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Copper-Catalyzed Dynamic Kinetic Asymmetric P–C Coupling of Secondary Phosphine Oxides and Aryl Iodides

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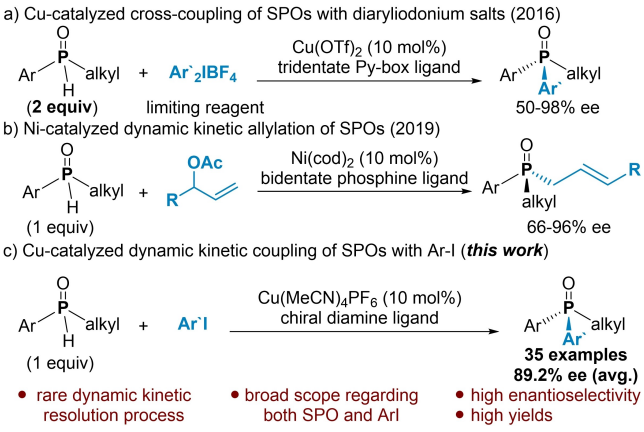
Abstract: Transition-metal-catalyzed enantioselective P–C cross-coupling of secondary phosphine oxides (SPOs) is an attractive method for synthesizing *P*-stereogenic phosphorus compounds, but the development of such a dynamic kinetic asymmetric process remains a considerable challenge. Here we report an unprecedented highly enantioselective dynamic kinetic intermolecular P–C coupling of SPOs and aryl iodides catalyzed by copper complexes ligated by a finely modified chiral 1,2-diamine ligand. The reaction tolerates a wide range of SPOs and aryl iodides, affording *P*-stereogenic tertiary phosphine oxides (TPOs) in high yields and with good enantioselectivity (average 89.2 % ee). The resulting enantioenriched TPOs were transformed into structurally diverse *P*-chiral scaffolds, which are highly valuable as ligands and catalysts in asymmetric synthesis.

Chiral phosphorus compounds are a class of important compounds and have found wide applications in drug development, agrochemistry, materials science, and asymmetric catalysis due to their unique structural and stereochemical properties.[1] In contrast to the well-studied chiral backbone-based (including central, axial, and planar) phosphines, synthesis of *P*-stereogenic compounds is relatively underdeveloped,[1a,2] which, in turn, largely limits their applications in both academia and industry. *P*-Stereogenic compounds are traditionally prepared by resolution or diastereomeric transformation of racemic mixtures,[3,4] which require stoichiometric resolving agents or chiral auxiliaries, but intrinsic limitations (e.g., low step- and chirality-economy, poor reproducibility, and high cost) associated with these processes make them less practical. The desymmetrization of prochiral phosphorus compounds is an alternative approach to preparing *P*-stereogenic compounds, and various reactions, including transition metal-catalyzed C–H bond functionalization,[5] alkene metathesis,[6] conjugate addition,[7] [2+2+2]-cycloaddition,[8] and other transformations,[9] have been applied in such a process. Although the aforementioned methods can provide *P*-chiral phosphorus compounds, the P–C bond-forming events do not occur in an enantioselective fashion.

In the last two decades, enantioselective P–C bond-forming reactions have gained increasing attention. Various transition metal-catalyzed transformations, such as addition reactions[10] and cross-couplings,[11,10i,12] have been developed, and in these transformations *secondary phosphines* (SPs; R^1R^2PH) are the commonly used reagents. However, the intrinsic properties of SPs lead to significant limitations. First, SPs are toxic, air- and moisture-sensitive, making them operationally inconvenient. Second, most SPs are not readily available, and their synthesis and modification are not trivial, largely limiting the product diversity. Moreover, both SPs and TPs have a strong coordinating ability with metals, which can be deleterious to the reactivity and selectivity of metal catalysts. Therefore, the development of new asymmetric P–C bond-forming reactions is still highly demanding.

