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Enantioselective Desymmetrization of Phosphinic Acids via Cu-Catalyzed O-Arylation

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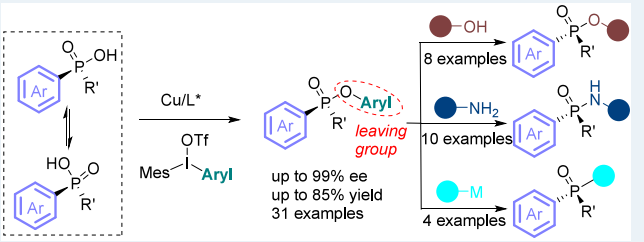
ABSTRACT: Enantioselective desymmetrization of phosphinic acid with two completely different carbon substituents on the P atom is an efficient way to obtain chiral P(V) compounds with high structural diversity. Herein, we reported a Cu-catalyzed asymmetric arylation of phosphinic acid, which turns the P-center to be a versatile electrophile for obtaining a series of chiral P(V) compounds, including phosphinates, phosphinamides, and tertiary phosphine oxides, in good yields and high enantioselectivities.



KEYWORDS: *Enantioselective desymmetrization, Copper catalysis, Chiral phosphorus compounds, Diaryliodonium salt, Phosphinic acid*

INTRODUCTION

P-chiral phosphorus compounds are essential molecules with diverse applications in fields such as agrochemicals,[1] pharmaceuticals,[2] and asymmetric catalysis[3] (Scheme 1a). Their versatile properties and wide-ranging utility have sparked continuous interest in their synthesis, leading to a vibrant and enduring area of research.[4] By exploring the synthesis and applications of P-chiral phosphorus compounds, researchers aim to unlock new possibilities for innovations and advancements in various industries. Historically, the synthesis of P-chiral phosphorus compounds has relied on classical resolution, separation of diastereomers or enantiomers by chromatography,[5] and chiral auxiliary-based diastereoselective methods.[6] While effective in generating P-chiral compounds, these traditional methods are often labor-intensive and can limit the efficiency of the overall synthesis process. As the demand for diverse and efficient synthetic routes for P-chiral phosphorus compounds continues to grow, researchers are exploring novel strategies to streamline their synthesis and enhance the accessibility of these valuable molecules.

Catalytic approaches to enantiopure P(V) compounds have emerged as a crucial and highly efficient strategy for the synthesis of P-chiral phosphorus compounds.[7] Generally, they can be subdivided into the following categories: (1) the diastereoselective coupling of P(V) electrophiles with enantiopure nucleophiles;[8] (2) the direct enantioselective arylation,[9] alkenylation,[10] allylation,[11] and alkylation[12] of secondary phosphine oxides (SPO) to obtain tertiary phosphine oxides; (3) enantioselective desymmetrization of prochiral P(V) compounds with the reaction site at the side chain indirectly[13] (Scheme 1b) or at the P atom directly;[14] and (4) conversion of P-chiral P(III) compounds obtained via catalytic asymmetric synthesis.[15] Although the development of these novel and clever synthetic strategies solved the preparation of diverse types of enantiopure P(V) compounds, the continuous exploration of a versatile pathway is necessary.

The phosphinic acid with two completely different carbon substituents on the P atom is a more suitable substrate for obtaining enantiopure P(V) compounds via enantioselective desymmetrization considering the structural diversity. Due to the easily available and stable properties, several racemic conversions of phosphinic acids have been developed.[16] However, there were very limited examples of such enantioselective conversions.[17] Trost and co-workers developed an enantioselective desymmetrization of phosphinic acid via Pd-catalyzed allylic alkylation[18] (Scheme 1c), and the electrophiles are limited to cyclic allylic bromides. Herein, we disclosed an enantioselective desymmetrization of phosphinic acid via Cu-catalyzed arylation, which allows the obtaining of a series of enantiopure phosphinates in good yields with high enantiomeric excess (ee) values (Scheme 1d). Moreover, the conversion of P(O)−OH into P(O)−OAr allows the P-center to be a useful electrophile for coupling with various N-, O-, or C-centered nucleophiles. Therefore, different enantiopure P(V) compounds could be obtained in an efficient way.

