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# Rhodium-Catalyzed Asymmetric Access to P-Chiral Triarylphosphine Oxides via Insertion of P−H Bonds into Diazonaphthoquinones

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**Abstract:** While significant progress has been made in enantioselective insertion of carbenes into heteroatom-hydrogen bonds, this chemistry is restricted to construction of carbon-based chirality. The asymmetric insertion of carbenes into P-H that delivers P-chiral products remains untouched. We herein report rhodium(I)-catalyzed enantioselective synthesis of P-chiral triarylphosphine oxides via asymmetric C-P coupling of a secondary phosphine oxide (SPO) with diazonaphthoquinone. Driven by aromatization, this protocol affords a variety of P-chiral triarylphosphine oxides tethered to a 2-naphthol functionality in excellent enantioselectivity by following a kinetic resolution reaction pattern. The diverse synthetic and catalytic applications of the P-chiral products highlight the value of this method, even though the derivatized trivalent chiral phosphine bears a rather low barrier of racemization.

## Introduction

Owing to wide applications of chiral phosphine (oxides) in materials,[1] biomedicines,[2] and asymmetric catalysis,[3] efficient access to enantioenriched P-chiral compounds has been attracting increasing attention.[4] Four catalytic synthetic strategies have been developed to address the asymmetric synthesis of this class of targets (Scheme 1a), namely, the chiral auxiliary strategy,[5] desymmetrization of tertiary phosphine oxides (TPOs),[6] hydrophosphonylation of π-bonds,[7] and cross-coupling of a secondary phosphine oxide (SPO) with a carbon electrophile.[8] Despite the progress, existing methods suffer from various limitations. The chiral auxiliary strategy requires the usage of at least one equivalent of chiral auxiliaries. The desymmetrization strategy relies on specific substrates. The employment of a SPO in P-H insertion or the cross-coupling strategy conduces to flexibility and modularity of the reaction. However, reactive π-bonds are employed and the SPOs are predominantly limited to alkyl-aryl substituents, while diaryl-substituted SPOs have been much less explored. This is ascribed to the challenge associated with differentiation of the two aryl substituents by the catalyst. Previously, aryl-pyridyl SPOs have been established as substrates with the P-pyridyl group serving as a chelator.[9] The limited reaction mode of diaryl SPOs and the structural constraint of the corresponding chiral TPO products leave large room for exploration of asymmetric synthesis.

As an important class of unsaturated species, carbene undergoes insertion into various heteroatom-hydrogen (E-H) bonds, which represents an efficient strategy to construct C-E bonds.[10] Carbene precursors have also been investigated in P-H insertion to construct tertiary phosphine oxides (Scheme 1b),[11] and the first example dated back to 1986 by Arbuzov.[11a] However, the asymmetric version of this insertion didn't emerge until 2023, when the Jiang group reported asymmetric P−H insertion into diazopyrazole amides by Cu(I) catalysis (Scheme 1b).[12] However, the product was restricted to C-chirality since only symmetric SPOs were engaged. To the best of our knowledge, there has been no report on asymmetric carbene insertion into a P-H bond that affords P-chiral products. In fact, in the context of insertion of $sp^3$ E-H bonds into carbenes, only sole example of Ge chiral center has been established through Ge-H insertion (Scheme 1c).[13]

In the reported related asymmetric N-H, O-H, and P-H insertion reactions that generate a carbon chiral center, proton transfer using a proton-shuttle catalyst has been rationalized as the enantiodetermining step.[14] The reliance on this specific chiral induction mode inspired our development of an asymmetric catalytic system of P-H insertion by following a different asymmetric induction mode. Given the strong ligating ability of a P atom to a rhodium center and abundance of Rh(I)-catalyzed transformation of carbenes,[15] we envisaged a Rh(I)-catalyzed inner-sphere pathway of carbene insertion that takes advantage of Rh-P migratory insertion as a key step. In this context, to avoid the protonolysis event being enantiodetermining, we designed diazonaphthoquinone as a carbene precursor with aromatization being the driving force. In addition, the structural rigidity of the

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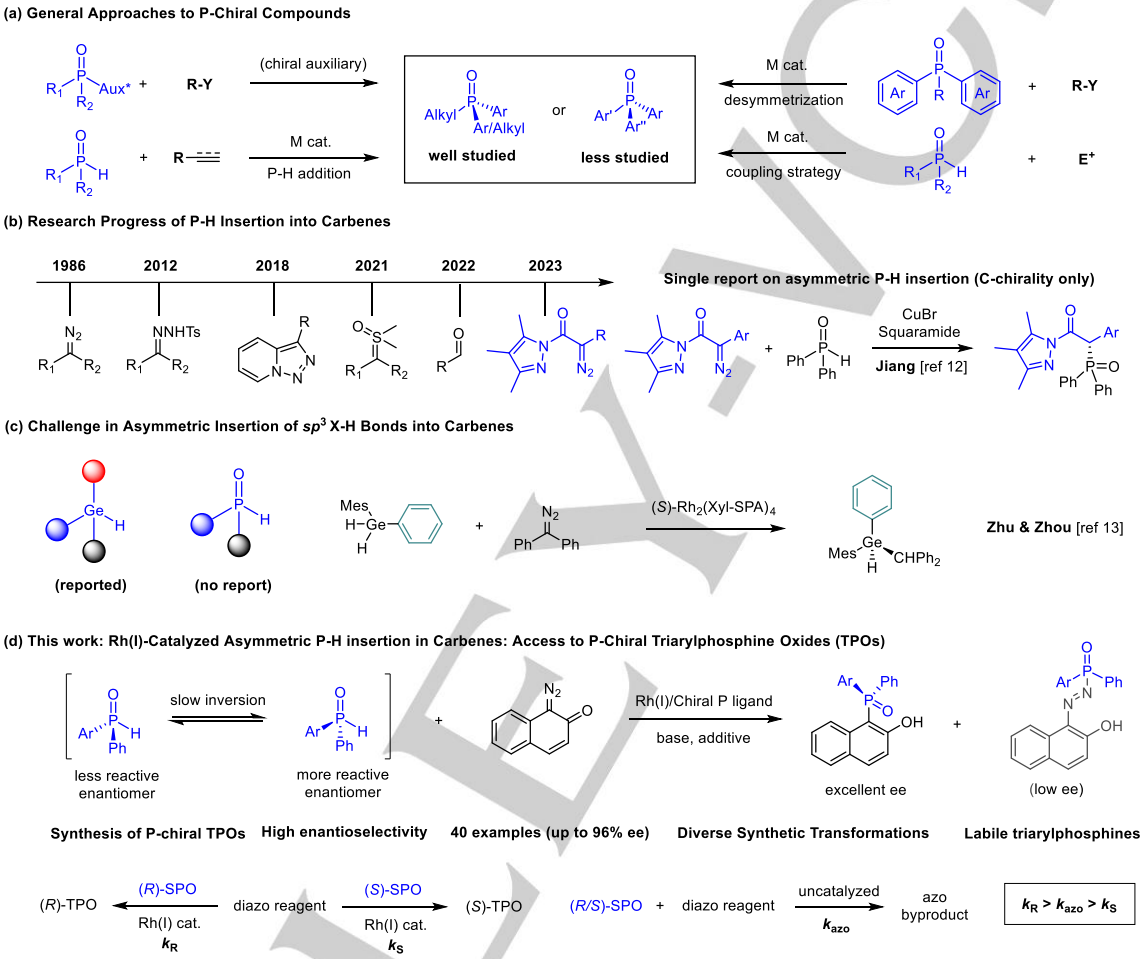
diazonaphthalenone-derived carbene also favors the spatial recognition of the two aryl groups in the ligated SPO.[16] The major obstacle in our system development is the substrate inhibition and the enantioselective control. In addition, a reactive diazo reagent also tends to give side reactions such as uncatalyzed nitrogen-retentive P-N coupling.[17] We now report rhodium-catalyzed asymmetric C-P coupling between SPOs and diazonaphthoquinone toward the synthesis of enantioenriched P-chiral TPOs (Scheme 1d). Synthetic transformations and catalytic applications of the chiral products further highlight the value of this method even though the derived trivalent chiral phosphine experiences a rather low barrier of racemization.

