z:* $[M+Na]^+$ calcd for $C_{17}H_{23}NO_2SNa$ 328.1347; Found *m/z* 328.1337.

(2*S*,5*S*)-2-Isopropyl-5-phenyl-1-tosyl-2,5-dihydro-1H-pyrrole (*cis*-5-2l)



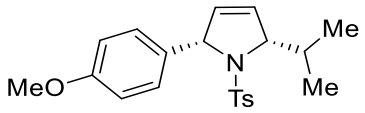
cis-**5-2l**

Following the general procedure B, **5-1l** (0.2 mmol, 68.3 mg), 5 mol % **(*S*)-L2-13**AuCl (9.2 mg), 10 mol% $NaBAr^F_4$ (17.6 mg) and 0.4 mL dry toluene were stirred at 110 ℃ for 24 h. The solvent was removed, and the residue was purified by flash column chromatography (hexane/EtOAc = 10:1) to afford *cis*-**5-2l** as a yellow oil (50.6 mg, 75% yield, *d.r.* > 50/1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.2 Hz, 2H), 7.44 (d, *J* = 8.6 Hz, 1H), 7.35 – 7.29 (m, 2H), 7.29 – 7.22 (m, 3H), 5.75 – 5.69 (m, 2H), 5.52 – 5.48 (m, 1H), 4.42 – 4.37 (m, 1H), 2.39 (s, 3H), 2.13 – 2.03 (m, 1H), 1.02 (d, *J* = 7.0 Hz, 3H), 0.83 (d, *J* = 6.8 Hz,

3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 143.4, 140.6, 134.9, 129.5, 129.3, 128.2, 127.7, 127.52, 127.51, 127.1, 73.9, 70.3, 33.0, 21.5, 20.2, 17.5. **HRMS (ESI)** *m/z:* $[M+Na]^+$ calcd for $C_{20}H_{23}NO_2SNa$ 364.1347; Found *m/z* 364.1334.

(2*S*,5*S*)-2-Isopropyl-5-(4-methoxyphenyl)-1-tosyl-2,5-dihydro-1H-pyrrole (*cis*-5-2m)

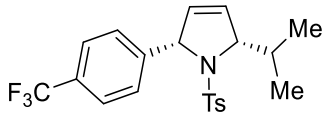


cis-**5-2m**

Following the general procedure B, **5-1m** (0.2 mmol, 74.8 mg), 5 mol % **(*S*)-L2-13**AuCl (9.2 mg), 10 mol% $NaBAr^F_4$ (17.6 mg) and 0.4 mL dry toluene were stirred at 110 ℃ for 48 h. The solvent was removed, and the residue was purified by flash column chromatography (hexane/EtOAc = 10:1) to afford *cis*-**5-2m** as a yellow solid (59.3 mg, 79% yield, *d.r.* > 50/1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 8.7 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 3H), 6.86 (d, *J* = 8.7 Hz, 2H), 5.72 (dt, *J* = 6.2, 1.9 Hz, 1H), 5.69 (dt, *J* = 6.3, 1.9 Hz, 1H), 5.47 (q, *J* = 2.2 Hz, 1H), 4.38 (dq, *J* = 4.3, 2.0 Hz, 1H), 3.80 (s, 3H), 2.40 (s, 3H), 2.11 – 2.03 (m, 1H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 159.0, 143.2, 135.1, 132.8, 129.45, 129.39, 129.0, 127.7, 126.9, 113.6, 73.8, 69.8, 55.2, 32.9, 21.5, 20.1, 17.5. **HRMS (ESI)** *m/z:* $[M+Na]^+$ calcd for $C_{21}H_{25}NO_3SNa$ 394.1453; Found *m/z* 394.1454.

(2*S*,5*S*)-2-Isopropyl-1-tosyl-5-(4-(trifluoromethyl)phenyl)-2,5-dihydro-1H-pyrrole (*cis*-5-2n)

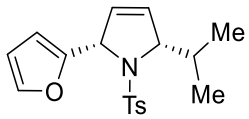


cis-**5-2n**

Following the general procedure B, **5-1n** (0.2 mmol, 81.9 mg), 5 mol % **(*S*)-L2-13**AuCl (9.2 mg), 10 mol% $NaBAr^F_4$ (17.6 mg) and 0.4 mL dry toluene were stirred at 110 ℃ for 48 h. The solvent was removed, and the residue was purified by flash column chromatography (hexane/EtOAc = 10:1) to afford *cis*-**5-2n** as a yellow solid (60.2 mg, 74% yield, *d.r.* > 50/1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.2 Hz, 2H), 7.60 – 7.52 (m, 4H), 7.25 (d, *J* = 7.7 Hz, 3H), 5.74 (dt, *J* = 6.3, 2.0 Hz, 1H), 5.71 (dt, *J* = 6.3, 2.1 Hz, 1H), 5.51 (q, *J* = 2.2 Hz, 1H), 4.39 (dq, *J* = 4.4, 2.1 Hz, 1H), 2.39 (s, 3H), 2.15 – 2.05 (m, 1H), 1.02 (d, *J* = 7.0 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 144.6 (q, *J* = 1.5 Hz), 143.8, 134.3, 129.7 (q, *J* = 32.3 Hz), 129.6, 128.5, 127.85, 127.77, 127.72, 125.2 (q, *J* = 3.8 Hz), 124.1 (q, *J* = 272.0 Hz), 74.0, 69.8, 33.0, 21.5, 20.2, 17.5. **^{19}F NMR (376 MHz, $CDCl_3$)** δ -61.83. **HRMS (ESI)** *m/z:* $[M+Na]^+$ calcd for $C_{21}H_{22}F_3NO_2SNa$ 432.1221; Found *m/z* 432.1208.

(2*S*,5*S*)-2-(furan-2-yl)-5-Isopropyl-1-tosyl-2,5-dihydro-1H-pyrrole (*cis*-5-2o)



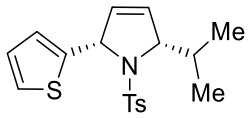
cis-**5-2o**

Following the general procedure B, **5-1o** (0.2 mmol, 66.2 mg), 5 mol % **(*S*)-L2-13**AuCl (9.2 mg), 10 mol% $NaBAr^F_4$ (17.6 mg) and 0.4 mL dry toluene were stirred at 110 ℃ for 38 h. The solvent was removed, and the residue was purified by flash column

chromatography (hexane/EtOAc = 10:1) to afford *cis*-**5-2o** as an orange oil (29.3 mg, 44% yield, *d.r.* = 96/4).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.3 Hz, 2H), 7.33 (dd, *J* = 1.8, 0.9 Hz, 1H), 7.28 – 7.23 (m, 2H), 6.36 – 6.25 (m, 2H), 5.75 (dt, *J* = 6.3, 2.1 Hz, 1H), 5.69 (dt, *J* = 6.3, 2.1 Hz, 1H), 5.54 (q, *J* = 2.2 Hz, 1H), 4.44 (dq, *J* = 4.4, 2.1 Hz, 1H), 2.40 (s, 3H), 2.16 – 2.05 (m, 1H), 0.99 (d, *J* = 7.0 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 153.2, 143.4, 142.1, 135.3, 129.5, 127.9, 127.6, 126.6, 110.4, 108.2, 73.6, 64.1, 32.8, 21.5, 19.9, 16.8. **HRMS (ESI)** *m/z:* $[M+Na]^+$ calcd for $C_{18}H_{21}NO_3SNa$ 354.1140; Found *m/z* 354.1145.

(2*S*,5*S*)-2-Isopropyl-5-(thiophen-2-yl)-1-tosyl-2,5-dihydro-1H-pyrrole (*cis*-5-2p)

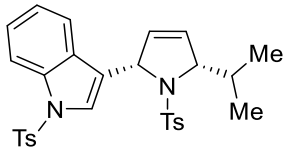


cis-**5-2p**

Following the general procedure B, **5-1p** (0.2 mmol, 69.3 mg), 5 mol % **(*S*)-L2-13**AuCl (9.2 mg), 10 mol% $NaBAr^F_4$ (17.6 mg) and 0.4 mL dry toluene were stirred at 110 ℃ for 44 h. The solvent was removed, and the residue was purified by flash column chromatography (hexane/EtOAc = 10:1) to afford *cis*-**5-2p** as an orange oil (35.0 mg, 50% yield, *d.r.* > 50/1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.3 Hz, 2H), 7.27 – 7.22 (m, 3H), 7.07 (dt, *J* = 3.5, 1.0 Hz, 1H), 6.95 (dd, *J* = 5.1, 3.5 Hz, 1H), 5.84 – 5.70 (m, 3H), 4.45 – 4.36 (m, 1H), 2.40 (s, 3H), 2.09 – 2.02 (m, 1H), 1.00 (d, *J* = 7.0 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 144.7, 143.4, 135.2, 129.5, 128.6, 127.65, 127.61, 126.4, 126.2, 125.5, 73.8, 65.8, 32.8, 21.5, 19.9, 17.3. **HRMS (ESI)** *m/z:* $[M+Na]^+$ calcd for $C_{18}H_{21}NO_2S_2Na$ 370.0912, found *m/z* 370.0917.

3-((2*S*,5*S*)-5-Isopropyl-1-tosyl-2,5-dihydro-1H-pyrrol-2-yl)-1-tosyl-1H-indole (*cis*-5-2q)

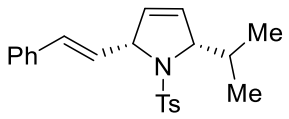


cis-**5-2q**

Following the general procedure B, **5-1q** (0.2 mmol, 106.9 mg), 5 mol % **(*S*)-L2-13**AuCl (9.2 mg), 10 mol% $NaBAr^F_4$ (17.6 mg) and 0.4 mL dry toluene were stirred at 110 ℃ for 48 h. The solvent was removed, and the residue was purified by flash column chromatography (hexane/EtOAc = 6:1) to afford *cis*-**5-2q** as a yellow solid (99.5 mg, 93% yield, *d.r.* > 50/1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.3 Hz, 1H), 7.77 – 7.73 (m, 3H), 7.68 (d, *J* = 8.3 Hz, 2H), 7.58 (s, 1H), 7.32 – 7.29 (m, 1H), 7.25 – 7.21 (m, 3H), 7.19 (d, *J* = 8.2 Hz, 2H), 5.85 (dt, *J* = 6.2, 2.1 Hz, 1H), 5.74 (dt, *J* = 6.2, 2.1 Hz, 1H), 5.68 – 5.63 (m, 1H), 4.37 (dq, *J* = 5.9, 2.0 Hz, 1H), 2.39 (s, 3H), 2.31 (s, 3H), 2.10 – 2.02 (m, 1H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 144.8, 143.6, 135.2, 135.0, 134.2, 129.8, 129.6, 128.9, 127.84, 127.78, 127.73, 126.8, 125.1, 124.6, 123.2, 123.0, 120.1, 113.6, 73.8, 63.4, 33.4, 21.5, 21.5, 20.2, 17.8. **HRMS (ESI)** *m/z:* $[M+Na]^+$ calcd for $C_{29}H_{30}N_2O_4S_2Na$ 557.1545; Found *m/z* 557.1545.

(2*S*,5*R*)-2-Isopropyl-5-((*E*)-styryl)-1-tosyl-2,5-dihydro-1H-pyrrole (*cis*-5-2r)



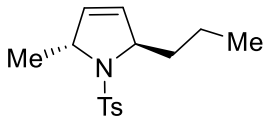
cis-**5-2r**

Following the general procedure B, **5-1r** (0.2 mmol, 73.5 mg), 5 mol % **(*S*)-L2-13**AuCl (9.2 mg), 10 mol% $NaBAr^F_4$ (17.6 mg) and 0.4 mL dry toluene were stirred at 110 ℃ for

72 h. The solvent was removed, and the residue was purified by flash column chromatography (hexane/EtOAc = 10:1) to afford *cis*-**5-2r** as a yellow solid (39.2 mg, 53% yield, *d.r.* > 50/1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.39 – 7.21 (m, 7H), 6.52 (dd, *J* = 16.0, 1.0 Hz, 1H), 6.11 (dd, *J* = 15.9, 7.1 Hz, 1H), 5.68 – 5.61 (m, 2H), 5.09 – 5.01 (m, 1H), 4.45 (dq, *J* = 4.0, 1.7 Hz, 1H), 2.39 (s, 3H), 2.24 – 2.14 (m, 1H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 143.4, 136.5, 135.4, 131.6, 129.6, 129.2, 128.7, 128.4, 127.71, 127.67, 126.7, 126.6, 73.4, 69.1, 32.6, 21.5, 19.7, 16.8. **HRMS (ESI)** *m/z:* $[M+Na]^+$ calcd for $C_{22}H_{25}NO_2SNa$ 390.1504; Found *m/z* 390.1503.

(2*R*,5*R*)-2-Methyl-5-propyl-1-tosyl-2,5-dihydro-1H-pyrrole (*trans*-5-2a)

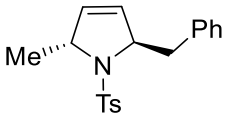


trans-**5-2a**

Following the general procedure B, **5-1a** (0.15 mmol, 41.9 mg), 5 mol % **(*R*)-L2-13**AuCl (6.6 mg), 10 mol% $NaBAr^F_4$ (13.2 mg) and 0.75 mL dry toluene were stirred at 110 ℃ for 72 h. The solvent was removed, and the residue was purified by flash column chromatography (hexane/EtOAc = 10:1) to afford *trans*-**5-2a** as a white solid (38.3 mg, 91% yield, *d.r.* = 92/8).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 – 7.71 (m, 2H), 7.29 – 7.23 (m, 2H), 5.62 – 5.55 (m, 2H), 4.64 – 4.58 (m, 2H), 2.40 (s, 3H), 1.94 – 1.81 (m, 1H), 1.78 – 1.69 (m, 1H), 1.33 (d, *J* = 6.1 Hz, 3H), 1.25 – 1.14 (m, 2H), 0.84 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 142.6, 139.6, 131.0, 129.3, 128.1, 126.8, 67.3, 63.5, 36.5, 21.4, 21.1, 17.5, 14.0.

(2*R*,5*R*)-2-Benzyl-5-methyl-1-tosyl-2,5-dihydro-1H-pyrrole (*trans*-5-2b)

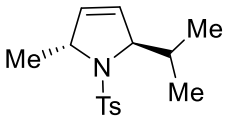


trans-**5-2b**

Following the general procedure B, **5-1b** (0.15 mmol, 49.1 mg), 5 mol % **(*R*)-L2-13**AuCl (6.6 mg), 10 mol% $NaBAr^F_4$ (13.2 mg) and 0.75 mL dry toluene were stirred at 110 ℃. After 24 h, 5 mol % **(*R*)-L2-13**AuCl (6.6 mg) and 10 mol% $NaBAr^F_4$ (13.2 mg) were added to the reaction mixture and the reaction was continued for 48 h. After completion, the solvent was removed, and the residue was purified by flash column chromatography (hexane/EtOAc = 15:1) to afford *trans*-**5-2b** as a colorless oil (43.6 mg, 89% yield, *d.r.* = 84/16).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84 – 7.78 (m, 2H), 7.34 – 7.24 (m, 4H), 7.24 – 7.13 (m, 3H), 5.55 – 5.46 (m, 2H), 4.79 (dddt, *J* = 8.9, 5.3, 3.5, 1.6 Hz, 1H), 4.60 – 4.46 (m, 1H), 3.57 (dd, *J* = 12.8, 3.7 Hz, 1H), 2.76 (dd, *J* = 12.8, 9.3 Hz, 1H), 2.42 (s, 3H), 1.30 (d, *J* = 6.4 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 142.8, 139.8, 137.6, 131.3, 129.8, 129.5, 128.2, 127.8, 126.8, 126.4, 68.6, 63.6, 42.0, 21.4, 20.8.

(2*R*,5*R*)-2-Isopropyl-5-methyl-1-tosyl-2,5-dihydro-1H-pyrrole (*trans*-5-2c)



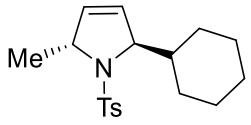
trans-**5-2c**

Following the general procedure B, **5-1c** (0.15 mmol, 41.9 mg), 5 mol % **(*R*)-L2-13**AuCl (6.6 mg), 10 mol% $NaBAr^F_4$ (13.2 mg) and 0.75 mL dry toluene were stirred at 110 ℃. After 24 h, 5 mol % **(*R*)-L2-13**AuCl (6.6 mg) and 10 mol% $NaBAr^F_4$ (13.2 mg) were added to the reaction mixture and the reaction was continued for 48 h. After completion, the solvent was removed, and the residue was purified by flash column

chromatography (hexane/EtOAc = 20:1 to hexane/EtOAc = 15/1) to afford *trans*-**5-2c** as a colorless oil (31.1 mg, 74% yield, *d.r.* = 85/15).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 – 7.59 (m, 2H), 7.26 – 7.15 (m, 2H), 5.60 (dt, *J* = 6.5, 1.8 Hz, 1H), 5.51 (dt, *J* = 6.5, 1.9 Hz, 1H), 4.60 – 4.53 (m, 1H), 4.47 (ddt, *J* = 5.6, 3.7, 1.9 Hz, 1H), 2.65 – 2.53 (m, 1H), 2.34 (s, 3H), 1.27 (d, *J* = 6.4 Hz, 3H), 0.83 (d, *J* = 7.1 Hz, 3H), 0.56 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 142.5, 139.6, 132.7, 129.3, 126.7, 124.2, 72.9, 64.00, 30.7, 21.4, 21.00, 19.4, 15.1.

(2*R*,5*R*)-2-Cyclohexyl-5-methyl-1-tosyl-2,5-dihydro-1H-pyrrole (*trans*-5-2d)

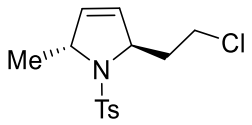


trans-**5-2d**

Following the general procedure B, **5-1d** (0.15 mmol, 47.9 mg), 5 mol % **(*R*)-L2-13**AuCl (6.6 mg), 10 mol% $NaBAr^F_4$ (13.2 mg) and 0.75 mL dry toluene were stirred at 110 ℃. After 24 h, 5 mol % **(*R*)-L2-13**AuCl (6.6 mg) and 10 mol% $NaBAr^F_4$ (13.2 mg) were added to the reaction mixture and the reaction was continued for 48 h. After completion, the solvent was removed, and the residue was purified by flash column chromatography (hexane/EtOAc = 20:1 to hexane/EtOAc = 15/1) to afford *trans*-**5-2d** as a colorless oil (39.0 mg, 81% yield, *d.r.* = 85/15).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 5.60 (tdd, *J* = 8.2, 6.4, 1.6 Hz, 2H), 4.60 – 4.48 (m, 2H), 2.40 (s, 3H), 2.30 – 2.19 (m, 1H), 1.85 – 1.70 (m, 2H), 1.57 – 1.50 (m, 1H), 1.36 (d, *J* = 6.3 Hz, 3H), 1.32 – 1.22 (m, 3H), 1.06 – 0.95 (m, 2H), 0.91 (qd, *J* = 12.6, 3.6 Hz, 1H), 0.71 (qd, *J* = 12.4, 3.6 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 142.5, 139.7, 132.1, 129.3, 126.7, 125.3, 72.6, 63.7, 40.8, 30.2, 26.62, 26.58, 26.1, 25.6, 21.4, 21.2.

(2*R*,5*R*)-2-(2-chloroethyl)-5-Methyl-1-tosyl-2,5-dihydro-1H-pyrrole (*trans*-5-2e)

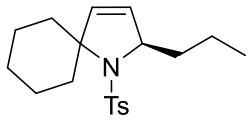


trans-**5-2e**

Following the general procedure B, **5-1e** (0.15 mmol, 45.0 mg), 10 mol % **(*R*)-L2-13**AuCl (13.2 mg), 20 mol% $NaBAr^F_4$ (26.4 mg) and 0.75 mL dry toluene were stirred at 110 ℃ for 72 h. The solvent was removed, and the residue was purified by flash column chromatography (hexane/EtOAc = 10:1) to afford *trans*-**5-2e** as a colorless oil (29.5 mg, 66% yield, 77% yield based on recovery, *d.r.* = 86/14) and recovered **5-1e** (6.9 mg).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 7.9 Hz, 2H), 5.70 – 5.62 (m, 2H), 4.74 – 4.61 (m, 2H), 3.52 (ddd, *J* = 10.9, 7.9, 5.7 Hz, 1H), 3.43 (dt, *J* = 10.9, 7.6 Hz, 1H), 2.41 (s, 3H), 2.45 – 2.33 (m, 2H), 1.32 (d, *J* = 6.2 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 143.0, 138.8, 132.0, 129.5, 127.0, 126.8, 65.1, 63.7, 40.5, 37.2, 21.4, 20.6.

(*R*)-2-Propyl-1-tosyl-1-azaspiro[4.5]dec-3-ene (5-2s)

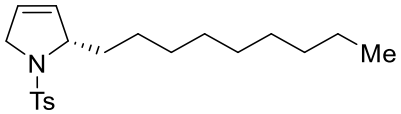


5-2s

Following the general procedure B, **5-1s** (0.15 mmol, 50.0 mg), 5 mol % **(*R*)-L2-18**AuCl (6.6 mg), 10 mol% $NaBAr^F_4$ (13.2 mg) and 0.3 mL dry $PhCF_3$ were stirred at 95 ℃ for 48 h. The solvent was removed, and the residue was purified by flash column chromatography (hexane/EtOAc = 10:1) to afford **5-2s** as a colorless oil (40.8 mg, 82% yield, *e.r.* = 97/3).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 6.12 (dd, *J* = 6.6, 1.7 Hz, 1H), 5.66 (dd, *J* = 6.6, 2.1 Hz, 1H), 4.53 – 4.46 (m, 1H), 2.53 (td, *J* = 13.1, 4.7 Hz, 1H), 2.40 (s, 3H), 2.34 (td, *J* = 13.1, 4.2 Hz, 1H), 2.05 – 1.95 (m, 1H), 1.87 – 1.79 (m, 1H), 1.77 – 1.59 (m, 4H), 1.46 – 1.19 (m, 6H), 0.91 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 142.3, 140.09, 140.08, 131.7, 129.2, 127.2, 127.0, 76.2, 67.7, 40.0, 39.1, 35.4, 25.2, 24.6, 24.5, 21.4, 18.2, 14.0. **HRMS (ESI)** *m/z:* $[M+Na]^+$ calcd for $C_{19}H_{27}NO_2SNa$ 372.1973; Found *m/z* 372.1983. ***e.r.* = 97/3**; HPLC(IC, Hexane/*i*PrOH = 90/10, flow rate = 1.0 mL/min, λ = 200 nm) t_R = 13.94 min (major), t_R = 23.88 min (minor).

(*S*)-2-Nonyl-1-tosyl-2,5-dihydro-1H-pyrrole (2u)

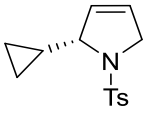


5-2u

Following the general procedure B, **5-1u** (0.15 mmol, 52.5 mg), 10 mol % **(*S*)-L2-13**AuCl (9.2 mg), 20 mol% $NaBAr^F_4$ (26.4 mg) and 0.3 mL dry $PhCF_3$ were stirred at 95 ℃ for 72 h. The solvent was removed, and the residue was purified by flash column chromatography (hexane/EtOAc = 10:1) to afford **5-2u** as a yellow oil (20.0 mg, 38% yield, 83% yield based on conversion) and recover starting material **5-1u** (28.3 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 5.62 – 5.53 (m, 2H), 4.51 – 4.41 (m, 1H), 4.16 – 4.05 (m, 2H), 2.41 (s, 3H), 1.82 – 1.68 (m, 2H), 1.34 – 1.18 (m, 15H), 0.88 (t, *J* = 6.8 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 143.2, 134.9, 129.8, 129.6, 127.4, 124.5, 67.4, 55.6, 36.1, 31.9, 29.62, 29.57, 29.3, 24.5, 22.7, 21.5, 14.1. **HRMS (ESI)** *m/z:* $[M+Na]^+$ calcd for $C_{20}H_{31}NO_2SNa$ 372.1973; Found *m/z* 372.1983. ***e.r.* = 94/6**; HPLC(IC, Hexane/iPrOH = 95/5, flow rate = 1.0 mL/min, λ = 200 nm) t_R = 33.03 min (major), t_R = 31.54 min (minor).

(*R*)-2-Cyclopropyl-1-tosyl-2,5-dihydro-1H-pyrrole (5-2v)

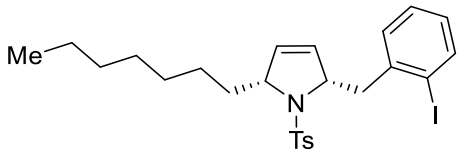


5-2v

Following the general procedure B, **5-1v** (0.2 mmol, 52.7 mg), 5 mol % **L2-2**AuCl (7.6 mg), 10 mol% $NaBAr^F_4$ (17.6 mg) and 0.4 mL dry toluene were stirred at 110 ℃ for 24 h. The solvent was removed, and the residue was purified by flash column chromatography (hexane/EtOAc = 10:1) to afford **5-2v** as a white solid (42.2mg, 80% yield, 90% *ee*).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 7.9 Hz, 2H), 5.61 (dq, *J* = 6.2, 1.8 Hz, 1H), 5.51 (dq, *J* = 6.3, 2.0 Hz, 1H), 4.17 – 4.08 (m, 3H), 2.38 (s, 3H), 1.06 – 0.98 (m, 1H), 0.52 – 0.47 (m, 2H), 0.47 – 0.41 (m, 1H), 0.31 – 0.24 (m, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 143.2, 135.5, 129.5, 128.9, 127.3, 125.2, 70.4, 55.6, 21.4, 16.3, 4.0, 1.6. These data are consistent with the literature.[21] **90% *ee***; HPLC(IC, Hexane/iPrOH = 90/10, flow rate = 1.0 mL/min, λ = 206 nm) t_R = 41.34 min (major), t_R = 53.00 min (minor).

(2*R*,5*S*)-2-Heptyl-5-(2-iodobenzyl)-1-tosyl-2,5-dihydro-1H-pyrrole (*cis*-5-2w)

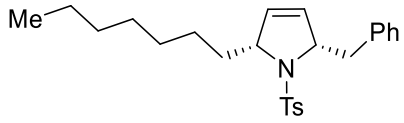


cis-**5-2w**

Following the general procedure B, **5-1w** (0.2 mmol, 107.4 mg), 10 mol % **(*S*)-L2-13**AuCl (18.4 mg), 20 mol% $NaBAr^F_4$ (26.4 mg) and 0.4 mL dry $PhCF_3$ were stirred at 95 ℃ for 72 h. The solvent was removed, and the residue was purified by flash column chromatography (hexane/EtOAc = 10:1) to afford *cis*-**5-2w** as a yellow oil (92.1 mg, 86% yield, *d.r.* = 93/7).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 – 7.71 (m, 1H), 7.69 (d, *J* = 8.3 Hz, 2H), 7.26 – 7.18 (m, 4H), 6.84 (ddd, *J* = 8.0, 5.3, 3.8 Hz, 1H), 5.47 (dt, *J* = 6.3, 2.0 Hz, 1H), 5.38 (dt, *J* = 6.3, 2.0 Hz, 1H), 4.53 (ddq, *J* = 8.6, 5.0, 1.9 Hz, 1H), 4.29 (ddq, *J* = 8.2, 3.9, 1.9 Hz, 1H), 3.43 (dd, *J* = 13.2, 4.8 Hz, 1H), 2.96 (dd, *J* = 13.1, 9.4 Hz, 1H), 2.33 (s, 3H), 1.77 – 1.63 (m, 1H), 1.33 – 1.04 (m, 11H), 0.86 – 0.79 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 143.3, 140.7, 139.6, 134.5, 131.6, 129.6, 129.5, 128.4, 128.1, 127.9, 127.6, 101.0, 48.0, 37.5, 31.8, 29.6, 29.2, 25.4, 22.7, 21.5, 14.1. **HRMS (ESI)** *m/z:* $[M+Na]^+$ calcd for $C_{25}H_{32}INO_2SNa$ 560.1096; Found *m/z* 560.1077.

(2*S*,5*R*)-2-Benzyl-5-heptyl-1-tosyl-2,5-dihydro-1H-pyrrole (*cis*-5-2x)



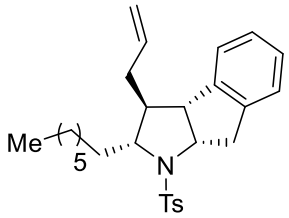
cis-**5**-**2x**

Following the general procedure B, **5-1x** (1.0 mmol, 411.6 mg), 5 mol % **(*S*)-L2-13**AuCl (46.0 mg), 10 mol% $NaBAr^F{}_4$ (88.0 mg) and 2.0 mL dry toluene were stirred at 110 ℃ for 72 h. The solvent was removed, and the residue was purified by flash column chromatography (hexane/EtOAc = 10:1) to afford *cis*-**5-2x** as a colorless oil (353.6 mg, 86% yield, *d.r.* = 93/7).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.3 Hz, 2H), 7.31 – 7.26 (m, 4H), 7.23 – 7.16 (m, 3H), 5.52 (dt, *J* = 6.3, 2.0 Hz, 1H), 5.44 (dt, *J* = 6.3, 2.0 Hz, 1H), 4.58 – 4.48 (m, 1H), 4.31 – 4.23 (m, 1H), 3.30 (dd, *J* = 13.0, 3.6 Hz, 1H), 2.83 (dd, *J* = 13.0, 9.3 Hz, 1H), 2.39 (s, 3H), 1.70 – 1.63 (m, 1H), 1.39 – 1.09 (m, 11H), 0.89 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 143.3, 137.4, 134.8, 130.0, 129.6, 129.4, 128.2, 128.1, 127.5, 126.5, 69.2, 68.3, 44.1, 37.3, 31.8, 29.5, 29.2, 25.4, 22.6, 21.5, 14.1. **HRMS (ESI)** *m/z:* $[M+Na]^+$ calcd for $C_{25}H_{33}NO_2SNa$ 434.2130; Found *m/z* 450.2122.

Applications

(2*R*,3*S*,3a*R*,8a*S*)-3-Allyl-2-heptyl-1-tosyl-1,2,3,3a,8,8a-hexahydroindeno[2,1-b]pyrrole (5-3)

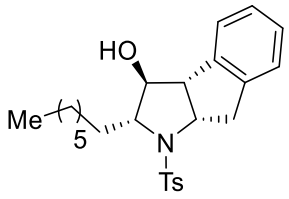


5-3

To a solution of the *cis*-**5-2w** (0.11 mmol, 52.9 mg) in benzene (1 mL) was added AIBN (0.022 mmol, 3.6 mg) and allyltributyltin (0.33 mmol, 0.11 mL). The reaction was heated to 80 ℃ in a sealed vial for 12 h. The reaction was cooled to room temperature, the solvent evaporated, and the crude product purified by flash chromatography (hexane/EA = 20/1) to afford **5-3** (31.8 mg, 64% yield) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 7.9 Hz, 2H), 7.16 (d, *J* = 7.2 Hz, 1H), 7.14 – 7.07 (m, 2H), 7.06 (d, *J* = 7.2 Hz, 1H), 5.49 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 4.90 (d, *J* = 9.2 Hz, 1fH), 4.66 (dq, *J* = 17.1, 1.6 Hz, 1H), 4.33 (t, *J* = 6.5 Hz, 1H), 3.40 (d, *J* = 17.2 Hz, 1H), 3.34 (d, *J* = 6.9 Hz, 1H), 3.29 (dd, *J* = 10.4, 4.4 Hz, 1H), 3.21 (dd, *J* = 17.2, 6.1 Hz, 1H), 2.38 (s, 3H), 2.20 (t, *J* = 7.7 Hz, 1H), 1.48 – 1.43 (m, 1H), 1.35 – 1.25 (m, 2H), 1.21 – 1.11 (m, 3H), 1.11 – 0.90 (m, 8H), 0.78 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 144.1, 143.3, 141.4, 135.9, 135.5, 129.6, 127.7, 127.4, 126.7, 125.3, 123.4, 117.1, 67.1, 64.2, 55.0, 47.3, 41.8, 38.6, 36.8, 31.7, 29.1, 28.9, 26.3, 22.6, 21.5, 14.1. **HRMS (ESI)** *m/z:* $[M+Na]^+$ calcd for $C_{28}H_{37}NO_2SNa$ 474.2443; Found *m/z* 474.2431.

(2*R*,3*S*,3a*R*,8a*S*)-2-Heptyl-1-tosyl-1,2,3,3a,8,8a-hexahydroindeno[2,1-b]pyrrol-3-ol (5-4)



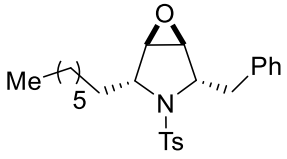
5-4

A solution of *cis*-**5-2w** (38.3 mg, 0.071 mmol) in anhydrous toluene (2.4 mL) was treated with a solution of TEMPO (32 mg, 0.22 mmol) in toluene (0.2 mL) and $(TMS)_3SiH$ (22 μL, 74 μmol). The solution was warmed to 80 ℃, TEMPO (2 × 28 mg in 0.6 mL toluene) and $(TMS)_3SiH$ (4 × 22 μL) were added in portions over the next 4 h. After 16 h, the reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The crude product was purified via chromatography (hexane/EA = 5/1) to afford a brown oil (42.7 mg). The brown oil was dissolved in a 3:1 mixture of THF-H_2O (0.9 mL) and treated with activated zinc powder (54 mg, 0.8 mmol) and HOAc (0.2 mL). The resulting suspension was warmed to 60 ℃ with vigorous stirring. After 12 h, additional Zn (54 mg) was added, and the reaction was stirred for 12 h. The zinc power was removed by filtration through Celite and washed with DCM. The solvent was removed under reduced pressure, and the resulting mixture was purified by chromatography (hexane/EA = 4/1) to afford **5-4** as a light brown oil (14.4 mg, 54% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.28 – 7.16 (m, 4H), 4.60 (td, *J* = 6.6, 1.2 Hz, 1H), 4.34 (s, 1H), 3.71 (dd, *J* = 7.0, 1.3 Hz, 1H), 3.63 (ddd, *J* = 9.8, 5.6, 1.3 Hz, 1H), 3.42 (d, *J* = 17.2 Hz, 1H), 3.33 (dd, *J* = 17.3, 6.2 Hz, 1H), 2.46 (s, 3H), 1.37 – 1.12 (m, 12H), 0.87 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 143.6, 141.8, 140.6, 135.2, 129.6, 127.9, 127.8, 126.9, 125.6, 123.8, 78.7, 77.3,

71.3, 63.6, 58.9, 41.8, 34.6, 31.6, 29.0, 28.8, 26.2, 22.6, 21.6, 14.1. **HRMS (ESI)** *m/z:* $[M+Na]^+$ calcd for $C_{25}H_{33}NO_3SNa$ 450.2079; Found *m/z* 450.2067.

(2*S*,4*R*,5*R*)-2-Benzyl-4-heptyl-3-tosyl-6-oxa-3-azabicyclo[3.1.0]hexane (5-5)

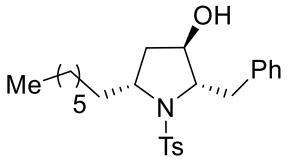


5-5

To a solution of *cis*-**5-2x** (138.1 mg, 0.34 mmol) in 3 mL DCM was added *m*CPBA (70%, 2 equiv., 165 mg) and the reaction mixture was stirred at room temperature for 24h. Upon completion, the reaction was diluted with DCM and wash with $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified via chromatography (hexane/EA = 10/1) to afford **5-5** as a colorless oil (104.1 mg, 75% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 7.6 Hz, 2H), 7.23 – 7.18 (m, 5H), 3.89 (dd, *J* = 10.6, 3.8 Hz, 1H), 3.66 (dd, *J* = 8.8, 5.7 Hz, 1H), 3.28 – 3.21 (m, 3H), 2.72 (dd, *J* = 13.7, 10.6 Hz, 1H), 2.33 (s, 3H), 1.65 – 1.57 (m, 1H), 1.46 – 1.13 (m, 12H), 0.83 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 143.4, 137.1, 135.1, 129.5, 129.4, 128.7, 127.7, 126.9, 62.5, 61.6, 58.4, 57.6, 40.8, 34.0, 31.8, 29.5, 29.1, 26.3, 22.6, 21.6, 14.1. **HRMS (ESI)** *m/z:* $[M+Na]^+$ calcd for $C_{25}H_{33}NO_3SNa$ 450.2079; Found *m/z* 450.2073.

(2*S*,3*R*,5*R*)-2-Benzyl-5-heptyl-1-tosylpyrrolidin-3-ol (5-6)

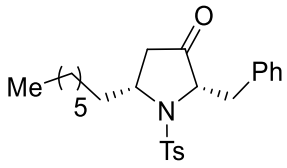


5-6

To a solution of **5-5** (187.7 mg, 0.44 mmol) in 5 mL THF solution under N_2 protection with an ethylene glycol/dry ice cooling bath, $LiBHEt_3$ (1.7 M, 2.6 ml, 10 equiv.) was added slowly, and the reaction was stirred for 18 h. Upon completion, the reaction was quench by slowly adding water and extract with Et_2O three times. The organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting crude product was purified via chromatography (hexane/EA = 3/1) to afford **5-6** as a colorless oil (142.2 mg, 76% yield, *rr* = 84/16).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (d, J = 8.3 Hz, 2H), 7.23 (td, J = 7.4, 1.7 Hz, 4H), 7.18 – 7.12 (m, 3H), 3.96 – 3.89 (m, 1H), 3.68 – 3.54 (m, 2H), 3.11 (dd, J = 13.7, 4.1 Hz, 1H), 2.56 (dd, J = 13.7, 10.2 Hz, 1H), 2.34 (d, J = 7.3 Hz, 3H), 2.00 – 1.89 (m, 1H), 1.80 – 1.67 (m, 1H), 1.67 – 1.59 (m, 1H), 1.40 – 1.30 (m, 1H), 1.29 – 1.08 (m, 10H), 0.83 (t, J = 7.1 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 143.5, 137.7, 134.6, 129.5, 129.5, 128.6, 127.8, 126.7, 72.8, 71.00, 59.8, 42.0, 38.2, 36.9, 31.8, 29.5, 29.2, 25.9, 22.6, 21.5, 14.1. **HRMS (ESI)** *m/z:* $[M+Na]^+$ calcd for $C_{25}H_{35}NO_3SNa$ 452.2235, found *m/z* 452.2219.

