

# THQphos in Ir-catalyzed Asymmetric Allylic Substitution Reactions

Xiao Zhang<sup>a</sup> and Shu-Li You<sup>\*ab</sup>

**Abstract:** The 1,2,3,4-tetrahydroquinoline phosphoramidites (**THQphos**) have been found to be efficient ligands for iridium-catalyzed asymmetric allylic substitution reactions. In this short review article, an overall introduction on the development of **THQphos**, involving their original design, preparation, mechanistic studies, applications and features will be described.

**Keywords:** Allylic substitution · Asymmetric catalysis · Iridium · THQphos



## Shu-Li You

was born in Henan, China, and received his BSc in chemistry from Nankai University. (1996). He obtained his PhD from Shanghai Institute of Organic Chemistry (SIOC)

in 2001 under the supervision of Prof. Li-Xin Dai before doing postdoctoral studies with Prof. Jeffery Kelly at The Scripps Research Institute. From 2004, he worked at the Genomics Institute of the Novartis Research Foundation as a principal investigator before returning to SIOC as a Professor in 2006. He is currently the director of the State Key Laboratory of Organometallic Chemistry. His research interests mainly focus on asymmetric C-H functionalization and catalytic asymmetric dearomatization (CADA) reactions.

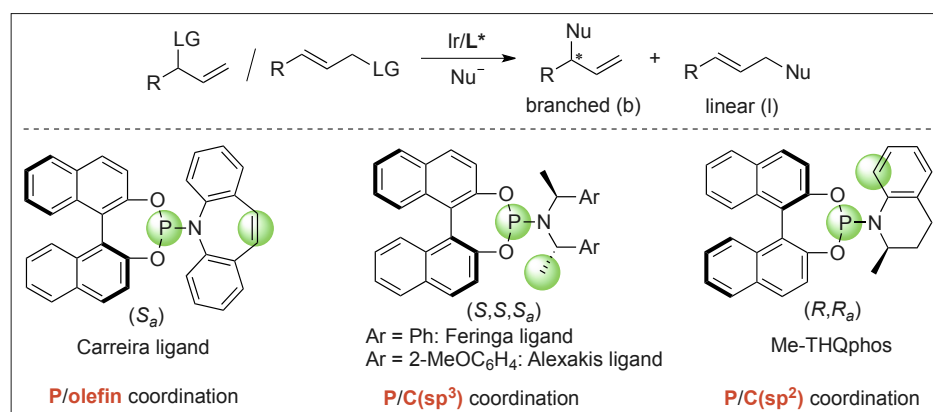
## 1. Introduction

Iridium-catalyzed asymmetric allylic substitution reactions have experienced tremendous advances during the past years, providing a powerful, efficient and reliable avenue for simultaneously incorporating stereocenters and allyl groups that are primed for further elaboration. These variants generally occur in a highly branched regio- and enantioselective fashion, which is largely due to the vital roles played by the coordinated chiral ligands.<sup>[1]</sup> Since the first enantioselective report introduced by Helmchen and co-workers, many privileged chiral ligands have been successfully applied in iridium catalytic system (Scheme 1).<sup>[2]</sup> Among them, Carreira's bidentate P/olefin coordination ligand is greatly appreciated since the catalyst derived thereof allows numerous highly selective transformations by directly using allylic alcohols as the substrates in the presence of an acidic additive.<sup>[3]</sup> With respect to non-acidic conditions, Ir-complexes derived from phosphoramidite ligands emerge as the most frequently used catalytic systems. For instance, the combination of iridium precursors such as  $[\text{Ir}(\text{cod})\text{Cl}]_2$  (cod=1,5-

cyclooctadiene) and Feringa-type ligands is applicable to a broad range of substrates with an excellent level of regio- and enantioselectivity. Mechanistically, the active iridacycle catalyst involving P/C(sp<sup>3</sup>) coordination, generated by cyclometalation of a methyl group of the ligand, is crucial for the activity and selectivity.<sup>[4]</sup> However, its sensitivity to steric hindrance somehow limits its application, resulting in poor reactivity in some cases. On the other hand, Ir/THQphos based on P/C(sp<sup>2</sup>) coordination constitutes another powerful catalytic system with a broader substrate scope including the challenging ones in previous studies.<sup>[5]</sup> This short review article describes the evolution of **THQphos**, in terms of original design, preparation, mechanistic studies, applications and features.