**Scheme 1**. P-Chiral Products via Asymmetric Insertion of Carbene into a P-H Bond.




## Results and Discussion

**Initial Optimization Studies.** We chose diazonaphthalenone **1** and diarylphosphine oxide **2** as the model substrates for optimization studies. The racemic reaction conditions were initially identified using a Rh(I) catalyst and an achiral phosphine ligand. The target racemic product **3** was isolated in high yield when DPPP was used as the ligand in the presence of a base additive (see Supporting Information for details). In contrast, no desired reaction occurred when other metal catalysts including Cu(I) were employed. Next, a large set of chiral phosphine ligands were screened for the asymmetric reaction (Scheme 2), but many commonly used ligands such as QuinoxP, Sadphos, ferrocenyl phosphines, and SpiroP all failed. Several diphosphine ligands (**L1** and **L3**) exhibited moderate reactivity with promising enantioselective control. However, increasing the steric hindrance of these ligands simply led to no reactivity (**L2** and **L4**). After screening of a series of biaryl-based $C_2$-symmetric bidentate phosphine ligands, it was found that the **L9** and **L10** ligands showed good enantioselective control albeit with rather low activity. The reaction enantioselectivity was further improved when an axially chiral bipyridyl-based PPhops ligand (**L12**) was used. Careful examination of the reaction byproducts revealed that decomposition of the diazo reagent and formation of an azo byproduct via an uncatalyzed P-N coupling were the major competitive side reactions. Therefore, further studies were directed to the suppression of these side reactions.

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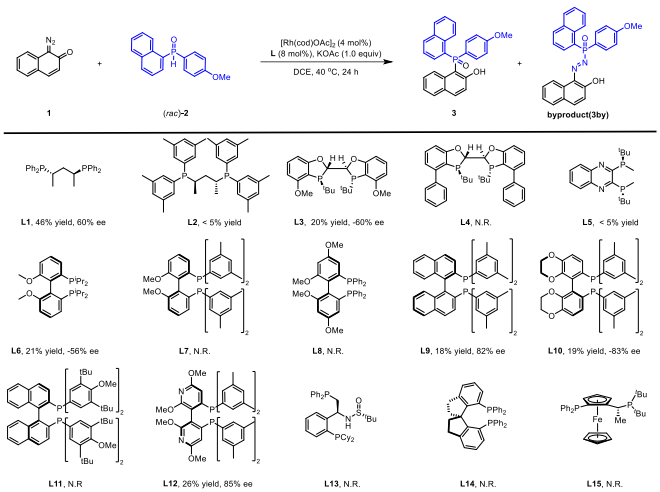
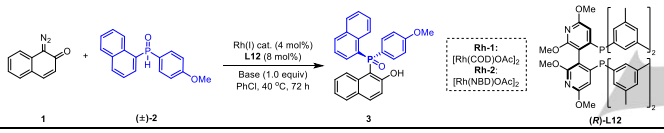
**Scheme 2.** Initial Screening of Chiral Ligands.[a]




[a] Reaction conditions: **1** (0.1 mmol), **2** (0.2 mmol), Rh(I) catalyst (4 mol%), ligand (8 mol%), and KOAc (1.0 equiv) in DCE (0.05 M) at 40 °C for 24 h under $N_2$; isolated yield. The ee was determined by HPLC using a chiral stationary phase.

**Table 1.** Further Optimization Studies.[a]




| Entry | Catalyst | Base | Additive | Solvent | Yield (%)/ Ee (%) |
|---|---|---|---|---|---|
| 1 | **Rh-1** | KOAc | -- | DCE | 26/85 |
| 2 | **Rh-1** | KOAc | -- | DCM | 28/86 |
| 3 | **Rh-1** | KOAc | -- | PhCl | 30/88 |
| 4 | **Rh-1** | NaOAc | -- | PhCl | <5/n.d. |
| 5 | **Rh-1** | $K_2HPO_4$ | -- | PhCl | 30/86 |
| 6 | **Rh-1** | KOAc | 3Å MS | PhCl | 49/93[b] |
| 7 | **Rh-2** | KOAc | 3Å MS | PhCl | 53/94 |
| 8 | **Rh-2** | NaOAc | 3Å MS | PhCl | 55/94 |
| 9 | **Rh-2** | NaOAc | 3Å MS | DCM | 60/92 |
| 10 | **Rh-2** | $K_2HPO_4$ | 3Å MS | DCM | 62/92 |
| 11 | **Rh-2** | $K_2HPO_4$ | 3Å MS | DCM/ACN (4:1) | 66/91 |
| 12[c] | **Rh-2** | $K_2HPO_4$ | 3Å MS | DCM/ACN (4:1) | 73/91 |

[a] Reaction conditions: **1** (0.1 mmol), **2** (0.2 mmol), Rh(I) catalyst (4 mol%), **L12** (8 mol%), base (1.0 equiv), solvent (0.05 M), 3Å MS (60 mg, if any) at 40 °C for 48 h under $N_2$; isolated yield. The ee was determined by HPLC using a chiral stationary phase. [b] The azo byproduct was isolated in 25% yield (14% ee). [c] *t* = 72 h.