Recently, secondary phosphine oxides (SPOs)—they are bench-stable, odorless, and less toxic and basic—have been pursued in the transition metal-catalyzed enantioselective P–C bond-forming reactions. In 2016, Gaunt and co-workers reported the first asymmetric cross-coupling of SPOs and diaryliodonium (Scheme 1a), in which copper complexes containing a pyridinebisoxazoline (pybox) was used as the catalyst.[12b] Subsequently, some excellent work has also been achieved,[10i,12a,c–f] however, most of these reactions occurred through the *kinetic resolution* of SPOs, which only provides the products in less than 50 % yields if high enantioselectivity is expected, thus being less practical.



Scheme 1. Transition-Metal-Catalyzed Dynamic Kinetic Asymmetric Transformations of SPOs.

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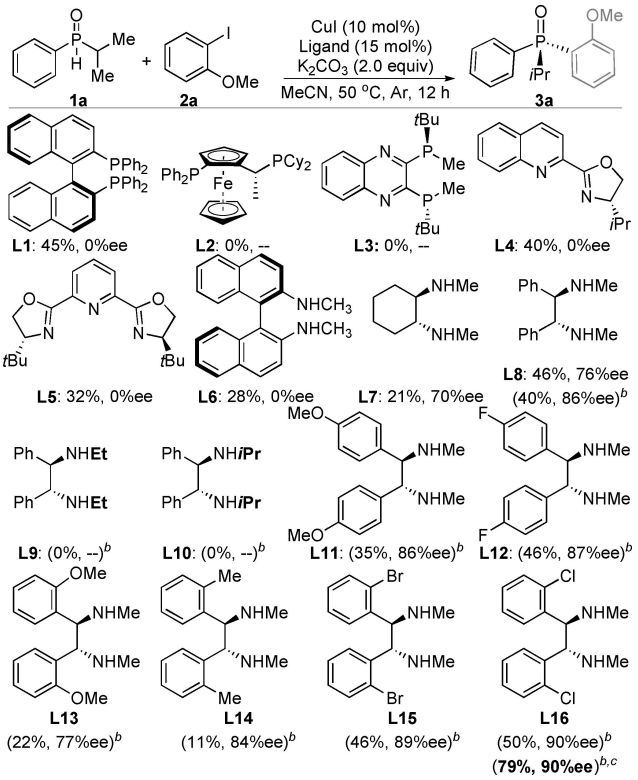
Dynamic kinetic asymmetric transformations (*DYKAT*) of SPOs are much more attractive, but the development of such a process is challenging because of the elusive racemization of SPOs, side reactions associated with SPOs, and/or the control of enantioselectivity. For example, although the aforementioned Gaunt's copper-catalyzed P–C coupling of SPOs and diaryliodonium salts demonstrated the opportunity for developing a dynamic kinetic resolution of SPOs, attempts to secure such a transformation failed due to the severe oxidation of SPOs.[12b] In 2019, Zhang and co-workers developed a dynamic kinetic asymmetric allylation of SPOs (Scheme 1b),[13] which was catalyzed by nickel catalysts containing a chiral bisphosphine ligand and represents the only successful examples of *DYKAT* of SPOs that occurs in an intermolecular fashion. Additionally, the scarcity of *DYKAT*s is not only limited to SPOs, any types of pentavalent phosphorus compounds in such processes is also rare.[14] Therefore, the construction of *P*-stereogenic centers by a *DYKAT* of SPOs is still in its infancy, and therefore the development of new transformations is in a high demand.

Here, we report the first copper-catalyzed intermolecular dynamic kinetic asymmetric P–C coupling of SPOs and aryl iodides (Scheme 1c), and the success of the reaction relies on the highly enantioselective copper complexes and the facile racemization of SPOs under the reaction conditions. This reaction tolerates a broad range of aryl iodides and SPOs, affording TPOs in good yields and with high enantioselectivity, and the resulting chiral TPOs were converted to structurally diverse chiral *P*-stereogenic scaffolds. During the review process, an *intramolecular* dynamic kinetic asymmetric arylation of SPOs catalyzed by copper complexes containing a simple diamine ligand was reported for the synthesis *P*-stereogenic cyclic phosphine oxides,[15] but the scope of the reaction was limited; only SPOs bearing a primary alkyl group are suitable substrates, and only seven membered cyclic products could be obtained with high enantioselectivity.