## 2. Original Design and Synthesis of THQphos

In 1997, Takeuchi and co-workers reported the first iridium-catalyzed allylic substitution reaction and it was found that the utilization of the strong  $\pi$ -acceptor ligand P(OPh)<sub>3</sub> plays a key role in obtain-



\*Correspondence: Prof. S.-L. You  
E-mail: slyou@sioc.ac.cn

<sup>a</sup>State Key Laboratory of Organometallic Chemistry  
Shanghai Institute of Organic Chemistry, University of  
Chinese Academy of Sciences  
Chinese Academy of Sciences, 345 Lingling Lu,  
Shanghai 200032, China

<sup>b</sup>Collaborative Innovation Center of Chemical Science  
and Engineering (Tianjin), 300072, China

Scheme 1. Representative ligands in Ir-catalyzed asymmetric allylic substitution reactions.

ing high reactivity and favoring branched selectivity.<sup>[6]</sup> Later on, Helmchen and co-workers revealed the true active species for such transformation is a P/C(sp<sup>2</sup>) co-ordinated iridium complex.<sup>[7]</sup> Inspired by these pioneering works, we initiated our investigation of **THQphos**, in which chiral factors were introduced in these bidentate P/C(sp<sup>2</sup>) coordination ligands (a, Scheme 2). Accordingly, commercially available achiral *N*-aryl amines and enantiopure 2-substituted tetrahydroquinolines<sup>[8]</sup> were used as the amine part. Then, **THQphos** ligands were prepared through the reactions of 1,1'-bi-2-naphthols with amines in a one-pot procedure (b, Scheme 2).<sup>[9]</sup>

### 3. Mechanistic Studies

With respect to reactivity and selectivity, (*R,R*)-Me-**THQphos** **L1b** functions as the optimal ligand in most cases. As an illustration, its cinnamyliridium complex **K1** was synthesized according to a known procedure developed by Helmchen and coworkers.<sup>[10]</sup> Despite the formation of an exclusive *exo* isomer at the very beginning, this complex was isolated in the form of *exo* and *endo* isomers with a ratio of 4:1 as a result of thermodynamic equilibrium (a, Scheme 3). Experimentally, the allylic alkylation of sodium dimethyl malonate with **K1** gave comparable results with that catalyzed by the catalyst generated *in situ*, further supporting the ( $\pi$ -allyl)-Ir complex **K1** as the key intermediate and active catalytic species (b, Scheme 3). In addition, the crystal structure of this complex led to the following observations: i) Despite the presence of Me group, the active iridacycle is formed through a C(sp<sup>2</sup>)-H bond insertion of tetrahydroquinoline in the ligand. ii) The Ir-C(3) bond of **K1** is longer than Ir-C(1) bond by 0.17 Å, which could be attributed to the strong *trans* influence of P atom combined with the stabilizing ability of neighbored phenyl ring. As a consequence, the subsequent nucleophile preferably attacks at the aryl or alkyl-substituted C(3) position resulting in a highly branched regioselectivity since C(3) is more electropositive than C(1). iii) The *Re*-face is well shielded by the chiral ligand, leading to the nucleophilic attack from the *Si*-face dominantly to afford the (*R*)-branched product. Compared with Ir-complexes derived from Feringa-type ligands, **K1** features less steric hindrance, thus permitting a good tolerance of bulky nucleophiles and *ortho*-substituted cinnamyl derivatives. The plausible explanation for high enantioselectivity induced by the catalytic amount of catalyst is that the nucleophile attacks at the kinetically favorable formation of the *exo* form of **K1**

much faster than its  $\pi$ - $\sigma$ - $\pi$  interconversion. Principally, the absolute configuration of branched products was controlled by the BINOL scaffold. It is worth noting that the employment of **THQphos** and Feringa-type ligands with same axial chirality led to the products with opposite absolute configuration.<sup>[5]</sup>

### 4. Application

Due to their unique properties, **THQphos** ligands have been successfully applied in several iridium-catalyzed allylic substitution reactions and found to be compatible with diverse nucleophiles.