Further optimization studies were carried out using the (*R*)-**L12** chiral ligand (**Table 1**). Our screening of solvents and bases failed to effectively improve the reaction efficiency and enantioselectivity (entries 1-5). The yield and enantioselectivity were greatly improved upon introduction of 3Å MS (entry 6). Nevertheless, the azo byproduct was still generated in 25% yield (14% ee). To suppress this side reaction, we then evaluated the Rh(I) source and found that $[Rh(nbd)OAc]_2$ slightly outperformed the others. Careful exploration of the base and reaction solvent indicated that a combination of $K_2HPO_4$ and DCM offered better yield and enantioselectivity (entries 7-10). Meanwhile, the azo byproduct was suppressed when MeCN was used as the solvent, although the reaction still suffered from low conversion. Consequently, a mixed solvent containing acetonitrile was used, and DCM/ACN (4:1) was established as the optimal one (entry 11). The reaction yield was further improved by extending the reaction time to 72 h, under which conditions the azo by-product was generated in ~ 5% yield and in 20% ee (entry 12). The absolute configuration of the (*R*)-**3** was determined by X-Ray crystallographic analyses.[18] Under these optimal conditions, the SPO substrate **2** was recovered in 43% yield and 46% ee. To improve the enantioselectivity of the recovered substrate, we further screened a number of bases and solvents. It was found that in the solvent of PhCl/ACN (3:1), when the ratio of substrates was 1:1.8 (60 h), substrate **2** (32%, 66% ee) was recovered together with product **3** (79% yield, 88% ee, see Supporting Information).

**The Reaction Scope.** With the establishment of the optimal reaction conditions, we then explored the scope of the diaryl SPO substrates. We first studied the effect of the *para* substituent in the benzene ring of the diaryl SPO, including the unsubstituted SPO (**4**) and that bearing an alkyl (**5-6**), phenyl (**7**), OBn (**8**), TMS (**9**), halogen (**10**), and trifluoromethyl group (**11**). The *para* substituent had a great influence on the reaction yield, but the enantioselectivity was largely unaffected (**4-11**, 90-93% ee). It should be noted that reaction in DCM solvent gave a higher yield for the unsubstituted and the alkyl-, phenyl-, and EWG-substituted substrates. The reaction efficiency seemed to be gradually reduced by a bulky substituent (**4-6** and **9**), and a similar trend was also followed for a series of *meta* substituent SPO substrates (**12**-**16**). Notably, the enantioselectivity of 3-Cl and -$OCF_3$ substrates were higher than that of the unsubstituted one. To further explore the scope of the SPO substrates, we investigated the reactivity of several di- and trisubstituted ones (**17**-**21**). The yield decreased (40-53%) with the increase of size of the substituent, but the enantioselectivity was improved (94-96% ee). We next investigated the effect of substituents on the naphthalene ring. The enantioselectivity was well maintained for the 4-alkyl, -phenyl, and -halogen substituted naphthalene ring (**22**-**25**). The reactivity of alkyl-substituted substrates decreased slightly, while that of halogen-substituted substrates further decreased. Surprisingly, the presence of an electron-donating methoxy group at the 3- or 4- positions of the naphthalene ring tends to give decreased enantioselectivity (**26**-**27**). The reaction also proceeded with comparable efficiency (**28**, 92% ee) when the naphthalene ring was extended to a phenanthrene. Extension to

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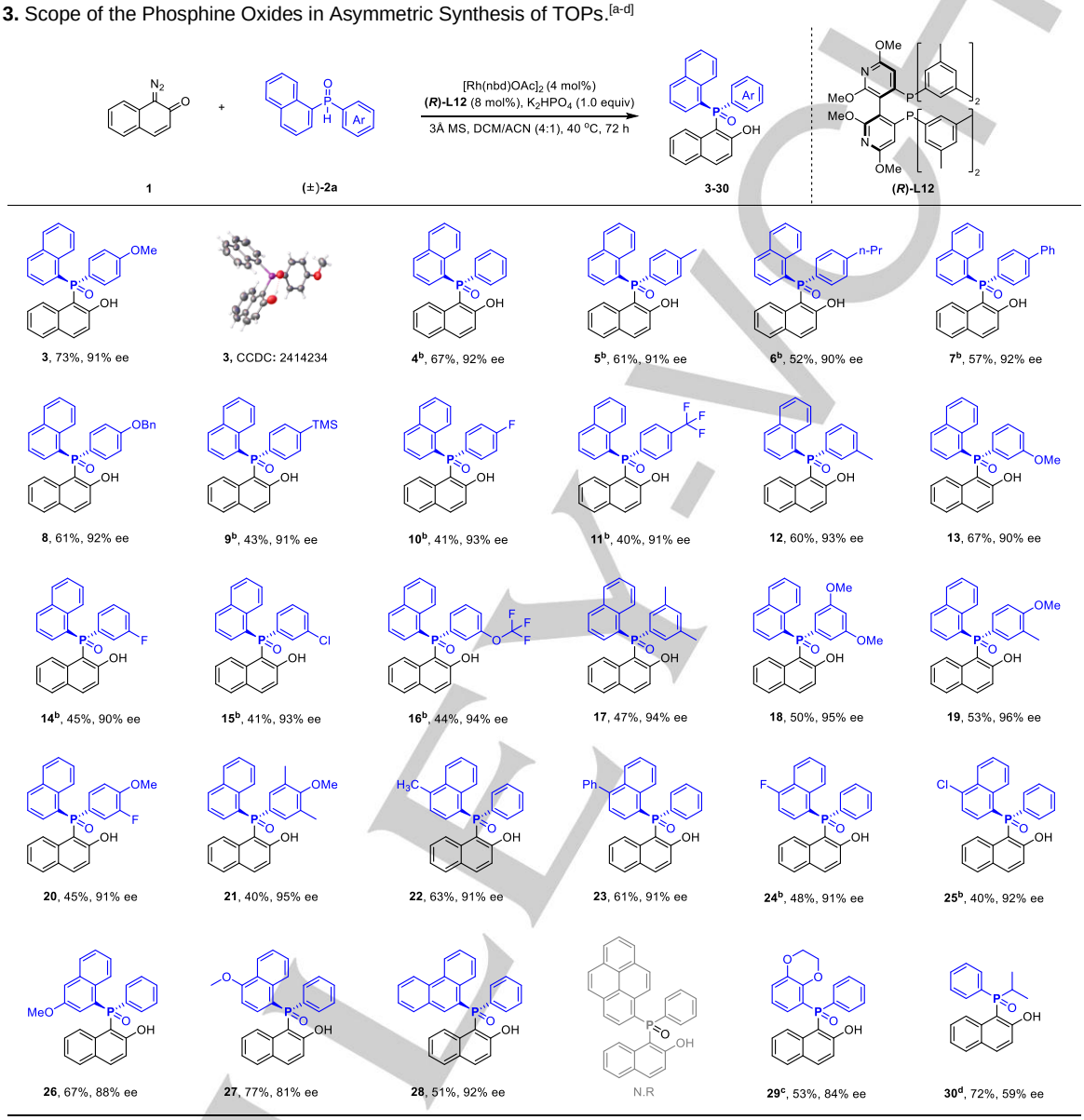
a larger fused ring met with difficulty, possibly caused by unfavorable π-π stacking. In addition to these phosphine oxides, we also investigated other types of SPOs. For example, the phosphine oxide of benzodioxanone reacted to give product **29** in 53% yield and 84% ee when using **L6** as a ligand. Extension of the phenyl group in the SPO to an $^{i}$Pr group, however, resulted in lower enantioselectivity (**30**).