(2*S*,5*R*)-2-Benzyl-5-heptyl-1-tosylpyrrolidin-3-one (5-7)



5-7

To a solution of **5-6** (102.2 mg, 0.24 mmol) in 5 mL DCM was added Dess-Martin periodinane (407.2 mg, 4.0 equiv.) and the reaction was heated to 40 ℃ for 24 h. Upon completion, the reaction was cooled down to room temperature and diluted with DCM. The organic layer was washed with $NaHCO_3$ and brine. The solvent was removed under

vacuum, and the crude product was purified via chromatography (hexane/EA = 10/1) to afford **5-7** as a colorless oil (77.3 mg, 76%, *rr* = 84/16).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.32 – 7.17 (m, 5H), 3.97 – 3.90 (m, 1H), 3.87 – 3.77 (m, 1H), 3.28 – 3.19 (m, 2H), 2.42 (s, 3H), 2.17 – 2.06 (m, 1H), 1.80 – 1.67 (m, 1H), 1.38 – 0.92 (m, 11H), 0.88 (t, *J* = 7.2 Hz, 3H), 0.49 – 0.35 (m, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 211.2, 144.1, 136.2, 134.1, 130.9, 130.00, 128.1, 127.4, 126.8, 65.4, 56.8, 42.2, 37.9, 37.0, 31.7, 29.0, 28.9, 25.8, 22.6, 21.5, 14.0. **HRMS (ESI)** *m/z:* $[M+Na]^+$ calcd for $C_{25}H_{33}NO_3SNa$ 450.2079; Found *m/z* 450.2073.

5.8. Reference

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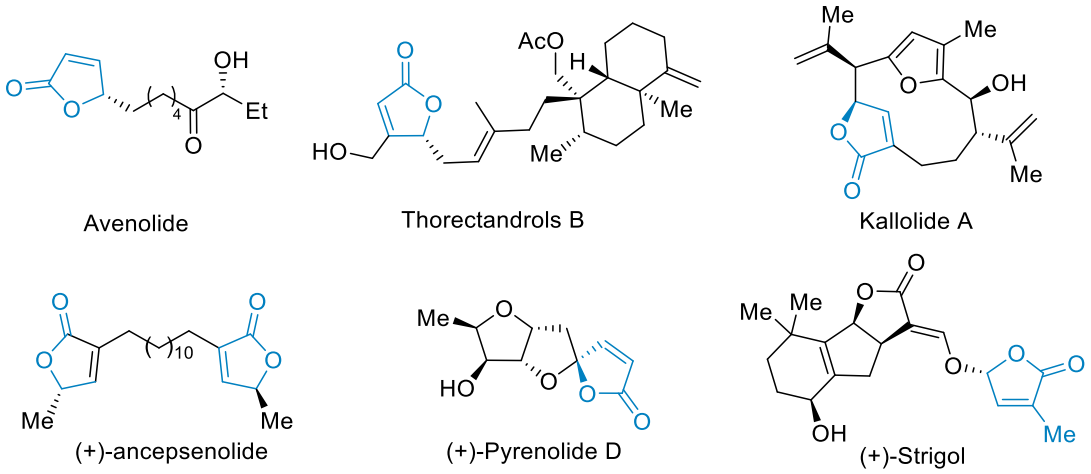
6. Formation of Chiral *α, β*-Butenolides via Highly Enantioselective *γ*-Protonation

6.1. Introduction and Design

Many natural products featuring chiral α, β-butenolide motifs possess various biological activities (Scheme 51). For example, avenolide can control the production of antibiotics in *Streptomyces avermitilis*;[1, 2] thorectandrols B inhibits the growth of MALME-3M (melanoma) and MCF-7 (breast) cancer cell lines;[3] kallolide A exhibits anti-inflammatory activity;[4, 5] (+)-ancepsenolide shows antitumoral, antimalarial, immunosuppressive, and pesticidal activities;[6] (+)-pyrenolide D exhibits cytotoxic activity toward HL-60 cells;[7] and (+)-strigol is a plant hormone for triggering the germination of parasitic plant seeds.[8]

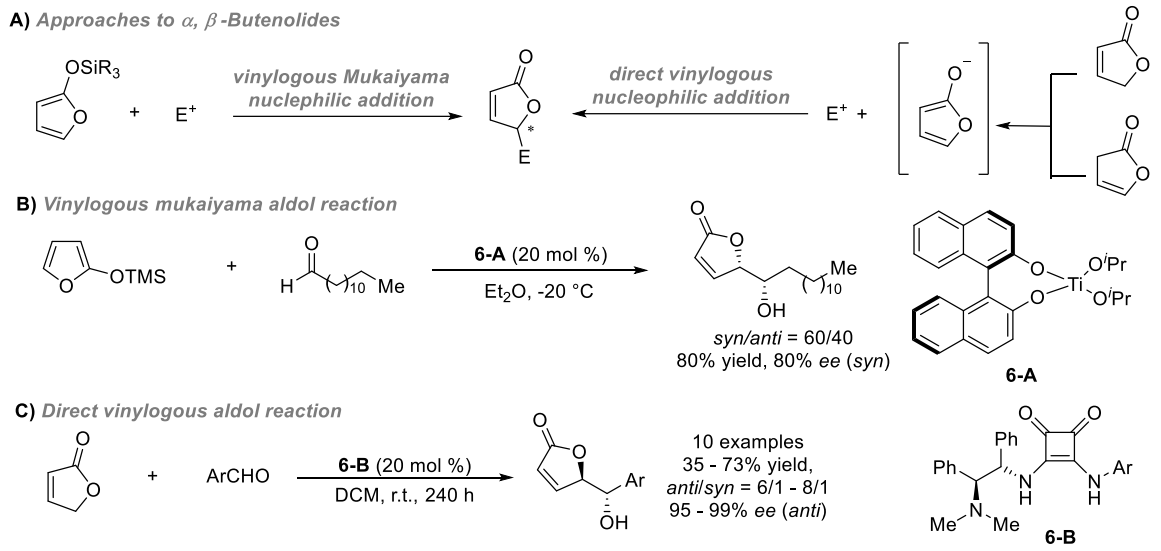
Scheme 51. Natural Products Containing *α, β*-Butenolide Structure Core



Various synthetic approaches have been developed to access chiral *α, β*-butenolide.[9, 10] They mostly entail the reactions of 2-siloxylfuran or enloated generated from *γ*-deprotonation of *α, β*-butenolides or α-deprotonation of *β, γ*-butenolides with electrophiles

(aldehyde, *α, β*-unsaturated ketone, imine) (Scheme 52A). In 1998, Figadere discovered the first catalytic enantioselective vinylogous mukaiyama aldol reaction.[11] With *in-situ* generated titanium catalyst **6-A**, 2-(trimethylsilyloxy)furan reacted with tridecanal to form the desired *α,β*-butenolides in 80% yield, and with *syn*/*anti* = 60/40 (Scheme 52B). The enantiomeric excess of *syn* product is 80%. In 2010, Paul reported the direct vinylogous aldol reaction between *α,β*-butenolides, and aromatic aldehydes which is catalyzed by the bifunctional aminosquaramide **6-B**. The chiral *α,β*-butenolides with an *anti*-configuration were formed as the major isomer and with excellent enantiomeric excess. (Scheme 52C).

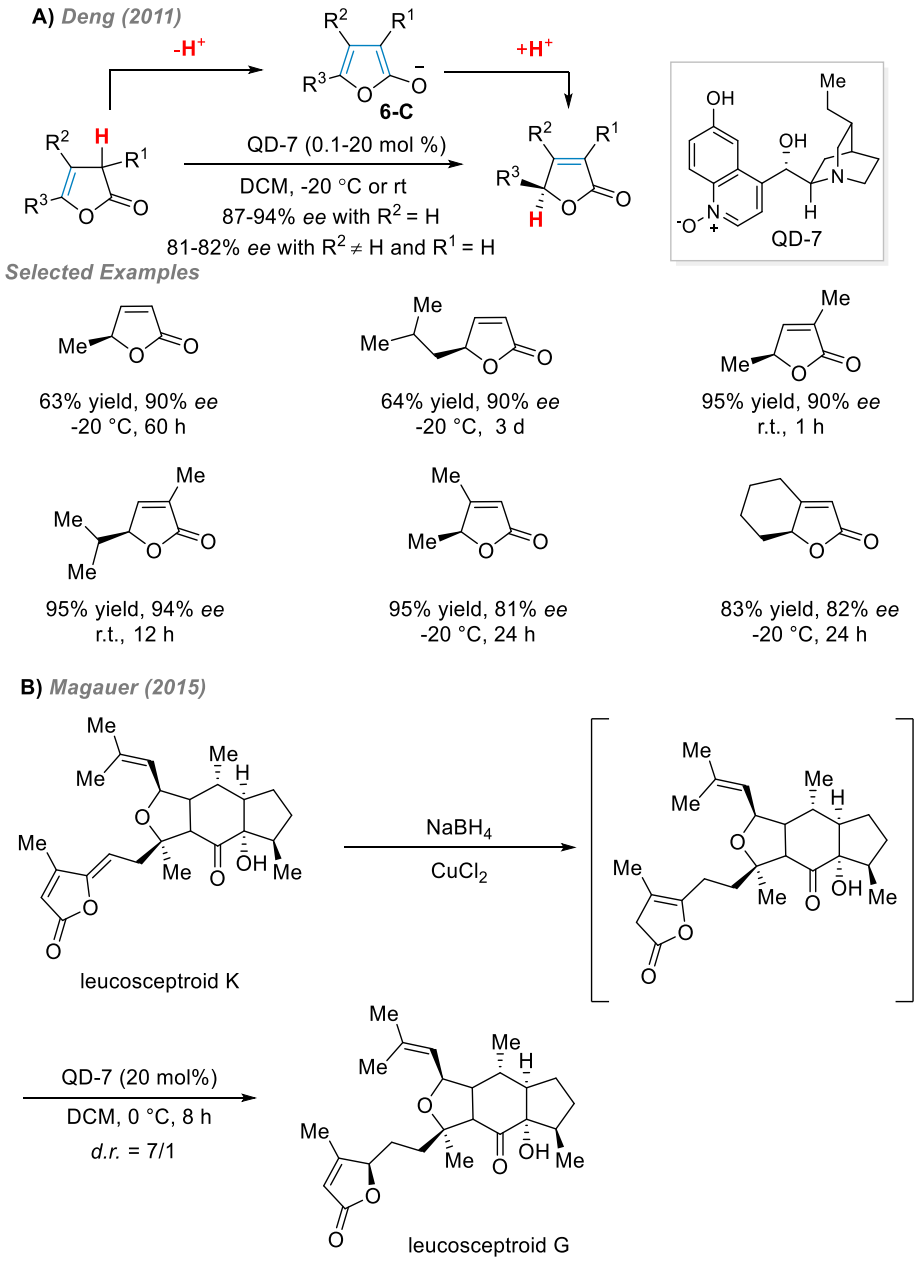
Scheme 52. Prior Strategies of Constructing Chiral *α, β* -Butenolides



The direct catalytic isomerization of racemic/achiral *β*, *γ*-butenolide into chiral *α, β*-butenolide via the achiral 2-furanoxyl anion **6-C** is an atom-economic and arguably the most straightforward approach (Scheme 53A), yet has been only sparsely explored. A notable advance in this strategy was achieved by Deng[12] in 2011 by employing a cinchona-derived organocatalyst. In this chemistry, good levels of enantioselectivities (87-94% *ee*) are achieved for *γ*-monosubstituted and α, *γ*-disubstituted *α, β*-butenolide products, but only

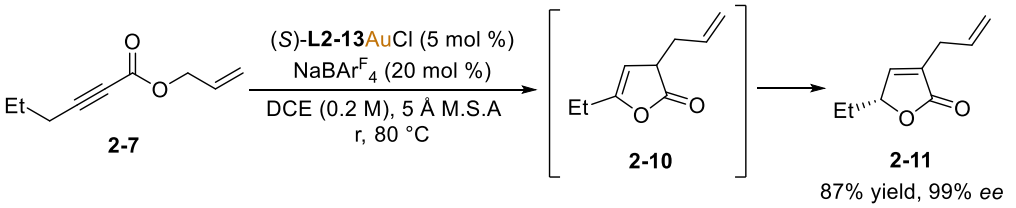
moderate *ee* values (81-82%) are reported for the *β*, *γ*-disubstituted *α, β*-butenolides. This chemistry was applied in the total synthesis of the Leucosceptroid G,[13] where a moderate diastereomeric ratio of 7/1 was reported with the latter butenolide type (Scheme 53B).

Scheme 53. Asymmetric Olefin Isomerization of Butenolides

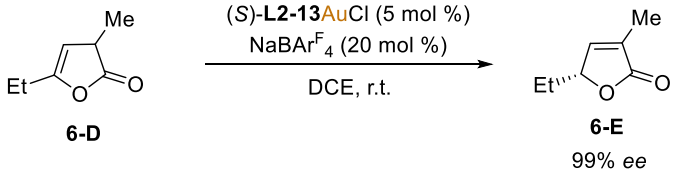


As we discussed in **Chapter 2.2.2**, promoted by the achiral bifunctional ligand **L2-2**, allylic alkynoate **2-7** was isomerized into *α, β*-disubstituted *α, β*-butenolide **2-11** via proton

transfer and Claisen rearrangement. To our surprise, when we used (*S*)-**L2-13**AuCl as the catalyst, chiral *α, β*-butenolides **2-11** was obtained in excellent yield and with exceptional enantioselectivity (Eq.11). Based on our proposed mechanism in **Chapter 2.2.2.**, chirality should be introduced from the asymmetric olefin isomerization of *β, γ*-butenolide **2-10**. To test our assumption, Dr. Conghui synthesized a simpler version of compound **2-10,** i.e., **6-D,** and subjected it to the gold catalysis to afford compound **6-E** with 99% *ee* value (Eq.12).



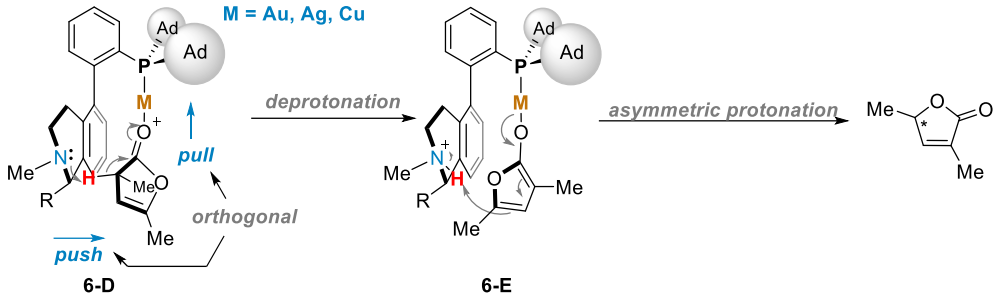
Eq. 11



Eq. 12

The proposed reaction mechanism is depicted in Scheme 54. Consistent with *soft enolization*,[14] we envisioned that an orthogonal organization of a 'pulling' cationic metal and a 'pushing' basic amino group can be readily achieved by the chiral ligand, as outlined in the structures **6-D**, which should permit *soft enolization* of *β, γ*-butenolides to generated the alkoxy furan intermediate **6-E**. This deprotonation should be amenable to both enantiomers of the *β, γ*-butenolides. The subsequent *γ*-protonation, being highly stereoselective, is achieved by intramolecular proton transfer from the chiral ligand amino nitrogen to the *γ* carbon.

Scheme 54. Proposed Reaction Mechanism for Asymmetric Isomerization

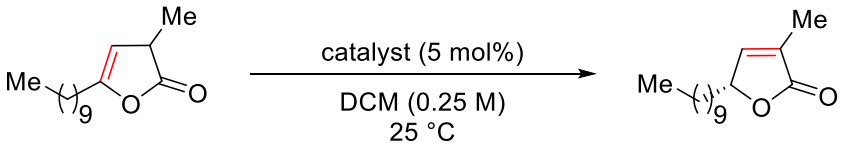


Since Cu^{I} and Ag^{I} can also adopt the same linear bis-coordinated structures with bulky phosphine,[15, 16] we anticipated that the corresponding Cu^{I} or Ag^{I} complexes featuring these bifunctional ligands could also be effective in this cooperative catalysis manifold.[17-19] Moreover, these harder and cheaper coinage metals may be advantageous in enolate chemistry over softer Au since the coordination/activation of hard carbonyl oxygen instead of soft C-C triple bond is desired. It is noteworthy that metal-ligand cooperative catalysis involving Cu^{I} [20-25] or Ag^{I} is scarce.

6.2. Reaction Condition and Scope Study

6.2.1. Reaction Condition Optimization

Table 12. Reaction Condition Optimization for Asymmetric Butenolide Isomerization



Entry[a]	Catalyst	Time	Conv.	Yield (%)[b]	*ee* (%)[c]
1	$[Cu(MeCN)_4]^+ PF_6^-$	3 h	2%	NA	NA
2	$[Cu(MeCN)_4]^+ PF_6^-/Et_3N$	3 h	3%	NA	NA
3	$[JohnPhosCu(MeCN)]^+ PF_6^-/Et_3N$	16 h	35%	6	NA
4	$[Cu(MeCN)_4]^+ PF_6^-$/**L2-2**	3 h	100%	99	NA
5	$[Cu(MeCN)_4]^+ PF_6^-$ /(*S*)-**L2-13**	3 h	100%	99	98

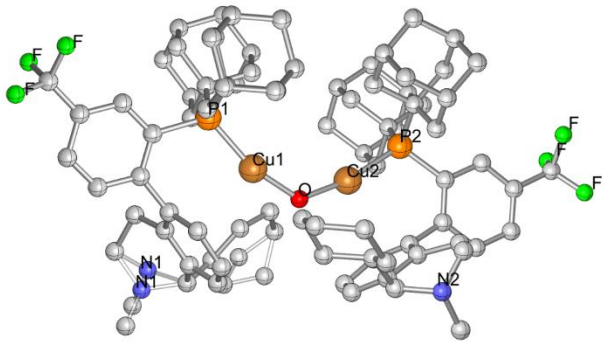
6	$[Cu(MeCN)_4]^+ PF_6^-$/(*S*)-**L2-18**	3 h	100%	98	94
7	[(*S*)-**L2-13**Cu(MeCN)]$^+ PF_6^-$	1 h	100%	99	97
8[d]	[(*S*)-**L2-13**Cu(MeCN)]$^+ PF_6^-$	0.5 h	100%	99[e]	98
9	$\{[(S)$-**L2-13**$Cu]_2(H_2O)\}^{2+} (PF_6^-)_2$	0.5 h	100%	99	98
10	(*S*)-**L2-13**	3 h	NA	NA	NA
11	$Cu(OTf)_2$ or $Cu(hfac)_2$/(*S*)-**L2-13**	24 h	<5%	<2	NA
12	(*S*)-**L2-13**AuCl/ $NaBAr^F_4$ (10 mol%)	0.5 h	100%	99	99
13	$[Ag(MeCN)_2]^+ BAr^F_4^-$ /(*S*)-**L2-13**	0.5 h	100%	99	98
14[f]	[(*S*)-**L2-13**Cu(MeCN)]$^+ PF_6^-$	1 h	100%	92[g]	99

[a] Reaction was performed at 0.05 mmol scale in 1-dram vials under air. [b] The NMR yield is calculated by assuming that the triplet at around 0.87 ppm corresponds to the terminal methyl groups of all compounds. [c] Detected using a chiral HPLC column. [d] Under argon protection. [e] Isolated yield. [f] Reaction was performed with 1 mol % of catalyst. [g] 0.99 g product isolated.

Guided by these considerations, we initiated our investigation by employing Cu(I) as the metal center and the *β*, *γ*-butenolide **6-1a** as the model substrate (Table 12). As expected, the Cu^I salt, $[Cu(MeCN)_4]^+ PF_6^-$, alone could not promote the isomerization of **6-1a** into the α,β-butenolide product **6-2a** to a noticeable extent (entry 1), nor was its combination with Et_3N (entry 2). [**JohnPhos**Cu(MeCN)]$^+ PF_6^-$[16] and Et_3N (5 mol % each) did lead to substantial conversion in 16 h at ambient temperature, albeit in 6% yield (entry 3). The reaction was, however, drastically improved when **JohnPhos** was replaced by the achiral tertiary amine-functionalized ligand **L2-2**.[26] With the *in-situ* generated **L2-2**Cu^+, the reaction proceeded to completion in 3 h and afforded **6-2a** in nearly quantitative yield (entry 4). This large enhancement of reactivity is consistent with the intended Cu-ligand cooperation. When the chiral ligand (*S*)-**L2-13** along with $[Cu(MeCN)_4]^+ PF_6^-$ was employed, the reaction again proceeded with excellent efficiency, and moreover, the *ee* of **6-2a** was 98% (entry 5). The (*R*)-configuration of **6-2a** is inferred by comparing the specific

optical rotations of its homologs **6-2b** and **6-2c** (see Table 12) with the literature data.[12] The replacement of (*S*)-**L2-13** with (*S*)-**L2-18** led to 94% *ee* (entry 6). To establish the structure of the Cu(I) catalyst, we prepared [(*S*)-**L2-13**Cu(MeCN)]$^+$ PF_6^- by following the related protocol for [JohnPhosCu(MeCN)]$^+$ PF_6^-.[16] With this preformed chiral cationic Cu(I) complex as the catalyst, the reaction time was shortened to 1 h, while the yield and *ee* remained excellent (entry 7). Performing the reaction under argon atmosphere further shortened the reaction time to 30 min (entry 8). This observation is consistent with Cu(I) catalysis as atmospheric oxygen might oxidize Cu(I) to likely nonreactive Cu(II).

Figure 17. CYL Drawing of the Dimeric Cu(I) Complex. [a]



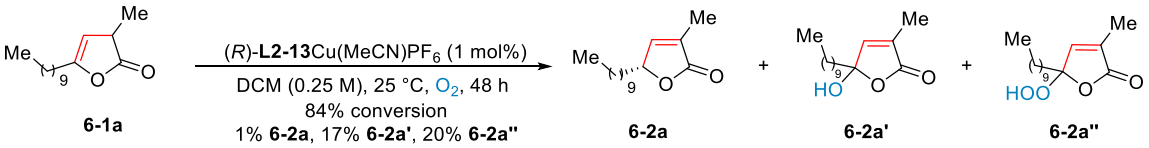
[a] The crystal solvent molecules, i.e., one MeCN and three Et_2O, are omitted for clarity. ∠P1-Cu1-O = 163.2° and ∠P2-Cu2-O = 167.8°

To further characterize the Cu(I) catalyst, we obtained its single crystals for X-ray diffraction studies. However, the solved structure, as shown in Figure 17, is a dimeric (*S*)-**L2-13**Cu(I) complex with the two-metal center bridged by a molecule of water. Nevertheless, it confirms that the Cu(I) center is bis-coordinated, with the angles of P-Cu-O being 167.8° and 163.2°, respectively. This structural feature supports our reaction design. Moreover, this dimeric complex is equally effective as the catalyst (Table 12, entry 9). In the control experiments, the ligand itself was not competent (entry 10), and Cu(II)

salts such as $Cu(OTf)_2$ and $Cu(hfac)_2$ could not serve as the copper source (entry 11). As expected, this catalytic system worked equally well with the other coinage metals. Hence, nearly identical results were obtained with Ag^I or Au^I at the metal center (entries 12 and 13). This interchangeability among the coinage metals is remarkable and rare. The scalability of this Cu(I) catalysis was demonstrated on a gram-scale reaction in entry 14. With 1 mol % of the catalyst, the reaction was completed in one hour and delivered 0.99 g of **6-2a** in 92% yield and 99% *ee*.

Oxygen is detrimental to this catalysis process. When the reaction was carried out under oxygen with 1 mol % catalyst loading, only a trace amount of desired butenolide **6-2a** was detected. The major products are **6-2a'** and **6-2a''** with oxidation at the γ position (Scheme 55).

Scheme 55. Reaction Performed Under Oxygen

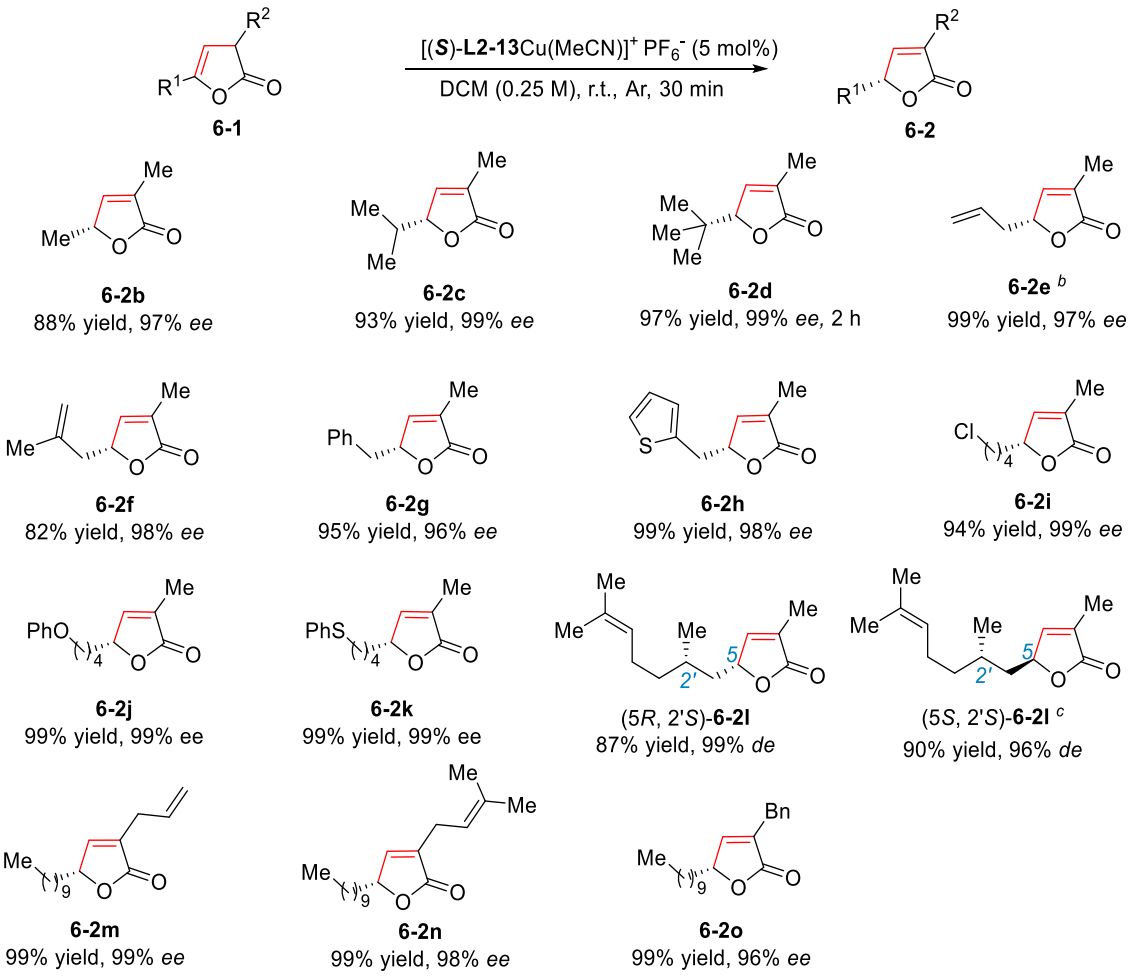


6.2.2. Reaction Scope Study

With the optimized reaction conditions (i.e., Table 12, entry 8) in hand, we explored the reaction scope. As shown in Scheme 56, a series of α, γ-disubstituted α, β-butenolides [(**6-2b**)-(**6-2o**)] were synthesized in yields ranging from 88% to 99% and with ≥96% *ee*. The R^1 group in this series can accommodate methyl (**6-2b**), isopropyl (**6-2c**), bulky t-butyl group (**6-2d**), and various functional groups, including C-C double bonds (**6-2e** and **6-2f**), phenyl (**6-2g**), thiophen-2-yl (**6-2h**), chloro (**6-2i**), phenyloxy (**6-2j**), and phenylthio (**6-2k**). From the substrate prepared from (*S*)-β-citronellol, (5*S*, 2'*S*)- **6-2l** was formed with 99% diastereomeric excess when (*S*)-**L2-13** was employed. By switching the chiral ligand

to its enantiomer, the diastereomer (5*R*, 2'*S*)-**6-2l** was formed with 96% diastereomeric excess. This ligand-enabled diastereomeric divergence permits flexible and selective access to stereochemical arrays. Little impact on the reactivities was noticed when the R^3 group was switched from methyl (**6-2a**) to allyl (**6-2m**), prenyl (**6-2n**), or benzyl groups (**6-2o**).

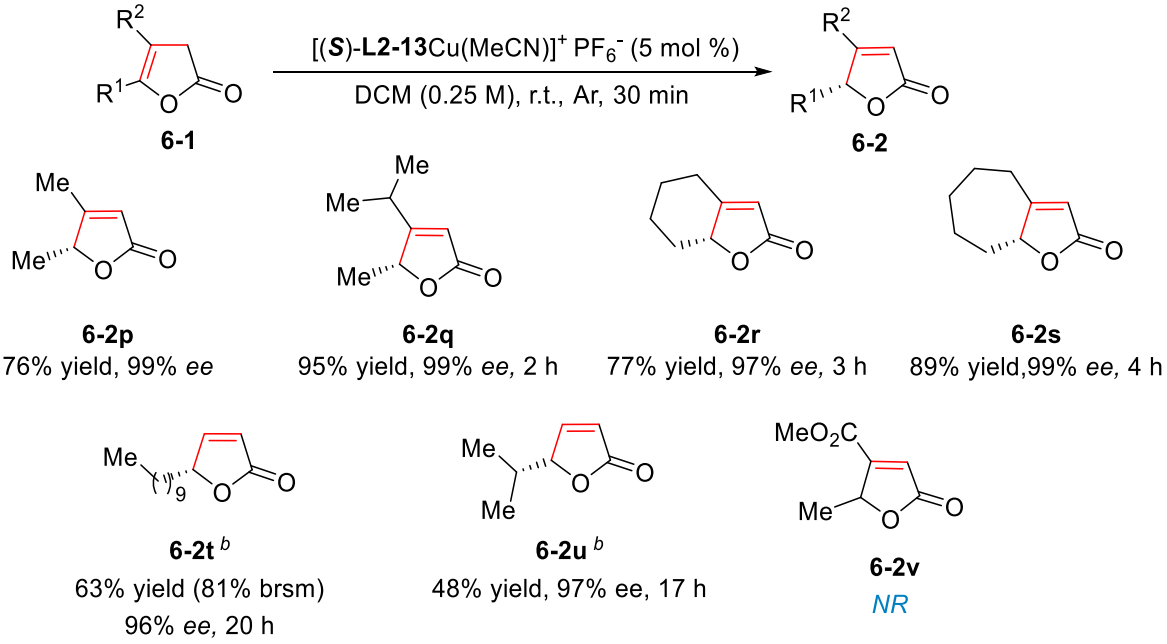
Scheme 56. Reaction Scope for the formation of *α*, *γ*-Disubstituted α,β-Butenolides [a]



[a] Reaction was performed in 2-dram sealed vials under argon at room temperature. Reaction scale is 0.3 mmol and reaction time is 0.5 h if not specified. [b] Reaction was performed at 0.15 mmol scale. [c] 5 mol % (*R*)-**L2-13**Cu(MeCN)PF_6 was used.

Next, we turned our attention to the synthesis of *β, γ*-disubstituted *α, β*-butenolides [(**6-2p)** - (**6-2s**)], which as aforementioned have rarely be accessed via highly enantioselective catalysis (Scheme 57). Much to our delight, they were also formed with ≥97% *ee*. The *β*-substituent, i.e., R^2, can be sterically demanding isopropyl (**6-2q**) or part of a 6-/7-membered ring connected to the *γ* substituent (**6-2r** and **6-2s**). Notably, no reaction was observed when R^2 is methyl ester (**6-2v**), probably due to the conjugation between the double bond and ester group, which makes the *β*, *γ*-butenolide (**6-1v**) more stable than the *α*, *β*-counterpart and hence the isomerization is thermodynamically disfavored.

Scheme 57. Reaction Scope for the Formation of *β, γ*-Disubstituted and γ-Monosubstituted *α, β*-Butenolides [a]

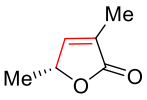


[a] Reaction was performed in 2-dram sealed vials under argon at room temperature. The reaction scale is 0.3 mmol, and the reaction time is 0.5 h if not specified. [b] Reaction was performed at 40 °C.

Finally, the preparation of chiral monosubstituted *α, β*-butenolides (**6-2t** and **6-2u**) was examined (Scheme 57). As expected, in the absence of α- and/or β-substituents to stabilize the product double bond, the energy differences between the substrates and the products appear to be small. As such, this asymmetric isomerization was sluggish and could not reach full conversion due to reaction equilibrium. 40 ˚C and 17 h were employed to improve the reaction yields without compromising the exceptional enantioselectivity. Due to volatility, the isolated yield of **6-2u** was moderate.

Compared to literature results,[12] which are shown Scheme 58, this asymmetric Cu(I) catalysis displays marked improvement in asymmetric induction. The difference is particularly significant in the cases of the *β, γ*-disubstituted *α, β*-butenolides **6-2p** and **6-2r**, where the *ee* values were improved from 81% to 99% and from 82% to 97%, respectively. Moreover, the reaction conditions improved substantially, i.e., r.t. and 0.5 h over -20 °C and 24 h.

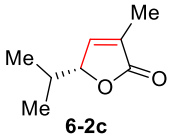
Scheme 58. Comparation with Literature Results



6-2b

Our work: **88% yield, 97% *ee*, 30 min**

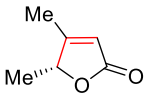
Deng: **95% yield, 90% ee, 1 h**



6-2c

Our work: **93% yield, 99% *ee*, 30 min**

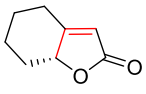
Deng: **95% yield, 94% ee, 12 h**



6-2p

Our work: **76% yield, 99% *ee*, *r.t.* 30 min**

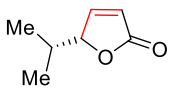
Deng: **95% yield, 81% *ee*, -20 ˚C, 24 h**



6-2r

Our work: **77% yield, 97% *ee*, *r.t.* 3 h**

Deng: **83% yield, 82% *ee*, -20 ˚C, 24 h**



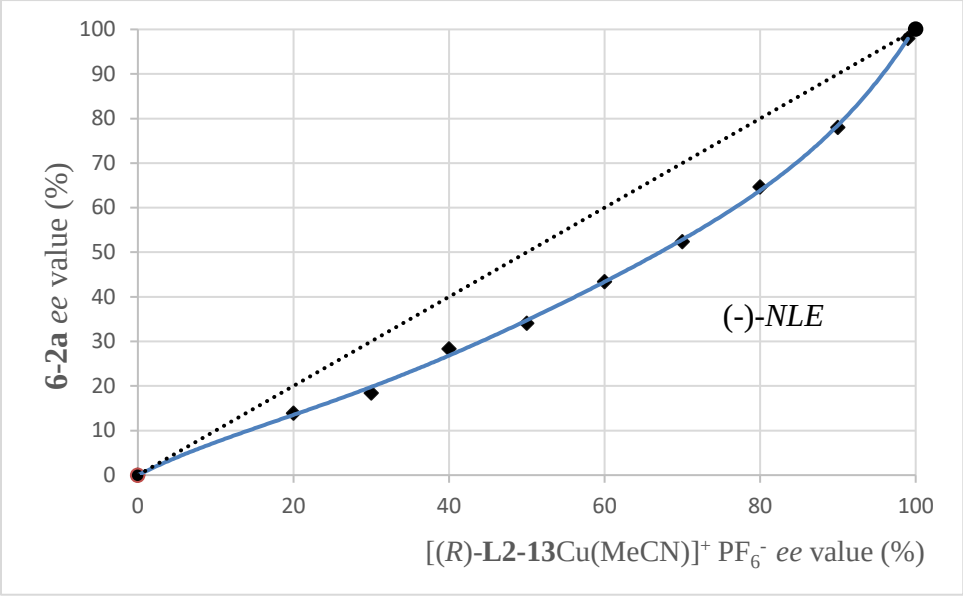
6-2u

Our work: **48% yield, 97% *ee*, 17 h**

Deng: **73% yield, 90% *ee*, 1 h**

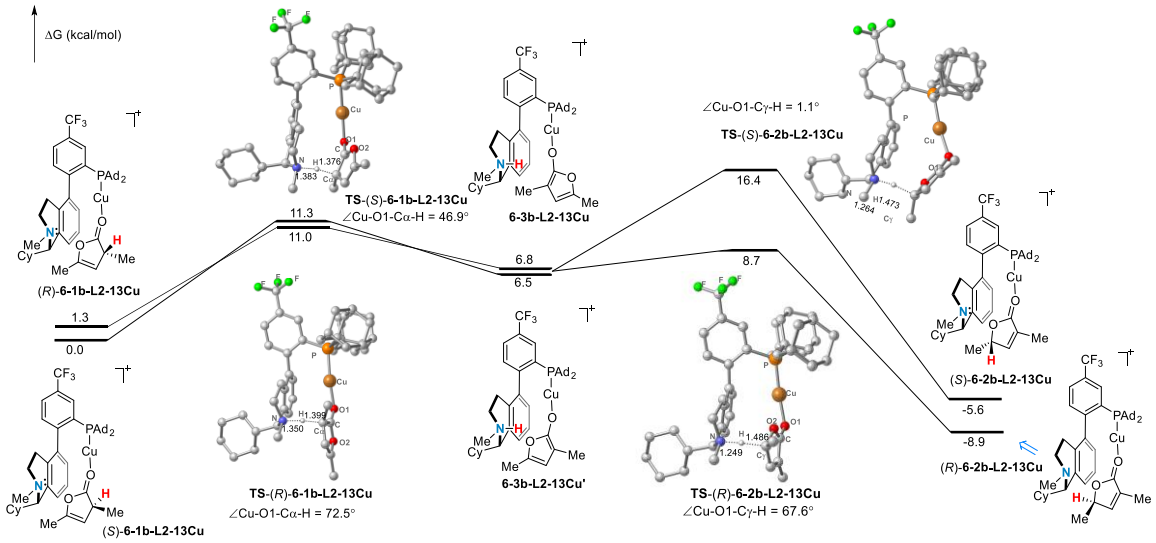
6.3. Non-Linear Effect Study and DFT Calculation

Scheme 59. Non-Linear Effect Study



To understand whether dimeric copper (I) catalyst, i.e. $\{[(S)\text{-}\mathbf{L2}Cu]_2\ H_2O\}^{2+}\ (PF_6)_2$, or monomeric copper(I) catalyst, i.e. $[(S)\text{-}\mathbf{L2\text{-}13}Cu(MeCN)]^+\ PF_6^-$, is the active catalyst in the reaction, we plotted the *ee* value of the catalyst, i.e. $[(R)\text{-}\mathbf{L2\text{-}13}Cu(MeCN)]^+\ PF_6^-$, against the *ee* value of **6-2a**. As shown in the Scheme 59, it reveals a moderate negative non-linear effect and suggests the monomeric catalyst as the active catalytic species and the formation of some catalytically inactive homochiral catalyst dimer/polymer in the reaction.[27] This phenomenon is consistent with the observation of the dimeric catalyst-water complex $\{[(S)\text{-}\mathbf{L2}Cu]_2\ H_2O\}^{2+}\ (PF_6^-)_2$ in the XRD study.