#### 4.1 Ir-Catalyzed Asymmetric Allylic Substitution Reactions with Carbon Nucleophiles

##### 4.1.1 Stabilized Enolates

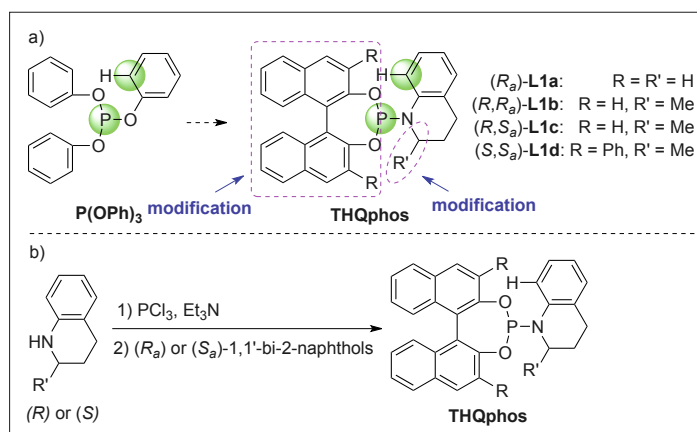
In 2012, our group reported an intensive investigation on **THQphos** including synthesis and mechanistic studies. With respect to their application, iridium-catalyzed asymmetric allylic alkylation of sodium dimethyl malonates was first studied. The reactions with various allylic carbonates all led to their desired products in good yields with excellent regio- and enantioselectivities. Particularly, the typical

ly unfavorable *ortho*-substituted cinnamyl carbonates could be well tolerated, further showcasing the generality of this catalytic system (Scheme 4).<sup>[5]</sup>

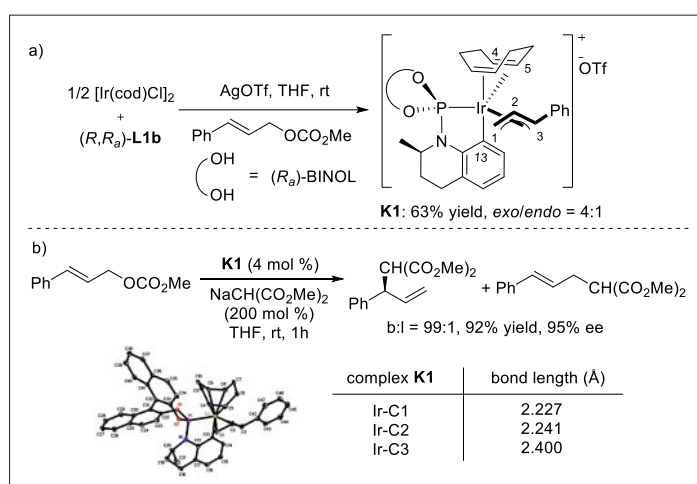
Stoltz and co-workers revealed an asymmetric allylic alkylation reaction of cyclic  $\beta$ -ketoesters in the iridium catalytic system, permitting the incorporation of vicinal tertiary and all-carbon quaternary centers in a highly regio- and enantioselective fashion. Despite of the difficulties associated with diastereocontrol of prochiral nucleophiles within this domain, Ir-complex derived from **L1b** performed outstandingly, leading to the desired product in excellent diastereoselectivity (>20:1 dr), which showed a significant advantage over other privileged ligands (1:1 or 1:2 dr in each case).<sup>[11]</sup> Furthermore, Stoltz and co-workers extended this catalytic system to achieve the asymmetric transformations based on acyclic  $\beta$ -ketoesters. Under the optimized conditions, diverse nucleophiles bearing various functional groups such as alkyl, heteroaryl, allyl, propargyl and keto functionalities at the  $\alpha$ -position were tested, delivering the desired  $\alpha$ -quaternary  $\beta$ -ketoesters in excellent yields and selectivities (Scheme 5).<sup>[12]</sup>

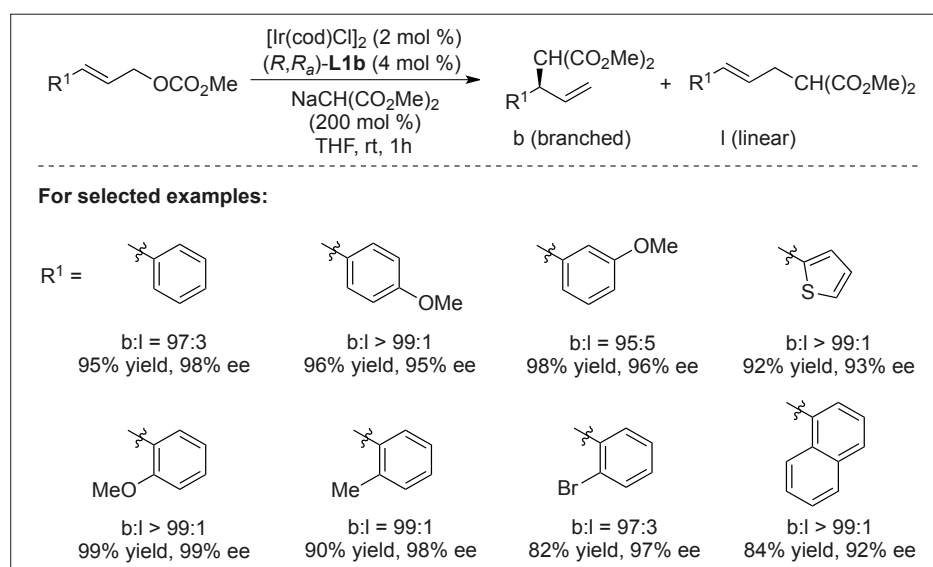
Later on, the Stoltz group disclosed an asymmetric allylic alkylation of  $\alpha,\beta$ -unsaturated malonates and ketoesters,