**Scheme 3.** Scope of the Phosphine Oxides in Asymmetric Synthesis of TOPs.[a-d]




[a] Reaction conditions: **1** (0.1 mmol), **2** (0.2 mmol), Rh catalyst (4 mol%), ligand (8 mol%), $K_2HPO_4$ (1.0 equiv), DCM/ACN (4:1) (0.05 M), 3Å MS (60 mg) at 40 °C for 72 h under $N_2$; isolated yield. The ee was determined by HPLC using a chiral stationary phase. [b] DCM (0.05 M), [c] **L** = **L6** [d] **L** = **L5.** The minor diazo byproduct was omitted.

Next, the scope of the diazonaphthoquinone substrate was evaluated under the standard reaction conditions. The 3-methyl or -methoxy-substituted diazonaphthoquinone reacted effectively with comparable enantioselectivity (**31** and **33**). However, both the yield and enantioselectivity slightly decreased for 7-methyl or 6-methoxy substituted diazonaphthoquinone (**32** and **34**). The introduction of a 6-halogen group maintained the high enantioselectivity, and the reaction yield was only slightly affected (**35**-**37**). We then varied the 6-substituent to an aryl group and investigated its effect. The electronic effect of these 4-aryl substituents (**38** and **39**) only had marginal influence on the yield (65-67%) or enantioselectivity (90-91% ee). In addition, extension to diazoanthraquinone met with no difficulty (**40**). Installation of a larger 1-naphthyl group at the 6-position also maintained the enantioselectivity of the product, although the yield was further reduced (**41**, 42% yield and 93% ee). A 6-ester substituted substrate was also applicable in this reaction (**42**, 51% yield and 93% ee).