Scheme 60. DFT Calculated Energetics of the Reaction Forming 6-2b [a]



[a] Performed at the PBE1PBE/6-31(d,p)/6-311g(d,p)(P)/SDD(Cu) level of theory with SMD (DCM).

To offer insight into the reaction mechanism and understand the extraordinary asymmetric induction, we conducted DFT studies of the reaction forming **6-2b** at the PBE1PBE level using the effective core potential SDD for Cu and the basis set 6-311g(d,p) for P and 6-31g(d,p) for the other atoms. The SMD model is employed for solvent DCM. As shown in Scheme 60, the deprotonation step eliminates the α-chiral center of the β, γ-butenolide **6-1b,** and exhibits only a minor difference in reaction barriers. The dihedral angles of Cu-O1-Cα-H in the transition state for the (*S*)- and (*R*)-**6-1b** substrates, a measure of the relative orientation of the 'push' and 'pull' in this soft enolization, are 46.9° and 72.5°, respectively, revealing deviation from orthogonality but supporting the cooperative nature of the metal and the ligand amino group in the deprotonation process. The formed (furan-2-yloxy) copper(I) intermediates **6-3b-L2-13Cu** and **6-3-L2-13Cu'** are conformers and differ little in free energy. The subsequent γ-protonation generates the butenolide γ-chiral center, and the two TS differ in free energy by 7.7 kcal/mol, which is consistent with

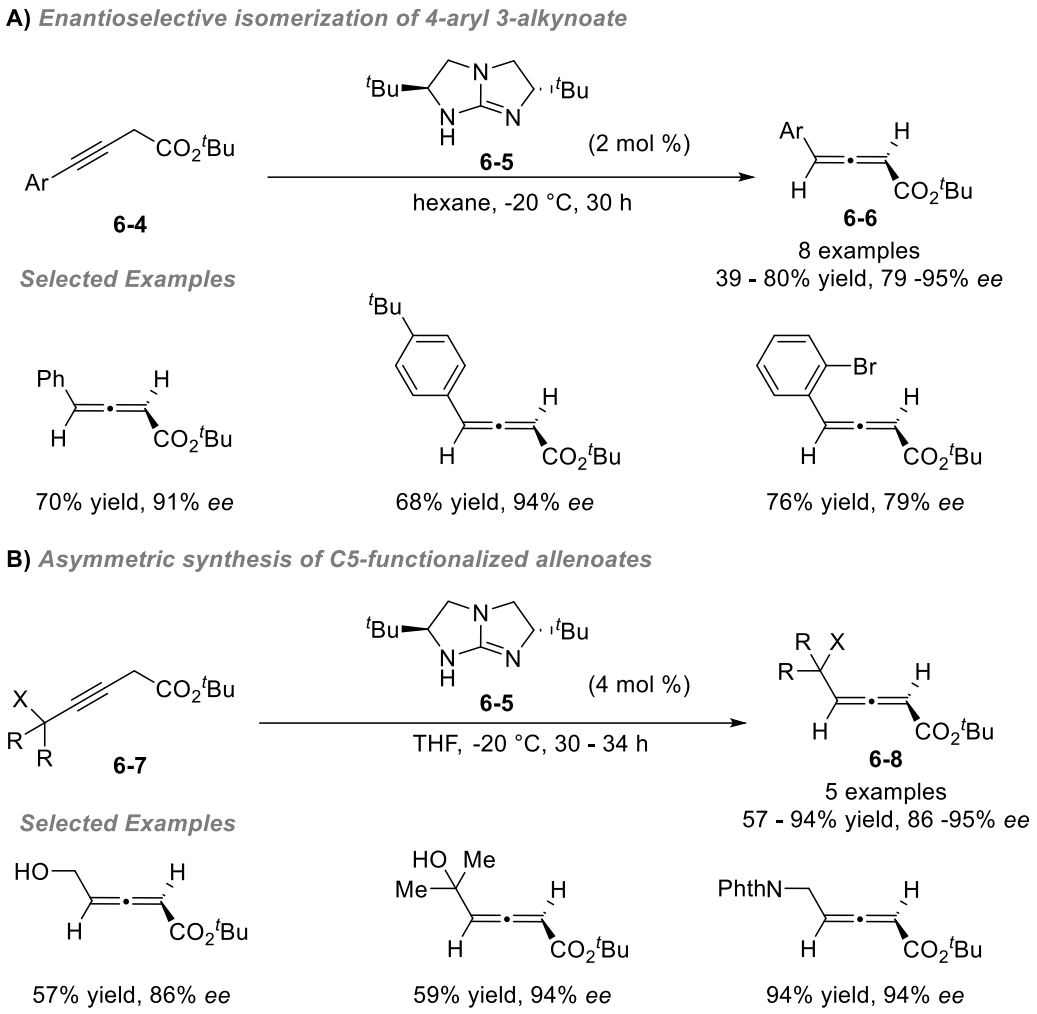
the observed excellent *ee* (i.e., 97%). In the favored TS structure **TS**-*(R)*-**6-2b**-**L2Cu** leading to the observed (*R*)- **6-2b**, the dihedral angle of Cu-O1-Cγ-H is 67.6°, while that for the disfavored TS is 1.1°. This stark difference in the relative orientation of Cu-O1 and Cγ-H reveals the former achieving substantially better metal-ligand cooperation and is attributed to the difference in reaction energy barriers. Additionally, the energy barrier of the preferred protonation is lower than that of deprotonating either of the **6-1b** enantiomers by ≥2.3 kcal/mol, suggesting that the stereo-eliminating deprotonation is the rate-limiting step, which is opposite to that revealed by the DFT studies of the Deng's chemistry.[28]

6.4. Extension to Other Substrates

In 2009, Tan reported[29] that chiral bicyclic guanidine **6-5** could catalyze the asymmetric isomerization of 3-alkynoates into chiral allenoates with high enantioselectivities (Scheme 61). The bulky *tert*-butyl ester group is essential to achieve high enantioselectivity. 4-Aryl 3-alkynoates **6-4** bearing electron-withdrawing or electron-donating substituents on the aromatic ring were well accommodated, and chiral allenoate **6-6** were formed with moderate to high enantioselectivities (Scheme 61A). Notably, albeit the yield based on the recovery of starting material is larger than 98%, the reaction was sluggish, i.e., 30 hours reaction time, and the reaction yield was moderate (39 – 80% yield). More catalyst loading, i.e., 4 mol %, was required to access the C5-functionalized allenoates **6-8** (Scheme 61B). The DFT calculations were used to evaluate the relative stabilities between alkyne/allene isomer pairs, suggesting that the allene is thermodynamic favorable. The calculated ΔG values for the reaction with moderate yield are between -3.0 kcal/mol and -4.3 kcal/mol. High conversion was observed in the case of *N*-Phthalimide (PhthN) protected propargylic

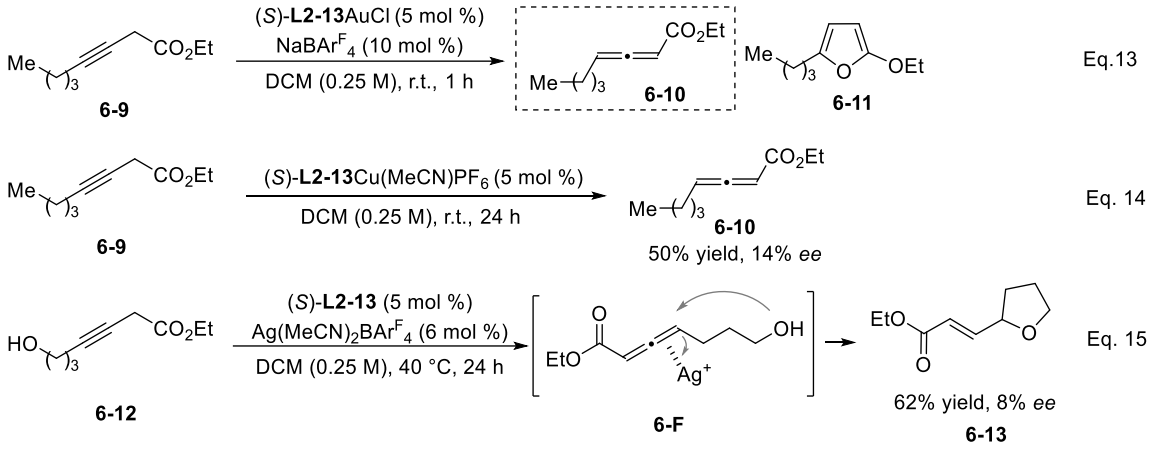
amine with a -6.5 kcal/mol ΔG values. These results indicated the calculated ΔG values correlate well with the observed yields.

Scheme 61. Asymmetric Isomerization of 3-Alkynoates into Chiral Allenoates

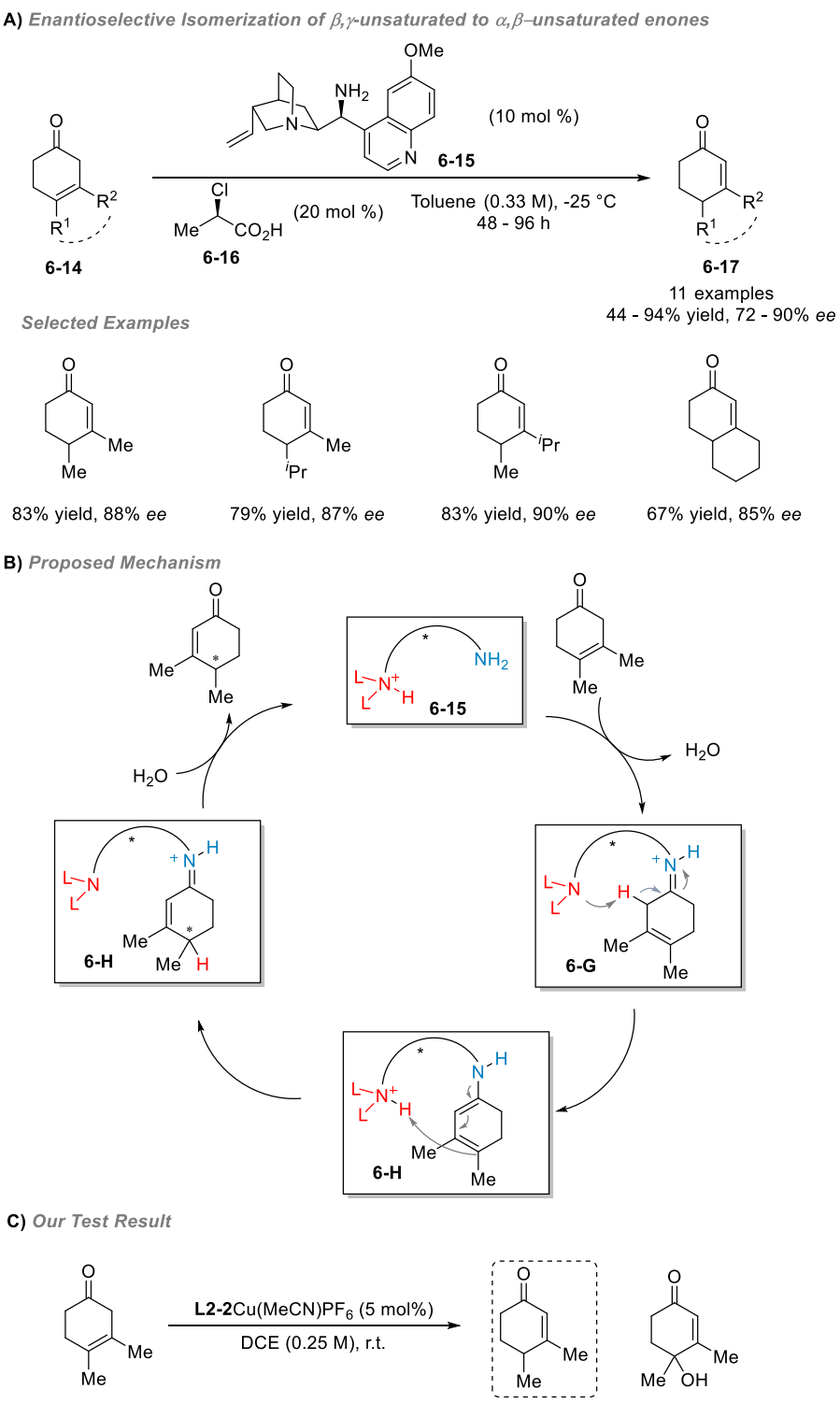


As discussed in **Chapter 3**, (*R*)-**L2-13**AuCl is found to catalyze the asymmetric cycloisomerization of propargylic alcohols into chiral 2,5-dihydrofurans via chiral allene intermediate. We envisioned a similar transformation would also apply to 3-alkynoate, leading to the formation of chiral allenes as the final product. To begin with, using ethyl oct-3-ynoate (**6-9**) as the substrate, we examined the reaction under gold catalysis. As we expected, no allene was observed in the reaction. The alkoxy furan **6-11** was formed

exclusively via tandem isomerization of alkyne and 5-*endo-dig* cyclization (Eq.13). As shown in Eq.14, ethyl oct-3-ynoate (**6-9**) was isomerized into chiral allene **6-10** without forming alkoxyl furan under copper catalysis. However, poor enantioselectivity and moderate conversion, i.e., 50%, were observed after 24 h. The poor enantioselectivity could be attributed to the reversible nature of the isomerization, leading to the racemization of the allene **6-10** during the prolonged reaction time. Thus, we proposed that gold-catalyzed intramolecular hydroalkoxylation of *in-situ* generated allene intermediate (**6-F**), as shown in Eq. 15, would convert it into the tetrahydrofuran product **6-13** with enantiomeric excess and hence avoid the racemization. To our disappointment, **6-13** was obtained in 62% yield and with only 8% *ee* from 3-alkynoate **6-12** in the presence of the shown silver catalyst (Eq. 15).



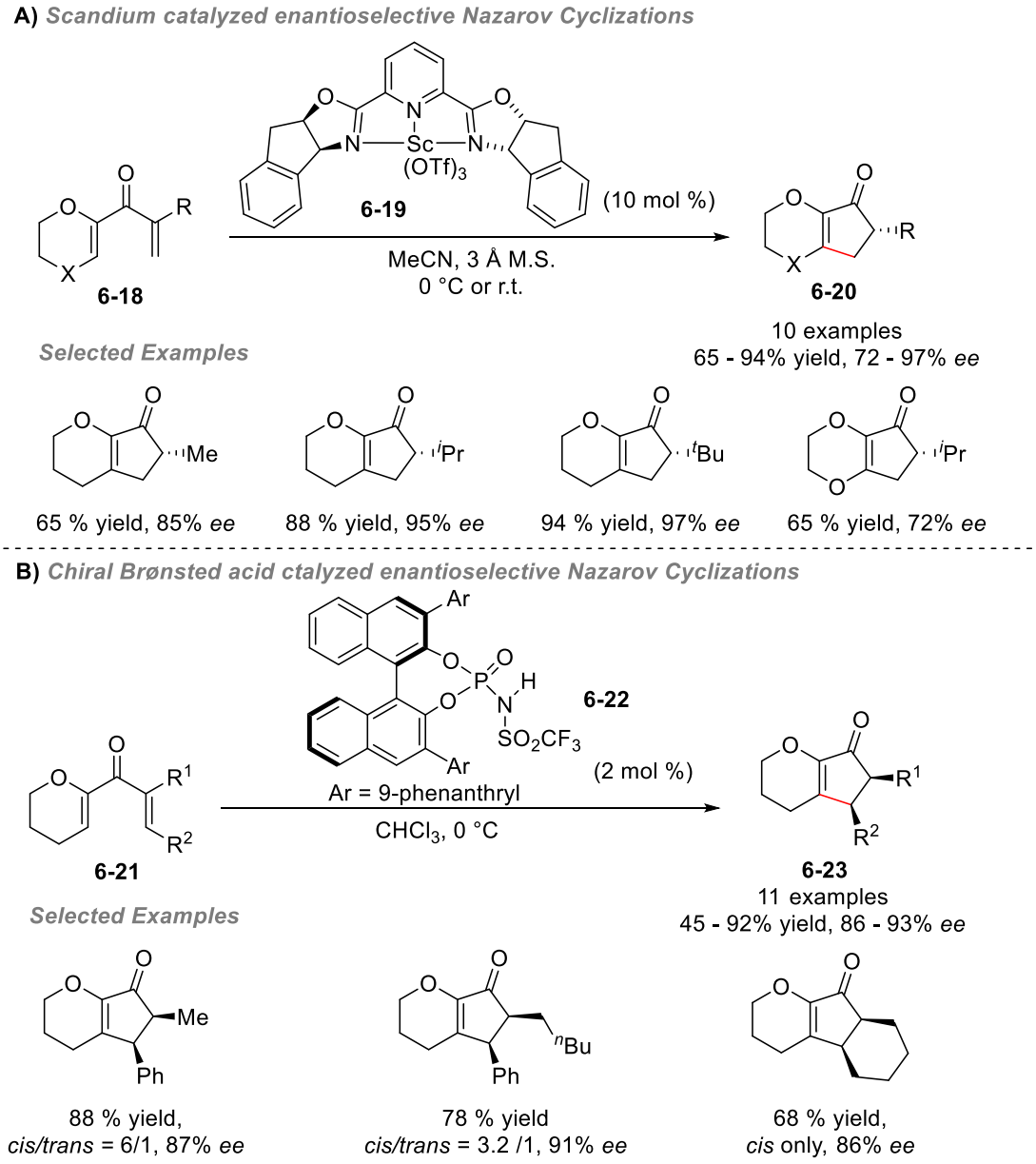
Scheme 62. Asymmetric Synthesis of Chiral Cyclohex-2-Enones



In 2012, Deng[30] reported the enantioselective isomerization of *β, γ*-unsaturated cyclohex-3-en-1-ones (**6-14**) to the corresponding *α, β*-unsaturated chiral enones (**6-17**) in moderate to high yields (Scheme 62A). The reaction was enabled by the organocatalyst **6-15** and a chiral carboxylic acid **6-16**. As shown in Scheme 62B, the proposed mechanism started with the condensation between **6-15** and β,γ-unsaturated enone **6-14a** in the presence of the carboxylic acid, affording the imine intermediate **6-G**. The amino group of **6-G** could then deprotonate the hydrogen alpha to the iminium moiety, followed by enantioselective γ-protonation to afford the chiral imine **6-H**. The catalytic cycle is closed by hydrolysis of **6-H** to give the chiral cyclohex-2-enone **6-17a** (Scheme 62B). Since this asymmetric transformation is also involved in asymmetric proton transfer, we envisioned that our chiral bifunctional ligand copper complex could also enable this transformation and may offer several advantages, i.e., room temperature, shorter reaction time, carboxylic acid-free, and higher enantioselectivity, in comparison to Deng's report. To our disappointment, with the achiral bifunctional ligand copper complex **L2-2**Cu(MeCN)PF_6 as the catalyst, no desired enone **6-17a** was observed after isomerization of **6-14a.** Instead, 4-hydroxyl-cyclohex-2-one was formed. In addition, we also observed the formation of another compound with the cyclohex-2-one motif but not fully characterized. We believed the deprotection step did happen in this transformation. However, the γ-protonation step turned out to be sluggish and was outcompeted by oxidation at the γ-position by atmospheric oxygen. Moreover, testing the same reaction under argon atmosphere using the Schlenk tube technique led to similar results. More rigorous oxygen-free conditions may be required to realize this reaction. In addition, nitrogen position on the ligand may need to be optimized to accommodate the longer distance between the carbonyl oxygen

and the γ-carbon as compared to the butenolide case. Further reaction condition optimization and substrate modification may also be required.

Scheme 63. Enantioselective Nazarov Cyclization

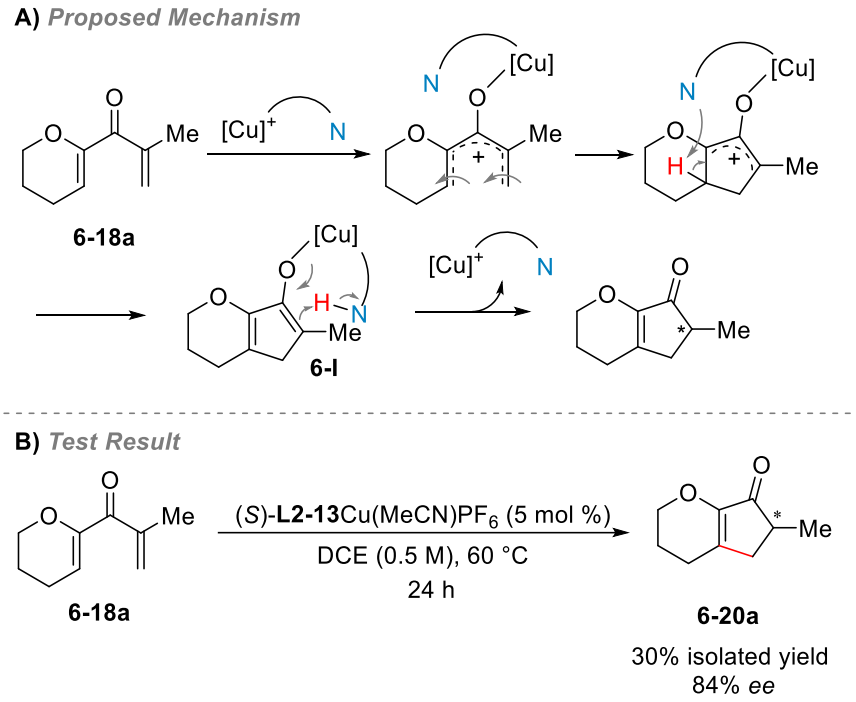


Nazarov cyclization is a well-established electrocyclic reaction[31] and is one of the most versatile methods for synthesizing five-membered rings. The reaction is typically catalyzed by Brønsted or Lewis acids. Although the reaction has been known for decades, the

asymmetric variant was not reported until 2003. In 2004, Trauner described that the chiral scandium triflate pybox complex **6-19** catalyzed an enantioselective Nazaro cyclization.[32] As shown in the Scheme 63, cyclization of dienone **6-18** led to cyclopentenone **6-20** in moderate to high yields and with good to excellent enantioselectivities. However, this reaction suffered poor diastereoselectivity and enantioselectivity when the alkene terminal position is not hydrogen. Rueping solved this problem in 2007. He reported a metal-free Nazarov reaction catalyzed by the chiral brønsted acid **6-22**.[33] Dienone **6-21** with a substituent at the alkene terminal position could cyclize to provide the corresponding *cis*-cyclopentenone **6-23** as the major diastereomer in good yields and with excellent enantioselectivity.

As depicted in Scheme 64A, we envisioned that our chiral bifunctional copper complex should be appliable to asymmetric Nazarov reaction with the asymmetric α-protonation of **6-I** serving as the key step. To our delight, chiral cyclopentenone **6-20a** was obtained in 30% isolated yield and with 84% *ee* after 24 hours (Scheme 64B). The reaction turned out to be sluggish with a large amount of unreacted dienone **6-18a**. Further reaction conditions optimization is required to accelerate this reaction and increase enantioselectivity.

Scheme 64. Copper-Catalyzed Asymmetric Nazarov Reaction



6.5. Conclusion

In summary, we have developed a rare Cu(I)-ligand cooperative catalysis enabled by a chiral bifunctional biphenyl-2-ylphosphine ligand. The reaction converts three-types of β, γ-butenolides into chiral *α, β*-butenolides with ≥96% *ee.* The ready and facile access to β, γ-disubstituted *α, β*-butenolides with high enantiopurity offers a needed approach to this important structural motif. The observed negative non-linear suggests the monomeric catalyst is the active catalytic species. DFT calculations support the cooperative nature between the Cu(I) center and the ligand remote amino group both in the soft deprotonation and the asymmetric γ-protonation steps.

In addition, this cooperative catalysis strategy was examined in several other enantioselective transformations, i.e., isomerization of 3-alkynoates or β, γ-unsaturated enones, and Nazarov reaction. The isomerization of 3-alkynoates suffered poor

enantioselectivity and only moderate conversion. The desired α, β -unsaturated enones were not found in the isomerization of β, γ-unsaturated enones. Although good enantioselectivity was observed in the Nazarov reaction, the sluggish reaction rate and the low conversion made this reaction still challenging. Further condition optimization, as well as substrates and ligands design, are required for these reactions.

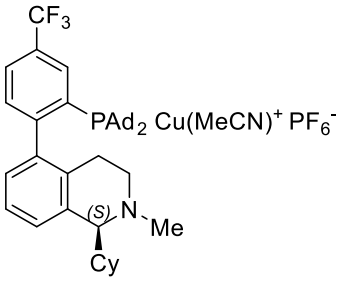
6.6. Experimental Section

General Information

Ethyl acetate (ACS grade), hexanes (ACS grade), dichloromethane (ACS grade) were purchased from Fisher Scientific and used without further purification. ACS grade 1,2-dichloroethane was purchased from Acros Organics and used directly. Commercially available reagents were used without further purification. Reactions were monitored by thin-layer chromatography (TLC) using Silicycle precoated silica gel plates. Flash column chromatography was performed over Silicycle silica gel (230-400 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 400 MHz, 500 MHz and 600 MHz spectrometers using residue solvent peaks as internal standards ($CDCl_3$, ^{1}H: 7.26 ppm; ^{13}C: 77.00 ppm. CD_2Cl_2, ^{1}H: 5.32 ppm; ^{13}C: 53.84 ppm) (multiplicity: s = singlet, d = doublet, t = triplet, q = quadruplet, quint = quintuplet, sext = sextuplet, sept = septuplet, oct = octuplet, non = nonuplet, m = multiplet).^{31}P NMR spectra were recorded on an Agilent 400MHz spectrometer calibrated by phosphoric acid peak (H_3PO_4, ^{31}P: 0.00 ppm). ^{19}F NMR spectra were recorded on an Agilent 400MHz spectrometer calibrated by trifluoroacetic acid peak (CF_3COOH, ^{19}F: -76.55 ppm). Mass spectra were recorded with Waters micro mass ZQ detector using the electrospray method.

Synthesis of Copper Catalyst and Rotation Barrier Study

[(*S*)-L2-13Cu(MeCN)]$^{+}$PF$_6^{-}$



The compound was synthesized according to the literature procedure, [34] (*S*)-**L2-13** (0.3 mmol, 202.2 mg) and [Cu(MeCN)$_4$]$^{+}$ PF$_6^{-}$ (0.3 mmol, 111.8 mg) were added into a flame-dried Schlenk flask under nitrogen protection, followed by the addition of 2 mL CH_2Cl_2. The mixture was stirred at room temperature for 30 min, and then the solvent was evaporated to afford [(*S*)-**L2-13**Cu(MeCN)]$^{+}$PF$_6^{-}$ (265.2 mg, 96% yield) as a white solid. Crystals for XRD were obtained by slow evaporation catalyst solution in a mixture of Et_2O/CH_2Cl_2 (2:1, v/v).

^{1}H NMR (600 MHz, CD_2Cl_2, mixture of two diastereomers**)** δ 8.14 – 8.00 (m, 1H), 7.82 (t, *J* = 8.3 Hz, 1H), 7.64 – 7.47 (m, 1H), 7.43 – 7.18 (m, 2H), 7.00 (t, *J* = 8.2 Hz, 1H), 3.71 – 3.17 (m, 1H), 3.12 – 2.88 (m, 1H), 2.81 – 2.34 (m, 4H), 2.17 (s, 3H), 2.05 – 0.76 (m, 43H). **^{13}C NMR (126 MHz, CD_2Cl_2**, mixture of two diastereomers , all peaks are listed due to being unable to determine coupling patterns) δ 152.17 (d, $^{2}J_{P\text{-}H}$ = 12.6 Hz), 152.05 (d, $^{2}J_{P\text{-}H}$ = 12.6 Hz), 141.77, 140.98, 139.41, 139.36, 139.12, 139.06, 135.71, 133.13, 133.11, 132.88, 132.83, 132.78, 132.24, 131.96, 129.72, 129.34, 129.05, 128.77, 128.69, 128.54, 128.38, 127.19, 124.22 ($^{1}J_{CF}$ = 272.6 Hz), 124.14 ($^{1}J_{CF}$= 272.6 Hz), 122.41, 120.08, 118.22, 70.67, 69.84, 50.22, 49.62, 46.16, 45.42, 45.11, 42.26, 42.22, 41.91, 41.87, 41.27, 41.10, 41.07, 40.42, 40.32, 40.28, 40.19, 39.81, 39.73, 39.47, 39.37, 36.59, 36.51, 36.45, 31.32, 31.12, 29.45, 29.07, 28.99, 28.95, 28.89, 28.82, 28.76, 28.69, 28.32, 27.14,

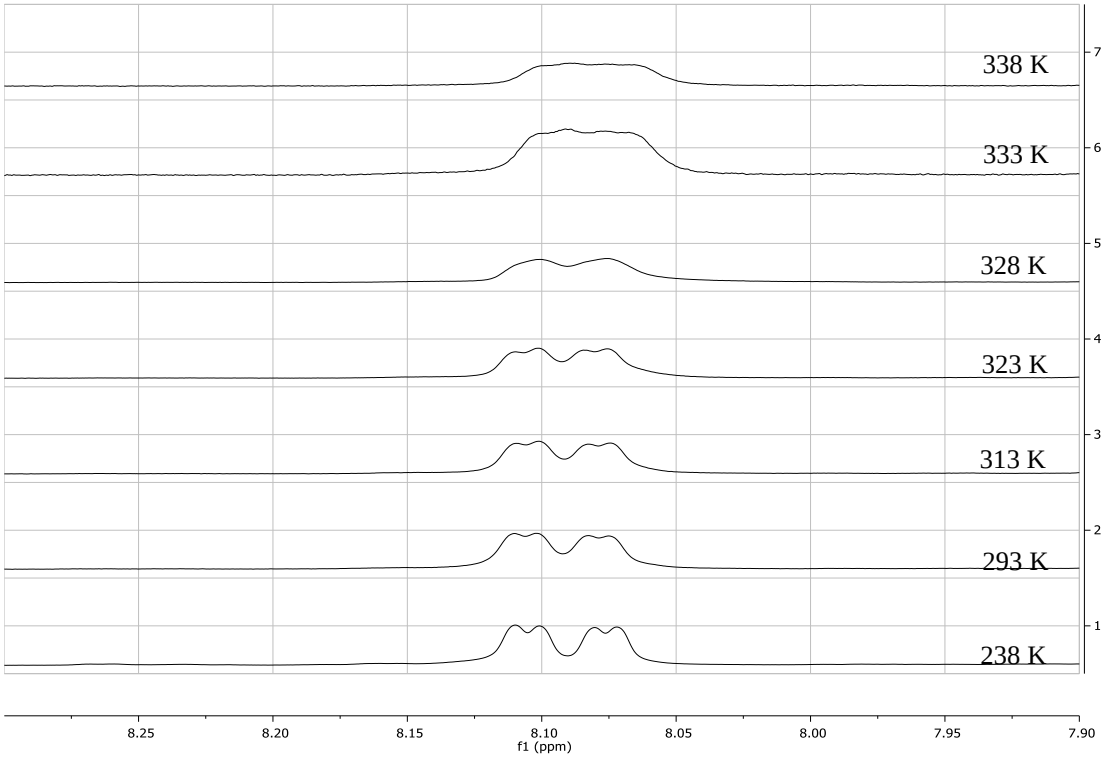
26.95, 26.80, 26.68, 25.42, 2.36. **^{19}F NMR (376 MHz, CD_2Cl_2)** δ -61.89, -71.96 (d, $^1J_{P\text{-}F}$ = 710.7 Hz). **^{31}P NMR (162 MHz, CD_2Cl_2)** δ 31.96, 31.45, -144.27 (hept, $^1J_{P\text{-}F}$ = 710.8 Hz). **HRMS (ESI-TOF)**: calculated for $[M\text{-}PF_6\text{-}CH_3CN]^+$ ($C_{43}H_{55}F_3NPCu$) requires *m/z* 736.3320, found *m/z* 736.3303.

[(*R*)-**L2-13**Cu(MeCN)]$^+PF_6^-$ was synthesized using the same method, and (*R*)-**L2-13** was used instead of (*S*)-**L2-13** in the synthesis process.

Axial Rotation Barrier Study

(*S*)-**L2-13** (0.02 mmol, 13.5 mg) and $[Cu(MeCN)_4]^+PF_6^-$ (0.02 mmol, 7.4 mg) were added into a flame-dried Schlenk flask under nitrogen protection, followed by the addition of 0.5 mL CH_2Cl_2. The mixture was stirred at room temperature for 30 min, and then the solvent was evaporated. The resulting solid was dissolved in $CDCl_3$ (0.7 mL) and injected into a sealed NMR tube under argon protection.

^{1}H NMR was collected at different temperatures with 10 min equilibrium time for each temperature increment. The hydrogen on the ortho-position of the trifluoromethyl group was used as the reference to study the axial rotation barrier.



The rate constants K_c was calculated at the coalescence temperature (T_c) employing the Gutowsky-Holm equation.[35]

$$\Delta v = (8.110\ ppm - 8.081\ ppm) \times 500 \frac{Hz}{ppm} = 14.5\ Hz$$

$$K_c = \frac{\pi \Delta v}{\sqrt{2}} = 29.99\ s^{-1}$$

Assuming the transmission coefficient *κ,* to be equal to one, the free energies of activation *(*$\Delta G^{\neq}$) were calculated according to the Eyring equation. Two $\Delta G^{\neq}$ values were calculated because we cannot determine the specific T_c.

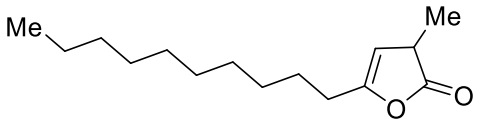
$\Delta G^{\neq} = RT_c[lnT_c - lnK_c + 23.76] = 74.4$ *kJ/mol* = 17.8 *kcal/mol* (*when* T_c = 333 K)

$\Delta G^{\neq} = RT_c[lnT_c - lnK_c + 23.76] = 75.6$ *kJ/mol* = 18.1 *kcal/mol* (*when* T_c = 338 K)

Synthesis of Compound 6-1

Compound **6-1** was synthesized according to previously reported literature.[36]

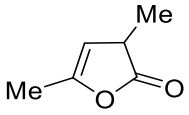
5-Decyl-3-methylfuran-2(3H)-one (6-1a)



6-1a

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.11 (dt, *J* = 2.5, 1.4 Hz, 1H), 3.28 – 3.18 (m, 1H), 2.30 – 2.23 (m, 2H), 1.53 (p, *J* = 7.5 Hz, 2H), 1.37 – 1.17 (m, 17H), 0.87 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 180.45, 155.86, 104.75, 39.63, 31.87, 29.54, 29.47, 29.28, 29.25, 28.97, 28.08, 25.65, 22.66, 15.90, 14.10; **HRMS (CI-TOF)**: calculated for $[M+H]^+$ ($C_{15}H_{27}O_2$) requires *m/z* 239.2011, found *m/z* 239.2007.

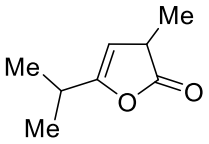
3,5-Dimethylfuran-2(3H)-one (6-1b)



6-1b

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.13 (dt, *J* = 2.3, 1.4 Hz, 1H), 3.30 – 3.17 (m, 1H), 1.98 (dd, *J* = 2.5, 1.5 Hz, 3H), 1.30 (d, *J* = 7.6 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 180.38, 151.85, 105.65, 39.86, 15.75, 13.94. ^{1}H and ^{13}C NMR are consistent with reported literature.[37]

5-Isopropyl-3-methylfuran-2(3H)-one (6-1c)

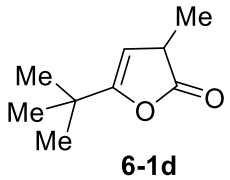


6-1c

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.09 (dt, *J* = 2.3, 1.5 Hz, 1H), 3.24 (qt, *J* = 7.6, 2.3 Hz, 1H), 2.60 – 2.49 (m, 1H), 1.31 (d, *J* = 7.6 Hz, 3H), 1.142 (d, *J* = 7.2 Hz, 3H), 1.139 (d, *J* =

7.2 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 180.51, 160.88, 102.73, 39.58, 27.61, 19.26, 19.18, 15.89. ^{1}H and ^{13}C NMR are consistent with reported literature.[38]

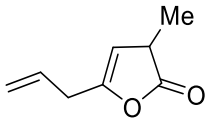
5-(*tert*-butyl)-3-Methylfuran-2(3H)-one (6-1d)



6-1d

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.07 (d, *J* = 2.4 Hz, 1H), 3.24 (qd, *J* = 7.6, 2.3 Hz, 1H), 1.31 (d, *J* = 7.6 Hz, 3H), 1.16 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 180.64, 163.37, 101.87, 39.75, 32.23, 27.10, 15.94; **HRMS (CI-TOF)**: calculated for $[M+H]^+$ ($C_9H_{15}O_2$) requires *m/z* 155.1072, found *m/z* 155.1064.

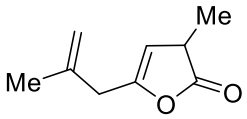
5-Allyl-3-methylfuran-2(3H)-one (6-1e)



6-1e

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.91 – 5.75 (m, 1H), 5.24 – 5.14 (m, 3H), 3.31 – 3.21 (m, 1H), 3.07 – 3.02 (m, 2H), 1.33 (d, *J* = 7.6 Hz, 3H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 180.06, 153.79, 131.09, 118.68, 105.56, 39.68, 32.58, 15.78; **HRMS (CI-TOF)**: calculated for $[M+H]^+$ ($C_8H_{11}O_2$) requires *m/z* 139.0759, found *m/z* 139.0756.