Scheme 2. Design and synthesis of **THQphos**.

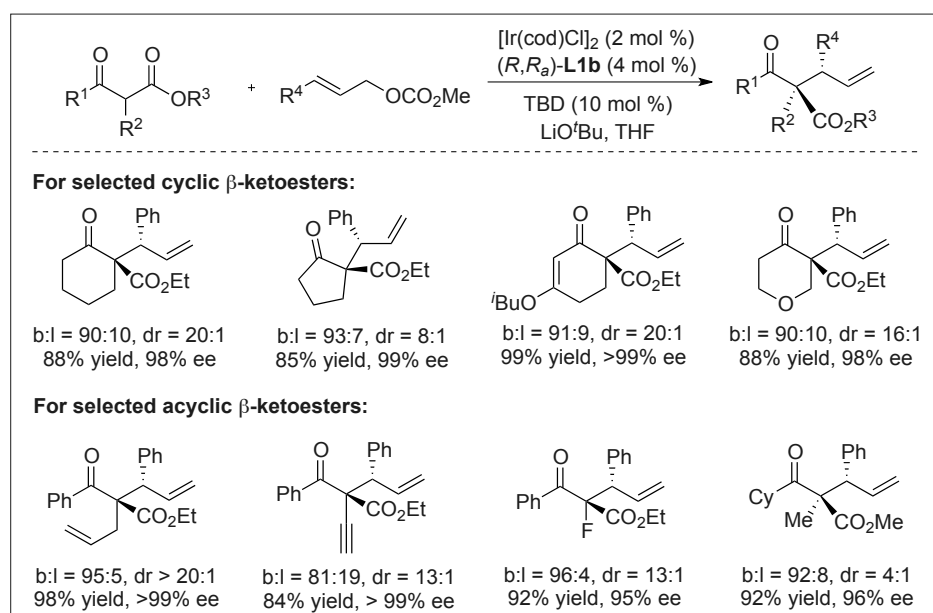


Scheme 3. Mechanistic studies.

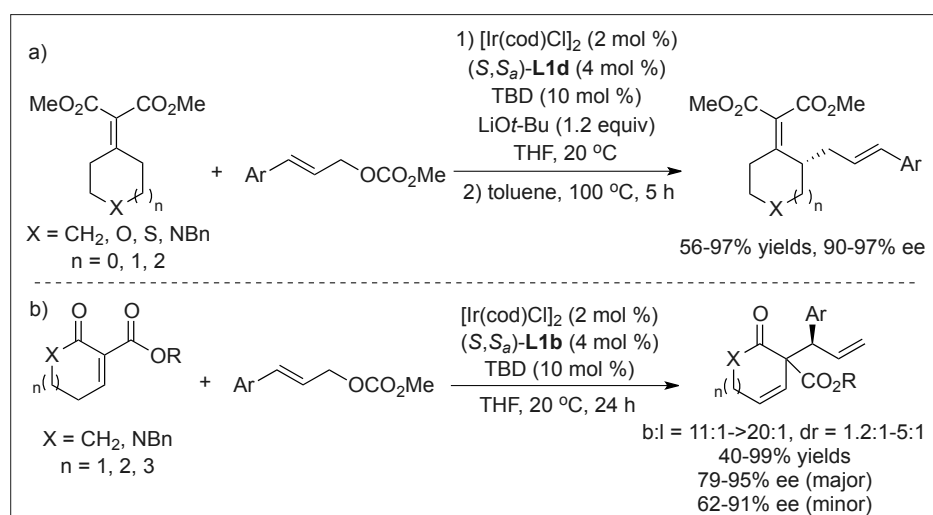




Scheme 4. Ir-catalyzed asymmetric allylic alkylation of sodium dimethyl malonates. THF = tetrahydrofuran.