We began by evaluating various commercially available chiral ligands for the enantioselective coupling of SPO **1a** and aryl iodide **2a** with CuI as the precatalyst and K_2CO_3 as the base in MeCN at 50 °C (Table 1). Among the tested chiral phosphine ligands (**L1**–**L3**), the reaction with BINAP (**L1**) formed the desired TPO **3a** in moderate yield but with no enantioselectivity, and the reactions with Josiphos **L2** and QuinoxP* **L3** did not form TPO **3a**. Nitrogen-containing ligands, including a bidentate quinoline oxazoline ligand (**L4**), a tridentate pyridine bisoxazoline ligand (**L5**), and diamine ligands **L6** and **L7** were also assessed; it was gratifyingly to find that the reaction with chiral cyclohexane-1,2-diamine **L7** formed TPO **3a** with 70 % ee, albeit in a low yield (21 %). When **L7** was replaced with 1,2-diphenylethylenediamine **L8**, both the efficiency and the selectivity of the reaction were increased, affording TPO **3a** in 46 % yield and with 76 % ee. Evaluation of other parameters, including copper salts, bases, solvents, and reaction temperature, led to a high enantioselectivity (86 % ee) but still moderate yield (40 %) under the conditions with $Cu(MeCN)_4PF_6$ as the precatalyst and K_3PO_4 as the base at lower temperature (0 °C) for 48 h (for details, see Supporting Information).

Table 1: Condition Optimizations.[a]

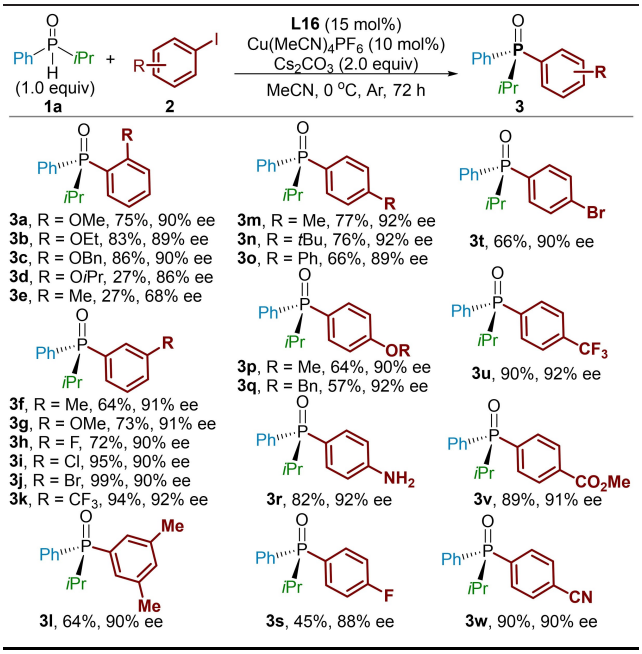


[a] Reaction was conducted with **1a** (0.1 mmol), and the yield was determined by ^{1}H NMR analysis with 2,4,6-trimethoxybenzene as the internal standard. [b] Reaction was conducted with $Cu(MeCN)_4PF_6$ and K_3PO_4 at 0 °C for 48 h. [c] Reaction was conducted with Cs_2CO_3 for 72 h.

To further increase the reactivity and selectivity of the copper catalysts, we studied the steric and electronic influences of the diamine ligand **L8** on the P–C coupling. Changing the methyl group on the nitrogen atoms of **L8** to a bulkier ethyl (**L9**) or isopropyl (**L10**) group resulted in no formation of the desired product **3a**, indicating that the reaction was very sensitive to the steric hindrance on the nitrogen atoms. The modification of the electronic (**L11** and **L12**) and steric (**L13**–**L16**) properties of the phenyl groups on **L8** showed that the ee value of **3a** could be further increased to 90 % while retaining a moderate yield (50 %) when the 1,2-bis(2-chlorophenyl)ethylenediamine **L16** was used. A practical yield (79 %) and high ee value (90 %) of **3a** were obtained when the reaction was conducted with Cs_2CO_3 as the base for a prolonged time (72 h).