3-Methyl-5-(2-methylallyl)furan-2(3H)-one (6-1f)

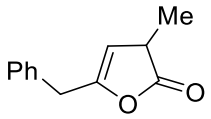


6-1f

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.17 – 5.12 (m, 1H), 4.86 – 4.82 (m, 1H), 4.80 – 4.77 (m, 1H), 3.26 – 3.15 (m, 1H), 2.95 – 2.91 (m, 2H), 1.71 (t, *J* = 1.1 Hz, 3H), 1.26 (d, *J* = 7.6

Hz, 3H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 180.11, 153.44, 139.35, 114.07, 106.45, 39.78, 36.82, 22.06, 15.86; **HRMS (CI-TOF)**: calculated for $[M+H]^+$ ($C_9H_{13}O_2$) requires *m/z* 153.0916, found *m/z* 153.0908.

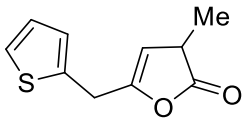
5-Benzyl-3-methylfuran-2(3H)-one (6-1g)



6-1g

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 – 7.31 (m, 2H), 7.29 – 7.23 (m, 3H), 5.10 – 5.03 (m, 1H), 3.63 – 3.58 (m, 2H), 3.29 – 3.21 (m, 1H), 1.31 (d, *J* = 7.6 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 180.04, 154.57, 135.15, 129.06, 128.61, 127.05, 106.25, 39.75, 34.75, 15.74; **HRMS (CI-TOF)**: calculated for $[M+H]^+$ ($C_{12}H_{13}O_2$) requires *m/z* 189.0916, found *m/z* 189.0912.

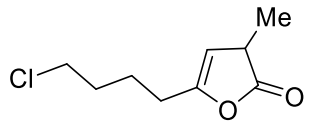
3-Methyl-5-(thiophen-2-ylmethyl)furan-2(3H)-one (6-1h)



6-1h

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.22 – 7.18 (m, 1H), 6.98 – 6.94 (m, 1H), 6.94 – 6.91 (m, 1H), 5.23 – 5.17 (m, 1H), 3.84 – 3.80 (m, 2H), 3.31 – 3.23 (m, 1H), 1.32 (d, *J* = 7.6 Hz, 3H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 179.72, 153.56, 136.72, 126.99, 126.65, 124.68, 106.33, 39.80, 28.89, 15.66; **HRMS (CI-TOF)**: calculated for $[M+H]^+$ ($C_{10}H_{11}O_2S$) requires *m/z* 195.0480, found *m/z* 195.0479.

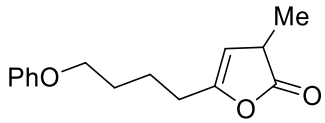
5-(4-chlorobutyl)-3-Methylfuran-2(3H)-one (6-1i)



6-1i

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.19 – 5.15 (m, 1H), 3.55 (t, *J* = 6.5 Hz, 2H), 3.29 – 3.21 (m, 1H), 2.36 – 2.30 (m, 2H), 1.87 – 1.81 (m, 2H), 1.76 – 1.70 (m, 2H), 1.32 (d, *J* = 7.6 Hz, 3H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 180.13, 154.96, 105.36, 44.44, 39.64, 31.73, 27.38, 23.08, 15.86; **HRMS (CI-TOF)**: calculated for $[M+H]^+$ ($C_9H_{14}ClO_2$) requires *m/z* 189.0682, found *m/z* 189.0678.

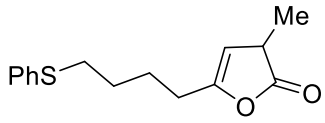
3-Methyl-5-(4-phenoxybutyl)furan-2(3H)-one (6-1j)



6-1j

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 – 7.17 (m, 2H), 6.90 – 6.84 (m, 1H), 6.84 – 6.79 (m, 2H), 5.12 – 5.06 (m, 1H), 3.91 (t, *J* = 6.1 Hz, 2H), 3.24 – 3.11 (m, 1H), 2.34 – 2.27 (m, 2H), 1.82 – 1.73 (m, 2H), 1.73 – 1.65 (m, 2H), 1.25 (d, *J* = 7.6 Hz, 3H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 180.25, 158.87, 155.30, 129.43, 120.65, 114.44, 105.21, 67.19, 39.64, 28.58, 27.84, 22.44, 15.88; **HRMS (CI-TOF)**: calculated for $[M+H]^+$ ($C_{15}H_{19}O_3$) requires *m/z* 247.1334, found *m/z* 247.1344.

3-Methyl-5-(4-(phenylthio)butyl)furan-2(3H)-one (6-1k)

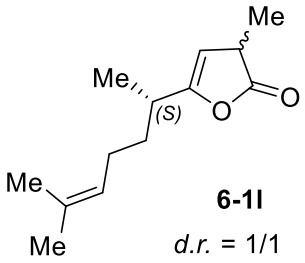


6-1k

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29 – 7.23 (m, 2H), 7.23 – 7.18 (m, 2H), 7.15 – 7.07 (m, 1H), 5.10 – 5.02 (m, 1H), 3.21 – 3.10 (m, 1H), 2.93 – 2.80 (m, 2H), 2.29 – 2.19 (m,

2H), 1.69 – 1.58 (m, 4H), 1.23 (d, *J* = 7.7 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 180.19, 155.07, 136.34, 129.18, 128.87, 125.93, 105.23, 39.61, 33.27, 28.29, 27.62, 24.72, 15.85; **HRMS (CI-TOF)**: calculated for $[M+H]^+$ ($C_{15}H_{19}O_2S$) requires *m/z* 263.1106, found *m/z* 263.1115.

3-Methyl-5-((*S*)-6-methylhept-5-en-2-yl)furan-2(3H)-one (6-1l)

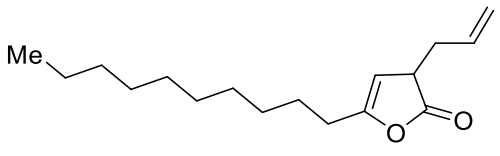


6-1l

d.r. = 1/1

^{1}H NMR (500 MHz, $CDCl_3$, mixture of two diastereomers) δ 5.06 – 4.97 (m, 2H), 3.17 (qt, *J* = 7.6, 2.0 Hz, 1H), 2.42 – 2.32 (m, 1H), 1.98 – 1.86 (m, 2H), 1.65 – 1.54 (m, 4H), 1.52 (s, 3H), 1.41 – 1.29 (m, 1H), 1.25 (d, *J* = 7.6 Hz, 3H), 1.07 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR (126 MHz, $CDCl_3$,** mixture of two diastereomers) δ 180.48, 180.47, 159.76, 159.66, 132.06, 132.05, 123.72, 103.93, 103.85, 39.52, 33.38, 33.34, 32.58, 32.51, 25.70, 25.33, 25.27, 17.68, 17.68, 17.23, 17.21, 16.02, 15.98; **HRMS (CI-TOF)**: calculated for $[M+H]^+$ ($C_{13}H_{21}O_2$) requires *m/z* 209.1542, found *m/z* 209.1540.

3-Allyl-5-decylfuran-2(3H)-one (6-1m)

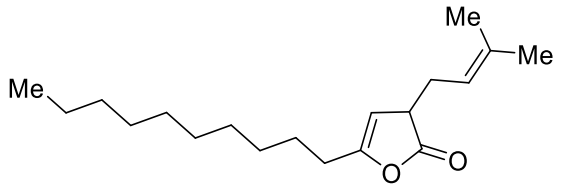


6-1m

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.80 – 5.70 (m, 1H), 5.15 – 5.07 (m, 3H), 3.33 – 3.26 (m, 1H), 2.62 – 2.55 (m, 1H), 2.36 – 2.23 (m, 3H), 1.60 – 1.49 (m, 2H), 1.36 – 1.20 (m, 14H), 0.87 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 178.98, 156.38, 133.69,

117.89, 102.58, 44.72, 34.95, 31.88, 29.55, 29.48, 29.29, 29.24, 28.93, 28.12, 25.66, 22.67, 14.11; **HRMS (CI-TOF)**: calculated for $[M+H]^+$ ($C_{17}H_{29}O_2$) requires *m/z* 265.2168, found *m/z* 265.2169.

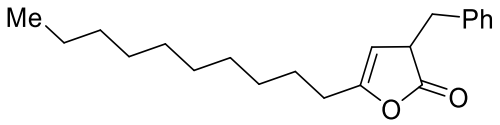
5-Decyl-3-(3-methylbut-2-en-1-yl)furan-2(3H)-one (6-1n)



6-1n

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.17 – 5.04 (m, 2H), 3.30 – 3.19 (m, 1H), 2.49 (dt, *J* = 12.8, 6.0 Hz, 1H), 2.38 – 2.26 (m, 3H), 1.71 (s, 3H), 1.63 (s, 3H), 1.58 – 1.49 (m, 2H), 1.39 – 1.22 (m, 14H), 0.89 (t, *J* = 6.9 Hz, 3H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 179.33, 156.12, 135.00, 119.29, 103.05, 45.32, 31.87, 29.56, 29.50, 29.38, 29.29, 29.26, 28.89, 28.12, 25.75, 25.71, 22.66, 17.90, 14.09; **HRMS (CI-TOF)**: calculated for $[M+H]^+$ ($C_{19}H_{33}O_2$) requires *m/z* 293.2480, found *m/z* 293.2490.

3-Benzyl-5-decylfuran-2(3H)-one (6-1o)

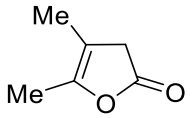


6-1o

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 7.25 – 7.21 (m, 1H), 7.20 – 7.15 (m, 2H), 5.07 – 5.01 (m, 1H), 3.53 – 3.46 (m, 1H), 3.20 (dd, *J* = 13.6, 4.9 Hz, 1H), 2.81 (dd, *J* = 13.6, 9.2 Hz, 1H), 2.25 – 2.17 (m, 2H), 1.49 – 1.41 (m, 2H), 1.35 – 1.16 (m, 14H), 0.88 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 178.82, 156.30, 137.63, 128.91, 128.49, 126.76, 102.58, 46.71, 37.05, 31.87, 29.55, 29.44, 29.29, 29.21, 28.78, 28.05,

25.60, 22.66, 14.11; **HRMS (CI-TOF)**: calculated for $[M+H]^+$ ($C_{21}H_{31}O_2$) requires *m/z* 315.2324, found *m/z* 315.2336.

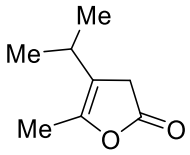
4,5-Dimethylfuran-2(3H)-one (6-1p)



6-1p

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.12 – 3.04 (m, 2H), 1.97 – 1.88 (m, 3H), 1.71 (q, *J* = 1.2 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 176.20, 146.22, 107.65, 37.89, 10.93, 10.79. ^{1}H and ^{13}C NMR are consistent with reported literature.[37]

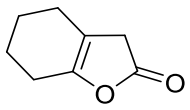
4-Isopropyl-5-methylfuran-2(3H)-one (6-1q)



6-1q

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.06 (qd, *J* = 2.4, 0.6 Hz, 2H), 2.65 (sept, *J* = 6.9 Hz, 1H), 1.92 (t, *J* = 2.5 Hz, 3H), 1.03 (d, *J* = 6.9 Hz, 6H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 176.33, 144.51, 117.84, 32.56, 25.02, 21.75, 11.09; **HRMS (CI-TOF)**: calculated for $[M+H]^+$ ($C_8H_{13}O_2$) requires *m/z* 141.0916, found *m/z* 141.0910.

4,5,6,7-Tetrahydrobenzofuran-2(3H)-one (6-1r)

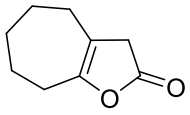


6-1r

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.12 – 3.01 (m, 2H), 2.25 – 2.20 (m, 2H), 2.08 – 2.04 (m, 2H), 1.80 – 1.76 (m, 2H), 1.71 – 1.66 (m, 2H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 176.56,

150.27, 110.58, 36.02, 22.47, 22.29, 22.27, 22.12. ^{1}H and ^{13}C NMR are consistent with reported literature.[39]

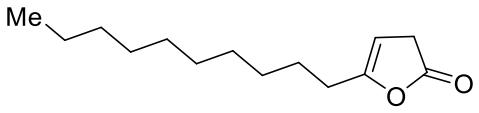
3,4,5,6,7,8-Hexahydro-2H-cyclohepta[b]furan-2-one (6-1s)



6-1s

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.17 – 3.11 (m, 2H), 2.49 – 2.39 (m, 2H), 2.17 – 2.10 (m, 2H), 1.73 – 1.62 (m, 6H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 176.53, 151.12, 113.27, 38.94, 28.66, 28.09, 27.99, 26.17, 25.83; **HRMS (CI-TOF)**: calculated for $[M+H]^+$ ($C_9H_{13}O_2$) requires *m/z* 153.0916, found *m/z* 153.0911.

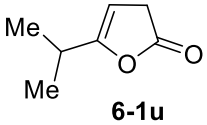
5-Decylfuran-2(3H)-one (6-1t)



6-1t

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.12 – 5.07 (m, 1H), 3.16 (q, *J* = 2.3 Hz, 2H), 2.30 – 2.24 (m, 2H), 1.54 (p, *J* = 7.5 Hz, 2H), 1.36 – 1.21 (m, 14H), 0.87 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 177.04, 157.31, 98.09, 33.92, 31.86, 29.54, 29.46, 29.28, 29.24, 28.98, 28.21, 25.67, 22.65, 14.09; **HRMS (CI-TOF)**: calculated for $[M+H]^+$ ($C_{14}H_{25}O_2$) requires *m/z* 225.1855, found *m/z* 225.1853.

5-Isopropylfuran-2(3H)-one (6-1u)

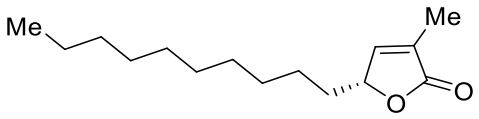


6-1u

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.08 – 5.01 (m, 1H), 3.14 (t, *J* = 2.4 Hz, 2H), 2.61 – 2.44 (m, 1H), 1.12 (d, *J* = 6.9 Hz, 6H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 177.09, 162.29, 96.11, 33.89, 27.76, 19.21. ^{1}H and ^{13}C NMR are consistent with reported literature[36].

Synthesis of Compound 6-2

(*R*)-5-Decyl-3-methylfuran-2(5H)-one (6-2a)



6-2a

To a 2-dram vial with **6-1a** (0.3 mmol. 67.3 mg) under argon protection, 5 mol% [(*S*)-**L2-13**Cu(MeCN)]$^+PF_6^-$ (13.8 mg) in 1.2 mL DCM was added and the reaction solution was stirred at room temperature for 30 min. The solvent was removed, and the residue was purified by flash column chromatography (hexanes/EtOAc = 10/1) to afford **6-2a** as a white solid (67.0 mg, 99% yield, 98% *ee*).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 – 6.96 (m, 1H), 4.91 – 4.80 (m, 1H), 1.94 – 1.84 (m, 3H), 1.72 – 1.54 (m, 2H), 1.50 – 1.04 (m, 16H), 0.85 (t, *J* = 6.7 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 174.32, 148.81, 129.72, 81.15, 33.46, 31.84, 29.51, 29.46, 29.36, 29.30, 29.25, 25.00, 22.63, 14.07, 10.58; **HRMS (CI-TOF)**: calculated for $[M+H]^+$ ($C_{15}H_{27}O_2$) requires *m/z* 239.2011, found *m/z* 239.2014; **$[\alpha]_D^{20}$** = -48.8° (*c* = 0.5, $CHCl_3$); **98% *ee*** [determined by HPLC: Chiralcel® Chiral IB column, Hexanes/*i*PrOH = 100/1, 1.0 mL/min, λ = 205 nm; t_R(major) = 9.959 min, t_R(minor) = 9.435 min].

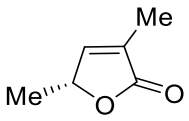
Gram-Scale Synthesis:

To a round bottom flask with substrate **6-1a** (4.5 mmol, 1.0727 g) under argon protection, 1 mol% [(*S*)-**L2-13**Cu(MeCN)]$^+PF_6^-$ (41.5 mg) in 18 mL DCM was added. The

reaction was stirred at room temperature for 1 h. Upon completion, the solvent was removed, and the residue was subjected to flash chromatography (hexanes/EA = 5/1) to afford **6-2a** as a white solid (988.2 mg, 92% yield, 99% *ee*).

99% *ee* [determined by HPLC: Chiralcel® Chiral IB column, Hexanes/*i*PrOH = 100/1, 1.0 mL/min, λ = 205 nm; t_R(major) = 8.930 min, t_R(minor) = 8.452 min].

(*R*)-3,5-Dimethylfuran-2(5H)-one (6-2b)

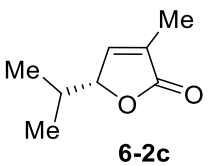


6-2b

To a 2-dram vial with **6-1b** (0.3 mmol. 33.6 mg) under argon protection, 5 mol% [(*S*)-**L2-13**Cu(MeCN)]$^+PF_6^-$ (13.8 mg) in 1.2 mL DCM was added and the reaction solution was stirred at room temperature for 30 min. The solvent was removed, and the residue was purified by flash column chromatography (hexanes/EtOAc = 5/1) to afford **6-2b** as a colorless oil (29.5 mg, 88% yield, 97% *ee*)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (p, *J* = 1.6 Hz, 1H), 5.03 – 4.91 (m, 1H), 1.90 (t, *J* = 1.8 Hz, 3H), 1.39 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 174.23, 149.83, 129.55, 77.30, 19.03, 10.52; ^{1}H NMR is consistent with reported literature.[36] **$[\alpha]_D^{20}$** = -53.1º (*c* = 0.16, $CHCl_3$); **97% *ee*** [determined by HPLC: Chiralcel® Chiral OJ-H column, Hexanes/*i*PrOH = 95/5, 1.0 mL/min, λ = 210 nm; t_R(major) = 14.373 min, t_R(minor) = 13.863 min].

(*R*)-5-Isopropyl-3-methylfuran-2(5H)-one (6-2c)

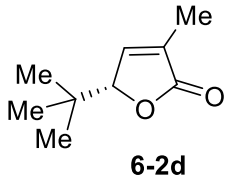


6-2c

To a 2-dram vial with **6-1c** (0.3 mmol. 42.3 mg) under argon protection, 5 mol% [(*S*)-**L2-13**Cu(MeCN)]$^{+}PF_6^{-}$ (13.8 mg) in 1.2 mL DCM was added and the reaction solution was stirred at room temperature for 30 min. The solvent was removed, and the residue was purified by flash column chromatography (hexanes/EtOAc = 5/1) to afford **6-2c** as a colorless oil (39.4 mg, 93% yield, 99% *ee*).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03 (p, *J* = 1.7 Hz, 1H), 4.67 (dp, *J* = 5.8, 1.9 Hz, 1H), 2.00 – 1.87 (m, 4H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 174.29, 147.20, 130.57, 85.69, 31.78, 17.83, 17.65, 10.65. ^{1}H NMR is consistent with reported literature.[36] **$[\alpha]_D^{20}$** = -48.5° (*c* = 0.21, $CHCl_3$); **99% *ee*** [determined by HPLC: Chiralcel® Chiral IB column, Hexanes/*i*PrOH = 100/1, 1.0 mL/min, λ = 210 nm; t_R(major) = 12.349 min, t_R(minor) = 11.826 min].

(*S*)-5-(tert-butyl)-3-Methylfuran-2(5H)-one (6-2d)



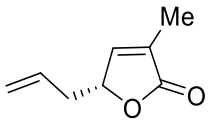
6-2d

To a 2-dram vial with **6-1d** (0.3 mmol. 46.3 mg) under argon protection, 5 mol% [(*S*)-**L2-13**Cu(MeCN)]$^{+}PF_6^{-}$ (13.8 mg) in 1.2 mL DCM was added and the reaction solution was stirred at room temperature for 2 h. The solvent was removed, and the residue was purified by flash column chromatography (hexanes/EtOAc = 5/1) to afford **6-2d** as a colorless oil (44.3 mg, 97% yield, 99% *ee*).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 – 7.01 (m, 1H), 4.57 – 4.53 (m, 1H), 1.92 (t, *J* = 1.8 Hz, 3H), 0.95 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 174.38, 146.56, 130.96, 88.61, 34.79, 25.38, 10.66. ^{1}H NMR is consistent with reported literature.[40] **$[\alpha]_D^{20}$** = -47.5° (*c* =

0.35, $CHCl_3$); **99% *ee*** [determined by HPLC: Chiralcel® Chiral IB column, Hexanes/*i*PrOH = 100/1, 1.0 mL/min, λ = 210 nm; t_R(major) = 9.947min, t_R(minor) = 8.961 min].

(*R*)-5-Allyl-3-methylfuran-2(5H)-one (6-2e)



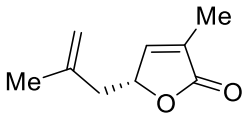
6-2e

To a 2-dram vial with **6-1e** (0.15 mmol. 23.7 mg) under argon protection, 5 mol% [(*S*)-**L2-13**Cu(MeCN)]$^+PF_6^-$ (6.9 mg) in 0.6 mL DCM was added and the reaction solution was stirred at room temperature for 30 min. The solvent was removed, and the residue was purified by flash column chromatography (hexanes/EtOAc = 5/1) to afford **6-2e** as a colorless oil (23.6 mg, 99% yield, 97% *ee*).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.05 – 7.01 (m, 1H), 5.74 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H), 5.19 – 5.12 (m, 2H), 4.94 – 4.87 (m, 1H), 2.51 – 2.44 (m, 1H), 2.44 – 2.37 (m, 1H), 1.90 (t, *J* = 1.8 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 174.02, 148.06, 131.34, 130.39, 119.26, 80.06, 37.58, 10.61.

^{1}H NMR and ^{13}C NMR are consistent with reported literature.[41] **$[\alpha]_D^{20}$** = -39.3° (*c* = 0.09, $CHCl_3$); **97% *ee*** [determined by HPLC: Chiralcel® Chiral IB column, Hexanes/*i*PrOH = 100/1, 1.0 mL/min, λ = 210 nm; t_R(major) = 15.681 min, t_R(minor) = 15.202 min].

(*R*)-3-Methyl-5-(2-methylallyl)furan-2(5H)-one (6-2f)

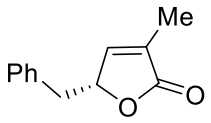


6-2f

To a 2-dram vial with **6-1f** (0.3 mmol. 45.6 mg) under argon protection, 5 mol% [(*S*)-**L2-13**Cu(MeCN)]$^{+}PF_6^{-}$ (13.8 mg) in 1.2 mL DCM was added and the reaction solution was stirred at room temperature for 30 min. The solvent was removed, and the residue was purified by flash column chromatography (hexanes/EtOAc = 5/1) to afford **6-2f** as a colorless oil (37.1 mg, 82% yield, 98% *ee*).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 – 7.02 (m, 1H), 5.02 – 4.96 (m, 1H), 4.91 – 4.87 (m, 1H), 4.81 – 4.78 (m, 1H), 2.40 (dd, *J* = 14.3, 7.3 Hz, 1H), 2.29 (dd, *J* = 14.3, 6.5 Hz, 1H), 1.90 (t, *J* = 1.8 Hz, 3H), 1.78 (t, *J* = 1.1 Hz, 3H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 173.97, 148.44, 139.89, 129.98, 114.07, 79.52, 41.53, 22.88, 10.56. ^{1}H NMR and ^{13}C NMR are consistent with reported literature.[42] **$[\alpha]_D^{20}$** = -70.7° (*c* = 0.26, $CHCl_3$); **98% *ee*** [determined by HPLC: Chiralcel® Chiral IB column, Hexanes/*i*PrOH = 100/1, 1.0 mL/min, λ = 210 nm; t_R(major) = 11.611 min, t_R(minor) = 10.744 min].

(*R*)-5-Benzyl-3-methylfuran-2(5H)-one (6-2g)



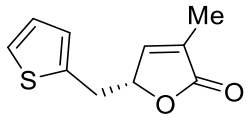
6-2g

To a 2-dram vial with **6-1g** (0.3 mmol. 56.6 mg) under argon protection, 5 mol% [(*S*)-**L2-13**Cu(MeCN)]$^{+}PF_6^{-}$ (13.8 mg) in 1.2 mL DCM was added and the reaction solution was stirred at room temperature for 30 min. The solvent was removed, and the residue was purified by flash column chromatography (hexanes/EtOAc = 5/1) to afford **6-2g** as a colorless oil (53.3 mg, 95% yield, 96% *ee*).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.30 (m, 2H), 7.29 – 7.25 (m, 1H), 7.25 – 7.20 (m, 2H), 7.04 – 6.97 (m, 1H), 5.12 – 5.03 (m, 1H), 3.10 (dd, *J* = 13.8, 6.6 Hz, 1H), 2.91 (dd, *J* = 13.8, 6.9 Hz, 1H), 1.88 (t, *J* = 1.8 Hz, 3H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 173.84,

147.95, 135.20, 130.34, 129.26, 128.53, 126.99, 81.15, 39.85, 10.52. ^{1}H NMR and ^{13}C NMR are consistent with reported literature.[43] **$[\alpha]_D^{20}$** = -96.9° (*c* = 0.39, $CHCl_3$); **96% *ee*** [determined by HPLC: Chiralcel® Chiral IC column, Hexanes/*i*PrOH = 90/10, 1.0 mL/min, λ = 210 nm; t_R(major) = 23.767 min, t_R(minor) = 29.650 min].

(*R*)-3-Methyl-5-(thiophen-2-ylmethyl)furan-2(5H)-one (6-2h)

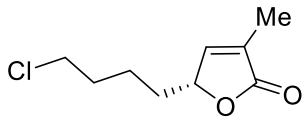


6-2h

To a 2-dram vial with **6-1h** (0.3 mmol. 55.2 mg) under argon protection, 5 mol% [(*S*)-**L2-13**Cu(MeCN)]$^{+}PF_6^{-}$ (13.8 mg) in 1.2 mL DCM was added and the reaction solution was stirred at room temperature for 30 min. The solvent was removed, and the residue was purified by flash column chromatography (hexanes/EtOAc = 7/1) to afford **6-2h** as light-yellow oil (54.5 mg, 99% yield, 98% *ee*).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.17 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.05 – 6.99 (m, 1H), 6.93 (dd, *J* = 5.1, 3.4 Hz, 1H), 6.87 (d, *J* = 3.4 fHz, 1H), 5.06 – 5.09 (m, 1H), 3.28 (dd, *J* = 14.9, 6.1 Hz, 1H), 3.16 (dd, *J* = 15.0, 6.7 Hz, 1H), 1.87 (t, *J* = 1.8 Hz, 3H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 173.69, 147.47, 136.48, 130.81, 126.99, 126.76, 124.63, 80.45, 33.65, 10.56; **HRMS (CI-TOF)**: calculated for $[M+H]^+$ ($C_{10}H_{11}O_2S$) requires *m/z* 195.0480, found *m/z* 95.0482; **$[\alpha]_D^{20}$** = -90.3° (*c* = 0.42, $CHCl_3$); **98% *ee*** [determined by HPLC: Chiralcel® Chiral IB column, Hexanes/*i*PrOH = 100/1, 1.0 mL/min, λ = 210 nm; t_R(major) = 16.333 min, t_R(minor) = 15.573 min].

(*R*)-5-(4-chlorobutyl)-3-Methylfuran-2(5H)-one (6-2i)

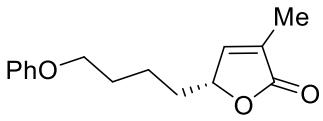


6-2i

To a 2-dram vial with **6-1i** (0.3 mmol. 56.6 mg) under argon protection, 5 mol% [(*S*)-**L2-13**Cu(MeCN)]$^{+}PF_6^{-}$ (13.8 mg) in 1.2 mL DCM was added and the reaction solution was stirred at room temperature for 30 min. The solvent was removed, and the residue was purified by flash column chromatography (hexanes/EtOAc = 10/1) to afford **6-2i** as a colorless oil (54.8 mg, 94% yield, 99% *ee*).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.02 (p, *J* = 1.6 Hz, 1H), 4.90 – 4.82 (m, 1H), 3.51 (t, *J* = 6.5 Hz, 2H), 1.89 (t, *J* = 1.8 Hz, 3H), 1.84 – 1.70 (m, 3H), 1.66 – 1.49 (m, 3H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 174.03, 148.35, 130.01, 80.68, 44.45, 32.62, 32.04, 22.37, 10.52; **HRMS (CI-TOF)**: calculated for $[M+H]^+$ ($C_9H_{14}ClO_2$) requires *m/z* 189.0682, found *m/z* 189.0675; **$[\alpha]_D^{20}$** = -44.7° (*c* = 0.38, $CHCl_3$); **99% *ee*** [determined by HPLC: Chiralcel® Chiral IB column, Hexanes/*i*PrOH = 100/1, 1.0 mL/min, λ = 210 nm; t_R(major) = 30.799 min, t_R(minor) = 29.326 min].

(*R*)-3-Methyl-5-(4-phenoxybutyl)furan-2(5H)-one (6-2j)

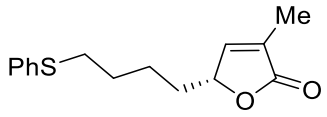


6-2j

To a 2-dram vial with **6-1j** (0.3 mmol. 73.9 mg) under argon protection, 5 mol% [(*S*)-**L2-13**Cu(MeCN)]$^{+}PF_6^{-}$ (13.8 mg) in 1.2 mL DCM was added and the reaction solution was stirred at room temperature for 30 min. The solvent was removed, and the residue was purified by flash column chromatography (hexanes/EtOAc = 10/1) to afford **6-2j** as a colorless oil (72.9 mg, 99% yield, 99% *ee*).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.24 (m, 2H), 7.04 (p, *J* = 1.6 Hz, 1H), 6.96 – 6.91 (m, 1H), 6.91 – 6.86 (m, 2H), 4.95 – 4.85 (m, 1H), 3.96 (t, *J* = 6.2 Hz, 2H), 1.92 (t, *J* = 1.8 Hz, 3H), 1.86 – 1.78 (m, 3H), 1.73 – 1.59 (m, 3H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 174.10, 158.76, 148.52, 129.81, 129.30, 120.51, 114.31, 80.82, 67.15, 33.08, 28.85, 21.72, 10.49; **HRMS (CI-TOF)**: calculated for $[M+H]^+$ ($C_{15}H_{19}O_3$) requires *m/z* 247.1334, found *m/z* 247.1342; **$[\alpha]_D^{20}$** = -38.5° (*c* = 0.46, $CHCl_3$); **99% *ee*** [determined by HPLC: Chiralcel® Chiral AS-H column, Hexanes/*i*PrOH = 90/10, 1.0 mL/min, λ = 210 nm; t_R(major) = 29.442 min, t_R(minor) = 17.002 min].

(*R*)-3-Methyl-5-(4-(phenylthio)butyl)furan-2(5H)-one (6-2k)

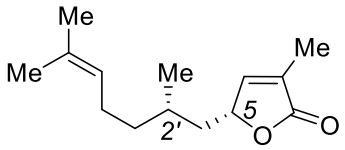


6-2k

To a 2-dram vial with **6-1k** (0.3 mmol. 78.7 mg) under argon protection, 5 mol% [(*S*)-**L2-13**Cu(MeCN)]$^+PF_6^-$ (13.8 mg) in 1.2 mL DCM was added and the reaction solution was stirred at room temperature for 30 min. The solvent was removed, and the residue was purified by flash column chromatography (hexanes/EtOAc = 10/1) to afford **6-2k** as a colorless oil (77.6 mg, 99% yield, 99% *ee*).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.23 (m, 4H), 7.20 – 7.14 (m, 1H), 7.00 (p, *J* = 1.6 Hz, 1H), 4.92 – 4.80 (m, 1H), 2.92 (t, *J* = 7.1 Hz, 2H), 1.91 (t, *J* = 1.8 Hz, 3H), 1.78 – 1.54 (m, 6H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 174.14, 148.38, 136.43, 130.10, 129.14, 128.89, 125.93, 80.78, 33.36, 33.01, 28.84, 24.17, 10.63; **HRMS (CI-TOF)**: calculated for $[M+H]^+$ ($C_{15}H_{19}O_2S$) requires *m/z* 263.1106, found *m/z* 263.1108; **$[\alpha]_D^{20}$** = -48.0° (*c* = 0.10, $CHCl_3$); **99% *ee*** [determined by HPLC: Chiralcel® Chiral AS-H column, Hexanes/*i*PrOH = 90/10, 1.0 mL/min, λ = 210 nm; t_R(major) = 22.721 min, t_R(minor) = 15.435 min].

(*R*)-3-Methyl-5-((S)-6-methylhept-5-en-2-yl)furan-2(5H)-one [(5*R*,2'S)-6-2l]

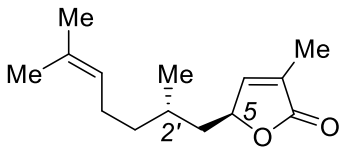


(5*R*, 2'*S*)-6-2l

To a 2-dram vial with **6-1l** (0.3 mmol. 62.5 mg) under argon protection, 5 mol% [(*S*)-**L2-13**Cu(MeCN)]$^{+}PF_6^{-}$ (13.8 mg) in 1.2 mL DCM was added and the reaction solution was stirred at room temperature for 30 min. The solvent was removed, and the residue was purified by flash column chromatography (hexanes/EtOAc = 10/1) to afford **(5*R*,2'S)-6-2l** as a colorless oil (54.3 mg, 87% yield, 99% *de*).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.00 (p, *J* = 1.6 Hz, 1H), 5.09 – 5.00 (m, 1H), 4.82 – 4.75 (m, 1H), 2.10 – 2.01 (m, 1H), 2.00 – 1.94 (m, 1H), 1.90 (t, *J* = 1.8 Hz, 3H), 1.85 – 1.78 (m, 1H), 1.66 (s, 3H), 1.57 (s, 3H), 1.51 – 1.43 (m, 1H), 1.25 – 1.17 (m, 1H), 0.87 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 174.40, 147.61, 131.99, 130.32, 123.65, 84.48, 35.67, 32.41, 25.63, 25.27, 17.62, 14.07, 10.61; **HRMS (CI-TOF)**: calculated for $[M+H]^+$ ($C_{13}H_{21}O_2$) requires *m/z* 209.1542, found *m/z* 209.1545; **$[\alpha]_D^{20}$** = -35.1° (*c* = 0.48, $CHCl_3$); **99% *de*** [determined by HPLC: Chiralcel® Chiral AS-H column, Hexanes/*i*PrOH = 90/10, 1.0 mL/min, λ = 210 nm; t_R(major) = 7.122 min, t_R(minor) = 5.707 min].

(*S*)-3-Methyl-5-((S)-6-methylhept-5-en-2-yl)furan-2(5H)-one [(5*S*,2'*S*)- 6-2l]



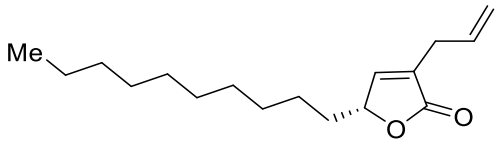
(5*S*, 2'*S*)-6-2l

To a 2-dram vial with **6-1l** (0.3 mmol. 62.5 mg) under argon protection, 5 mol% [(*R*)-**L2-13**Cu(MeCN)]$^{+}PF_6^{-}$ (13.6 mg) in 1.2 mL DCM was added and the reaction solution

was stirred at room temperature for 30 min. The solvent was removed, and the residue was purified by flash column chromatography (hexanes/EtOAc = 10/1) to afford **(5*S*,2'*S*)-6-2l** as a colorless oil (56.2 mg, 90% yield, 99% *de*).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.01 (p, *J* = 1.7 Hz, 1H), 5.10 – 4.98 (m, 1H), 4.80 – 4.71 (m, 1H), 2.12 – 2.01 (m, 1H), 2.01 – 1.92 (m, 1H), 1.90 (t, *J* = 1.8 Hz, 3H), 1.87 – 1.80 (m, 1H), 1.65 (d, *J* = 1.4 Hz, 3H), 1.57 (s, 3H), 1.52 – 1.45 (m, 1H), 1.25 – 1.16 (m, 1H), 0.88 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 174.16, 147.05, 132.01, 130.61, 123.63, 84.90, 35.93, 32.14, 25.60, 25.24, 17.59, 14.53, 10.60; **$[\alpha]_D^{20}$** = +95.7° (*c* = 0.43, $CHCl_3$); **99% *de*** [determined by HPLC: Chiralcel® Chiral AS-H column, Hexanes/*i*PrOH = 90/10, 1.0 mL/min, λ = 210 nm; t_R(major) = 5.682 min, t_R(minor) = 7.143 min].

(*R*)-3-Allyl-5-decylfuran-2(5H)-one (6-2m)



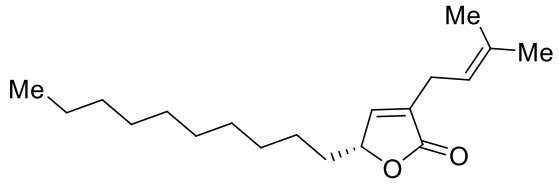
6-2m

To a 2-dram vial with **6-1m** (0.3 mmol. 79.6 mg) under argon protection, 5 mol% [(*S*)-**L2-13**Cu(MeCN)]$^+PF_6^-$ (13.6 mg) in 1.2 mL DCM was added and the reaction solution was stirred at room temperature for 30 min. The solvent was removed, and the residue was purified by flash column chromatography (hexanes/EtOAc = 10/1) to afford **6-2m** as a white solid (79.3 mg, 99% yield, 99% *ee*).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.02 (q, *J* = 1.6 Hz, 1H), 5.87 (ddt, *J* = 16.9, 10.1, 6.8 Hz, 1H), 5.19 – 5.10 (m, 2H), 4.88 – 4.91 (m, 1H), 3.02 (dp, *J* = 6.6, 1.6 Hz, 2H), 1.75 – 1.66 (m, 1H), 1.66 – 1.57 (m, 1H), 1.47 – 1.20 (m, 16H), 0.87 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR**

(101 MHz, $CDCl_3$) δ 173.44, 148.82, 133.18, 132.73, 117.67, 81.48, 33.50, 31.86, 29.55, 29.54, 29.48, 29.37, 29.32, 29.28, 25.02, 22.66, 14.10; **HRMS (CI-TOF)**: calculated for $[M+H]^+$ ($C_{17}H_{29}O_2$) requires *m/z* 265.2168, found *m/z* 265.2170; **$[\alpha]_D^{20}$** = -23.5° (*c* = 0.53, $CHCl_3$); **99% *ee*** [determined by HPLC: Chiralcel® Chiral IB column, Hexanes/*i*PrOH = 100/1, 1.0 mL/min, λ = 205 nm; t_R(major) = 8.373 min, t_R(minor) = 7.954 min].