Scheme 5. Ir-catalyzed asymmetric allylic alkylation of  $\beta$ -ketoesters. TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene; Cy = Cyclohexyl.



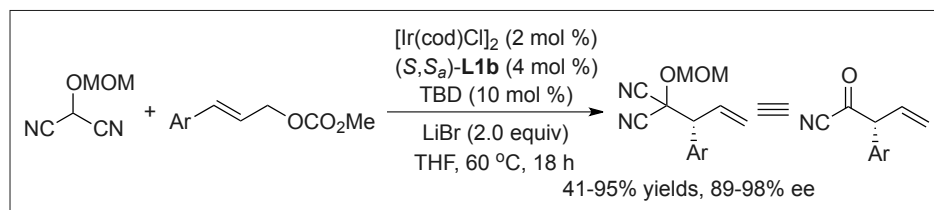
Scheme 6. a) Sequential (one-pot) Ir-catalyzed asymmetric allylic alkylation/cope rearrangement; b) Ir-catalyzed asymmetric allylic alkylation of cyclic  $\alpha,\beta$ -unsaturated  $\beta$ -ketoesters.

in which exclusive  $\gamma$ -selectivity was observed through a sequential  $\alpha$ -alkylation of the extended enolate and thermal cope rearrangement. In this case, **L1d** functions as the optimal ligand in terms of both yields and selectivities (Scheme 6).<sup>[13]</sup> Very recently, the masked acyl cyanide reagents, recognized as acyl cyanide equivalents, have been successfully applied in Ir-catalyzed asymmetric allylic alkylation reactions, thus allowing easy access to vinylic  $\alpha$ -aryl carbonyl derivatives in a highly enantioselective fashion (Scheme 7).<sup>[14]</sup>

#### 4.1.2 Electron-rich Arenes

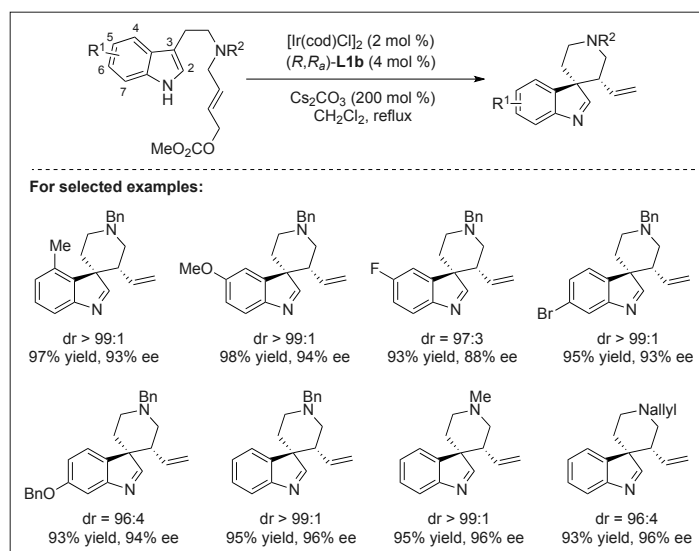
**Indoles:** The earliest example using **THQphos** was dated back to 2009 in the asymmetric Friedel-Crafts reaction of indoles with allylic carbonates. In the presence of ligand **L1b**, the corresponding alkylation products could be obtained in high branched regioselectivity and enantioselectivity.<sup>[9]</sup> After that, our group disclosed the first intramolecular dearomatization of indoles by introducing an allylic carbonate link at C(3), thus providing a straightforward access to enantioenriched spiroindolenines bearing all-carbon quaternary stereogenic centers in excellent yields with excellent diastereo- and enantioselectivity (up to >99/1 dr and 97% ee) (Scheme 8).<sup>[15]</sup> Interestingly, when symmetric bis(indol-3-yl) substituted allylic carbonates were used, the corresponding spiroindolenine products bearing three contiguous stereogenic centers were generated as a single diastereoisomer with high enantiomeric purity (up to 99% ee) in the presence of a catalyst derived from  $[\text{Ir}(\text{dbcot})\text{Cl}]_2$  (dbcot = dibenzocyclooctatetraene) and 3,3'-diphenyl substituted ligand **L1d** (a, Scheme 9). Further treatment of the products with a catalytic amount of *p*-toluenesulfonic acid (TsOH) in refluxing THF delivered hexahydroazepino[4,5-*b*]indoles with high diastereoselectivity. Based on the observation of reversed configuration of migratory carbon, such unprecedented six-to-seven-membered ring expansion reactions were assumed to proceed through free vinyliminium intermediates and to reestablish the stereochemistry during the subsequent cyclization step (b, Scheme 9).<sup>[16]</sup>