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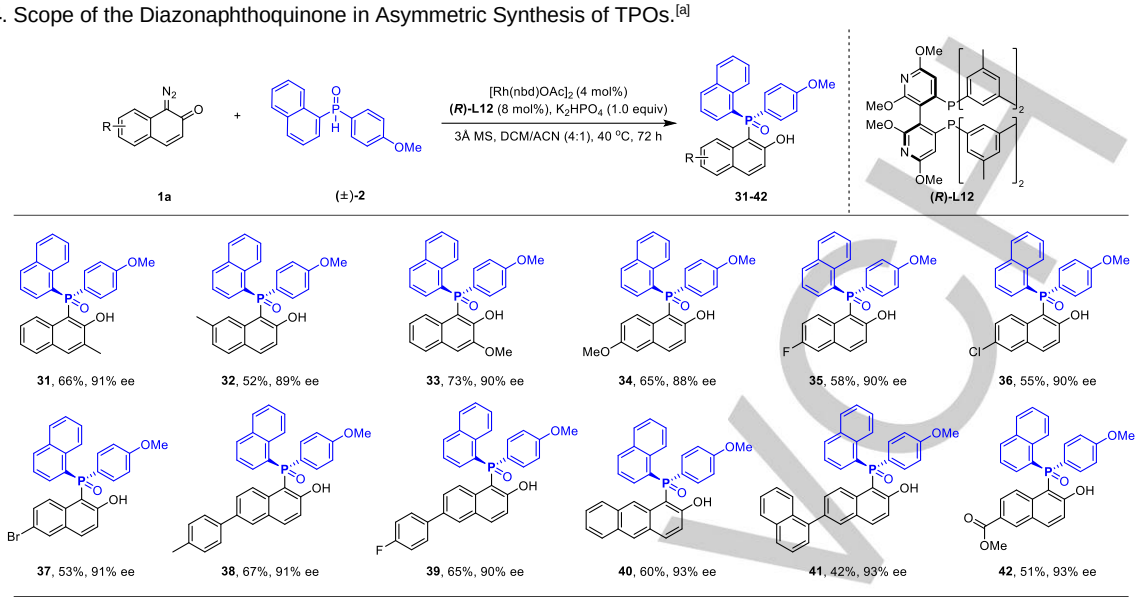
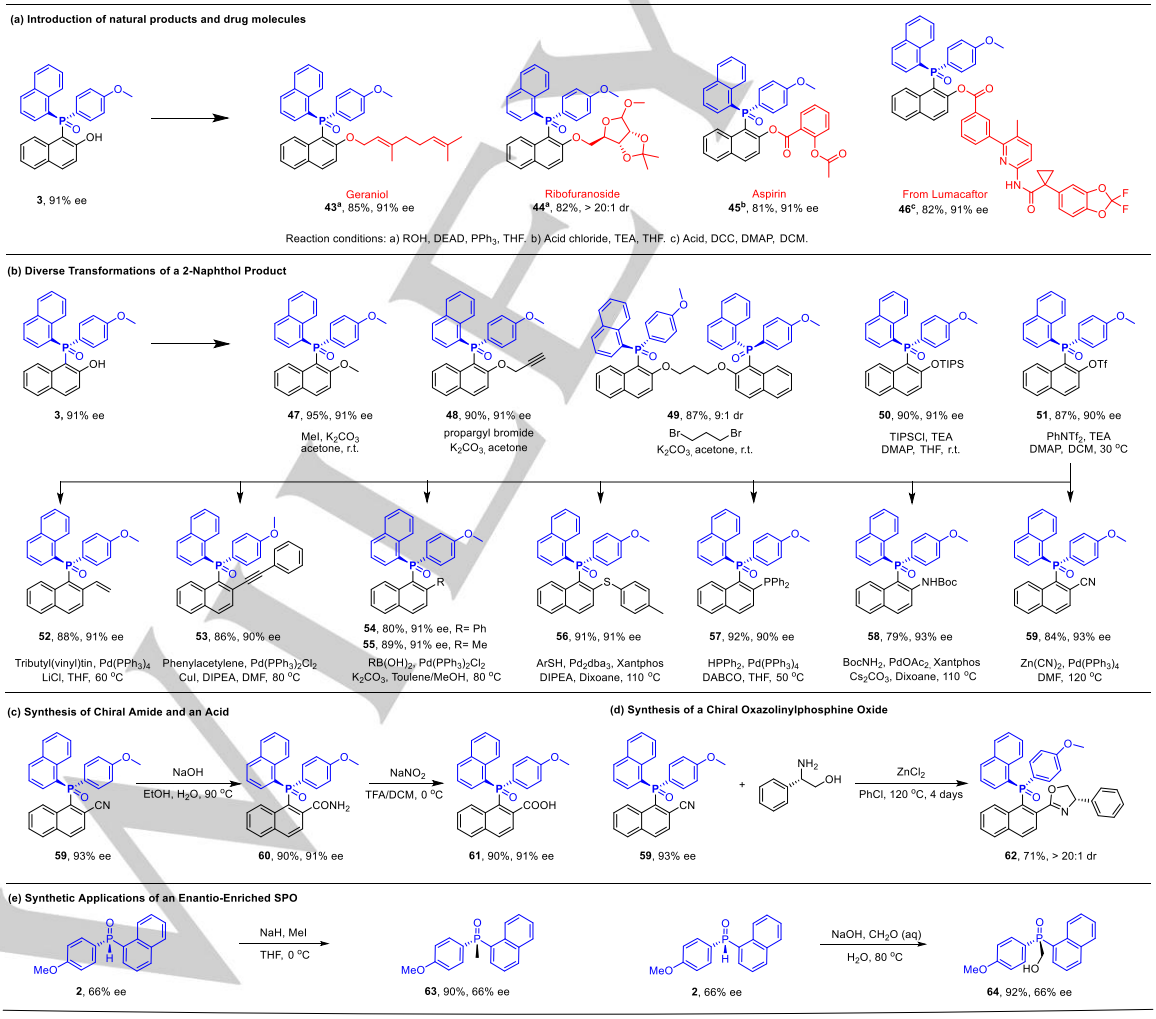
**Scheme 4**. Scope of the Diazonaphthoquinone in Asymmetric Synthesis of TPOs.[a]




[a] Reaction conditions: **1** (0.1 mmol), **2** (0.2 mmol), Rh(I) cat. (4 mol%), **L12** (8 mol%), $K_2HPO_4$ (1.0 equiv), DCM/ACN (4:1) (0.05 M), 3Å MS (60 mg) at 40 °C for 72 h under $N_2$; isolated yield. The ee was determined by HPLC using a chiral stationary phase