(*R*)-5-Decyl-3-(3-methylbut-2-en-1-yl)furan-2(5H)-one (6-2n)



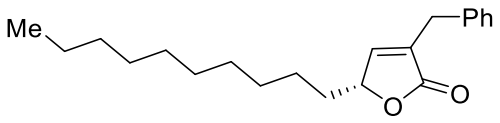
6-2n

To a 2-dram vial with **6-1n** (0.3 mmol. 88.1 mg) under argon protection, 5 mol% [(*S*)-**L2-13**Cu(MeCN)]$^+PF_6^-$ (13.6 mg) in 1.2 mL DCM was added and the reaction solution was stirred at room temperature for 30 min. The solvent was removed, and the residue was purified by flash column chromatography (hexanes/EtOAc = 10/1) to afford **6-2n** as a white solid (87.1 mg, 99% yield, 98% *ee*).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (q, *J* = 1.7 Hz, 1H), 5.29 – 5.18 (m, 1H), 4.91 – 4.84 (m, 1H), 2.95 (d, *J* = 7.1 Hz, 2H), 1.75 (s, 3H), 1.73 – 1.56 (m, 2H), 1.64 (s, 3H), 1.50 – 1.19 (m, 16H), 0.88 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 173.79, 147.89, 134.94, 133.71, 118.75, 81.45, 33.54, 31.87, 29.55, 29.49, 29.39, 29.34, 29.28, 25.65, 25.02, 24.16, 22.66, 17.80, 14.10; **HRMS (CI-TOF)**: calculated for $[M+H]^+$ ($C_{19}H_{33}O_2$) requires *m/z* 293.2480, found *m/z* 293.2471.

$[\alpha]_D^{20}$ = -6.8° (*c* = 0.66, $CHCl_3$); **98% *ee*** [determined by HPLC: Chiralcel® Chiral IB column, Hexanes/*i*PrOH = 100/1, 1.0 mL/min, λ = 205 nm; t_R(major) = 7.137 min, t_R(minor) = 6.886 min].

(*R*)-3-Benzyl-5-decylfuran-2(5H)-one (6-2o)

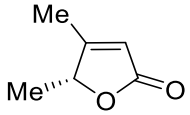


6-2o

To a 2-dram vial with **6-1o** (0.3 mmol. 93.9 mg) under argon protection, 5 mol% [(*S*)-**L2-13**Cu(MeCN)]$^{+}PF_6^{-}$ (13.6 mg) in 1.2 mL DCM was added and the reaction solution was stirred at room temperature for 30 min. The solvent was removed, and the residue was purified by flash column chromatography (hexanes/EtOAc = 10/1) to afford **6-2o** as a white solid (93.5 mg, 99% yield, 96% *ee*).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.29 (m, 2H), 7.28 – 7.25 (m, 1H), 7.24 – 7.21 (m, 2H), 6.81 (q, *J* = 1.7 Hz, 1H), 4.91 – 4.84 (m, 1H), 3.64 – 3.54 (m, 2H), 1.75 – 1.53 (m, 2H), 1.46 – 1.19 (m, 16H), 0.88 (t, *J* = 6.9 Hz, 3H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 173.43, 149.24, 137.48, 134.25, 128.88, 128.71, 126.74, 81.46, 33.42, 31.86, 31.75, 29.53, 29.46, 29.35, 29.29, 29.27, 24.96, 22.66, 14.09; **HRMS (CI-TOF)**: calculated for $[M+H]^+$ ($C_{21}H_{31}O_2$) requires *m/z* 315.2324, found *m/z* 315.2321; **$[\alpha]_D^{20}$** = -3.7° (*c* = 0.51, $CHCl_3$); **96% *ee*** [determined by HPLC: Chiralcel® Chiral IB column, Hexanes/*i*PrOH = 100/1, 1.0 mL/min, λ = 205 nm; t_R(major) = 10.641 min, t_R(minor) = 10.063 min].

(*R*)-4,5-Dimethylfuran-2(5H)-one (6-2p)



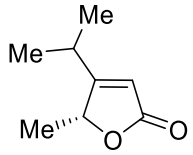
6-2p

To a 2-dram vial with **6-1p** (0.3 mmol. 33.8 mg) under argon protection, 5 mol% [(*S*)-**L2-13**Cu(MeCN)]$^{+}PF_6^{-}$ (13.6 mg) in 1.2 mL DCM was added and the reaction solution was stirred at room temperature for 30 min. The solvent was removed, and the residue was

purified by flash column chromatography (hexanes/EtOAc = 3/1) to afford **6-2p** as a colorless oil (25.6 mg, 76% yield, 99% *ee*).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 – 5.69 (m, 1H), 4.95 – 4.82 (m, 1H), 2.07 – 2.03 (m, 3H), 1.43 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 173.00, 169.68, 116.36, 80.94, 18.01, 13.63. ^{1}H NMR and ^{13}C NMR are consistent with reported literature.[44] **99% *ee*** [determined by HPLC: Chiralcel® Chiral OJ-H column, Hexanes/*i*PrOH = 90/10, 1.0 mL/min, λ = 210 nm; t_R(major) = 14.619 min, t_R(minor) = 14.066 min].

(*R*)-4-Isopropyl-5-methylfuran-2(5H)-one (6-2q)

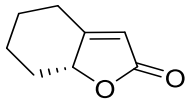


6-2q

To a 2-dram vial with **6-1q** (0.3 mmol. 42.2 mg) under argon protection, 5 mol% [(*S*)-**L2-13**Cu(MeCN)]$^+PF_6^-$ (13.6 mg) in 1.2 mL DCM was added and the reaction solution was stirred at room temperature for 2 h. The solvent was removed, and the residue was purified by flash column chromatography (hexanes/EtOAc = 3/1) to afford **6-2q** as a colorless oil (40.0 mg, 95% yield, 99% *ee*).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77 – 5.69 (m, 1H), 5.05 – 4.98 (m, 1H), 2.56 (sept, *J* = 6.5 Hz, 1H), 1.44 (d, *J* = 6.8 Hz, 3H), 1.24 (d, *J* = 6.7 Hz, 3H), 1.15 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 179.89, 173.07, 113.55, 79.52, 27.49, 21.49, 20.41, 18.33. ^{1}H NMR is consistent with reported literature.[45] **$[\alpha]_D^{20}$** = -13.8° (*c* = 0.19, $CHCl_3$); **99% *ee*** [determined by HPLC: Chiralcel® Chiral IC column, Hexanes/*i*PrOH = 80/20, 1.0 mL/min, λ = 210 nm; t_R(major) = 18.539 min, t_R(minor) = 27.492 min].

(*R*)-5,6,7,7a-Tetrahydrobenzofuran-2(4H)-one (6-2r)

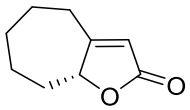


6-2r

To a 2-dram vial with **6-1r** (0.3 mmol. 42.0 mg) under argon protection, 5 mol% [(*S*)-**L2-13**Cu(MeCN)]$^{+}PF_6^{-}$ (13.6 mg) in 1.2 mL DCM was added and the reaction solution was stirred at room temperature for 3 h. The solvent was removed, and the residue was purified by flash column chromatography (hexanes/EtOAc = 4/1) to afford **6-2r** as a white solid (32.5 mg, 77% yield, 97% *ee*).

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.81 – 5.61 (m, 1H), 4.73 – 4.61 (m, 1H), 2.83 – 2.87 (m, 1H), 2.57 – 2.49 (m, 1H), 2.30 – 2.21 (m, 1H), 2.06 – 1.99 (m, 1H), 1.95 – 1.88 (m, 1H), 1.46 (qt, *J* = 13.6, 3.2 Hz, 1H), 1.38 – 1.24 (m, 2H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 173.45, 171.95, 112.42, 81.45, 34.41, 28.19, 26.63, 22.55. ^{1}H NMR and ^{13}C NMR are consistent with reported literature.[46] **$[\alpha]_D^{20}$** = -113.5° (*c* = 0.23, $CHCl_3$); **97% *ee*** [determined by HPLC: Chiralcel® Chiral IC column, Hexanes/*i*PrOH = 70/30, 1.5 mL/min, λ = 210 nm; t_R(major) = 20.724 min, t_R(minor) = 23.399 min].

(*R*)-4,5,6,7,8,8a-Hexahydro-2H-cyclohepta[b]furan-2-one (6-2s)



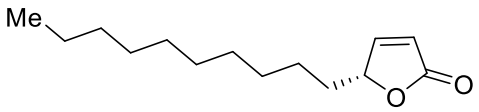
6-2s

To a 2-dram vial with **6-1s** (0.3 mmol. 45.7 mg) under argon protection, 5 mol% [(*S*)-**L2-13**Cu(MeCN)]$^{+}PF_6^{-}$ (13.6 mg) in 1.2 mL DCM was added and the reaction solution was stirred at room temperature for 4 h. The solvent was removed, and the residue was

purified by flash column chromatography (hexanes/EtOAc = 4/1) to afford **6-2s** as a white solid (40.8 mg, 89% yield, 99% *ee*).

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.76 – 5.77 (m, 1H), 4.99 – 4.92 (m, 1H), 2.79 – 2.72 (m, 1H), 2.72 – 2.64 (m, 1H), 2.36 – 2.30 (m, 1H), 1.91 – 1.76 (m, 3H), 1.63 – 1.45 (m, 3H), 1.40 – 1.29 (m, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 174.93, 173.46, 115.56, 85.04, 33.24, 29.60, 28.60, 25.94, 25.72. ^{1}H NMR and ^{13}C NMR are consistent with reported literature.[47] **$[\alpha]_D^{20}$** = -124.3° (*c* = 0.29, $CHCl_3$); **99% *ee*** [determined by HPLC: Chiralcel® Chiral IA column, Hexanes/*i*PrOH = 90/10, 1.0 mL/min, λ = 210 nm; t_R(major) = 10.075 min, t_R(minor) = 11.123 min].

(*R*)-5-Decylfuran-2(5H)-one (6-2t)



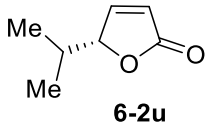
6-2t

To a 2-dram vial with **6-1t** (0.3 mmol. 67.3 mg) under argon protection, 5 mol% [(*S*)-**L2-13**Cu(MeCN)]$^+PF_6^-$ (13.6 mg) in 1.2 mL DCM was added and the reaction solution was stirred at 40 ℃ for 20 h. The solvent was removed, and the residue was purified by flash column chromatography (hexanes/EtOAc = 10/1) to afford **6-2t** as a white solid (42.1 mg, 63% yield, 81% yield based on conversion, 96% *ee*) and recovery 15.5 mg **6-1t**.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 (dd, *J* = 5.7, 1.4 Hz, 1H), 6.09 (dd, *J* = 5.7, 2.0 Hz, 1H), 5.02 (ddt, *J* = 7.3, 5.3, 1.8 Hz, 1H), 1.79 – 1.71 (m, 1H), 1.69 – 1.61 (m, 1H), 1.48 – 1.19 (m, 16H), 0.87 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 173.14, 156.29, 121.45, 83.42, 33.15, 31.84, 29.51, 29.45, 29.33, 29.26, 29.25, 24.93, 22.63, 14.07. ^{1}H NMR and ^{13}C NMR are consistent with reported literature.[46] **$[\alpha]_D^{20}$** = -47.9° (*c* = 0.29,

$CHCl_3$); **96% *ee*** [determined by HPLC: Chiralcel® Chiral IC column, Hexanes/*i*PrOH = 90/10, 1.0 mL/min, λ = 210 nm; t_R(major) = 28.693 min, t_R(minor) = 33.485 min].

(*R*)-5-Isopropylfuran-2(5H)-one (6-2u)



6-2u

To a 2-dram vial with **6-1u** (0.3 mmol. 37.9 mg) under argon protection, 5 mol% [(*S*)-**L2-13**Cu(MeCN)]$^+PF_6^-$ (13.6 mg) in 1.2 mL DCM was added and the reaction solution was stirred at 40 ℃ for 17 h. The solvent was removed, and the residue was purified by flash column chromatography (hexanes/EtOAc = 3/1) to afford **6-2u** as a colorless oil (18.1 mg, 48% yield, 97% *ee*).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 5.8, 1.4 Hz, 1H), 6.14 (dd, *J* = 5.8, 2.0 Hz, 1H), 4.85 (dt, *J* = 5.7, 1.7 Hz, 1H), 2.06 – 1.98 (m, 1H), 0.996 (d, *J* = 6.6 Hz, 3H), 0.992 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 173.13, 154.80, 122.23, 87.95, 31.60, 17.85, 17.56. ^{1}H NMR and ^{13}C NMR are consistent with reported literature.[36] **$[\alpha]_D^{20}$** = -92.9º (*c* = 0.08, $CHCl_3$); **97% *ee*** [determined by HPLC: Chiralcel® Chiral IB column, Hexanes/*i*PrOH = 100/1, 1.0 mL/min, λ = 210 nm; t_R(major) = 18.964 min, t_R(minor) = 18.172 min].

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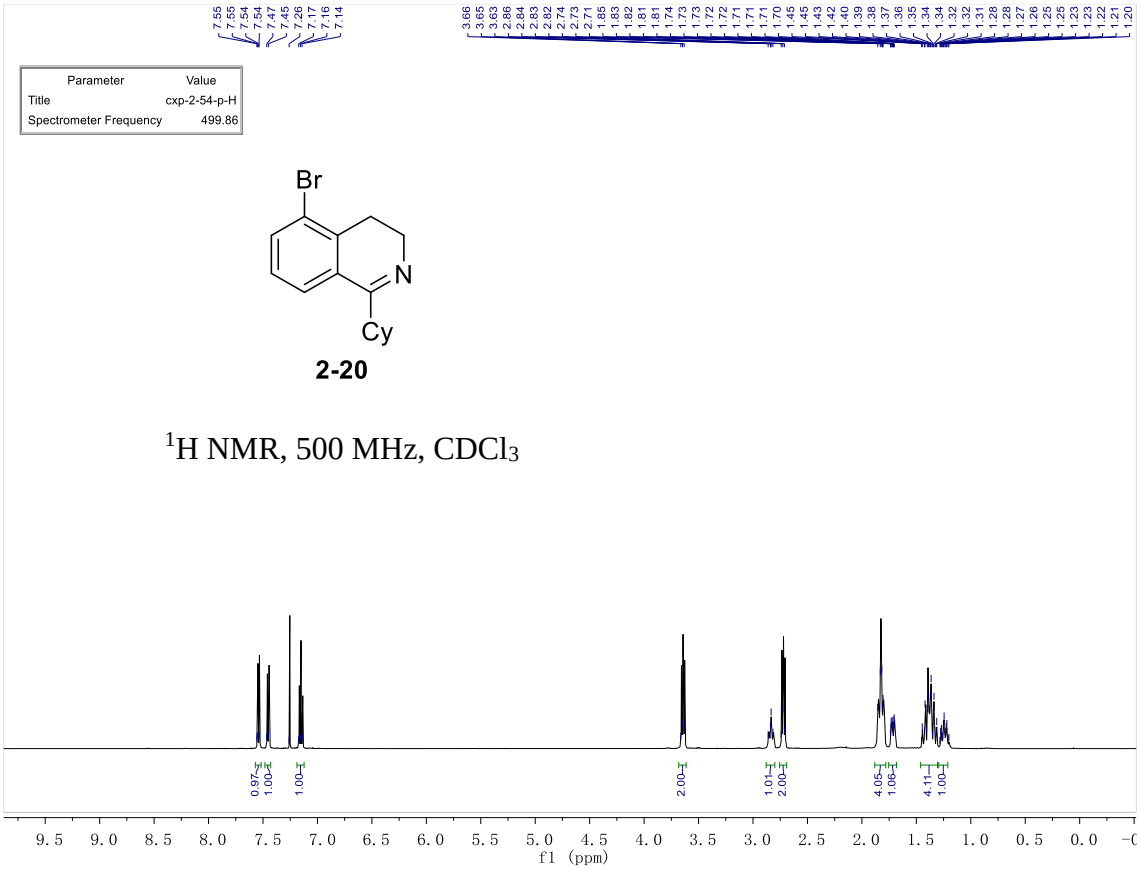
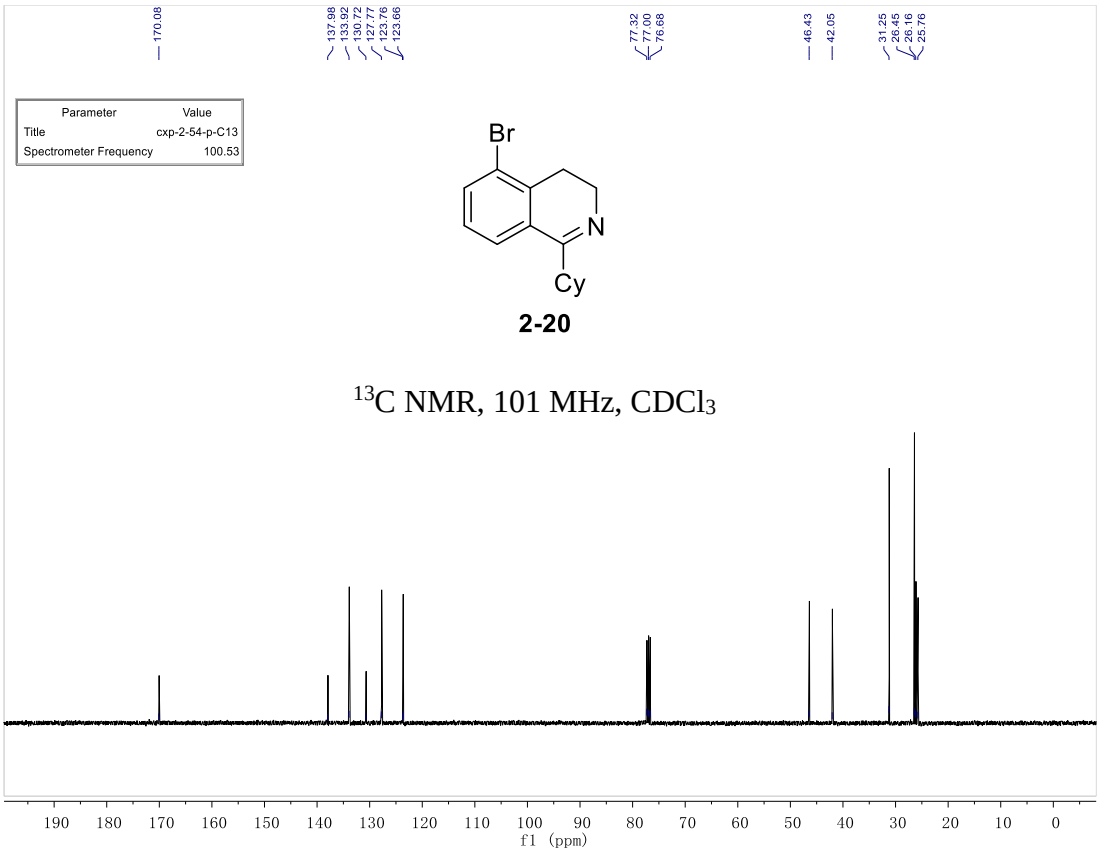
7. Selected Ligands and Catalyst Spectrum





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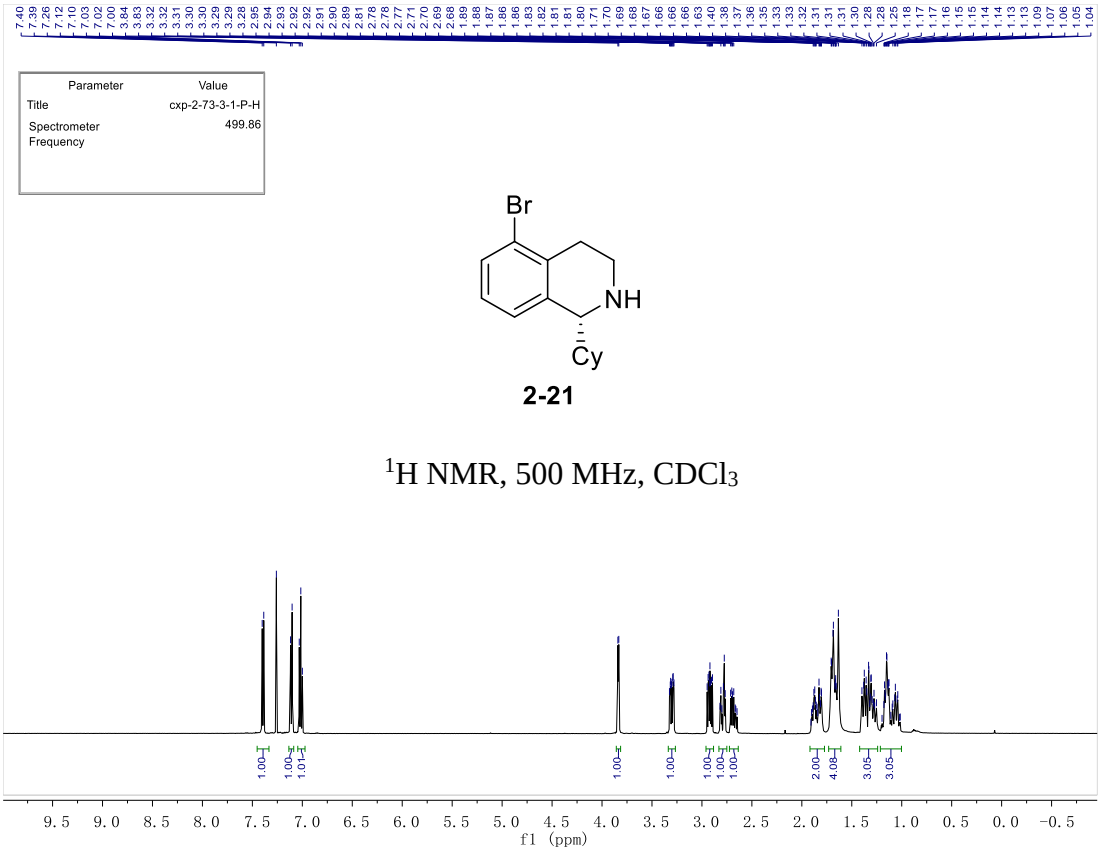

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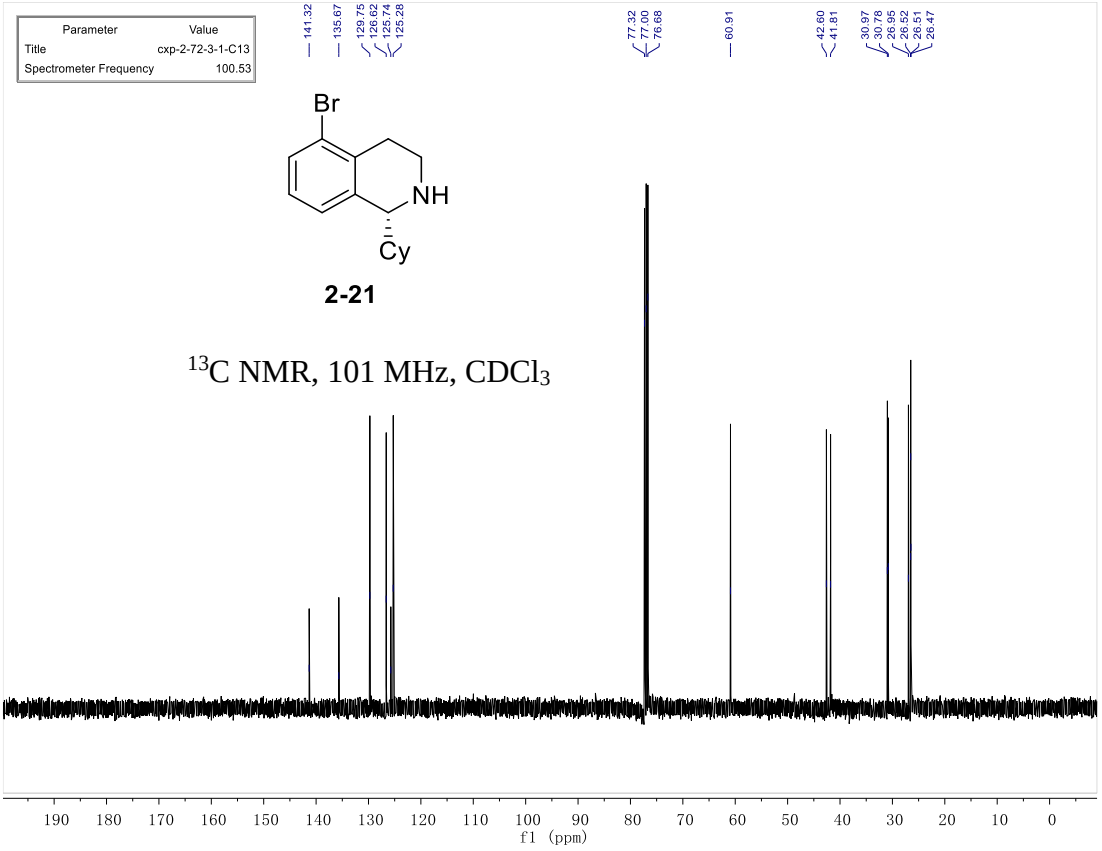
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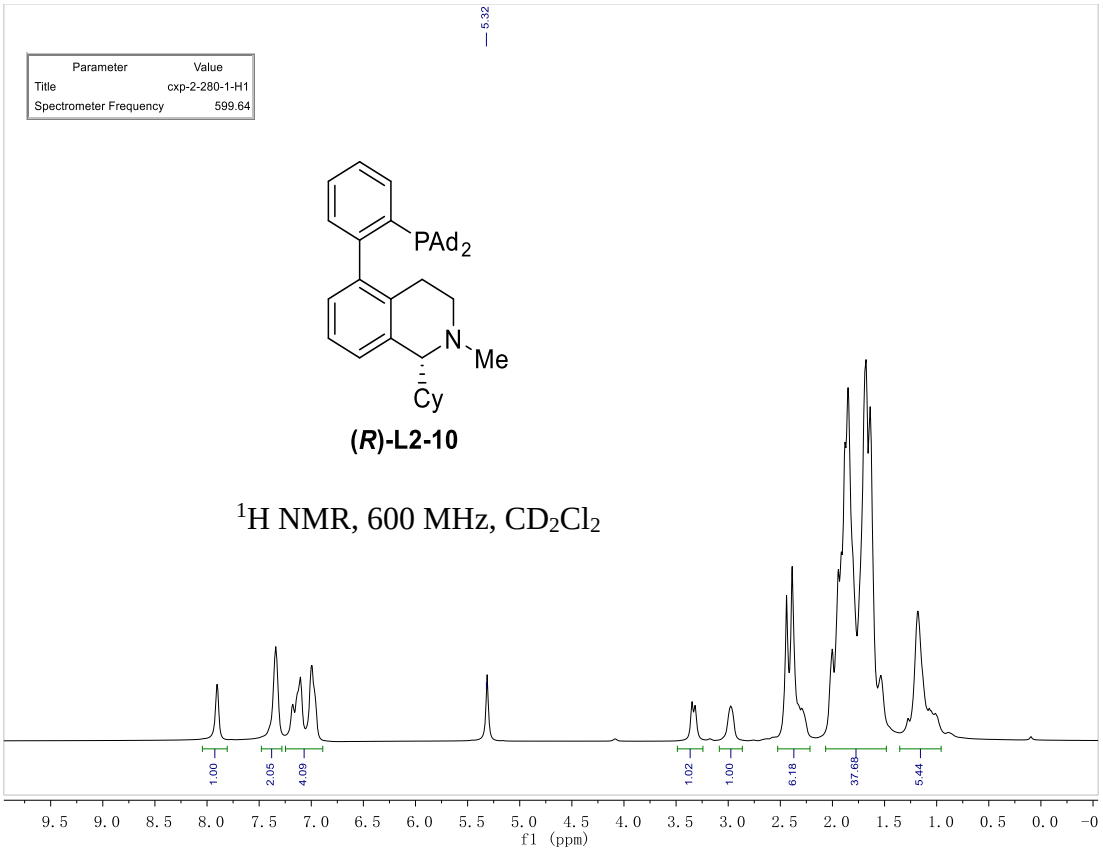
26.47
Br
NH
Cy
2-21
13C NMR, 101 MHz, CDCl3
f1 (ppm)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1.00
6.18
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5.44
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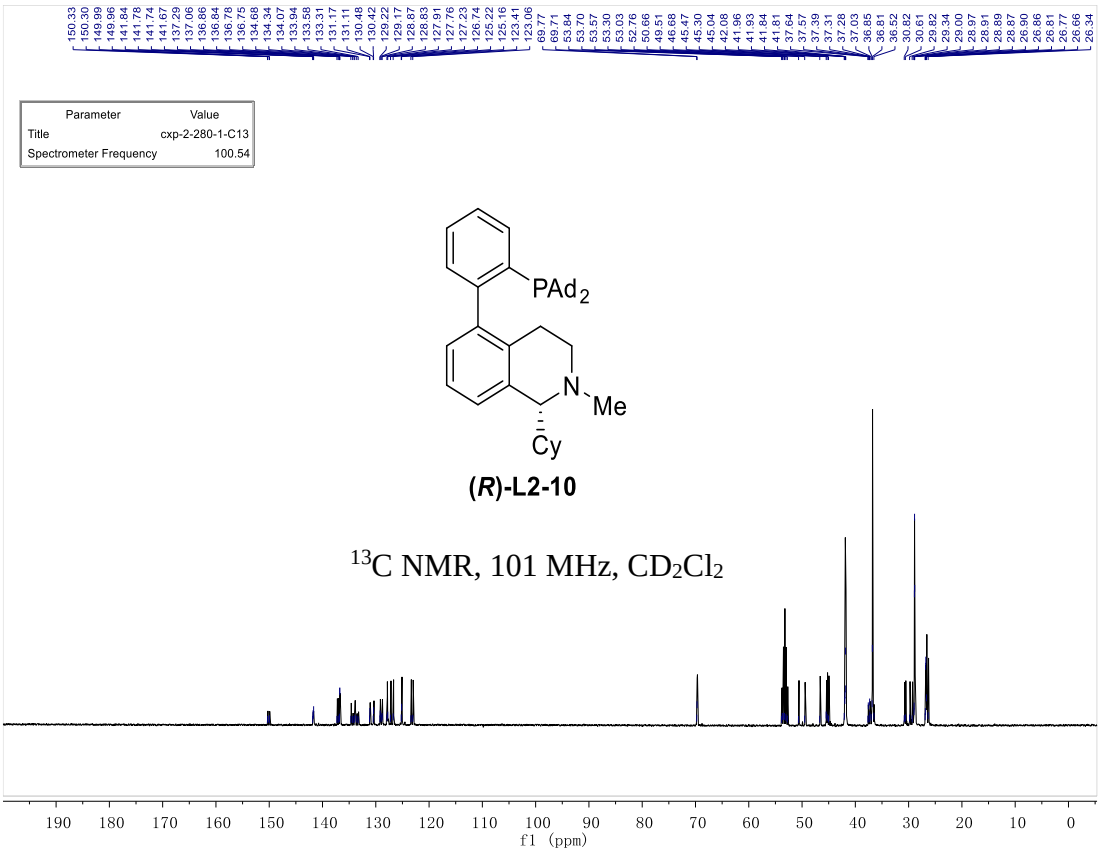
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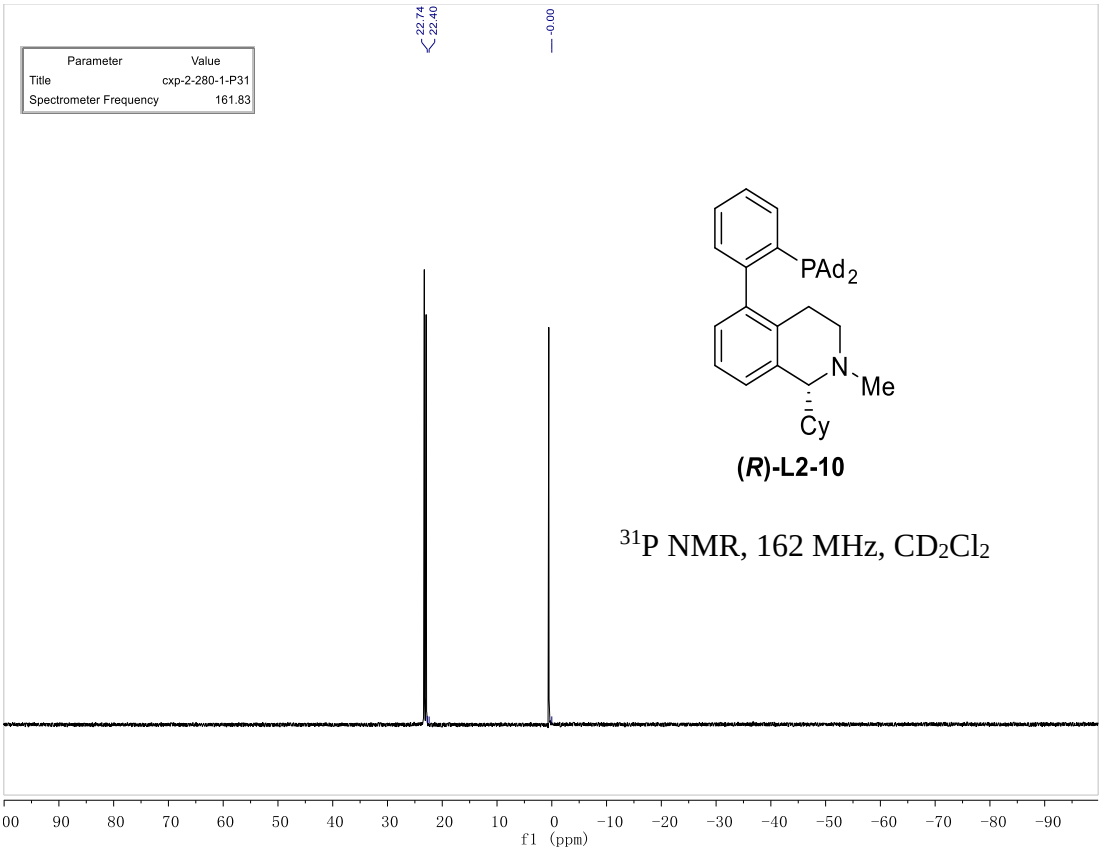
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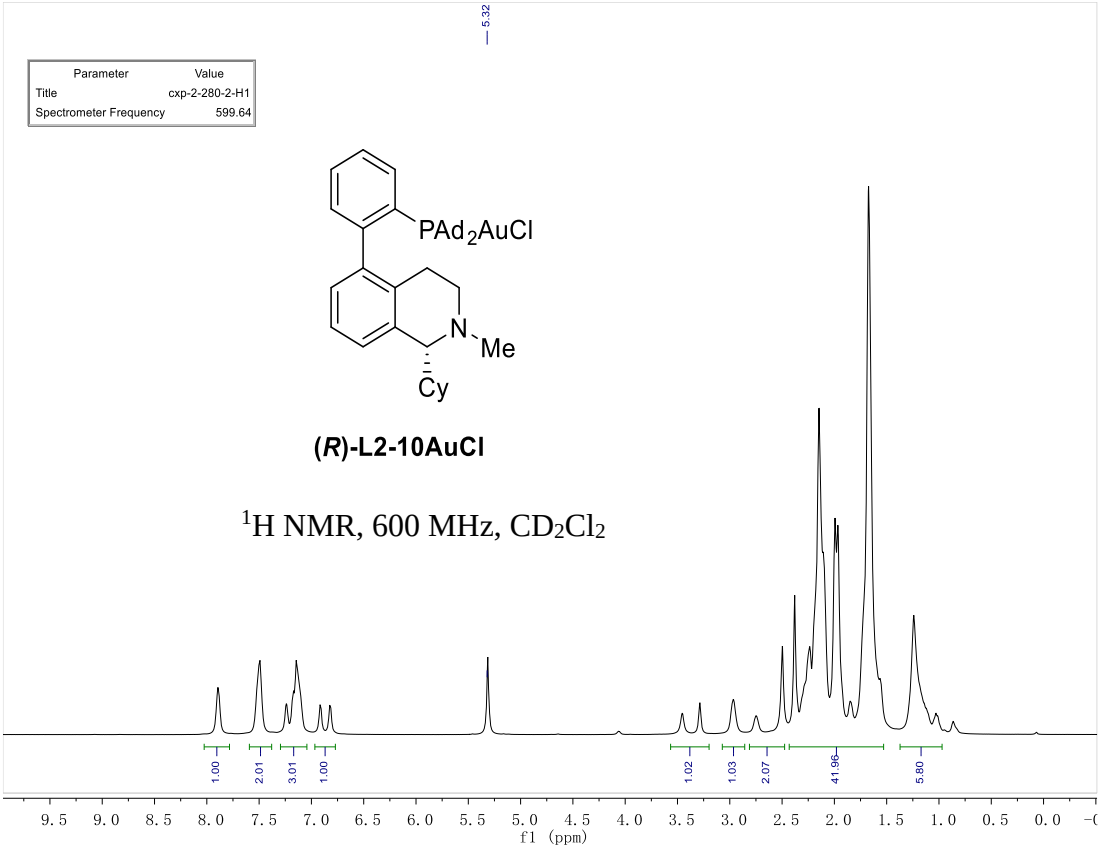
f1 (ppm)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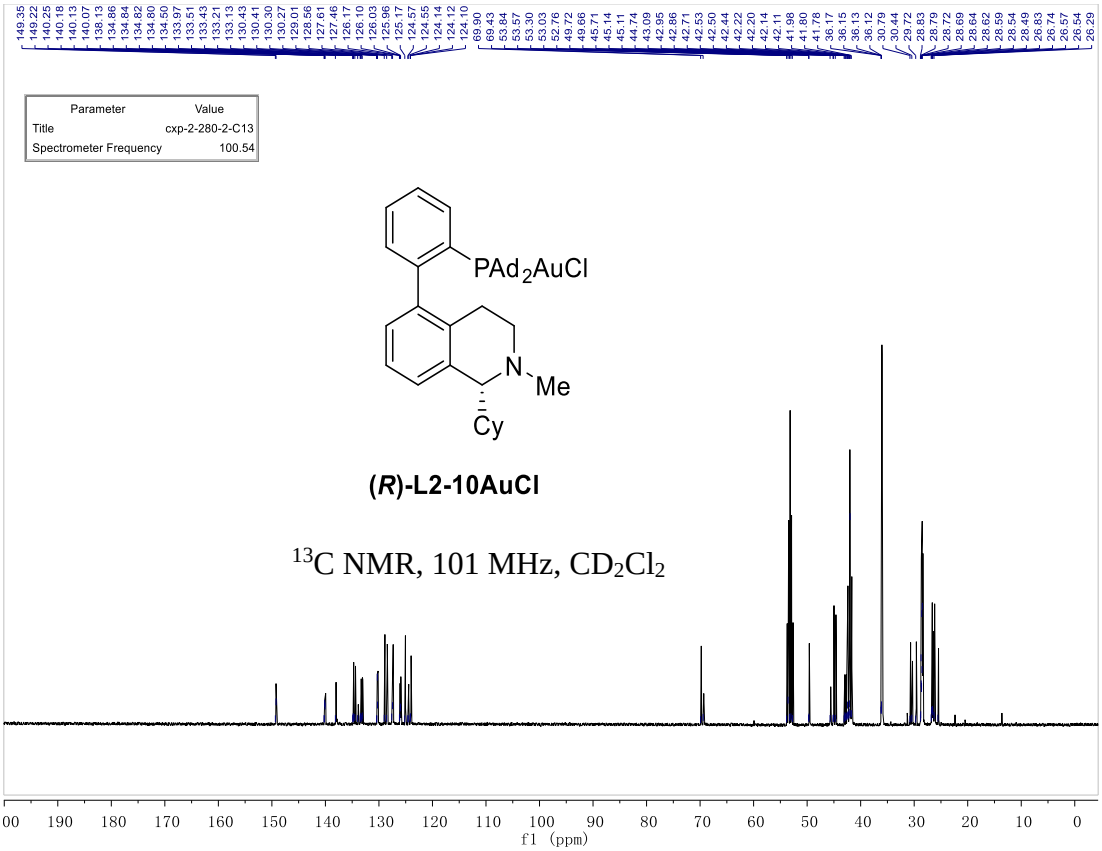
f1 (ppm)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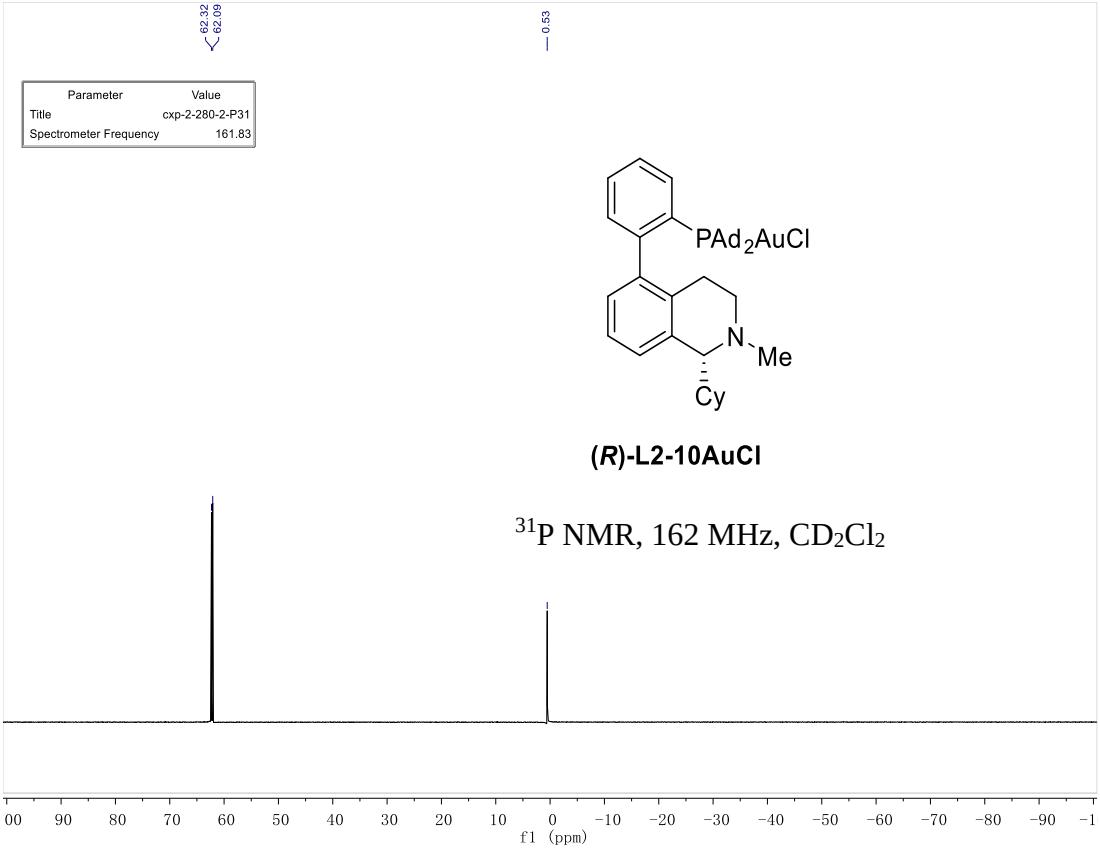
f1 (ppm)