METHODS

Early in 2015, Yin and co-workers reported the arylation of phosphinic acid with diaryliodonium salts (DAISs) under high reaction temperature.[19] Considering that the combination of

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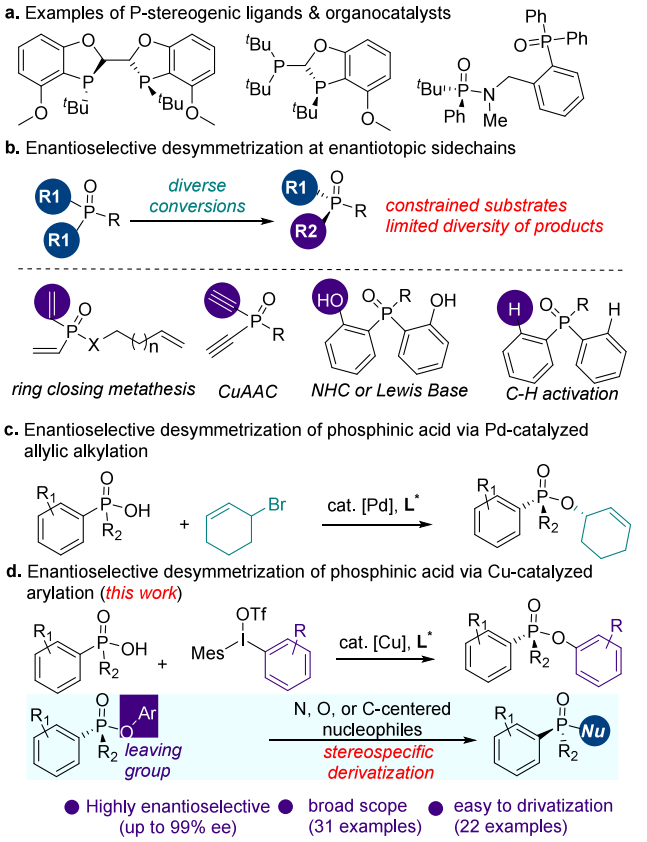
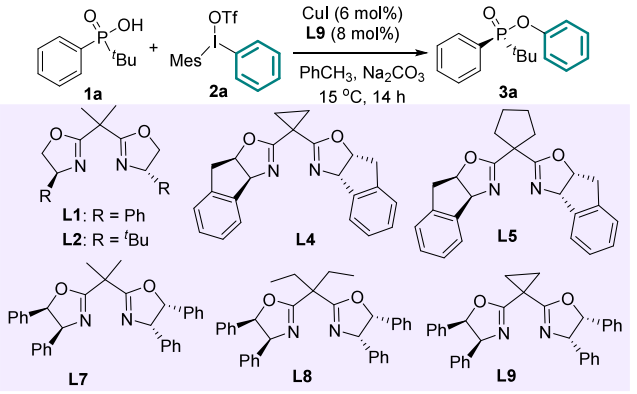
Scheme 1. Introduction of the Catalytic Asymmetric Synthesis of P(V) Compounds and Our Work. (a) Examples of P-Stereogenic Ligands and Organocatalysts. (b) Previous Ways of Enantioselective Desymmetrization at Enantiotopic Side Chains of P(V). (c) Previous Way of Enantioselective Desymmetrization of Phosphinic Acid via Pd-Catalyzed Allylic Alkylation. (d) This Work: Enantioselective Desymmetrization of Phosphinic Acid via Cu-Catalyzed Arylation



DAISs and Cu catalysts would generate an aromatic electrophile equivalent in the form of a putative Cu(III)−aryl intermediate,[20] we optimized the reaction conditions for the enantioselective desymmetrization arylation of phosphinic acid **1a** by screening a series of simple Cu catalyst, C2 symmetric bisoxazoline ligands (Table 1). The chiral phosphinate **3a** could be obtained in 76% yield and 93% ee under the following optimal reaction conditions: **1a** (0.1 mmol), **2a** (0.13 mmol), Na_2CO_3 (0.2 mmol), **L9** (8 mol %), and CuI (6 mol %) in toluene under argon atmosphere at 15 °C for 14 h (Table 1, entry 1). The reaction afforded very little product (<5%) without the addition of CuI (Table 1, entry 2). Meanwhile, other ligands afforded **3a** with lower enantioselectivities (Table 1, entries 3−8). Base as an additive is crucial for both the reaction yield and ee. For example, Li_2CO_3 as a base additive is ineffective (Table 1, entry 9). Moreover, the choice of DAISs is quite important. Symmetric DAISs such as diphenyliodonium salt afforded **3a** in slightly lower yield and ee, in comparison with unsymmetric DAIS **2a** (Table 1, entry 10). For details about the optimization of the reaction conditions, see the Supporting Information.