In addition, the intermolecular allylic dearomatization of indoles was established to provide the polycyclic indoline compounds bearing three contiguous stereocenters in a highly site-, regio-, diastereo- and enantioselective fashion. Critical to this method is the employment of **MeTHQphos L1b**. The reaction features a broad substrate scope, in which different allylic carbonates as well as a variety of indoles including tryptophols, tryptamines,

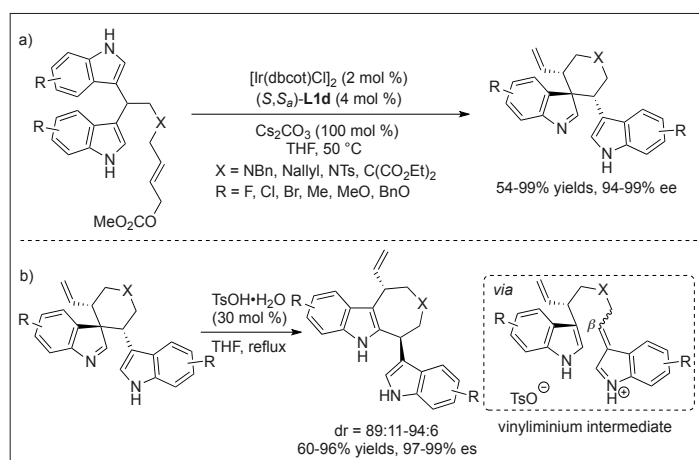


Scheme 7. Ir-catalyzed asymmetric allylic alkylation of masked acyl cyanide (MAC) reagents. MOM = methoxymethyl.

Scheme 8. Ir-catalyzed intramolecular asymmetric allylic dearomatization of indoles.



Scheme 9. a) Ir-catalyzed desymmetrizing allylic dearomatization reaction of indoles; b) Spiroindolenines migration reaction. Bn = benzyl; Ts = 4-toluenesulfonyl.

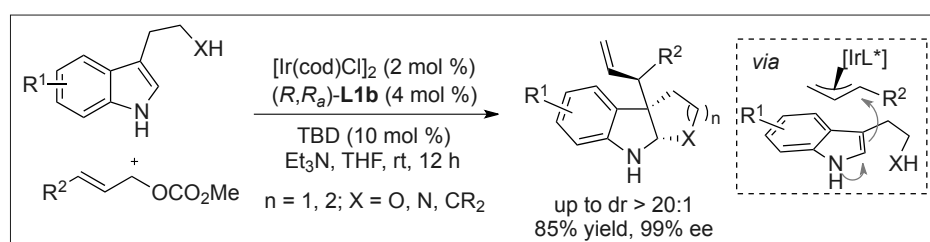


indoles with an carbon nucleophile side chain and tryptophan derivatives were well accommodated (Scheme 10).<sup>[17]</sup>

**Pyrroles:** Pyrroles tethered with an allylic carbonate are also amenable to the dearomatization processes catalyzed by the above iridium catalytic system consisting of  $[\text{Ir}(\text{cod})\text{Cl}]_2$  and Me-THQphos **L1b**. Although similar reactivity generally displayed at C(2) and C(3) positions of pyrroles, spiro-2*H*-pyrrole derivatives were obtained in good yields with excellent regio-, diastereo- and enantioselectivity under slightly modified conditions (Scheme 11). The utility of this method was further demonstrated by diverse transformations to afford various spirocycles.<sup>[18]</sup>

**Naphthols:** Since the nucleophilic 2-OH group is located at the *ortho* posi-

tion to an electrophilic allylic group, the intramolecular asymmetric allylic dearomatization of naphthol derivatives becomes particularly challenging due to the competition between C and O alkylation. Ultimately, our group discovered that the catalyst generated from  $[\text{Ir}(\text{dbcot})\text{Cl}]_2$  and



Scheme 10. Ir-catalyzed intermolecular asymmetric allylic dearomatization of 3-substituted indoles.