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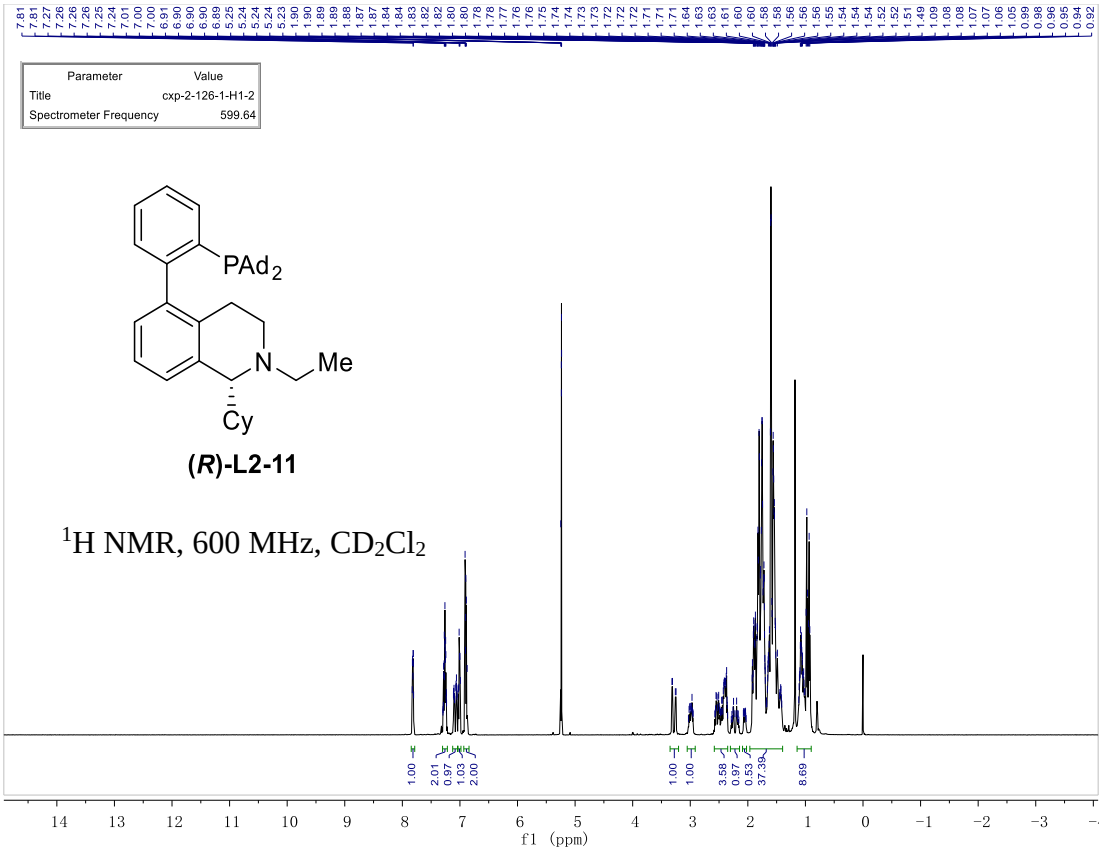