**Scheme 5.** Synthetic Transformations of Enantioenriched Products.



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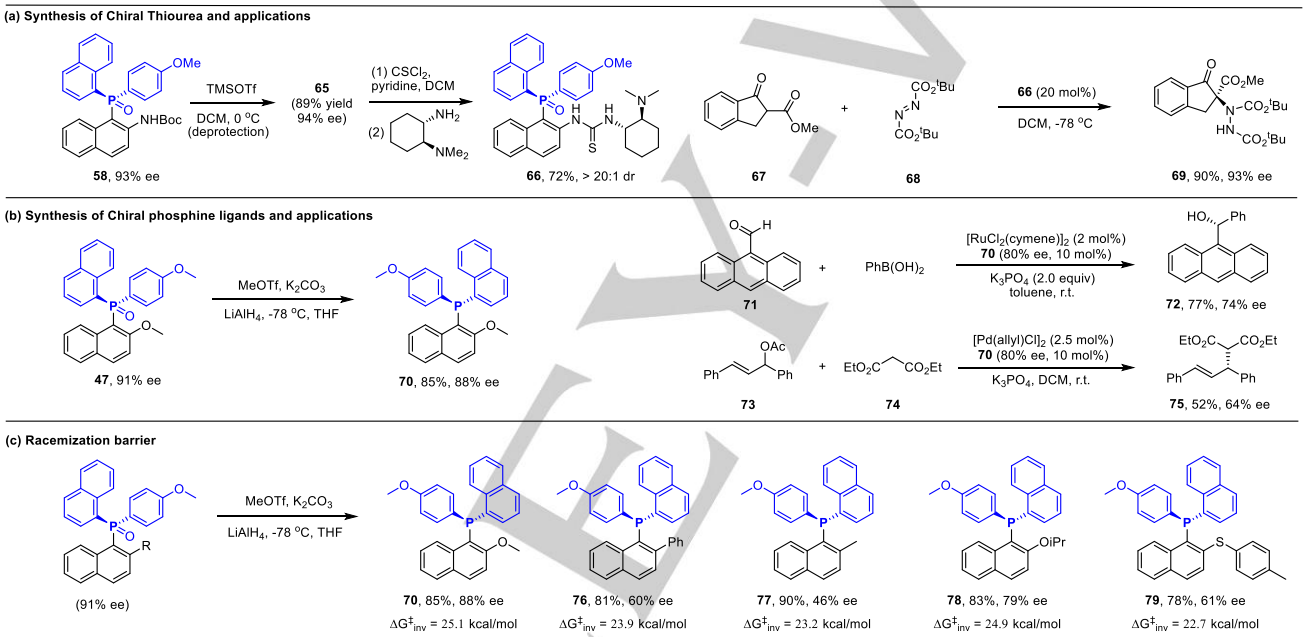
**Diverse Transformations.** To demonstrate the synthetic utility of this system, we examined the scalability of the reaction and synthetic applications of selected products (Scheme 5). The reaction was successfully scaled up to a mmol without loss of enantioselectivity (63%, 91% ee). The naphthol moiety in the product offers an important synthetic handle. Through the Mitsunobu reaction, a naturally occurring alcohol was installed in excellent yield (**43** and **44**). In addition, acyl chlorides and drug-related carboxylic acids also underwent esterification with the naphthol unit (**45-46**). Thus, in the presence of a condensation reagent, Lukasipine reacted to give a chiral phosphine oxide-tethered ester (**46**) in excellent diastereoselectivity. Meanwhile, the hydroxyl group in the product underwent smooth substitution with halogenated hydrocarbons or chlorosilanes to give diverse protected products (**47**-**50**). The OH group was also converted into a better leaving group (OTf) that can be engaged in various Pd-catalyzed cross-coupling reactions such as alkenylation (**52**), alkynylation (**53**), alkylation (**54**), and arylation (**55**). Besides, we further successfully extended the coupling reaction to a S-H, P-H, N-H, or a cyanide nucleophile (**56**-**59**). In all cases, the enantiopurity of these products was essentially unaffected. The product **59** was further converted a chiral amide (**60**) and a chiral acid (**61**) under different hydrolytic conditions. The cyano group underwent cyclization with a chiral amino alcohol under Zn(II) catalysis, affording a TPO-tethered oxazoline (**62**). We also utilized the recovered enantiomerically enriched **(*S*)-2** (66% ee) to synthesize two TPO derivatives (**63** and **64**, Scheme 5e).

**Scheme 6.** Catalytic Applications.




**Catalytic Applications.** The catalytic applications of the derived P-chiral product was demonstrated as a ligand or organocatalyst (Scheme 6). Deprotection of amide **58** gave to a primary amine (**65**), whose enantiopurity was improved to 94% ee possibly caused by recrystallization of the enantiomeric mixtures during the separation. Treatment of amine **65** with $CSCl_2$ and a chiral diamine afforded a bifunctional thiourea **66** in excellent diastereoselectivity (Scheme 6a). This thiourea proved to be an outstanding organocatalyst for enantioselective α-amination of β-ketoester **67** with an azodicarboxylate **68**.[19] The phosphine oxide functionality in **47** was reduced to chiral monodentate phosphine (**70**) upon reduction by MeOTf/$LiAlH_4$ with inversion of the stereochemistry. In the presence of a $K_2CO_3$ additive, the trivalent phosphine **70** was obtained in 88% ee (Scheme 6b). To our surprise, this phosphine is stereochemically labile with a racemization barrier of only 25.1 kcal/mol (40 °C, experimental data). Nevertheless, chiral phosphine **70** (80% ee) was employed as a chiral ligand in ruthenium-catalyzed addition of phenylboronic acid to an aromatic aldehyde, and the corresponding tertiary alcohol **72** was obtained in 74% ee (77% yield). This ligand also showed enantioselective control in Pd-catalyzed enantioselective allylic substitution of **73,** affording product **75** in 64% ee**.** To further explore the configurational stability of related triarylphosphines, we prepared a series of chiral phosphines bearing different alkyl and aryl substituents in the naphthalene ring (**76**-**79**, Scheme 6c). The energy barrier decreased when the OMe substituent was replaced by an aryl, alkyl or thioether group (**76, 77,** and **79**), indicating poor stereochemical stability of all the products.[20]

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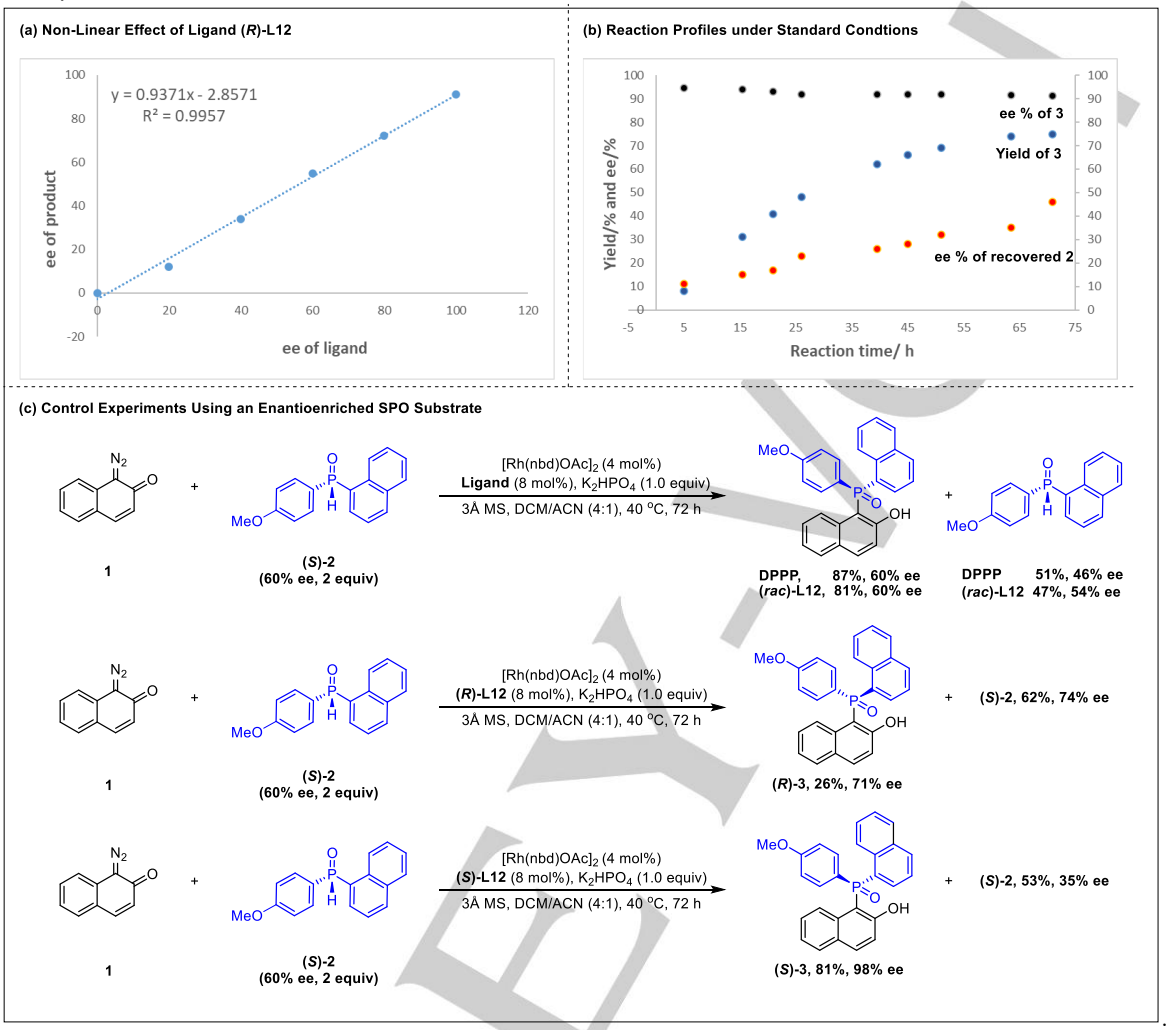
**Scheme 7.** Experimental Mechanistic Studies.