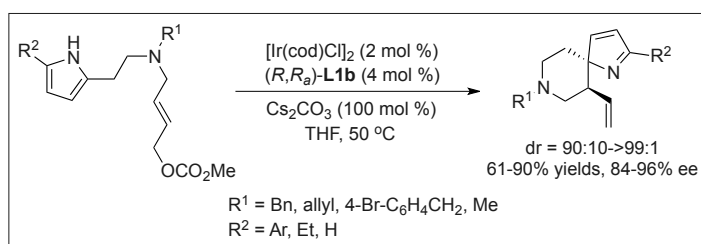
3,3'-diphenyl-substituted ligand **L1d** could enable the intramolecular variants to afford the corresponding naphthalenones with excellent chemo-, diastereo-, and enantioselective control. Notably, the electron-deficient and sterically hindered protecting groups introduced at the nitrogen atom are beneficial for superior selectivities (Scheme 12).<sup>[19]</sup>

#### 4.2 Ir-Catalyzed Asymmetric Allylic Substitution Reactions with Nitrogen Nucleophiles

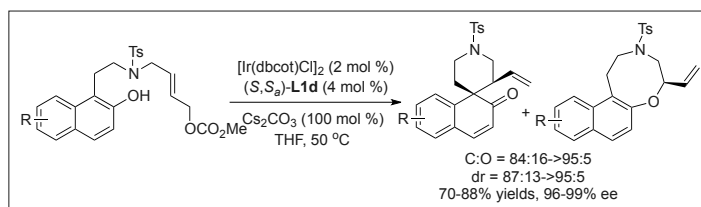
Iridium-catalyzed intramolecular asymmetric allylic amination reaction provides a straightforward route towards the pyrrole-fused piperazine derivatives with high yields. Notably, the enantioselectivity of the reaction with bromo-substituted pyrrole containing amide substrates could be dramatically improved by switching the ligand to Me-THQphos **L1b** or 3,3'-diphenyl-substituted ligand **L1d** (Scheme 13).<sup>[20]</sup> Moreover, Me-THQphos **L1b** has been largely applied in the intramolecular asymmetric allylic dearomatization of nitrogen-containing heterocycles. For instance, Me-THQphos **L1b** was found to be more efficient than other tested ligands in the dearomatization of diverse six-membered-ring electron-poor aromatics such as pyrazines and certain quinolines and isoquinolines, furnishing the desired products with high levels of yield and enantioselectivity (a, Scheme 14).<sup>[21]</sup> Meanwhile, a variety of five-membered-ring heterocycles bearing two heteroatoms including benzoxazoles, benzothiazoles and benzimidazoles were also compatible with the dearomatization protocol enabled by *in situ* formed Ir-catalyst. In all the cases, highly functionalized target molecules were obtained in good yields and excellent enantioselectivity (b, Scheme 14).<sup>[22]</sup>

In 2016, our group reported that the iridium catalyst derived from 3,3'-diphenyl-substituted ligand **L1d** can catalyze asymmetric intermolecular allylic amination reactions with anilines, indolines, benzylamines and 2-vinylanilines. Good yields and high to excellent regio- and enantioselectivities could be achieved for various allylic carbonates, especially for the previously challenging *ortho*-substi-

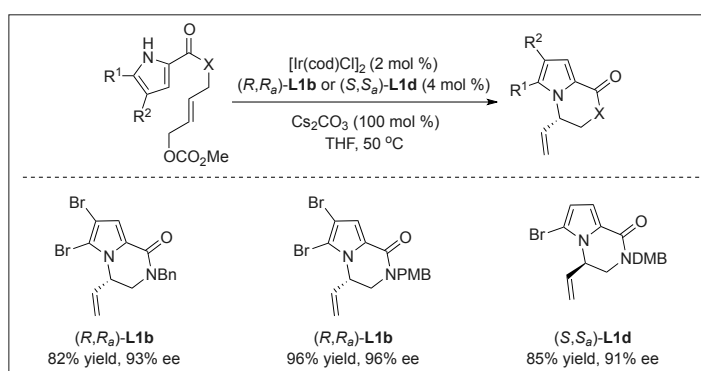
Scheme 11. Ir-catalyzed intramolecular asymmetric allylic dearomatization of pyrroles.



Scheme 12. Ir-catalyzed intramolecular asymmetric allylic dearomatization of naphthol derivatives.