Having identified conditions to obtain high yield and enantioselectivity for the formation of TPO **3a**, we first examined the scope of the aryl iodide component in this enantioselective P–C coupling reaction (Table 2). Generally, the reaction tolerates *ortho*-, *meta*- or *para*-substituted aryl iodides (**2a**–**2w**), affording the corresponding TPOs (**3a**–**3w**) in good yields and with high ee values. Various *ortho*-substituted aryl iodides were first examined: reactions of

Table 2: Scope of the Aryl Iodides.[a]



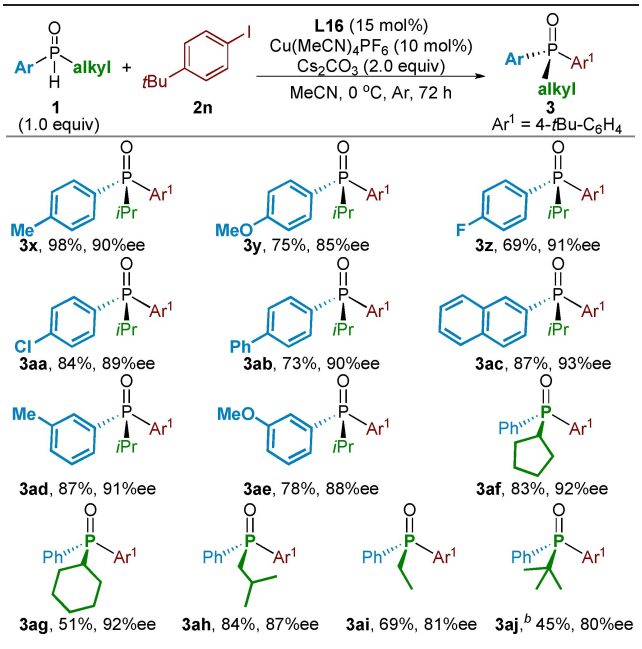
[a] Reactions were conducted with **1a** (0.1 mmol), the yields refer to isolated yields, and the ee values were determined by chiral HPLC analysis.

aryl iodides bearing less sterically demanding alkoxy groups, such as OMe, OEt, and OBn (**2a**–**2c**), formed the corresponding TPOs (**3a**–**3c**) in good yields (75 %–86 %) and high ee values (89 %–90 %), but bulkier substituents at the *ortho*-position (**2d** and **2e**) resulted in decreased yield and/or enantioselectivity. Installation of bulky substituents at the *ortho*-position of the aryl group on TPOs could be achieved through a two-step transformation of TPO **3c**: the conversion of the benzyloxy group in TPO **3c** to a triflate and subsequent transformation of OTf to various functionalities under palladium catalysis (detailed information is presented in the section of diversification of TPOs). Reactions with aryl iodides containing a variety of *meta*-substituents, including electron-donating methyl and methoxy groups (**2f**, **2g**, and **2l**), halogens (**2h**–**2j**; F, Cl, and Br), and electron-withdrawing trifluoromethyl group, underwent smoothly, forming the corresponding TPOs **3f**–**3l** in high yields and good to excellent enantioselectivities (≥ 90 % ee). Aryl iodides with various functionalities at the *para*-position were also assessed, affording products **3m**–**3w** with 88 %–92 % ee values. These functionalities include alkyl and aryl groups (**2m**–**2o**), electron-rich alkoxy groups (**2p** and **2q**) and a free amino group (**2r**), halides (**2s** and **2t**), and electron-poor groups (e.g., a trifluoromethyl group (**2u**), an ester (**2v**), and a cyanide (**2w**)). The absolution configuration of **3o** was determined to be S_P by comparing the retention time of HPLC traces and the optical rotation of **3o** with reported ones in the literature (for detailed information, see Supporting Information),[12d] and the stereochemistry in other TPO products was assigned by analogy.