**Mechanistic Studies.** A series of experimental studies have been conducted to probe the mechanism of the coupling of diazonaphthoquinone **1** and phosphine oxide **2** (Scheme 7). First, a linear correlation between the ee of (*R*)-**L12** and that of product **3** was observed (Scheme 7a), suggesting a 1:1 ratio of the chiral ligand and the rhodium during the enantioselective control. Next, we monitored the reaction yield and enantioselectivity versus time (Scheme 7b). During the whole reaction process (72 h), the ee of product **3** decreased slightly from 94% to 91%. Meanwhile, the recovered SPO **2** was enriched in the (***S***) configuration whose enantiopurity eventually reached 45% ee. This may suggest relevancy of a KR event. In order to further explore the reaction details, we prepared a moderately enantioenriched substrate (***S***)-**2** (60% ee) and subjected it to control experiments. Under modified reaction conditions using DPPP as an achiral ligand (Scheme 7c), the product **3** was isolated in 60% ee in the ***S***-configuration together with recovery of the (***S***)-2 in 46% ee. Under modified reaction conditions using **(*rac*)-L12** as a ligand, the optical purity of the recovered **2** was slightly reduced (54% ee). We also studied the factors that cause racemization of the recovered **(*S*)-2** by performing a series of control experiments (see Supporting Information for details). These results collectively confirmed that the reaction pattern is predominantly kinetic resolution, and racemization of the SPO substrate occurred very slowly under the standard conditions. As expected, when the **(*R*)-12** ligand was used for the conversion of (***S***)-**2**, both low yield and low enantioselectivity were observed ((***R***)-**3**, 26% yield, 71% ee), indicating mismatch between this chiral ligand and the (***S***)-substrate. In contrast, both the yield and enantioselectivity ((***S***)-**3**, 81% yield, 98% ee) were greatly improved when the (***S*)-12** ligand was used. These data further suggest the operation of KR in this system.

Density functional theory (DFT) calculations were then conducted to gain a better understanding of the reaction mechanism and the origins of the enantioselectivity. At the outset, the diazonaphthalenone **1** and SPO (*R*)-**2** were selected as the model substrates to establish the reaction mechanism, with dppp being the achiral ligand (Figure 1a). Starting from the active catalyst species **CAT**, the reaction is initiated by the deprotonation of SPO (*R*)-**2** via transition state **TS1**, leading to trivalent

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phosphine intermediate **IM1**. The computations show that **IM1** is relatively unstable, and it can rapidly undergo isomerization via transition state **TS1** to give a more stable intermediate **IM2**. Then, with the incoming diazonaphthoquinone **1**, the denitrogenation occurs via transition state **TS3**, giving rise to a rhodium carbene intermediate **IM3**. The ensuing migratory insertion through transition state **TS4** was found to be kinetically feasible, resulting in the formation of the oxa-π-allylrhodium **IM4**. Finally, the catalytic cycle is completed by the protonation with HOAc via transition state **TS5** to deliver the final product (*R*)-**3** together with regeneration of the active catalyst species **CAT**.