Then we turned to investigate the reaction scope. Initially, a series of unsymmetric DAISs displaying a variety of electronic and steric properties were tested. The results indicated that the

Table 1. Optimization of the Reaction Conditions[a]



entry	variation from sd	yield[b] (%)	enantiomeric excess, ee[c] (%)
1	none	76	93
2	without Cu	<5	–
3	**L1** instead of **L9**	50	35
4	**L2** instead of **L9**	41	5
5	**L4** instead of **L9**	54	15
6	**L5** instead of **L9**	50	0
7	**L7** instead of **L9**	55	71
8	**L8** instead of **L9**	59	43
9	Li_2CO_3 instead of Na_2CO_3	32	62
10	diphenyliodonium instead of **2a**	55	85

[a]Reaction conditions: to a flame-dried tube charged with **1a** (0.1 mmol), **2a** (0.13 mmol) and Na_2CO_3 (0.2 mmol), was added the catalyst formed by mixing **L9** (8 mol %) and CuI (6 mol %) in toluene for 30 min under an argon atmosphere. The reaction proceeded for 14 h and was directly purified by silica gel column. [b]Isolated yield. [c]Determined by HPLC with chiral column.

corresponding chiral phosphinates could be obtained in moderate to good yields with high ee values (Table 2). Electron-withdrawing groups at the para position were well-tolerated, and enantioenriched **3f**−**3i** were obtained in moderate yields and excellent ee values. Halogenated arenes were also transferred smoothly to afford **3b**, **3c**, and **3m** in good yields and enantioselectivities. The effect of steric hindrance was investigated, which indicated big substituent at the para position (**3e** and **3j**) were well-tolerated, while substituent at the ortho position was detrimental to the reaction ee (**3n**). After recrystallization, **3j** was obtained as a single enantiomer, and its X-ray structure confirmed the absolute stereochemistry of the enantioenriched phosphinates. In general, the ortho-substituted, meta-substituted, or para-substituted DAISs are effective in this process. The possible side product formed from 2,4,6-trimethyl phenyl were not found in these reactions, which might be ascribed to its big steric hindrance and inhibited the formation of the putative Cu(III)−aryl intermediate.

Next, we moved on to evaluate the scope of the substituent on P atom of phosphinic acids by using DAIS **2i** as the electrophile (Table 3). Substituents at the para-position (**4a**, **4d**, **4h**, **4i**, **4k**), meta-position (**4b**, **4g**, **4j**, **4l**), and ortho-position (**4c**, **4f**) of phenyls were well-tolerated and afforded the corresponding products in high efficiency. Steric hindrance at the para- or meta-position (**4g** and **4h**) did not affect the reaction yields and ee values as well. Replacing the phenyl group in **1a** with a 2-thienyl substituent gave rise to **4m** in a 73% yield and 96% ee. Then we tried to investigate the alkyl