Scheme 13. Ir-catalyzed intramolecular asymmetric allylic amination reaction of pyrrole derivatives.



tuted cinnamyl substrates. Interestingly, the use of (*S,S<sub>a</sub>*)-**L1d**, its diastereomer (*R,S<sub>a</sub>*)-**L1d** or a mixture of identical amount of the two diastereomers all led to identical results, which suggested the stereocenter in 2-methyl-1,2,3,4-tetrahydroquinoline was not necessary in this case.<sup>[23]</sup>

#### 4.3 Ir-Catalyzed Asymmetric Allylic Substitution Reactions with Oxygen Nucleophiles

The catalytic asymmetric synthesis towards chiral *N,O*-heterocycles is a challenging task. In 2014, Feringa and co-workers revealed a highly efficient iridium-catalyzed intramolecular allylic substitution with amide oxygen nucleophile to access such scaffolds. In the presence of the catalyst generated *in situ* from  $[\text{Ir}(\text{cod})\text{Cl}]_2$  and **THQphos L1a**, a wide range of heterocycles such as oxazoline, oxazine and benzoxazine derivatives were constructed in good yields with high enantiomeric purity (Scheme 15).<sup>[24]</sup>

#### 5. Conclusions

Since the introduction of **THQphos** ligands, considerable progress has been made in their applications in Ir-catalyzed asymmetric allylic substitutions. This class of ligand is structurally simple, configurationally stable and synthetically accessible

in large scale. Mechanistic studies suggest the active iridacycle catalyst is based on *P/C*(*sp*<sup>2</sup>) coordination. Due to the combined influence of electronic effect and

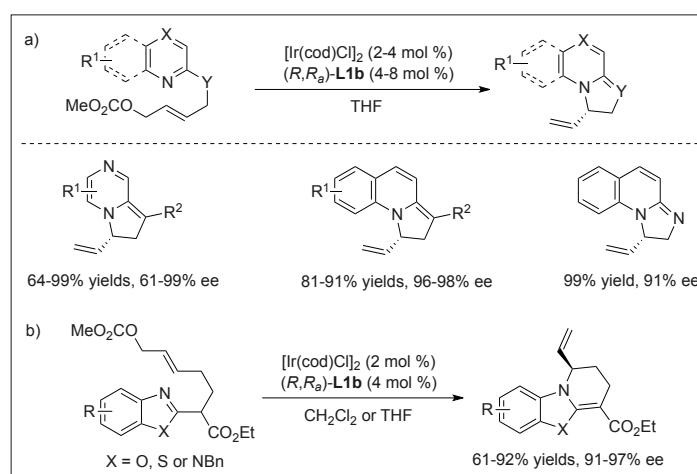
steric-hindrance effect, **THQphos** ligands are capable of providing high activity, branched regioselectivity and asymmetric induction. Particularly intriguing, the generally unfavorable *ortho*-substituted cinnamyl carbonates are well tolerated under such catalytic system. In many cases, **THQphos** ligands also display excellent diastereoselectivity when prochiral nucleophiles are employed. Future work on **THQphos** needs to explore new types of stereo-controlled reactions beyond Ir-catalyzed AAS.<sup>[25]</sup>

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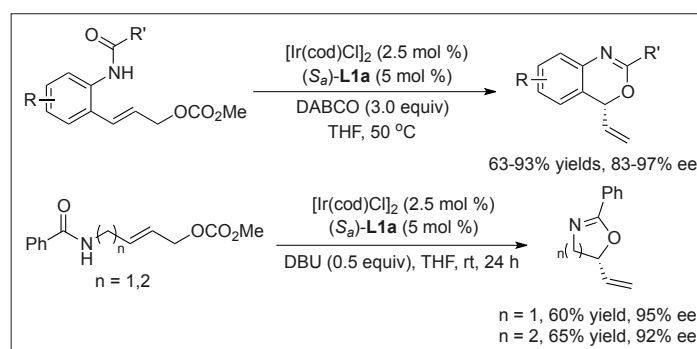
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Scheme 14. Ir-catalyzed intramolecular asymmetric allylic dearomatization of pyrazines, quinolones, benzoxazoles, benzothiazoles and benzimidazoles.



Scheme 15. Ir-catalyzed intramolecular asymmetric allylic substitution reaction with amide oxygen nucleophiles. DABCO = 1,4-diazabicyclo[2.2.2]octane; DBU = diazabicyclo[5.4.0]undec-7-ene.

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