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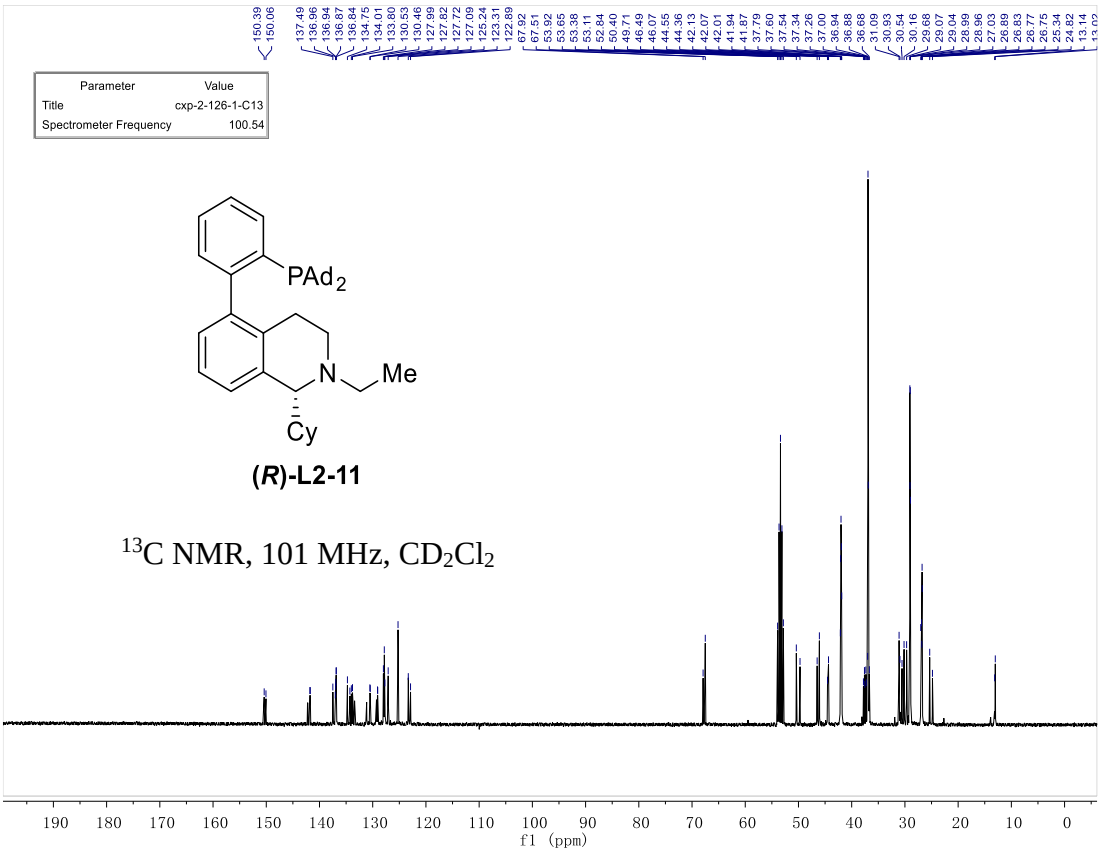
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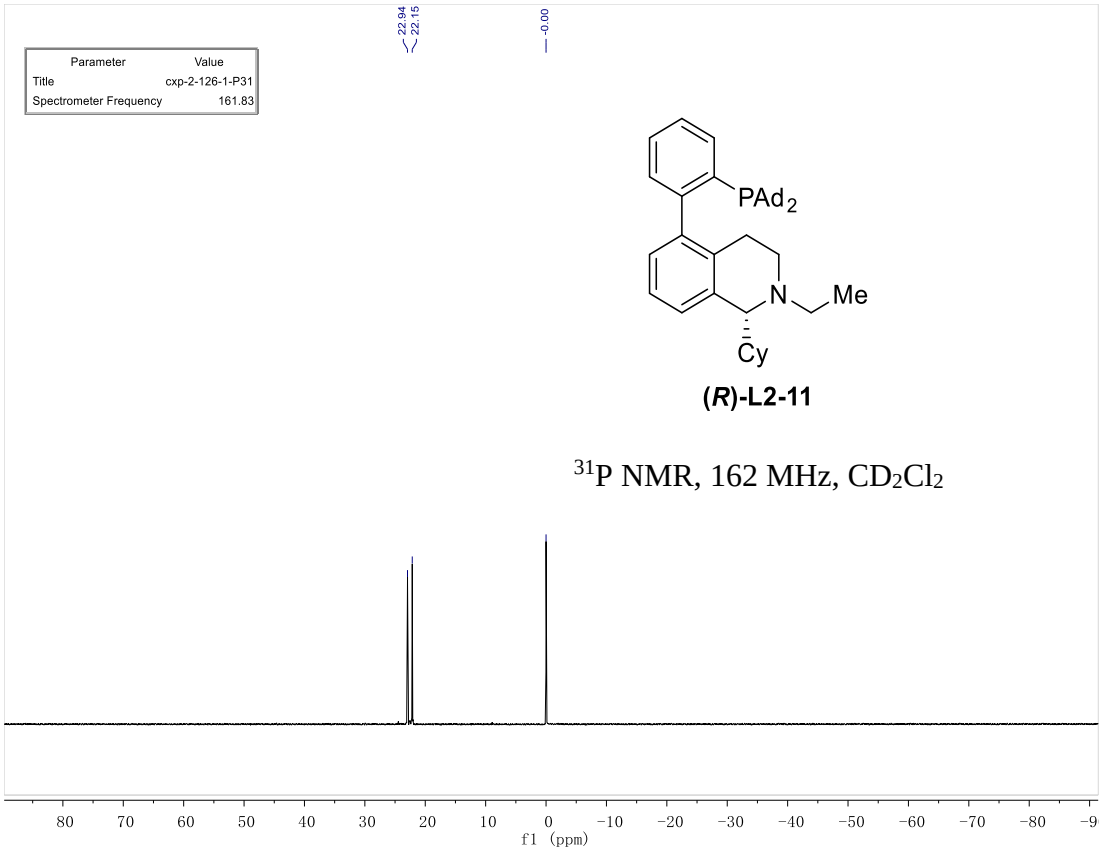
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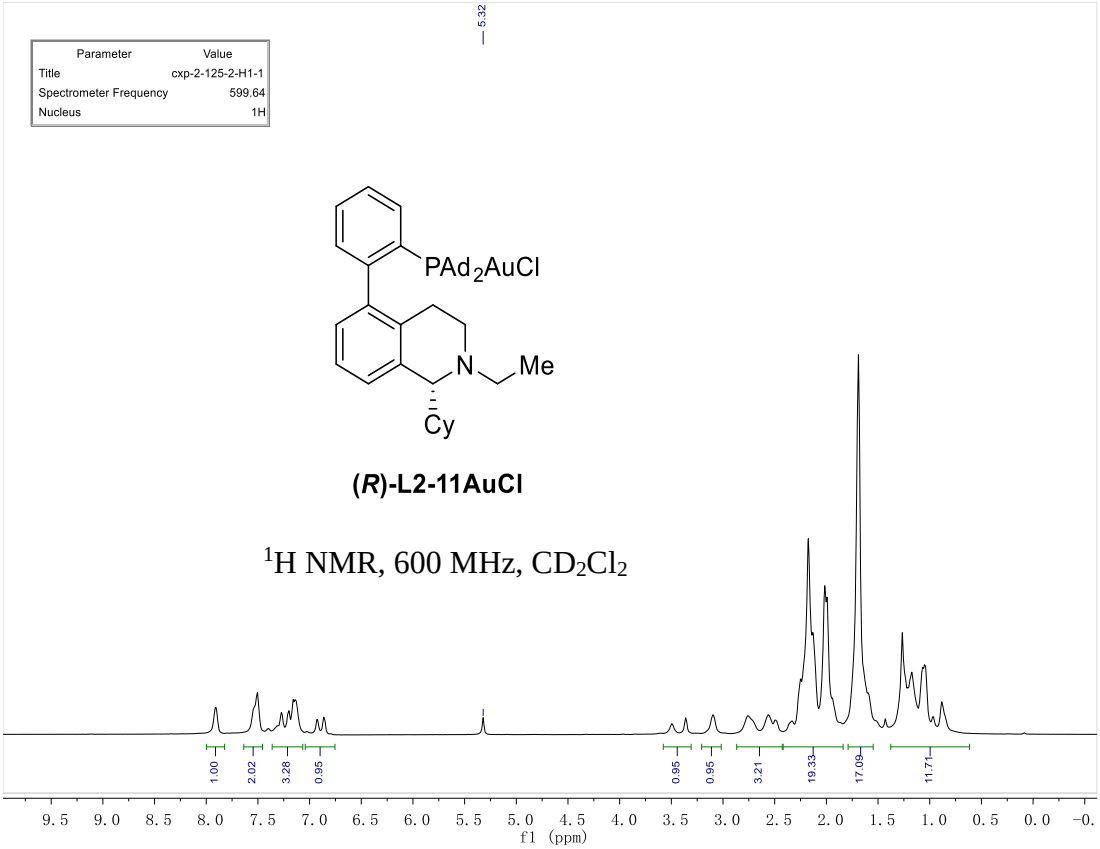
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0.95
0.95
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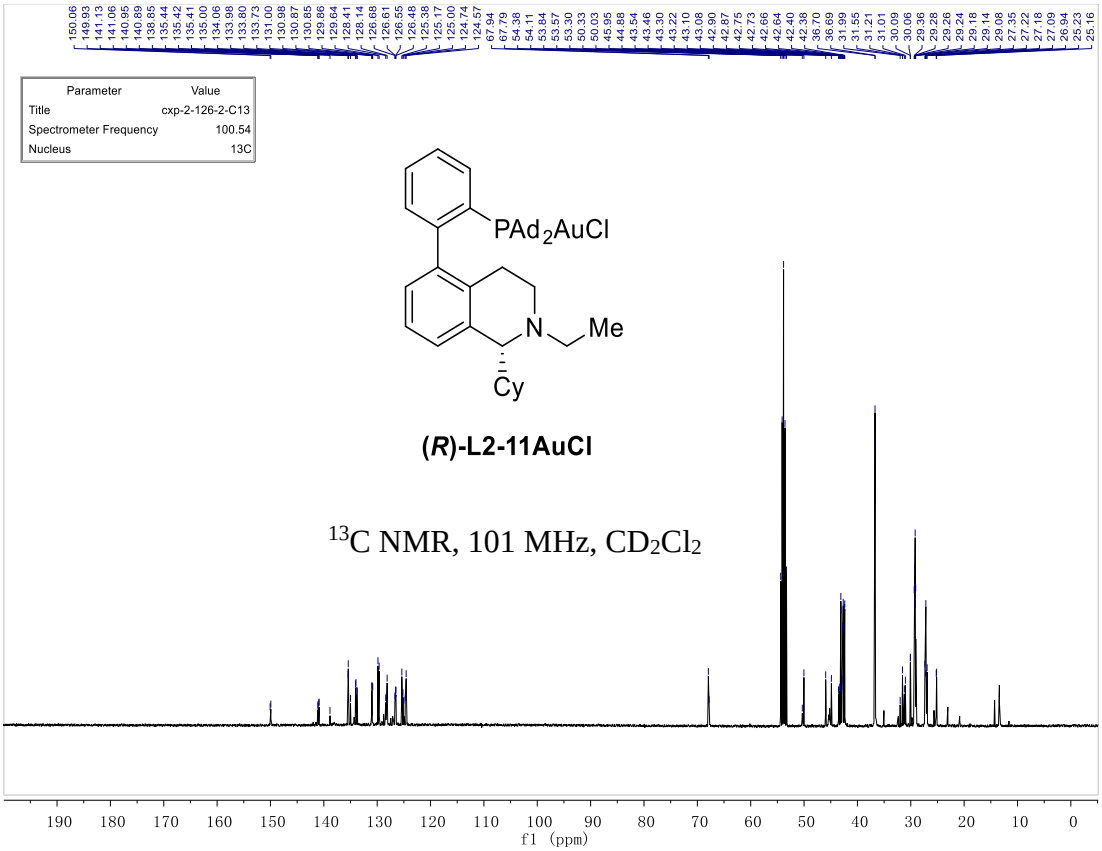
11.71
f1 (ppm)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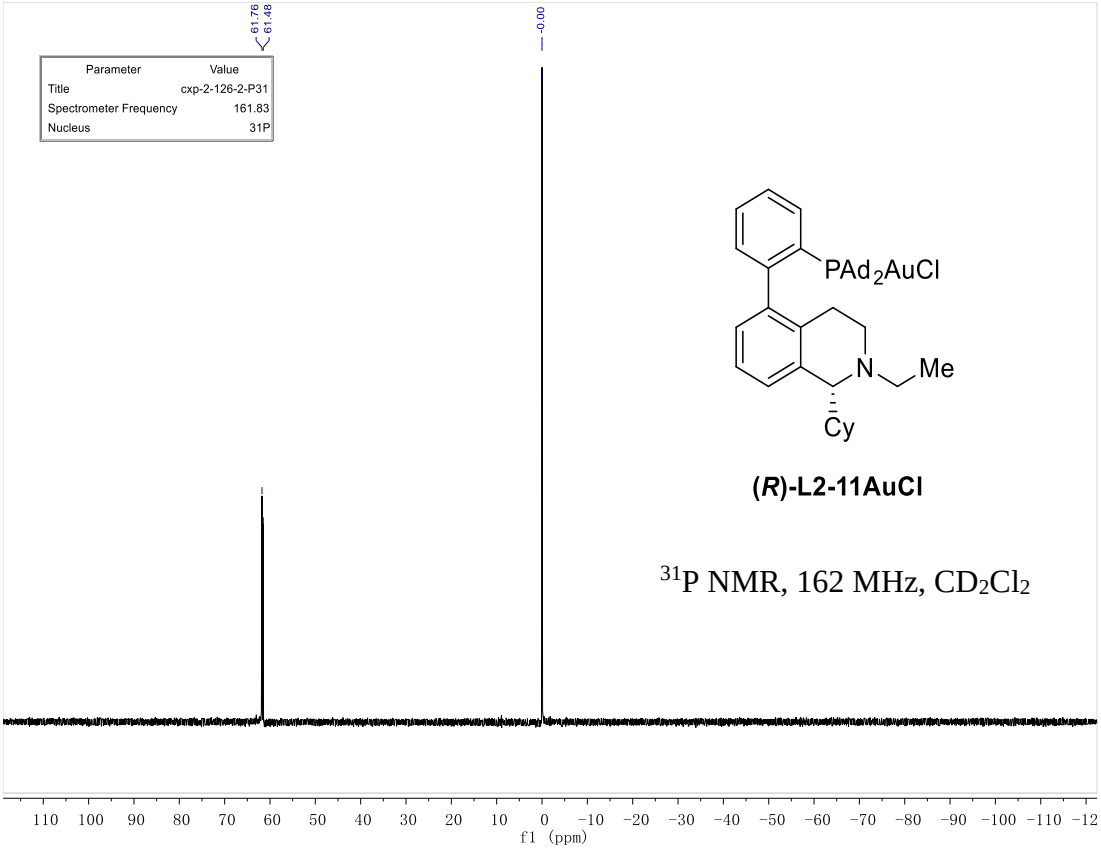
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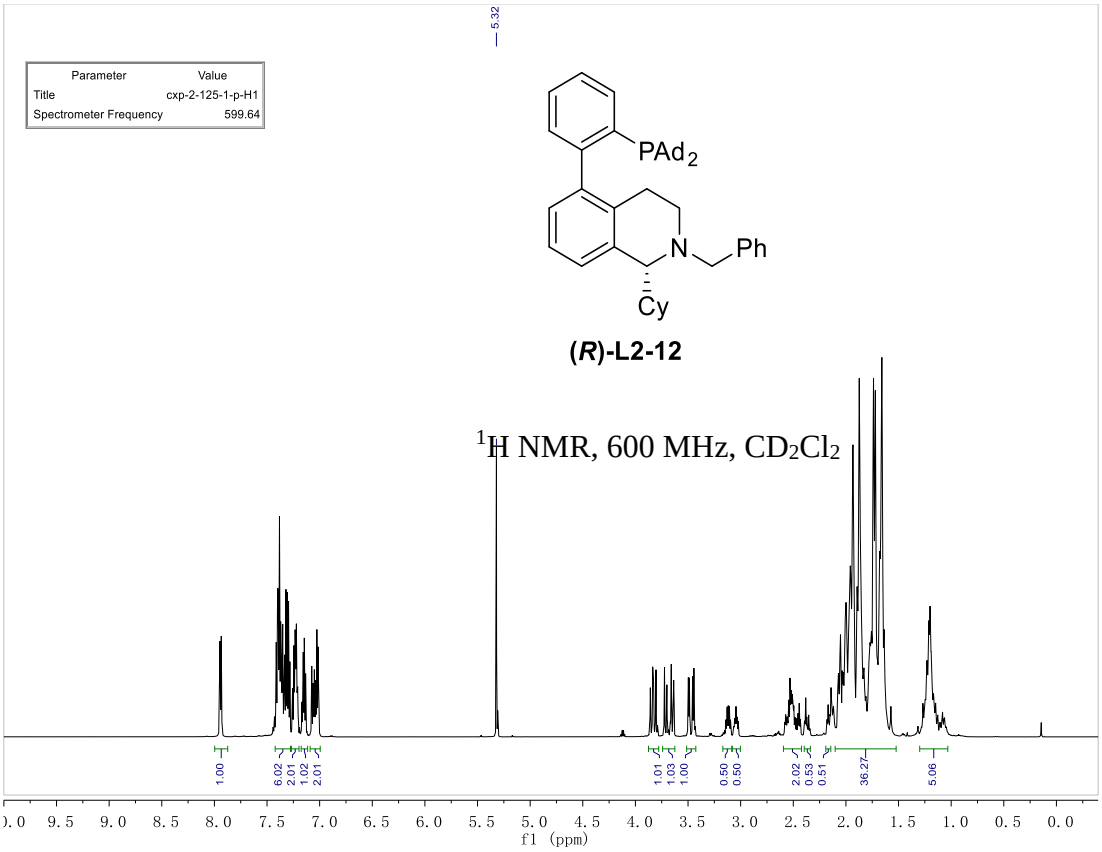
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1.02
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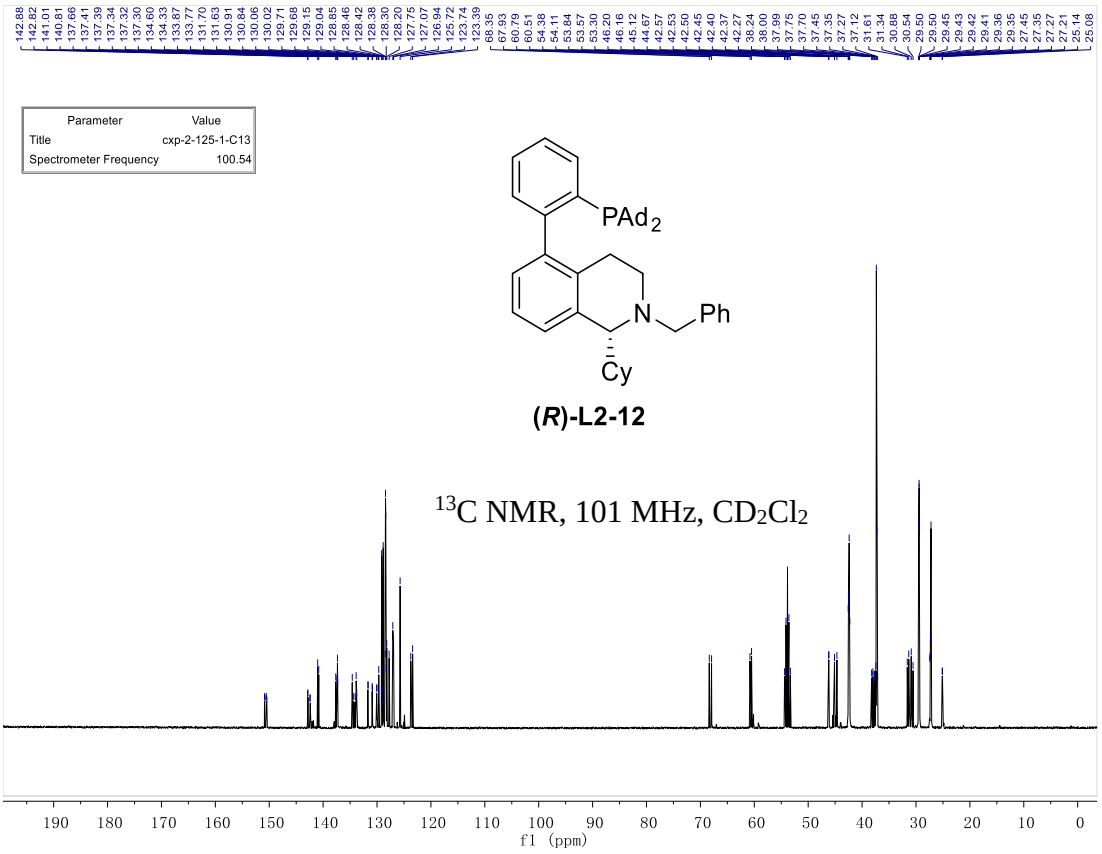
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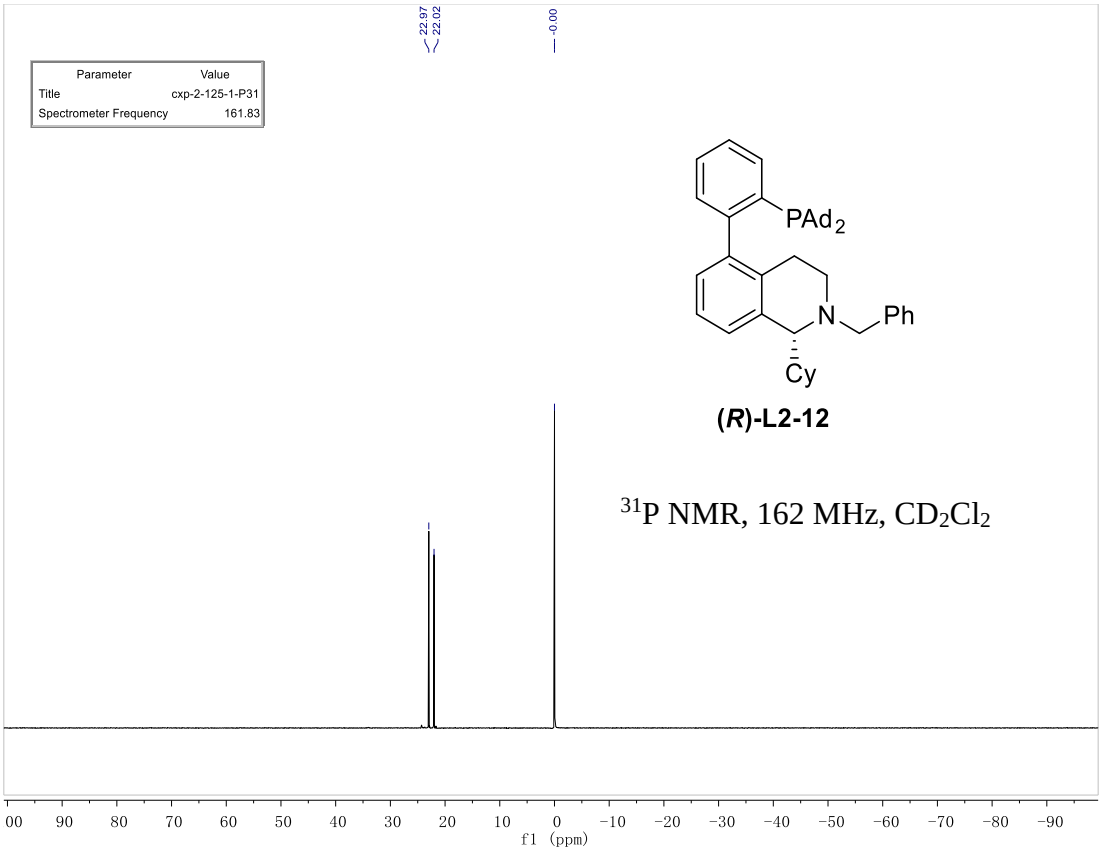
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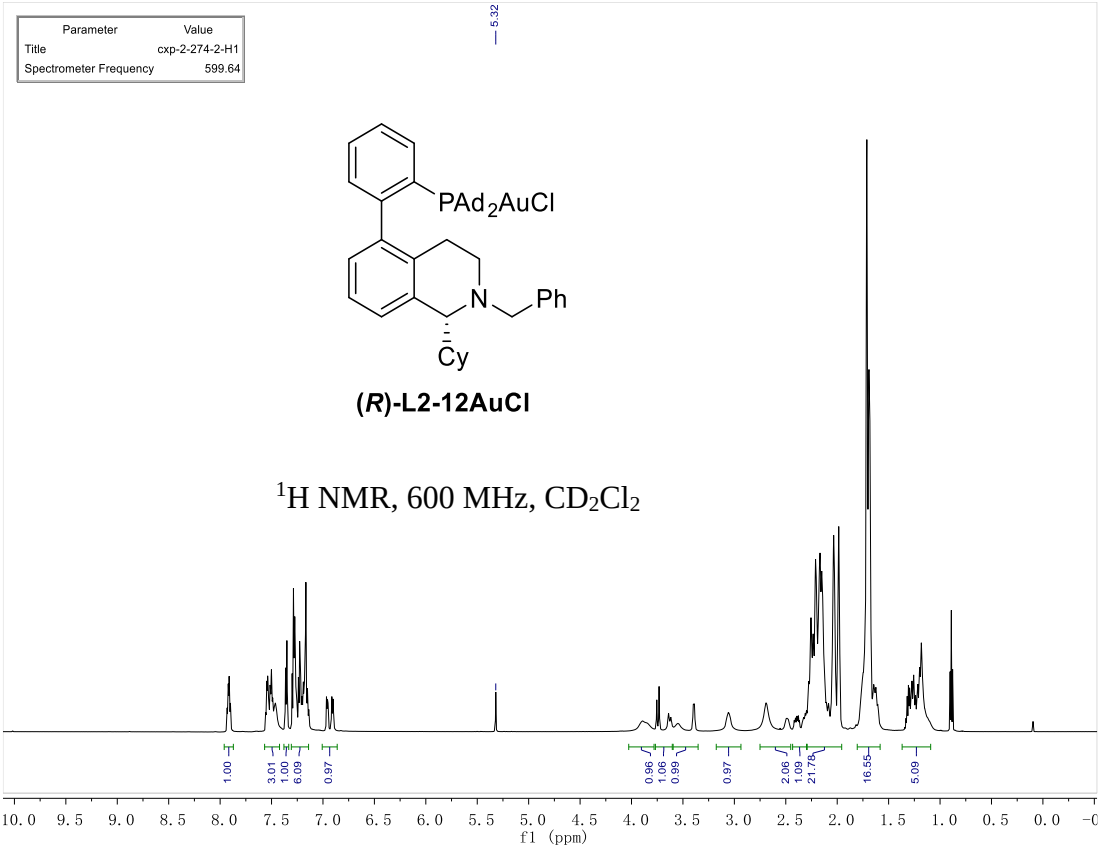
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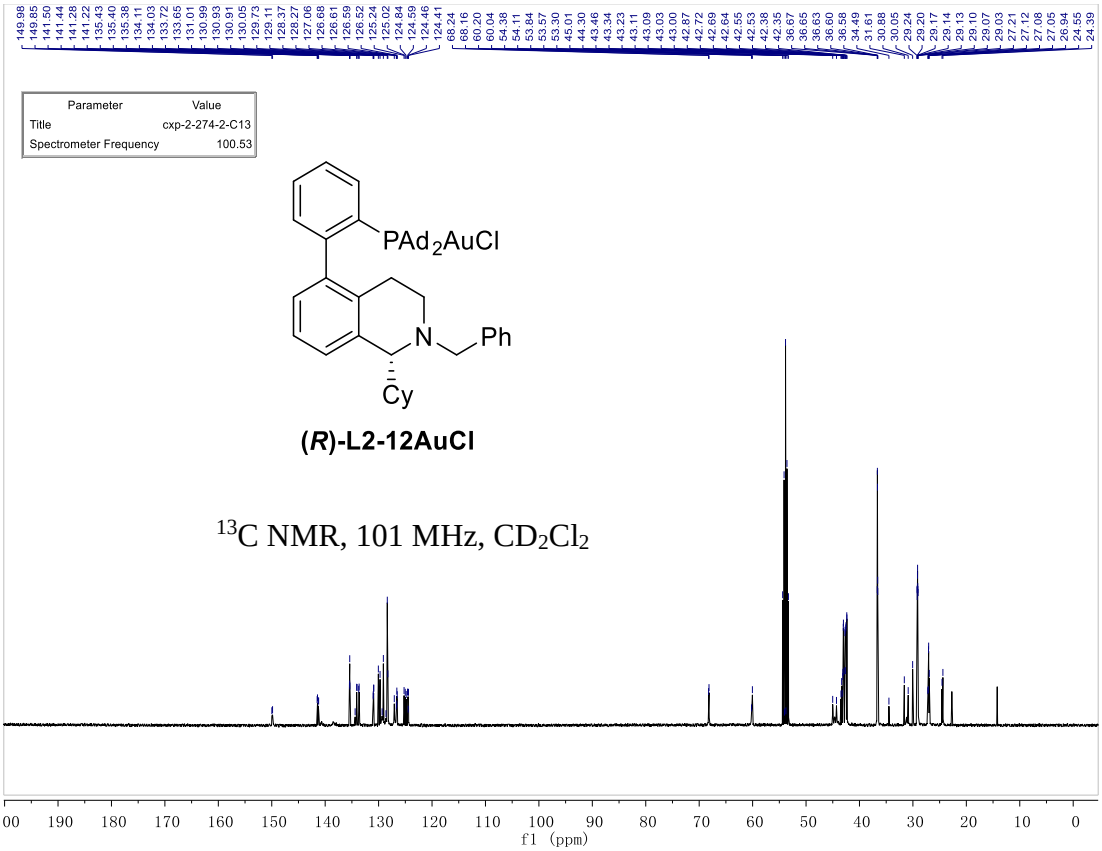
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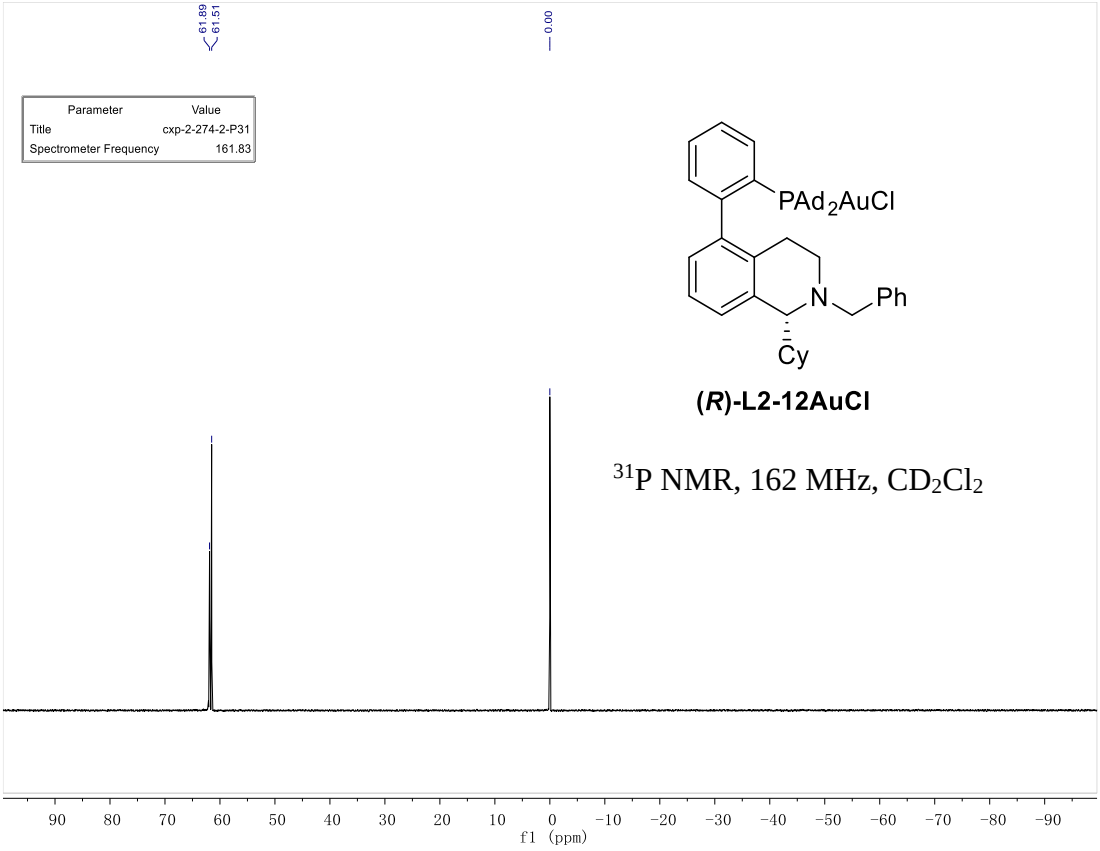
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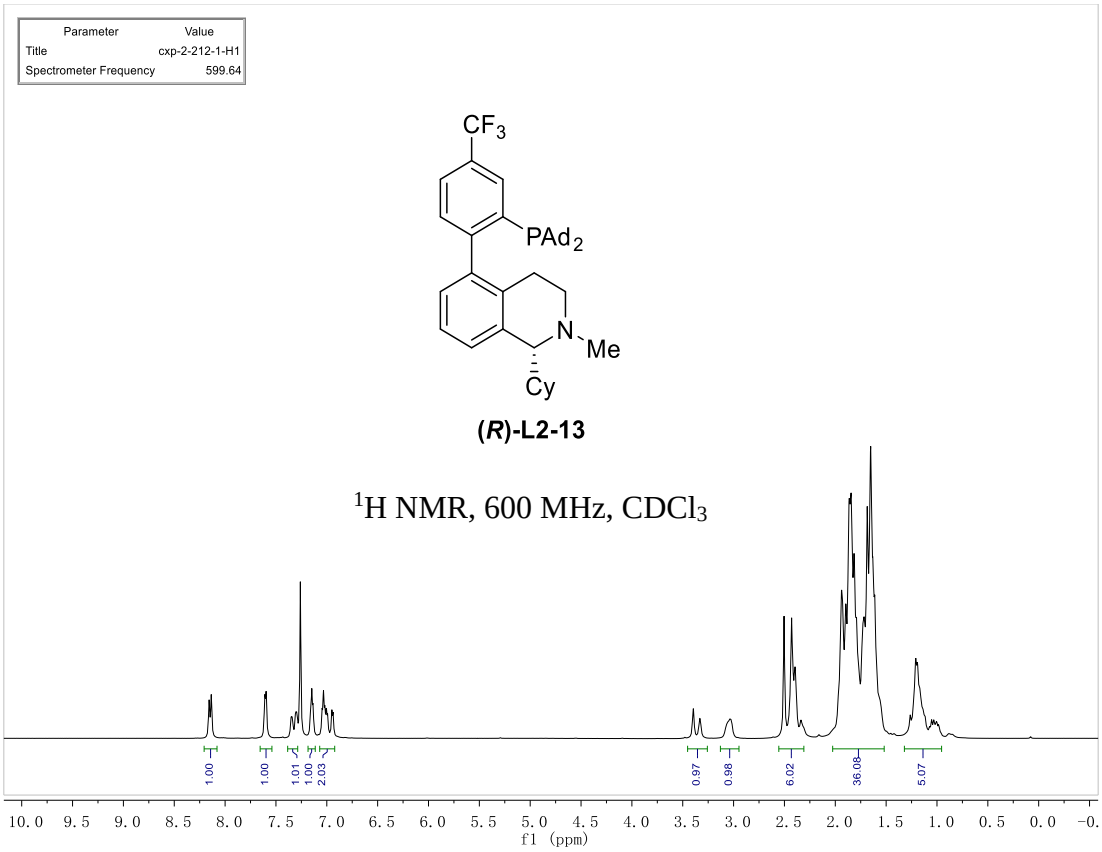
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0.98
6.02
36.08
5.07
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.
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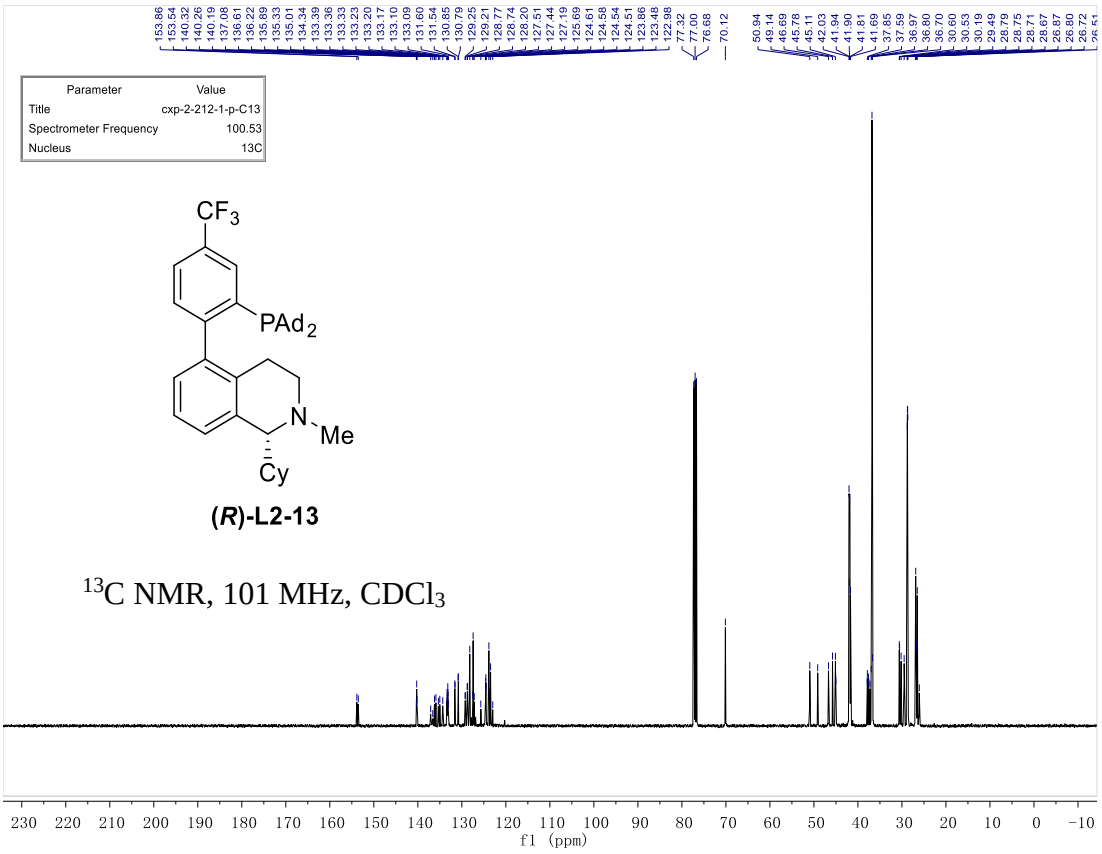
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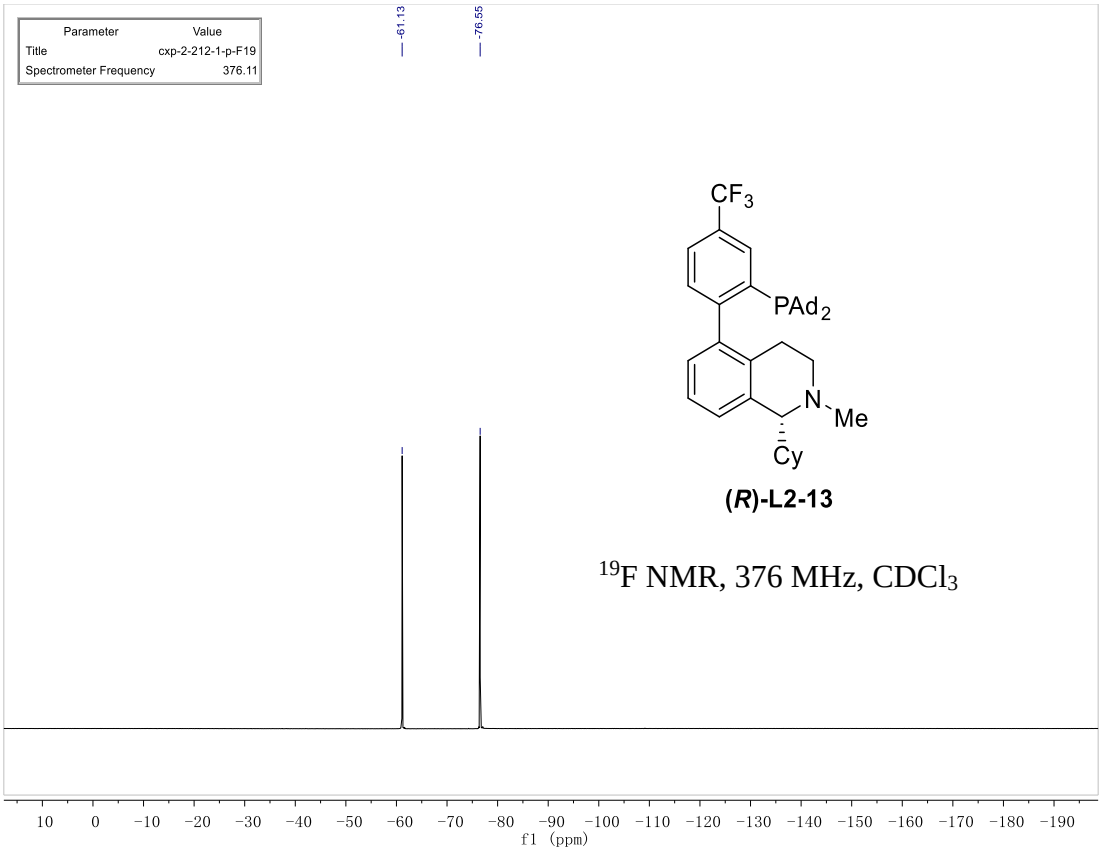
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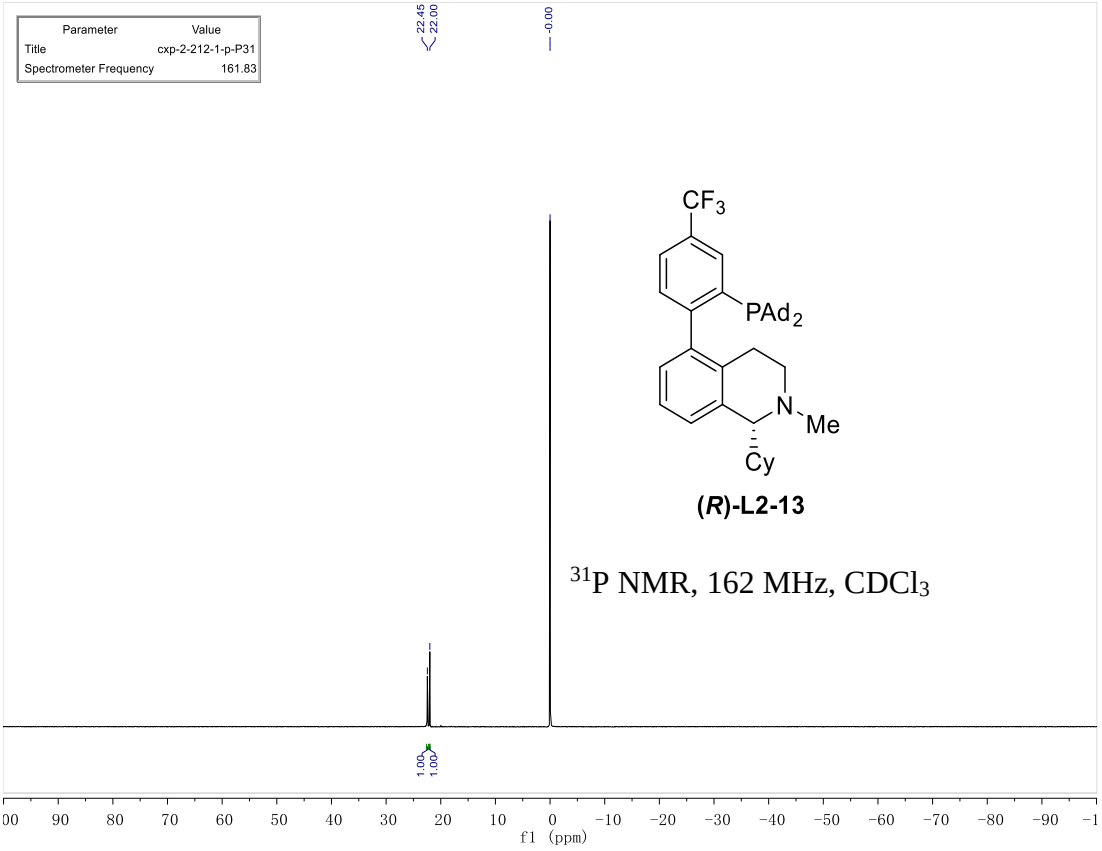
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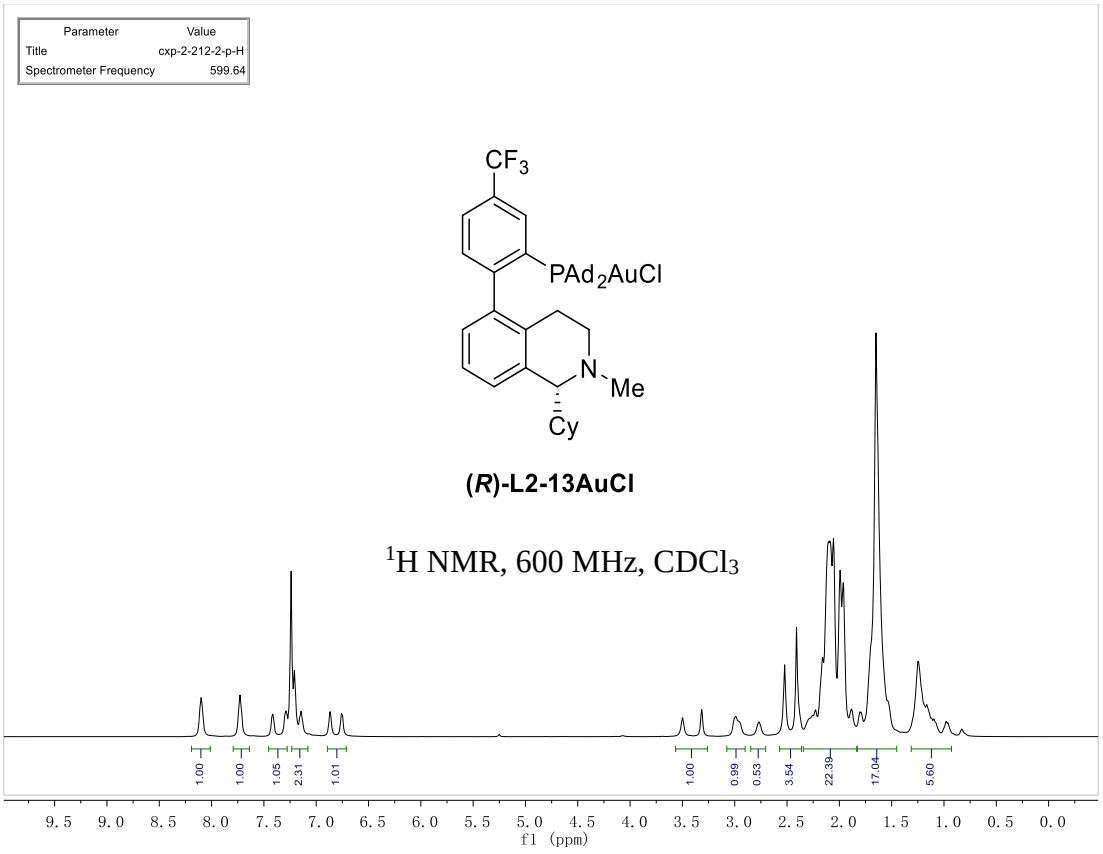
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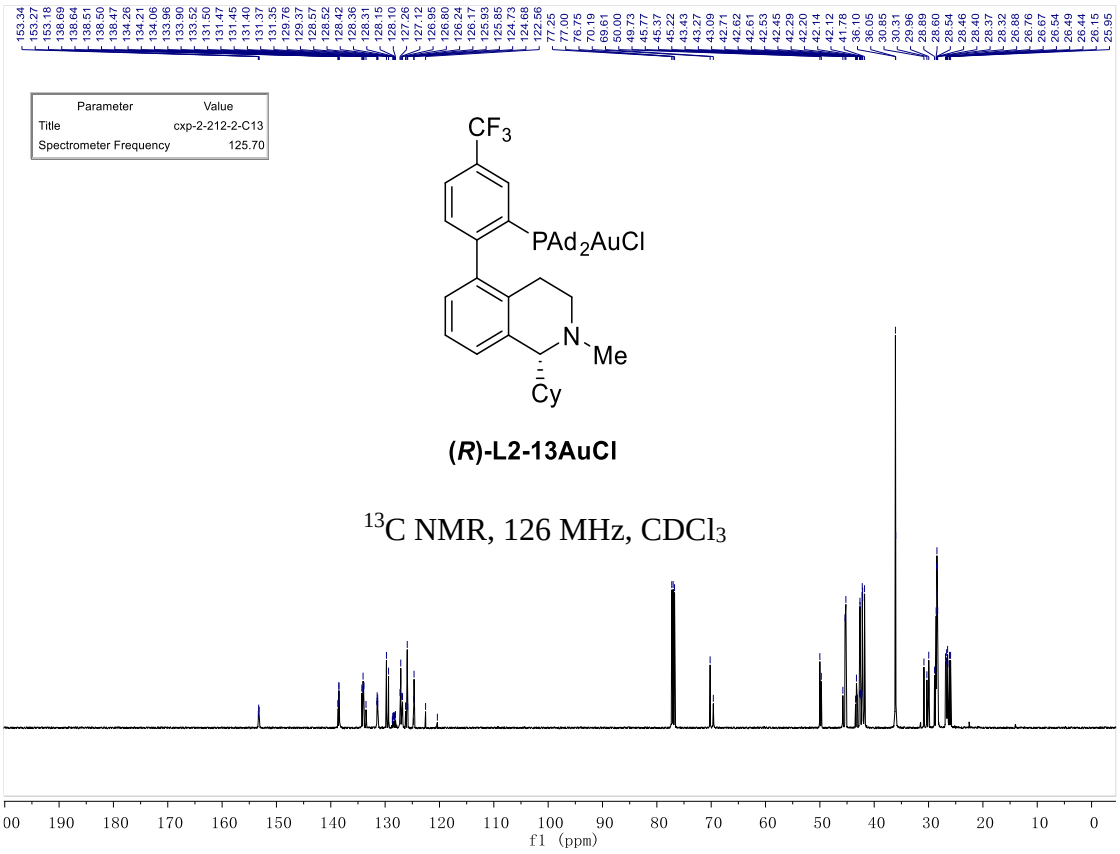
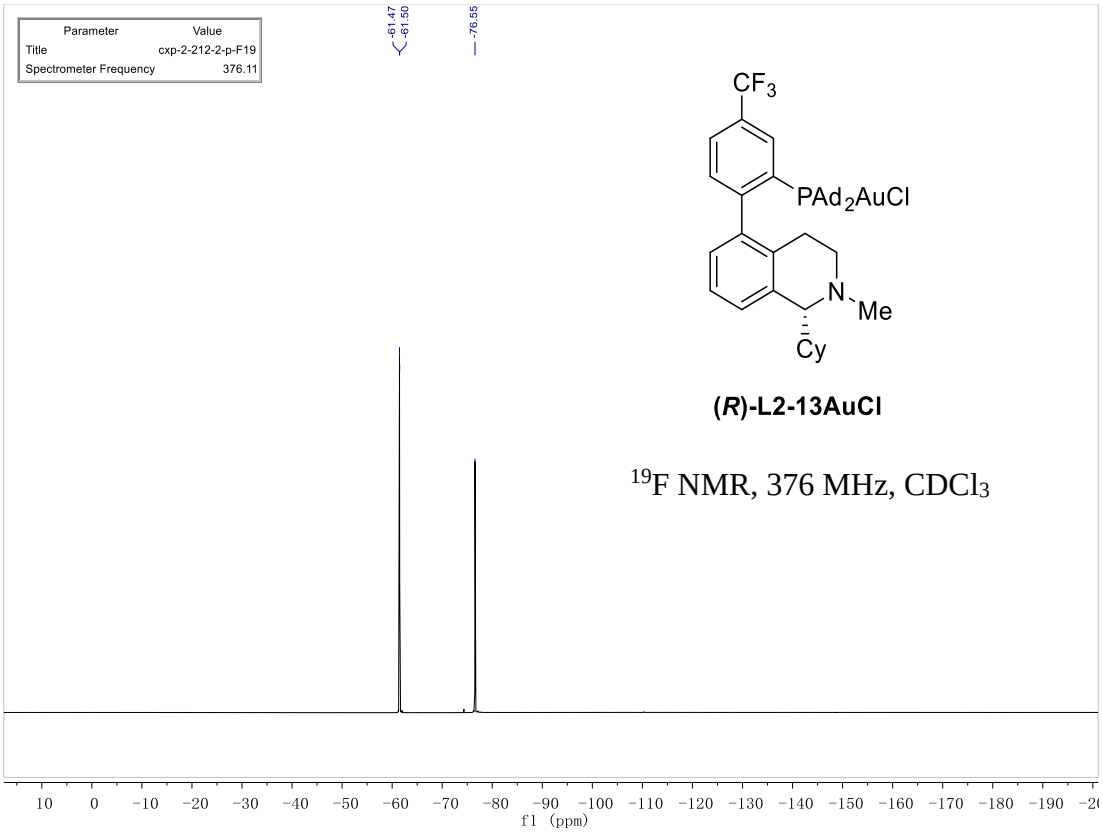
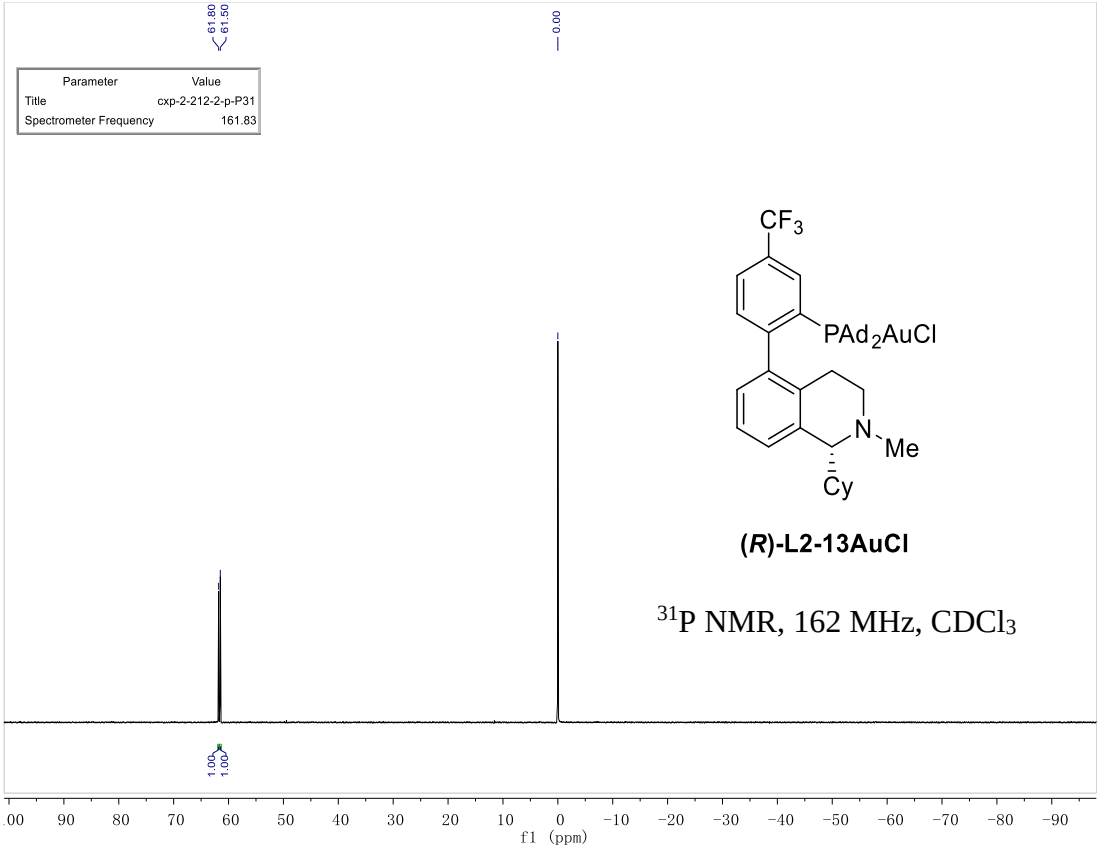
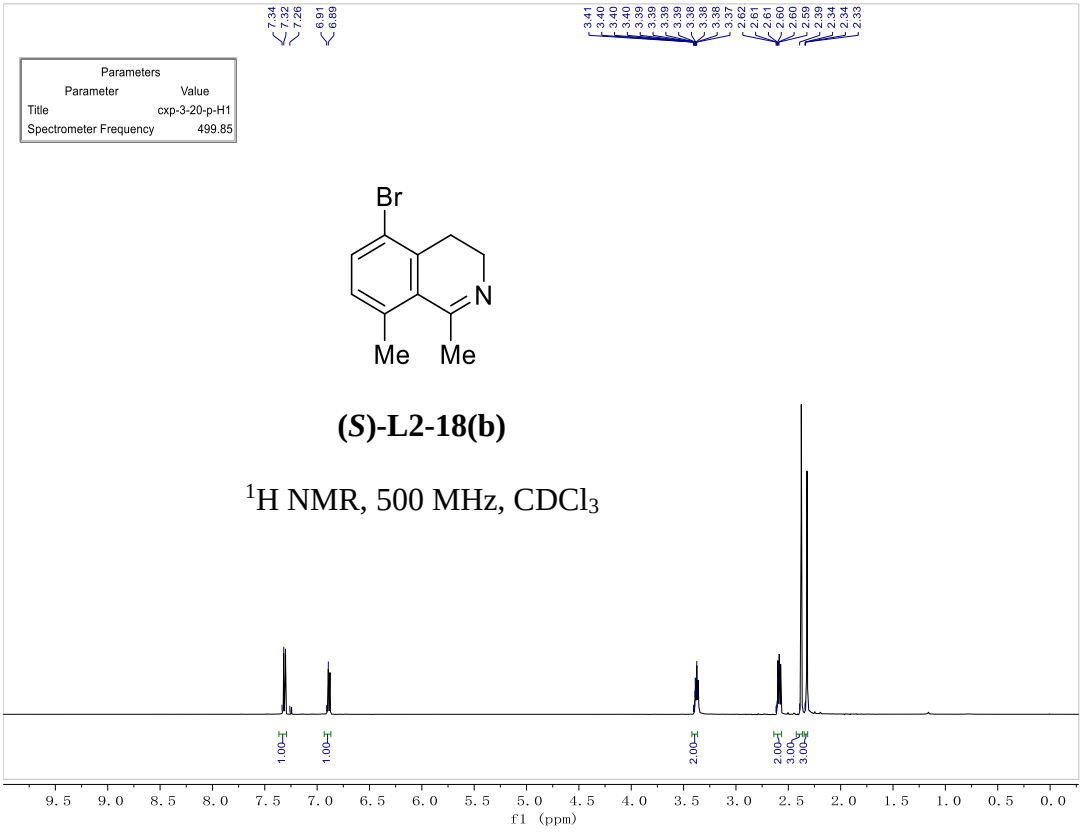
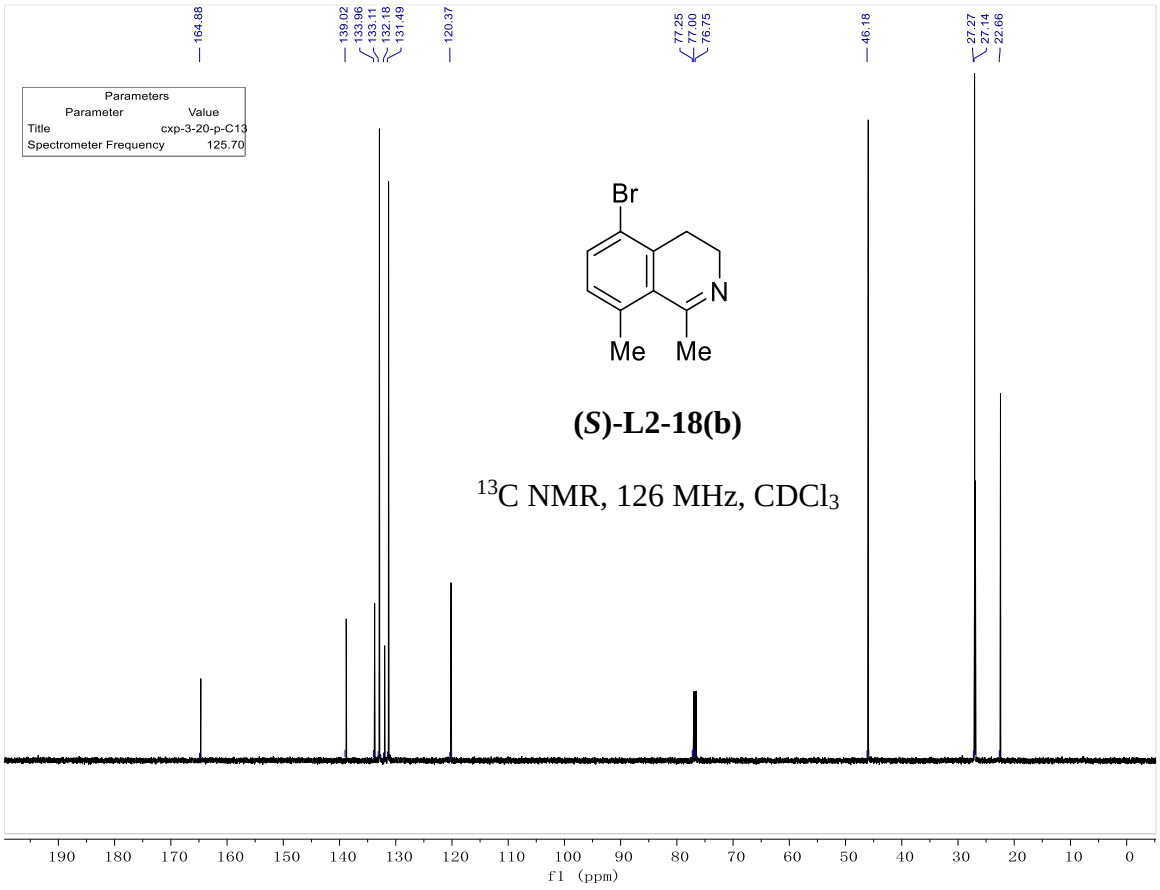
CF3
PAd2AuCl
N
Me
Cy
(R)-L2-13AuCl
1H NMR, 600 MHz, CDCl3
1.00
1.00
1.05
2.31
1.01
1.00
0.99
0.53
3.54
22.39
17.04
5.60
f1 (ppm)

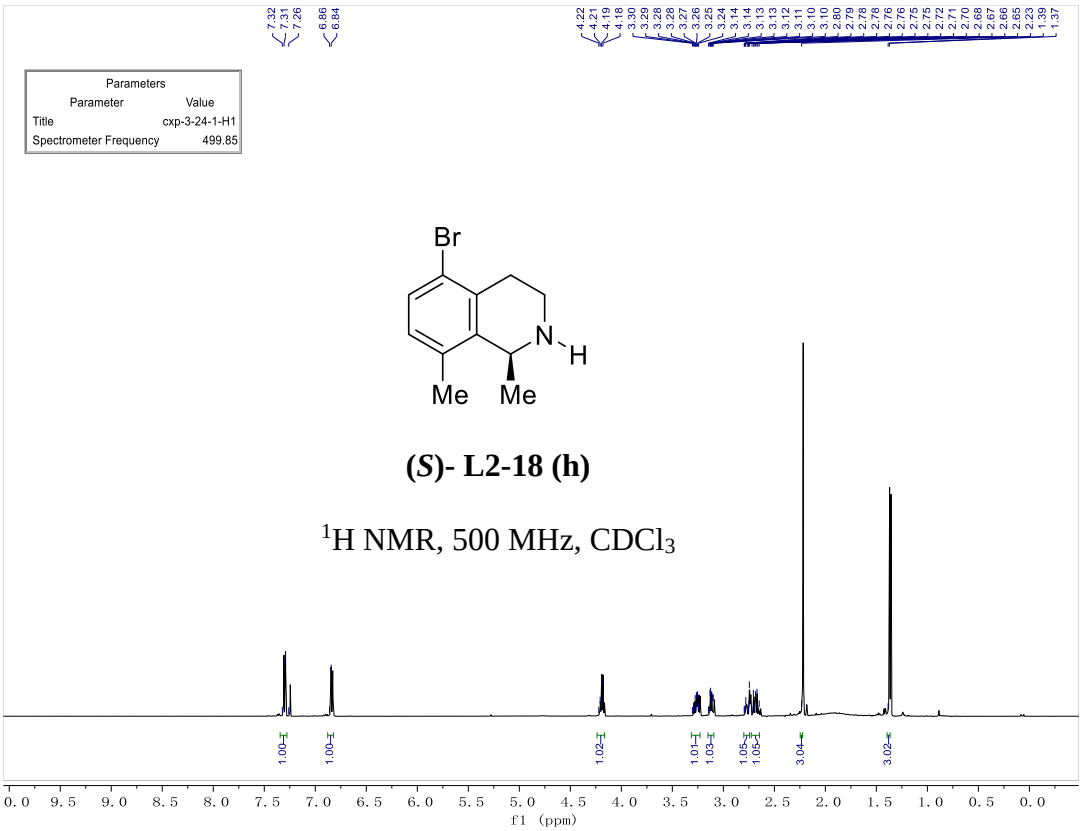

Parameter Value
Title cxp-2-212-2-C13
Spectrometer Frequency 125.70
CF3
PAd2AuCl
N
Me
Cy
(R)-L2-13AuCl
13C NMR, 126 MHz, CDCl3
f1 (ppm)


Parameter Value
Title cxp-2-212-2-p-F19
Spectrometer Frequency 376.11
-61.47
-61.50
-76.55
CF3
PAd2AuCl
N
Me
Cy
(R)-L2-13AuCl
19F NMR, 376 MHz, CDCl3
f1 (ppm)


61.80
61.50
0.00
Parameter Value
Title cxp-2-212-2-p-P31
Spectrometer Frequency 161.83
CF3
PAd2AuCl
N
Me
Cy
(R)-L2-13AuCl
31P NMR, 162 MHz, CDCl3
1.00
1.00
f1 (ppm)

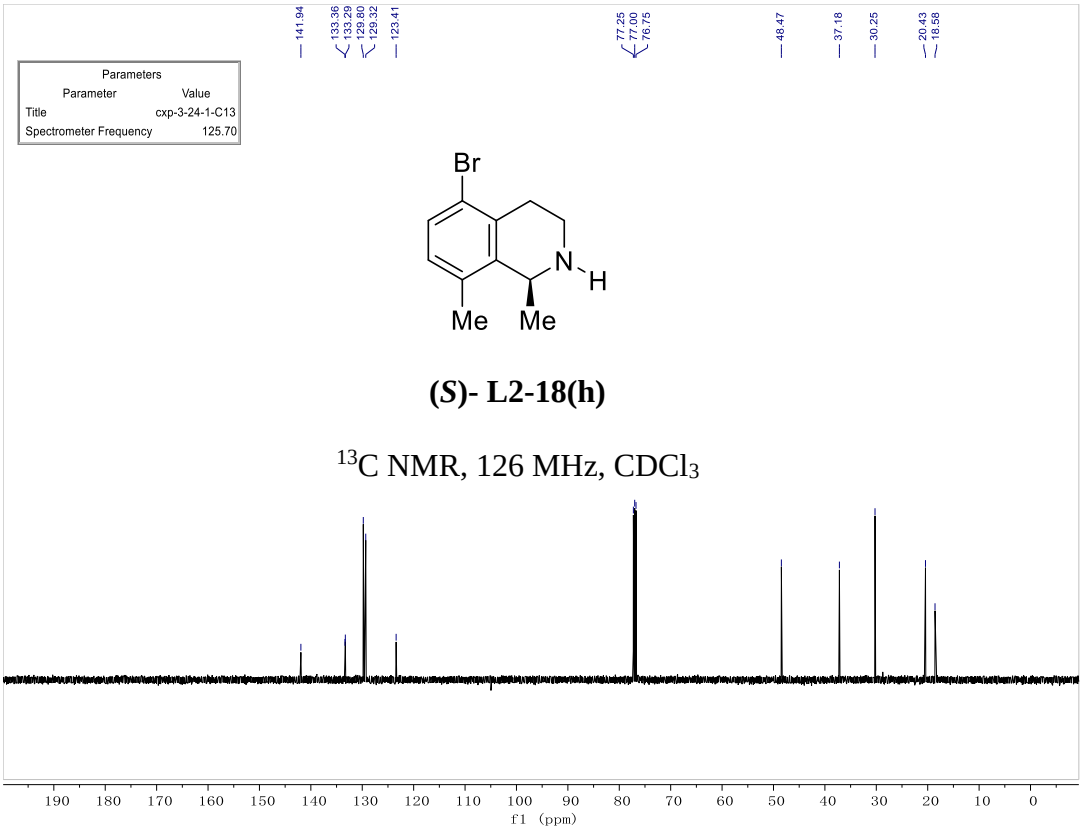

7.34
7.32
7.26
6.91
6.89
Parameters
Parameter Value
Title cxp-3-20-p-H1
Spectrometer Frequency 499.85
Br
N
Me
Me
(S)-L2-18(b)
1H NMR, 500 MHz, CDCl3
1.00
1.00
2.00
2.00
3.00
3.00
f1 (ppm)