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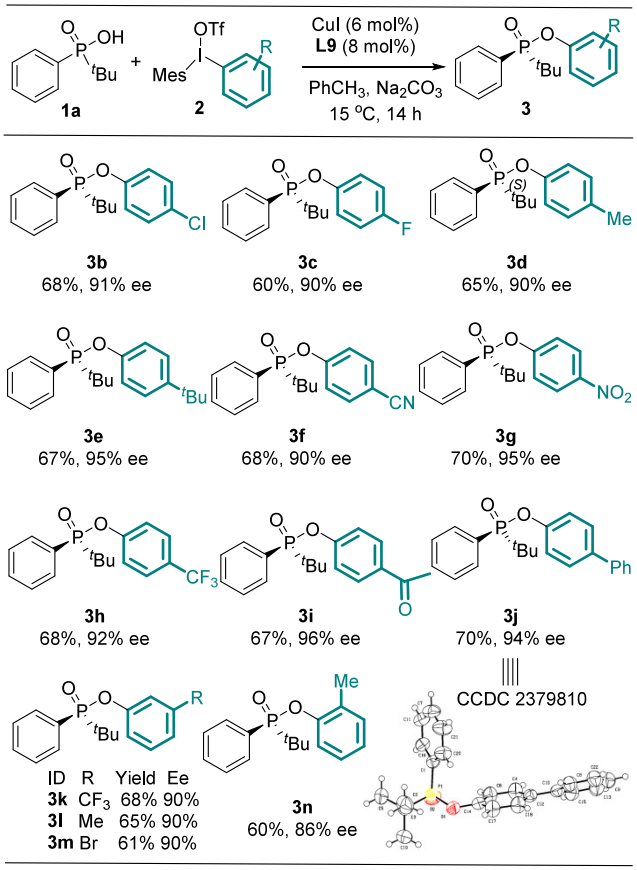
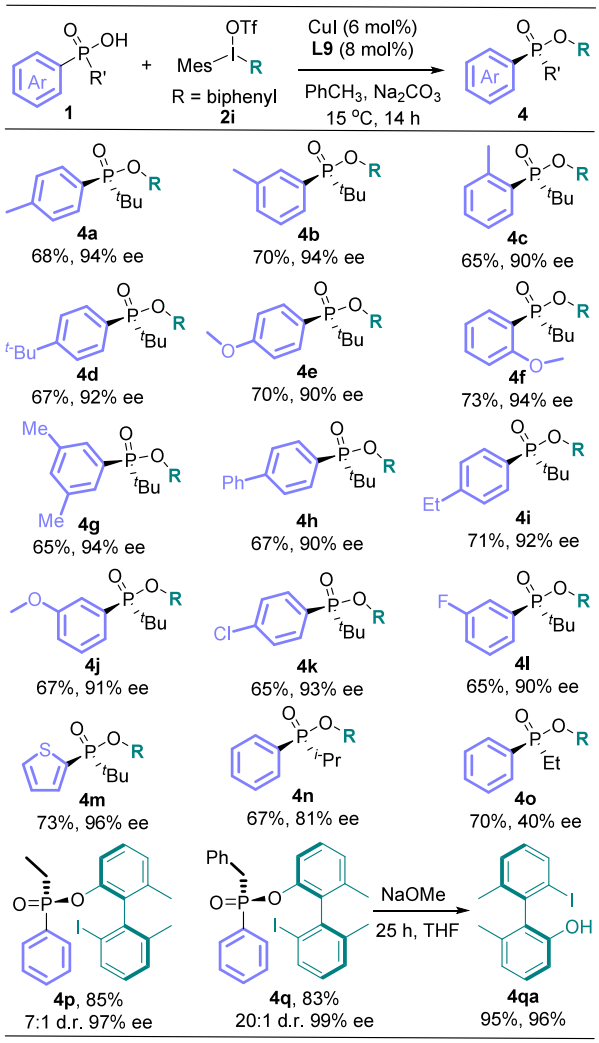
Table 2. Scope of DAISs[a]



[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.

Table 3. Scope of Phosphinic Acids[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. For **4p** and **4q**, the cyclic DAIS and **L8** were used instead.

substituent adjacent to the phosphorus center. Replacing the bulk *tert*-butyl group in **1a** with an iso-propyl substituent gave rise to **4n** in 67% yield and 81% ee. To further replace it with a smaller ethyl group afforded **4o** in 70% yield and 40% ee. These results indicated that the bulk substituent adjacent to the phosphorus center is beneficial for the reaction enantioselectivity. To solve this problem, we tried another type of DIAS **2p**, which were successfully used for obtaining axially chiral products. We speculated that **2p** allows for the formation of putative Cu(III)−aryl intermediate with bigger steric hindrance, which is beneficial for the nucleophilic attack of phosphinic acid with smaller steric hindrance. After rescreening the bisoxazoline ligands, we found ligand **L8** could smoothly catalyze the reaction and afforded the corresponding **4p** in 85% yield, 97% ee, and 7:1 diastereomeric ratio (dr). Furthermore, replacing ethyl with benzyl could afford **4q** in 83% yield, 99% ee, and 20:1 dr. The absolute configuration of the axial chirality was confirmed by derivatization of **4q** to the corresponding chiral phenol **4qa** and contrast with previous literature. For reactions with dialkyl substituted phosphinic acid, the corresponding products was not obtained. For reactions with aryl and alkoxyl substituted phosphinic acid, the corresponding products were obtained in moderated yield and low ee (Scheme S1 in the Supporting Information).