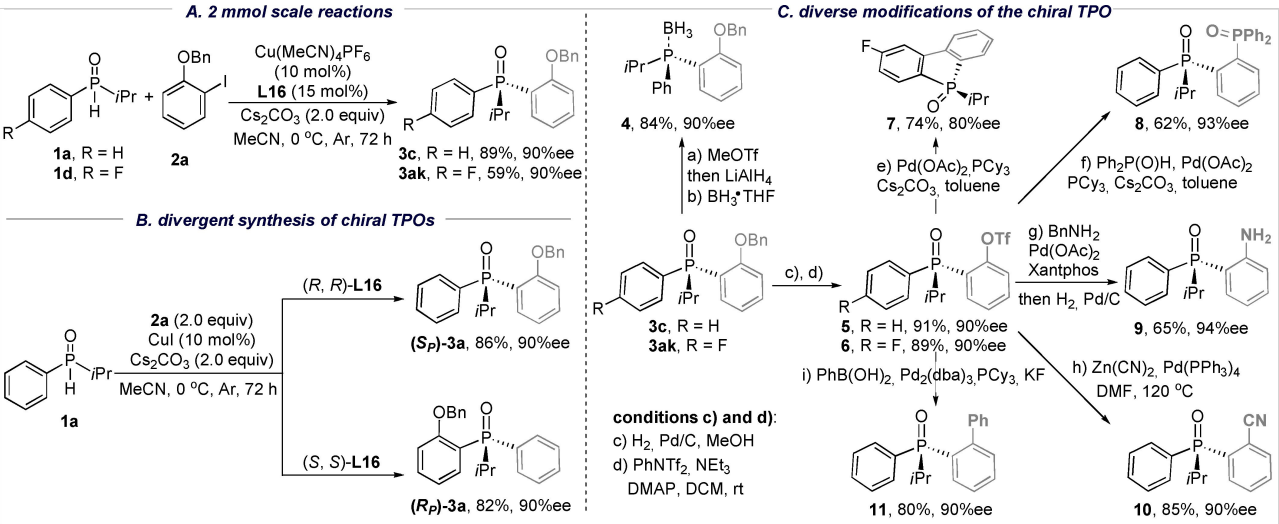
The scope of the SPO component in this enantioselective P–C coupling reaction was then evaluated, and variation of both the aryl and alkyl groups on the SPO was proven to be feasible (Table 3). Both *para*- and *meta*-substituted aryls—regardless of electronically rich or poor—on the SPOs (**1x**–**1ae**) are compatible with this reaction, and the corresponding TPO products (**3x**–**3ae**) were obtained in good to excellent yields (69 %–98 %) and with high enantioselectivities (85 %–93 % ee). SPOs containing *ortho*-substituted aryl (structures not shown) were not suitable for this P–C coupling, most probably due to the steric property adjacent to the phosphorus atom. Variation of the alkyl group on the SPO showed that SPOs bearing either a secondary or a primary alkyl group (e.g., isopropyl, cyclopentyl, cyclohexanyl isobutyl, and ethyl group) can be arylated efficiently, affording the desired TPOs (**3a** and **3af**–**3ai**) with 81 %–92 % ee. The SPO bearing a bulky tert-butyl group can also undergo the arylation at an elevated temperature (room temperature), affording TPO **3aj** with comparable enantioselectivity (80 % ee) but in a lower yield (45 %).

To demonstrate the utility of this reaction, we examined the scalability of the reaction, enantiodivergent synthesis of both TPO enantiomers, and diverse structural modification of the TPOs. The reactions of **1a** and **1d** on a 2 mmol scale delivered TPOs **3c** and **3ak** in comparable yields and enantioselectivity with those from reactions conducted on a 0.1 mmol scale (Scheme 2A). Enantiodivergent synthesis is attractive in asymmetric synthesis,[16] because it provides access to both enantiomers of a chiral compound by simply changing reaction conditions. (R_P)-**3c** was readily obtained in good yield (82 %) and with high ee value (90 %) by simply switching the (*R*, *R*)-**L16** to its antipod (*S*, *S*)-**L16** (Scheme 2B). To expand the structural diversity of the resulting chiral TPOs, various transformations were conducted (Sche-