164.88
139.02
133.96
133.11
132.18
131.49
120.37
77.25
77.00
76.75
46.18
27.27
27.14
22.66
Parameters
Parameter Value
Title cxp-3-20-p-C13
Spectrometer Frequency 125.70
Br
N
Me
Me
(S)-L2-18(b)
13C NMR, 126 MHz, CDCl3
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



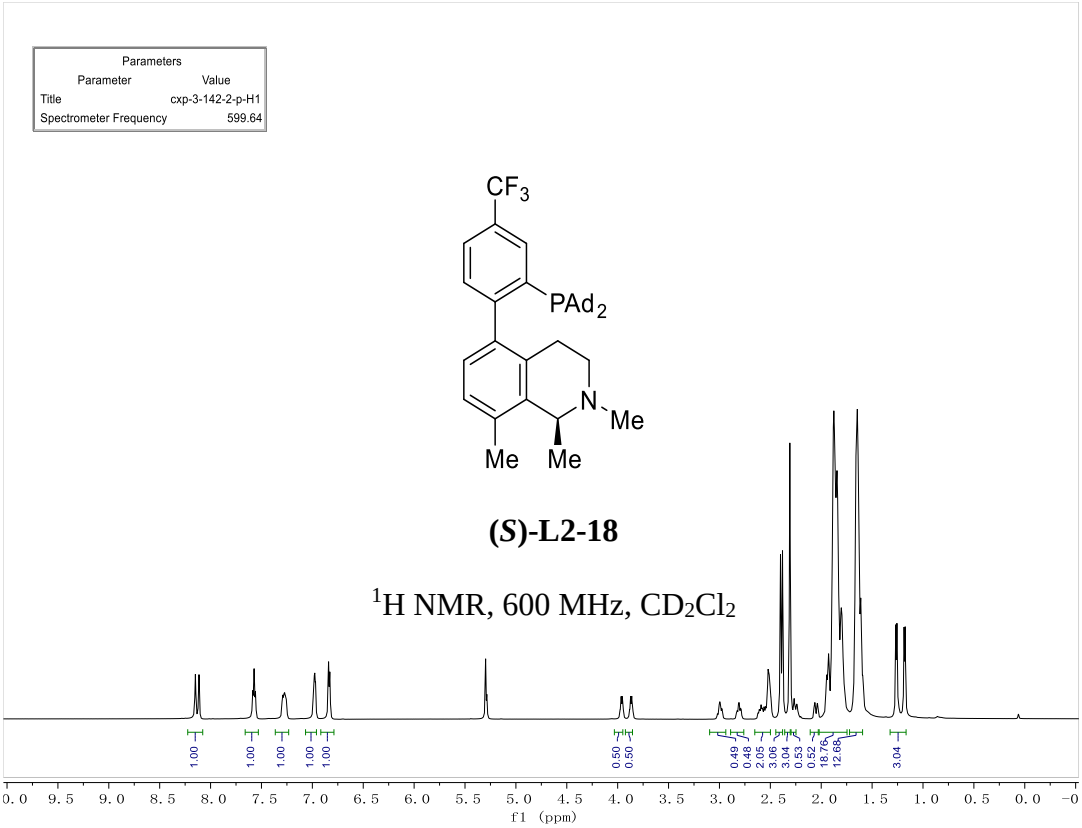
(*S*)- L2-18 (h)

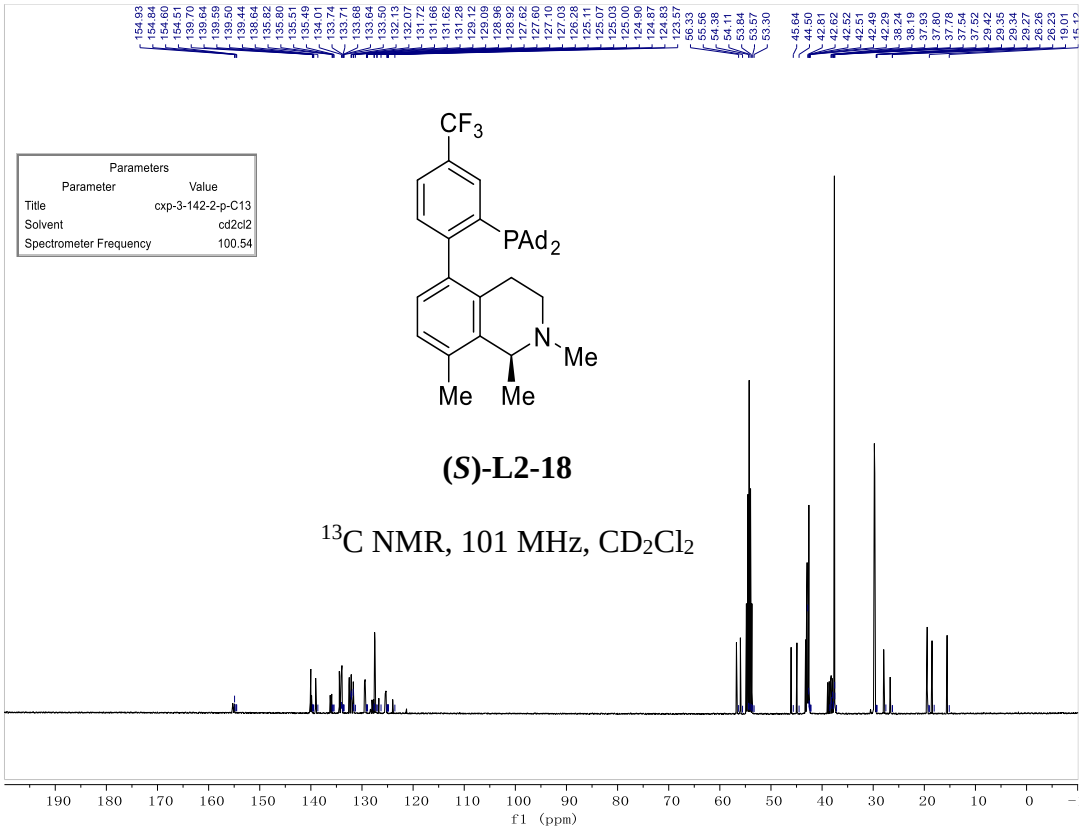
^{1}H NMR, 500 MHz, $CDCl_3$

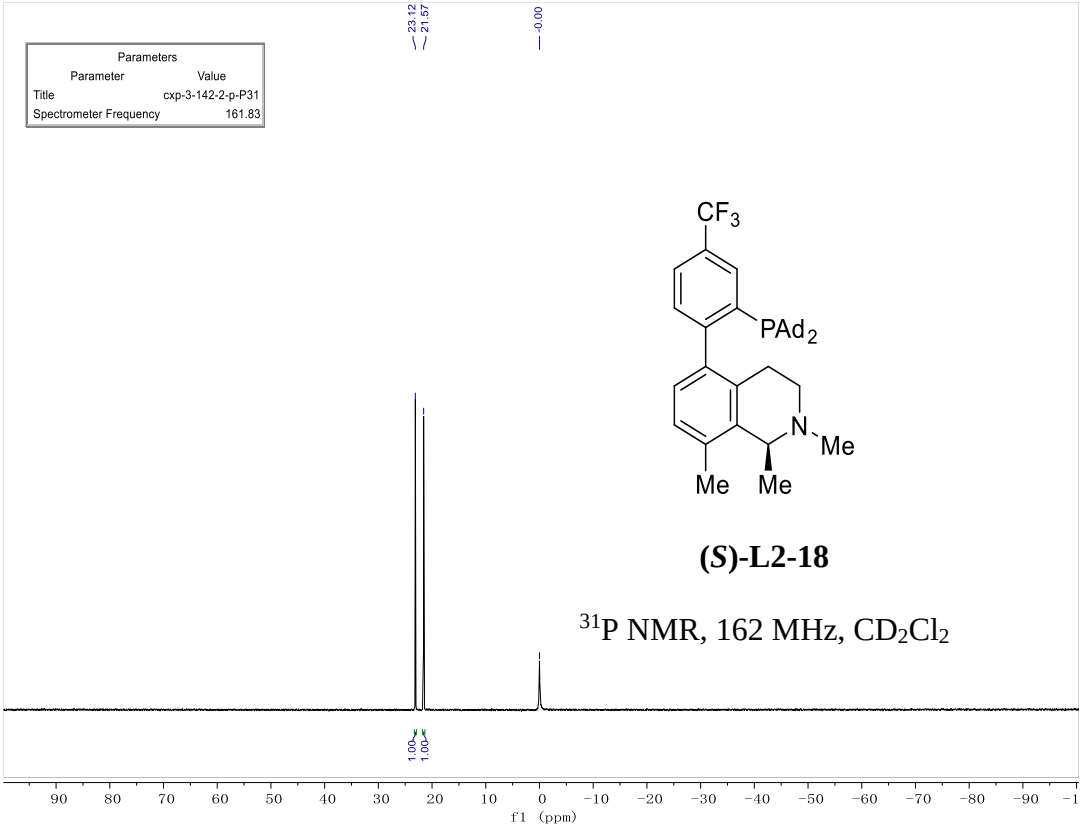


(*S*)- L2-18(h)

^{13}C NMR, 126 MHz, $CDCl_3$

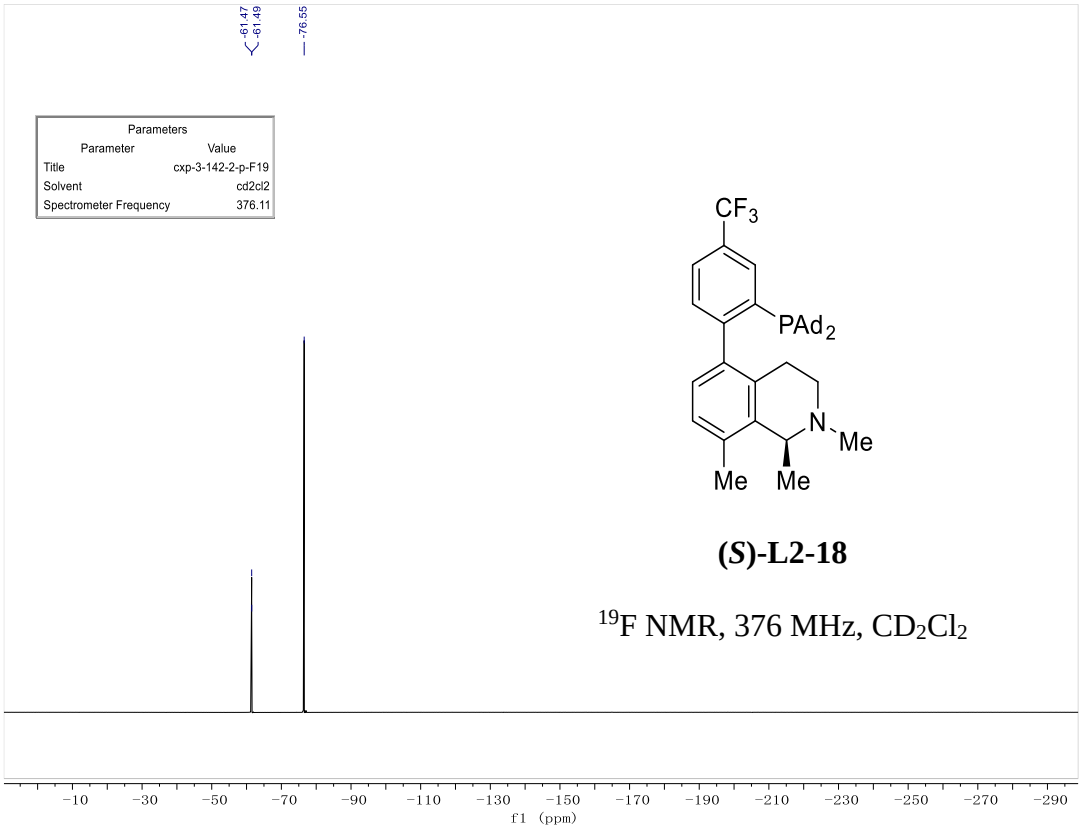

Parameters
Parameter Value
Title cxp-3-142-2-p-H1
Spectrometer Frequency 599.64
CF3
PAd2
N
Me
Me Me
(S)-L2-18
1H NMR, 600 MHz, CD2Cl2
f1 (ppm)


Parameters
Parameter Value
Title cxp-3-142-2-p-C13
Solvent cd2cl2
Spectrometer Frequency 100.54
CF3
PAd2
N
Me
Me Me
(S)-L2-18
13C NMR, 101 MHz, CD2Cl2
f1 (ppm)



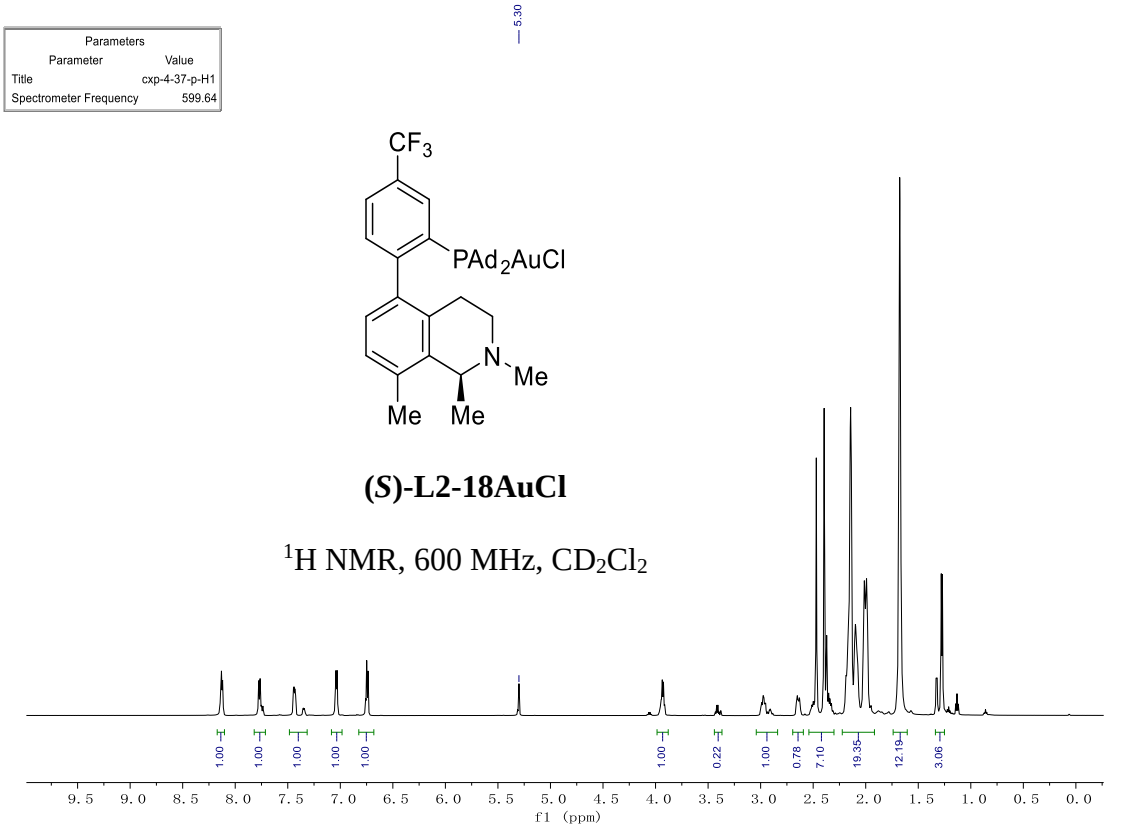
(*S*)-L2-18

^{31}P NMR, 162 MHz, CD_2Cl_2



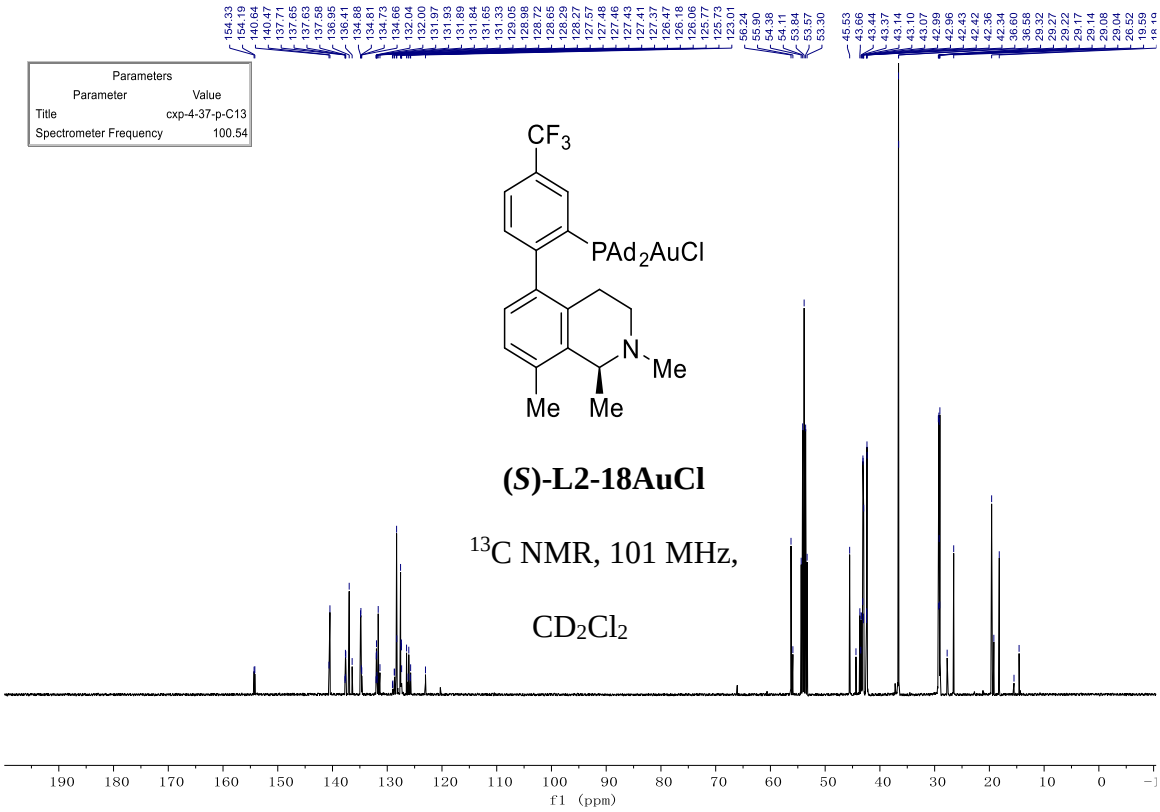
(*S*)-L2-18

^{19}F NMR, 376 MHz, CD_2Cl_2



(*S*)-L2-18AuCl

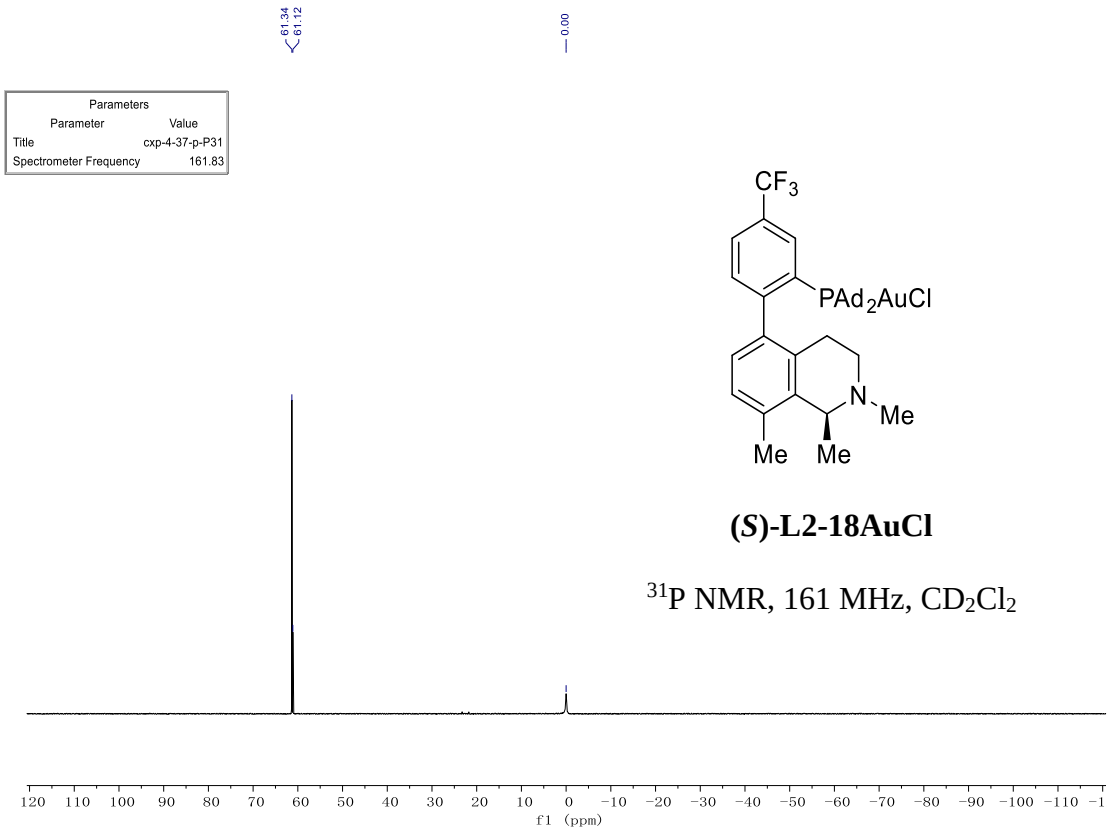
^{1}H NMR, 600 MHz, CD_2Cl_2



(*S*)-L2-18AuCl

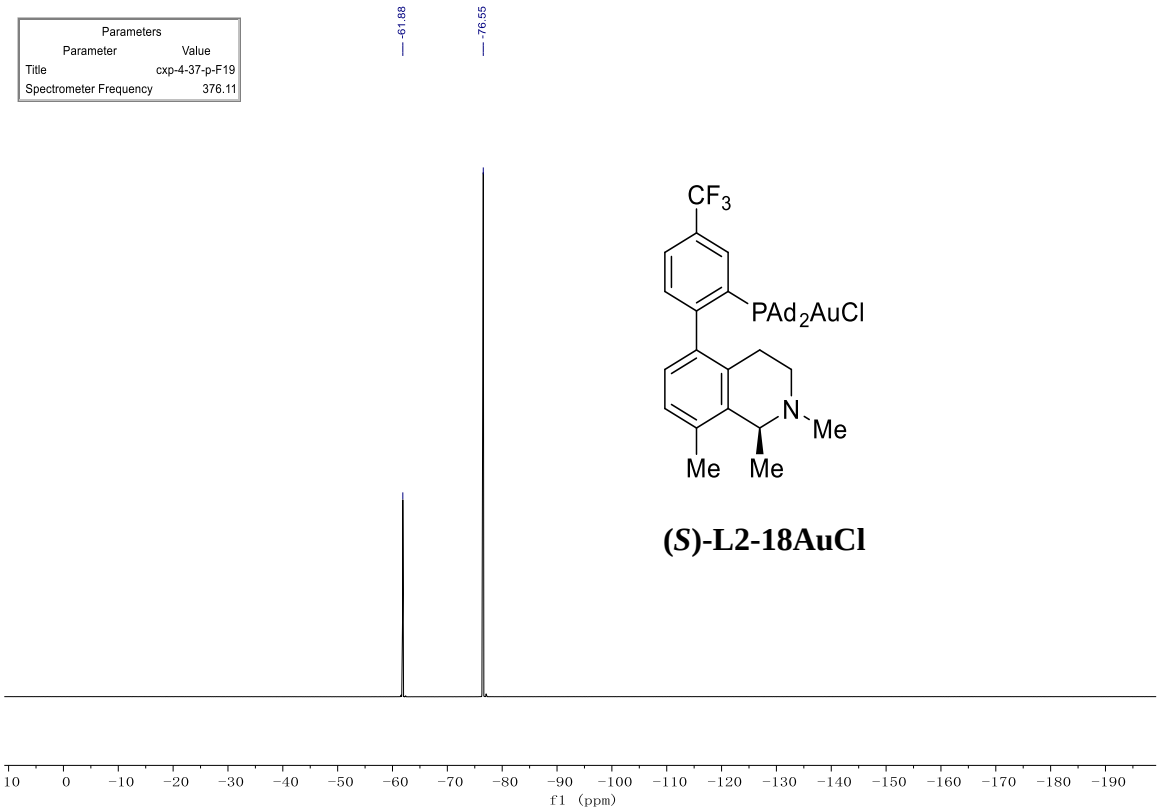
^{13}C NMR, 101 MHz,

CD_2Cl_2

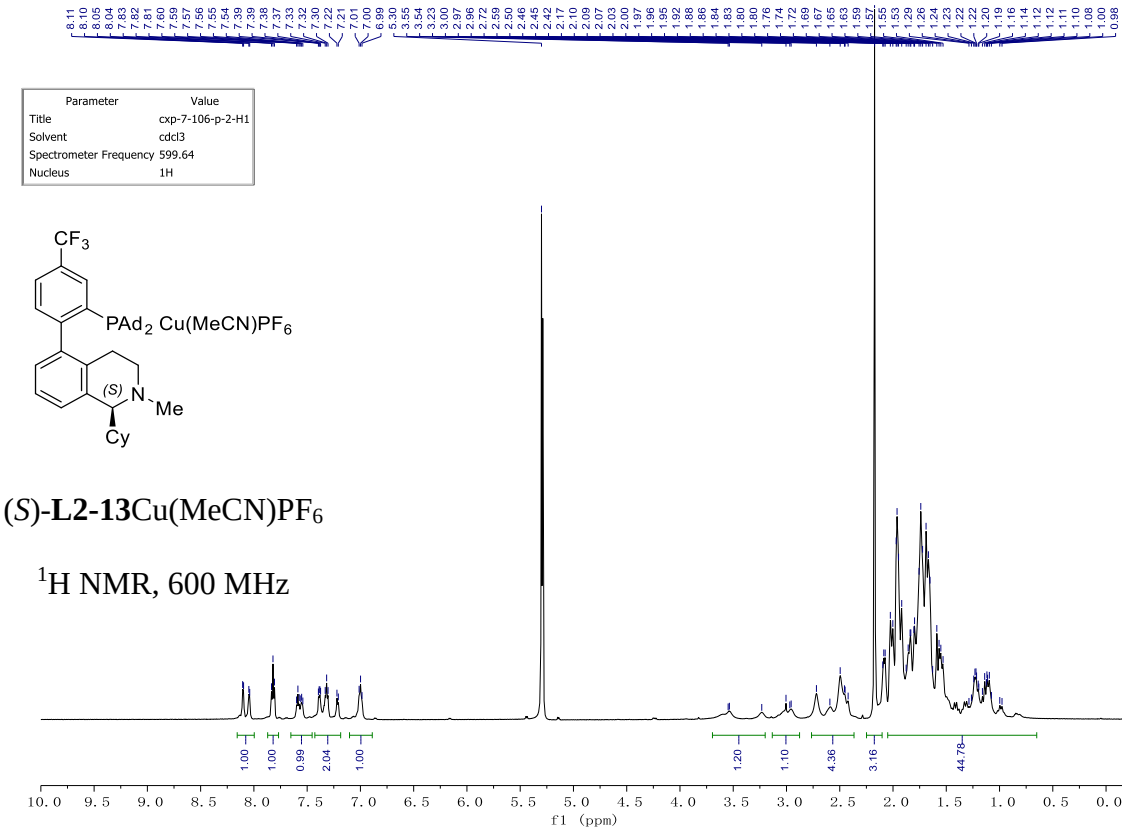


(*S*)-L2-18AuCl

^{31}P NMR, 161 MHz, CD_2Cl_2

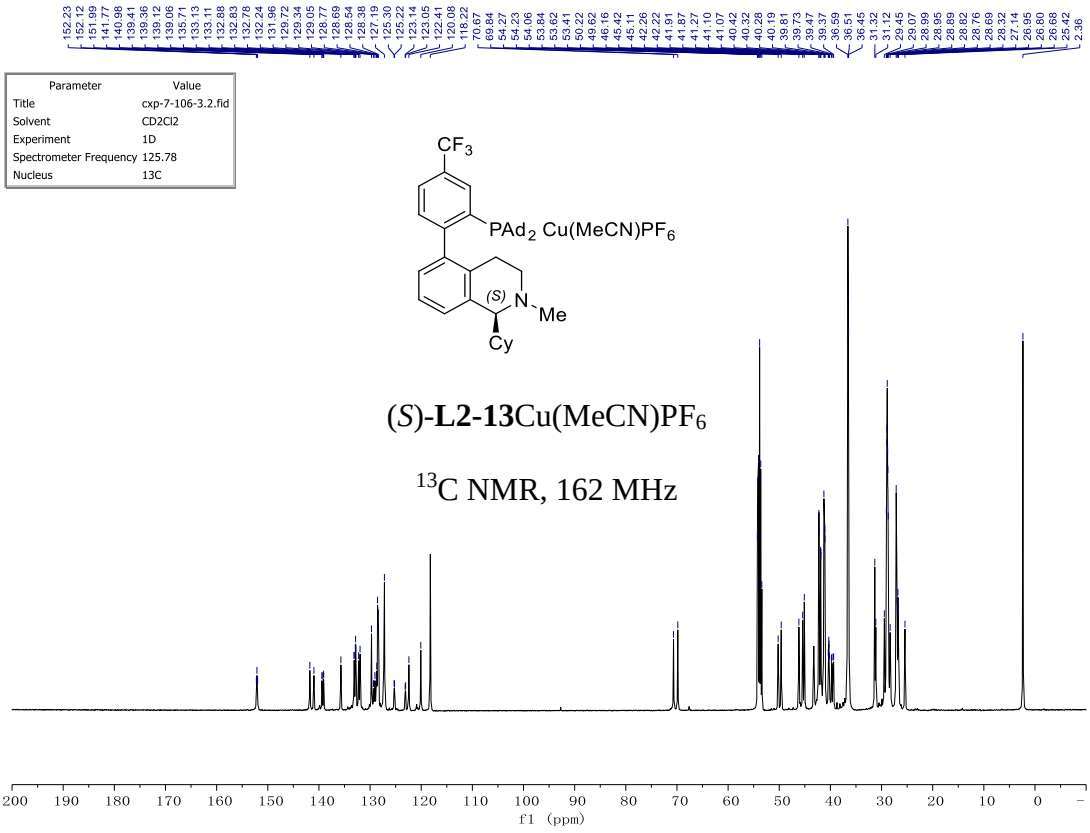


(*S*)-L2-18AuCl



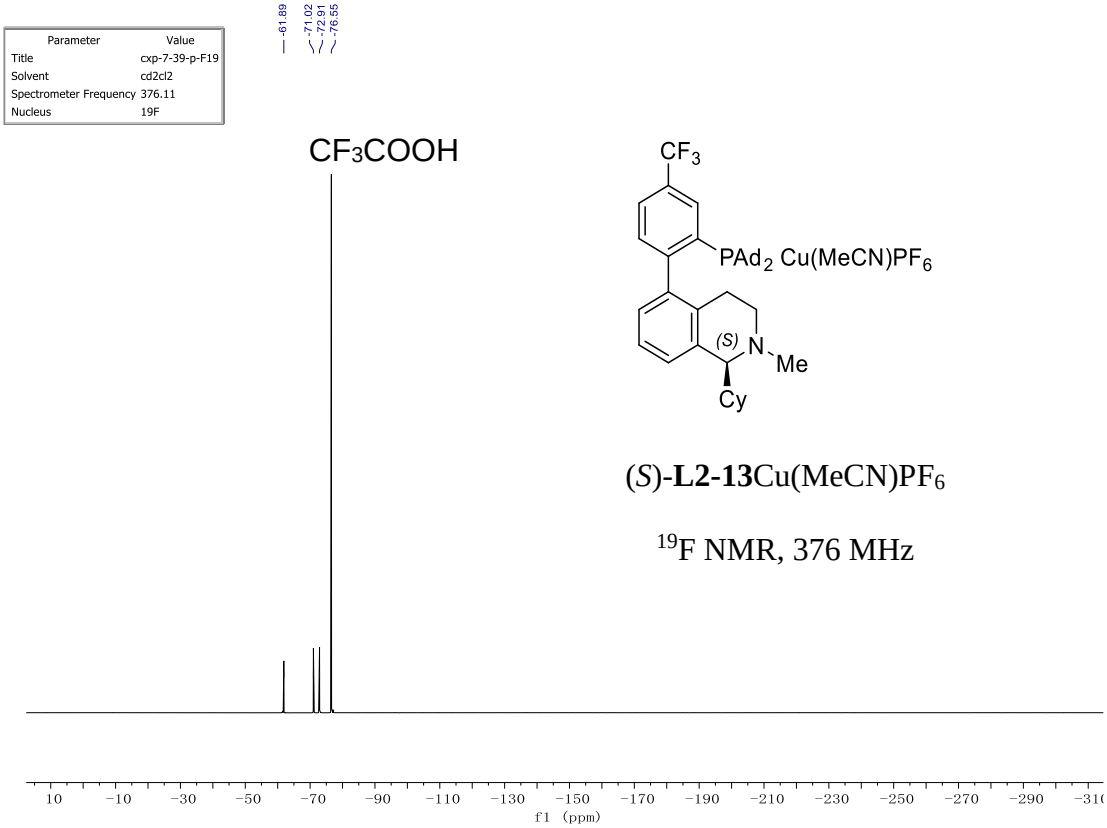
(*S*)-**L2-13**Cu(MeCN)PF_6

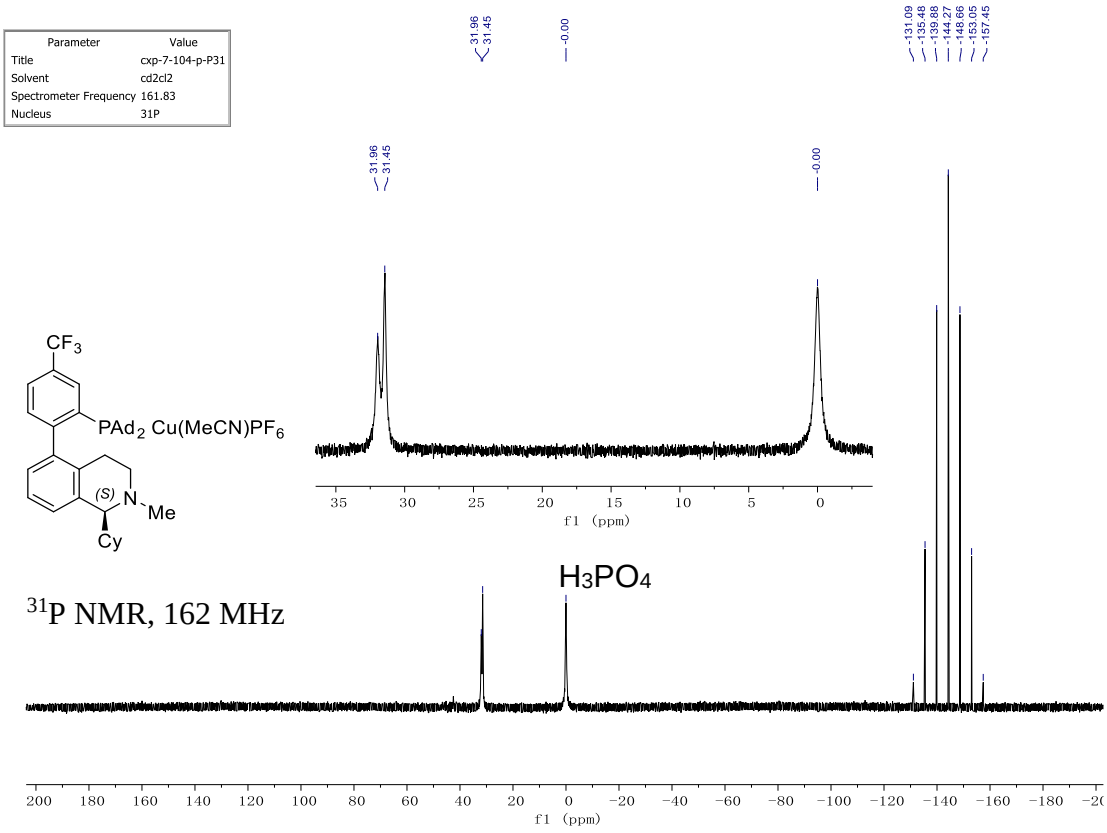
^{1}H NMR, 600 MHz



(*S*)-**L2-13**Cu(MeCN)PF_6

^{13}C NMR, 162 MHz


Parameter Value
Title cxp-7-39-p-F19
Solvent cd2cl2
Spectrometer Frequency 376.11
Nucleus 19F
-61.89
-71.02
-72.91
-76.55
CF3COOH
CF3
PAd2 Cu(MeCN)PF6
(S)
N
Me
Cy
(S)-L2-13Cu(MeCN)PF6
19F NMR, 376 MHz
f1 (ppm)


Parameter Value
Title cxp-7-104-p-P31
Solvent cd2cl2
Spectrometer Frequency 161.83
Nucleus 31P
31.96
31.45
-0.00
-131.09
-135.48
-139.88
-144.27
-148.66
-153.05
-157.45
CF3
PAd2 Cu(MeCN)PF6
(S)
N
Me
Cy
H3PO4
31P NMR, 162 MHz
f1 (ppm)