To demonstrate the utility of this reaction, the reaction was readily scaled up to 2 mmol scale for the preparation of **3f** in 72% yield and 95% ee (Scheme 2a). Meanwhile, enantiodivergent synthesis was investigated,[21] which indicated the other enantiomer of **3a** could be obtained in 74% yields and 94% ee by simply switching the ligand **L9** to its antipod (Scheme 2b). Due to the conversion of the P(O)−OH to P(O)−OAr, the P-center became electrophilic. Therefore, the structural diversity of the resulting chiral phosphinates could be easily expanded by reaction with various nucleophiles. First, phosphinate **3g** with para-NO_2 phenyl substituted was chosen as a suitable electrophile. To our delight, para-NO_2−PhO− was used as a good leaving group, which ensured the stereoselective ester exchange to afford the corresponding chiral phosphinates in good yields and ees (Scheme 2c). The ortho-methoxy phenolate was initially used, which afforded the corresponding **5a** in 90% yield with 90% ee. This result indicated that it is an alternative route to chiral phosphinates which was difficult to obtain via the above enantioselective desymmetrization arylation. The other enantiomer of **3i** was obtained by using the corresponding 4-phenyl phenolate as a nucleophile. This indicated that the ester exchange proceeded in an S_N2 substitution way. A series of functionalized phenols with

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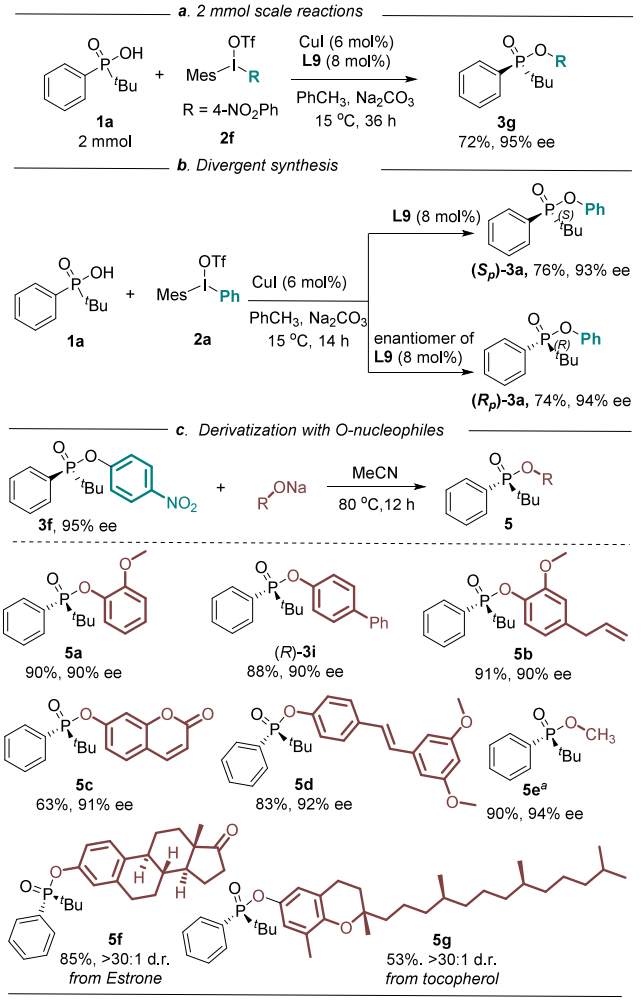
Scheme 2. Scalability, Divergent Synthesis, and Derivatization with O-Nucleophiles: (a) Investigation of the Reaction under 2 mmol Scale; (b) Divergent Synthesis of the Different Enantiomers; and (c) Derivatization by Using O-Nucleophiles*