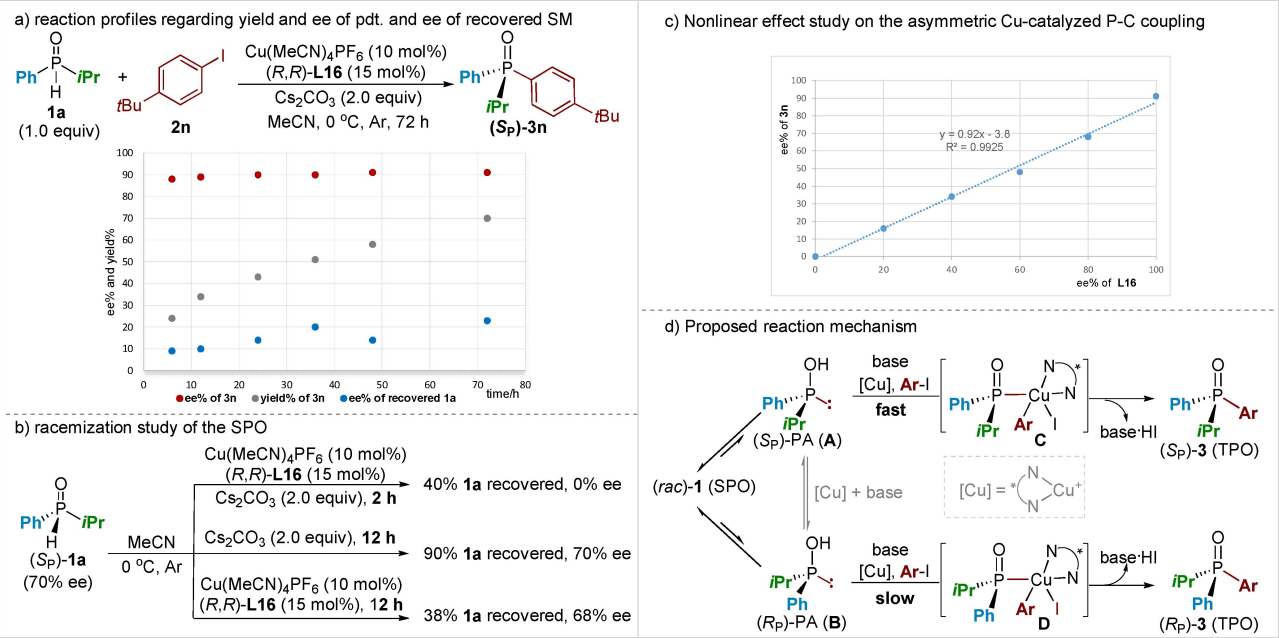
Table 3: Scope of the Secondary Phosphine Oxides.[a]



[a] Reactions were conducted with **1** (0.1 mmol), the yields refer to isolated yields, and the ee values were determined by chiral HPLC analysis. [b] Reaction was conducted at room temperature.



Scheme 2. Scalability, Divergent Synthesis, and Diverse Transformations.



Scheme 3. Mechanistic Studies and Proposed Catalytic Cycle.

me 2C). The pentavalent TPO **3c** was reduced to trivalent phosphine borane complex **4** in 84% yield and 90% ee under conditions with MeOTf and $LiAlH_4$, followed by protection with borane. Conversion of the OBn group in TPOs **3c** and **3ak** to an OTf group, providing compounds **5** and **6** with a convenient handle for further modification at the *ortho*-position of the chiral phosphinyl group. The cyclic chiral phosphine oxide **7** was formed efficiently through a palladium-catalyzed intramolecular C–H arylation of compound **6**, albeit with slight erosion of the enantiopurity. Under palladium-catalyzed conditions, *P*-stereogenic compound **5** underwent C–P cross-coupling to form the unsymmetrical chiral 1,2-bisphosphine oxides **8**, C–N cross-coupling (followed by debenzylation) to form 1-amino-2-phosphinylbenzene **9**, and C–C cross-couplings to afford 1-nitrile-2-phosphinylbenzyne **10** and 1-aryl-2-phosphinylbenzene **11**; these transformations underwent efficiently and without the erosion of *P*-enantiopurity. These transformations largely increase the structural diversity of the *P*-stereogenic phosphorus compounds, largely increasing their utility in the development of chiral ligands and asymmetric synthesis.[1a,c,e,17]