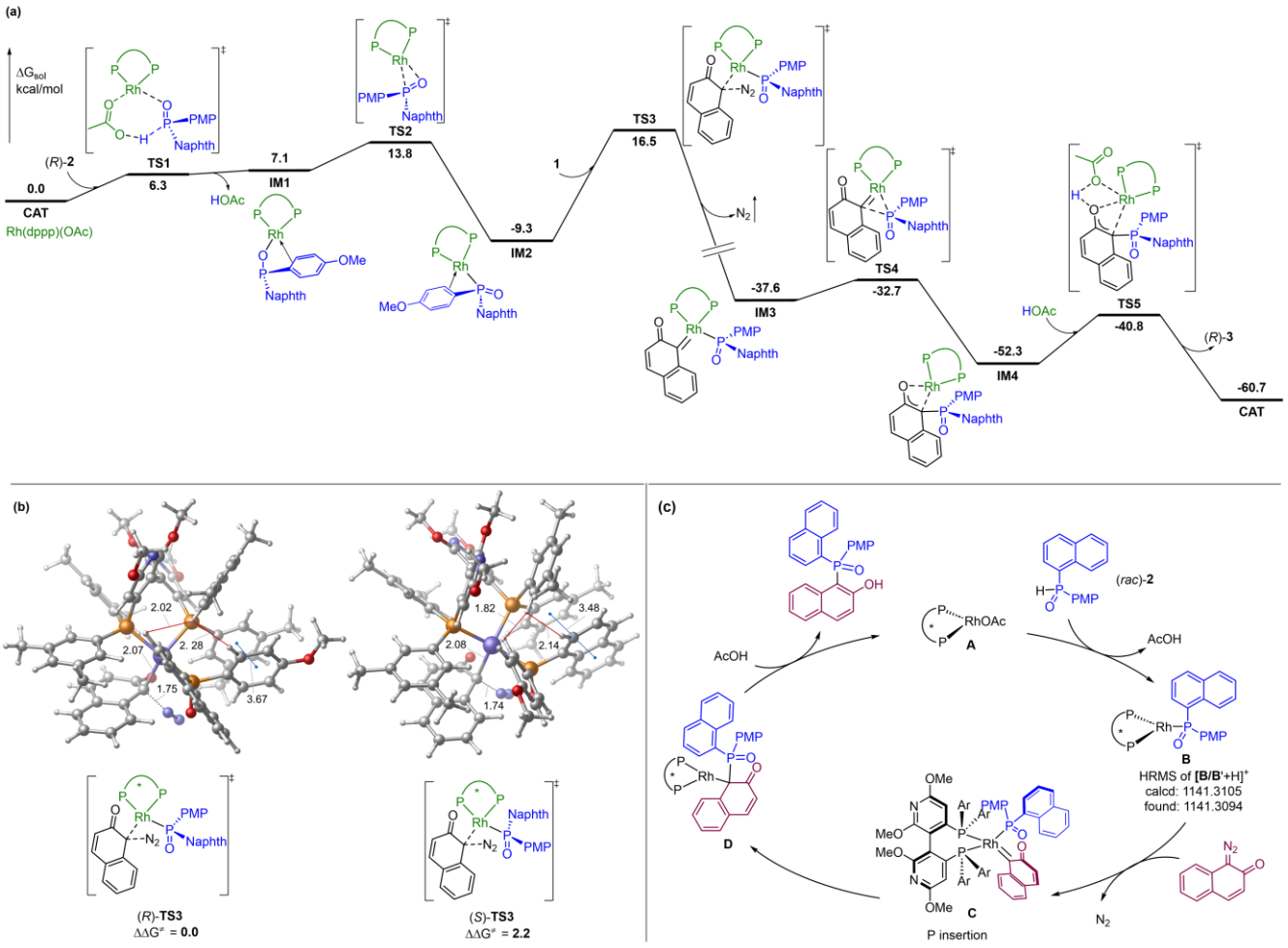


Figure 1. (a) Calculated energy profile of Rh(dppp)(OAc)-catalyzed reaction of (*R*)-**2** with **1**. (b) Key denitrogenation transition states with the chiral ligand (*R*)-**L12**. (c) Proposed reaction mechanism. Energies and bond distances are given in kcal/mol and Å, respectively.

The computations show that the denitrogenation is the rate- and enantio-determining step of the overall reaction. To further elucidate the origins of the enantioselectivity, the key denitrogenation transition states with the chiral ligand (*R*)-**L12** were investigated (Figure 1b). The computations show that transition state (*R*)-**TS3** is lower in energy than (*S*)-**TS3** by 2.2 kcal/mol, which is consistent with the experimentally observed enantioselectivity. Scrutiny of the optimized geometries reveal the presence of the π---π interaction between chiral ligand and the SPO moiety. The enantioselectivity is primarily attributed to the stronger steric repulsion between the chiral ligand and the SPO moiety in (*S*)-**TS3** compared to (*R*)-**TS3** (1.82 and 2.14 Å versus 2.02 and 2.28 Å), thus making (*S*)-**TS3** higher in energy than (*R*)-**TS3**.

Based on mechanistic experiments, DFT calculations and previous reports, a plausible mechanism is proposed (Figure 1c).[12] A Rh(I) catalyst **A** is formed from a pre-catalyst $[Rh(nbd)OAc]_2$ and **L12**. Upon deprotonation, the racemic SPOs coordinates to the Rh(I) center to give intermediates **B,** which was evidenced by mass spectrometry. Coordination and denitrogenation of diazonaphthalenone produces a rhodium carbene species **C** as the enantiodetermining step. Subsequent migration gives rise to an enolate intermediate **D** which is readily protonated to give the final product **3**.

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## Conclusion

In summary, we have developed the first example of asymmetric insertion of P-H into carbene reagents for direct construction of P-chiral TPOs. Through system design using a suitable Rh(I) catalyst, chiral ligand, substrates, additive, and solvent, the coupling system enabled efficient and enantioselective recognition of difficult-to-distinguish racemic diarylphosphine oxide. The catalytic system features good activity, mild reaction conditions, and high enantioselectivity. Mechanistic studies indicate that the SPO substrate undergo kinetic resolutions (KRs) as the major reaction pattern together with slow dynamic kinetic transformation. The chiral products have been demonstrated in diverse asymmetric synthetic and catalytic transformations. The conformational stability of the derived chiral triarylphosphine compounds have also been evaluated, and their rather low stability further highlighted the synthetic challenges. The work offers a new avenue to prepare useful chiral phosphine compounds. The synthetic method and the new stereoinduction model in asymmetric functionalization of $sp^3$-hybridized heteroatom X-H bond may offer important insight into construction of heteroatom-based stereogenic centers.

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**Keywords**: P-chirality, chiral phosphine oxides, rhodium, carbene, asymmetric P−H Insertion**.**

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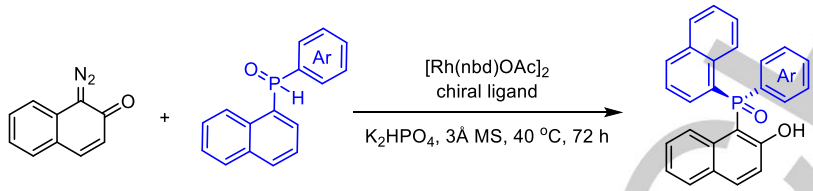
RESEARCH ARTICLE

# Rhodium-Catalyzed Asymmetric Access to P-Chiral Triarylphosphine Oxides via Insertion of P−H Bonds into Diazonaphthoquinones

Yulong Kang, Yue Shi, Genping Huang,* and Xingwei Li*




- Asymmetric P-H Addition to Carbene
- P-Chiral Triarylphosphine Oxide Products
- 40 Examples (up to 96% ee)
- Synthetic & Catalytic Applications

Asymmetric insertion of P-H bond into carbene has been developed to access P-chiral phosphine oxides in excellent enantioselectivity.