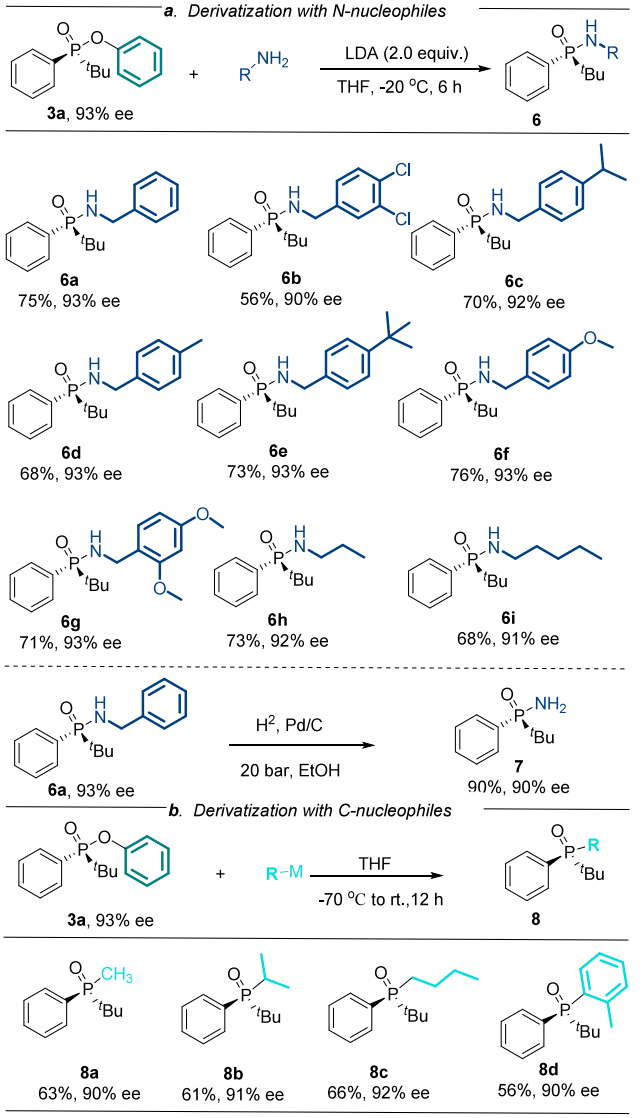


*The superscripted "a" footnote character indicates that the data are from (R_p)-3a, 94% ee.

terminal olefin (**5b**), internal olefin (**5d**), and lactone (**5c**) were smoothly converted to the corresponding products. Sodium alcoholate, such as methoxide, was also successfully applied to afford the chiral phosphinate **5e** in 90% yield and 94% ee. Furthermore, the modification of natural products such as estrone and tocopherol were investigated, which afforded **5f** and **5g** in pleasant yields and dr values.

The P-chiral phosphinamides were important functional groups distributed in bioactive compounds[22] and asymmetric catalysts.[23] Although much efforts have been put on their preparations such as the nucleophilic substitution with electrophilic P(III) precursors,[24] chiral auxiliaries-assisted preparations,[25] and catalytic asymmetric methods,[26] more-efficient synthetic methods are highly desirable. To further expand the utility of the reactions, N-centered nucleophiles were investigated with phosphinate **3a** as electrophile (Scheme 3a). According to the results, primary amines could effectively react with **3a** using lithium diisopropylamide (LDA) as a base. A series of P-chiral products (**6a**−**6i**) could be obtained in a smooth amine ester exchange reaction. Moreover, the N−H

Scheme 3. Derivatization of Phosphinate with N- or C-Nucleophiles:[a] (a) Derivatization by Using N-Nucleophiles and (b) Derivatization by Using C-Nucleophiles



[a]For **8a**−**8c**, the corresponding lithium were used as nucleophiles. For **8d**, the corresponding Grignard reagent was used as nucleophile.

free P-chiral phosphinamide **7**, which was used as a useful chiral auxiliary,[27] was obtained in 90% yield and 90% ee by debenzylation under Pd/C conditions.

Finally, we tried to derivatize phosphinate **3a** into tertiary phosphine oxides by using C-centered nucleophiles (Scheme 3b). Generally, alkyl Grignard reagent or aromatic Grignard reagent could smoothly react to afford the corresponding tertiary phosphine oxides **8a**−**8d** in moderate yields and high ee values.

CONCLUSION

In summary, by using phosphinic acid with two completely different carbon substituents on the P atom as nucleophiles and unsymmetric diaryliodonium salt as electrophiles, a copper(I)-catalyzed enantioselective desymmetrization arylation was achieved. A variety of P-chiral phosphinates were prepared in moderate to good yields with high enantioselectivities. Due to the conversion of the P(O)−OH to P(O)-

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OAr, the P-center became electrophilic. Therefore, a series of P-chiral compounds such as phosphinates, phosphinamides, and tertiary phosphine oxides were obtained with O-, N-, or C-centered nucleophiles. The utility of the reaction was also proven by gram-scale preparation and enantiodivergent synthesis of both enantiomers.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.5c00439.

General procedures, tables of reaction optimizations, analytical data, characterization data for all the products, and X-ray crystal structure data for **3j** (CCDC 2379810) (PDF)

Accession Codes

CCDC 2379810 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: + 44 1223 336033.

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Notes

The authors declare no competing financial interest.

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