This highly enantioselective P–C coupling reaction with SPO as the limiting reagent should operate as a dynamic kinetic resolution process, which was validated by the observation of consistently high ee (89%–91%) of the

coupling product (S_P)-**3n** throughout the reaction (Scheme 3a). The recovered unreacted SPO **1a** showed 9 %–23 % ee (with (R_P)-**1a** enriched) throughout the reaction, indicating that the reaction of (S_P)-**1a** with aryl halide **2n** was much favored than that of its antipod (R_P)-**1a**, and the coupling event was also slightly faster than the racemization of the in situ generated enantioenriched (R_P)-**1a** under the standard conditions. To gain more insights into the racemization of SPO, we prepared the enantioenriched (S_P)-**1a**[12d] and subjected it to various conditions (Scheme 3b). (S_P)-**1a** was completely racemized in 2 h in the presence of the copper complexes and the base but was hardly racemized in 12 h under the conditions with only the copper complexes or the base, implying that both the copper complexes and the base are indispensable for the racemization of SPOs. A linear correlation between the ee of **L16** and the product **3n** was observed (Scheme 3c), suggesting a 1:1 ratio of the chiral ligand and the copper in the copper complexes.

Based on these observations and related reports in literature,[13,18] a possible mechanism was proposed (Scheme 3d). Tautomerization of pentavalent racemic SPO **1a** leads to trivalent phosphinous acids (S_P)–PA (**A**) and (R_P)–PA (**B**), and interconversion between them proceeds easily under the reaction conditions. The coupling of (S_P)–PA (**A**) and Ar–I undergoes in a stereoretention fashion,[12d] most possibly through a trivalent copper intermediate **C**, to form the arylated TPO product (S_P)-**3**; this process is matched with the copper catalyst ligated by (*R*, *R*)-**L16** and is much faster than the corresponding coupling between (R_P)–PA and Ar–I. The facile racemization of SPO and high enantioselectivity of the copper catalysts together result in the successful implementation of the highly enantioselective dynamic kinetic P–C coupling.

In conclusion, we developed the first copper-catalyzed dynamic kinetic asymmetric intermolecular P–C coupling of SPOs and aryl iodides to form *P*-chiral TPOs in high yields and with high enantioselectivities. The structurally finely modified chiral 1,2-diaryl-1,2-ethylendiamine ligand (**L16**) is crucial for achieving the high enantioselectivity, and the facile racemization of SPOs under the reaction conditions is vital for developing such a *DYKAT* process. Versatile transformations of the resulting TPOs largely expand the diversity of *P*-stereogenic scaffolds, thus promoting their potential utility in asymmetric synthesis.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Asymmetric Synthesis · Chiral Phosphorus Compounds · Copper Catalysis · *P*-Stereogenic Compounds · Transition Metal Catalysis

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Communications

Asymmetric Catalysis

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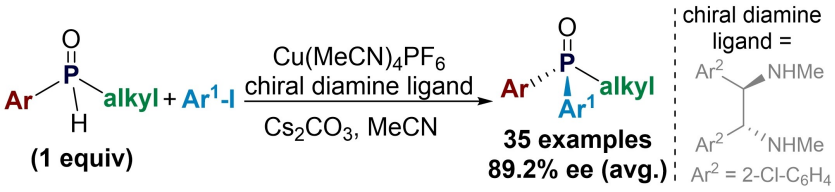
Copper-Catalyzed Dynamic Kinetic Asymmetric P–C Coupling of Secondary Phosphine Oxides and Aryl Iodides



An intermolecular dynamic kinetic asymmetric P–C coupling of secondary phosphine oxides and aryl iodides is catalyzed by copper complexes with a carefully tuned diamine ligand. The reaction features a broad substrate scope and affords the corresponding products with high yields and enantioselectivities. Versatile transformations of these products gave diverse P-chiral scaffolds, which are valuable in asymmetric catalysis.