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# Copper(I)-Catalyzed Asymmetric Alkylation of Unsymmetrical Secondary Phosphines

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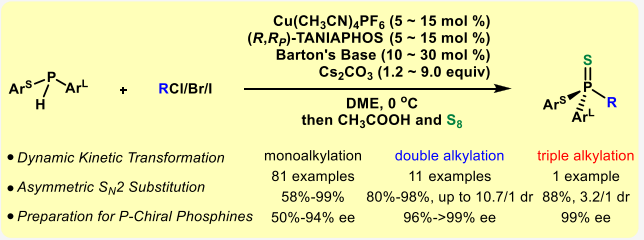
**ABSTRACT:** A copper(I)-catalyzed asymmetric alkylation of $HPAr^1Ar^2$ with alkyl halides is uncovered, which provides an array of *P*-stereogenic phosphines in generally high yield and enantioselectivity. The electrophilic alkyl halides enjoy a broad substrate scope, including allyl bromides, propargyl bromide, benzyl bromides, and alkyl iodides. Moreover, 11 unsymmetrical diarylphosphines ($HPAr^1Ar^2$) serve as competent pronucleophiles. The present methodology is also successfully applied to catalytic asymmetric double and triple alkylation, and the corresponding products were obtained in moderate diastereo- and excellent enantioselectivities. Some $^{31}P$ NMR experiments indicate that bulky HPPhMes exhibits weak competitively coordinating ability to the Cu(I)-bisphosphine complex, and thus the presence of stoichiometric $HPAr^1Ar^2$ does not affect the enantioselectivity significantly. Therefore, the high enantioselectivity in this reaction is attributed to the high performance of the unique Cu(I)-($R,R_P$)-TANIAPHOS complex in asymmetric induction. Finally, one monophosphine and two bisphosphines prepared by the present reaction are employed as efficient chiral ligands to afford three structurally diversified Cu(I) complexes, which demonstrates the synthetic utility of the present methodology.




## INTRODUCTION

*P*-Chiral stereogenic centers not only exist in pharmaceuticals (such as sofosbuvir, remdesivir, and cytoxan), pesticides (such as salithion), and bioactive molecules (such as cyclophostin, salinipostin A, and phostine), but also exist in powerful phosphine ligands (such as QUINOXP*, BENZP*, and DUANPHOS).[1−7] The classical synthetic methods mainly rely on resolution with stoichiometric chiral reagents and diastereoselective synthesis with chiral auxiliaries. The continuing flourish of asymmetric catalysis offers an alternative for the efficient synthesis of *P*-stereogenic centers, which enjoys the advantages of chirality economy, diversified methodologies, and high synthetic efficiency. However, only limited success has been achieved so far. It is obvious that more structurally diversified *P*-chiral phosphines would lead to the generation of more transition metal complexes, which would serve as new and efficient chiral metal catalysts in asymmetric catalysis. Therefore, it is highly desirable to develop new and powerful methodologies toward the synthesis of diversified *P*-chiral phosphines.

The strategies available for the catalytic asymmetric synthesis of *P*-chiral phosphines are mainly divided into four types, including molecular desymmetric reactions,[8−24] kinetic resolution of secondary phosphine oxides,[25−29] dynamic kinetic resolution of secondary phosphines, their oxides, and their borane complexes,[30−54] and other miscellaneous reactions.[55−59] The first strategy usually requires a synthetic handle on the starting molecules bearing P(V) to enable the desymmetric functionalization. The second strategy generally transforms 50% racemic phosphine oxides to the desired chiral products, in which the yield is less than 50%. The third strategy is more advantageous, as all of the racemic phosphines or phosphine derivatives are converted to the target chiral products in high yields. Moreover, various methods could be employed to accomplish the dynamic kinetic resolution, including Ni-catalyzed asymmetric allylation of secondary phosphine oxides,[30] palladium- or platinum-catalyzed asymmetric arylation,[31−36] Cu-catalyzed asymmetric arylation of secondary phosphine oxides with diaryliodonium salts,[37] transition-metal-catalyzed asymmetric conjugate addition of secondary phosphines to $\alpha,\beta$-unsaturated compounds,[38−44] palladium-catalyzed asymmetric addition of unsymmetrical diarylphosphines to benzoquinones,[45] and transition-metal-catalyzed asymmetric alkylation of secondary phosphines.[46−54] Other notable miscellaneous catalytic asymmetric methods for accessing *P*-chiral phosphines include pincer-nickel-complex-catalyzed asymmetric synthesis of secondary phosphineboranes,[55] asymmetric alkylation of phenylphosphine borane complexes under phase-transfer catalysis,[56] Brønsted acid-catalyzed addition of phosphoramidic acid to alkenes,[57]

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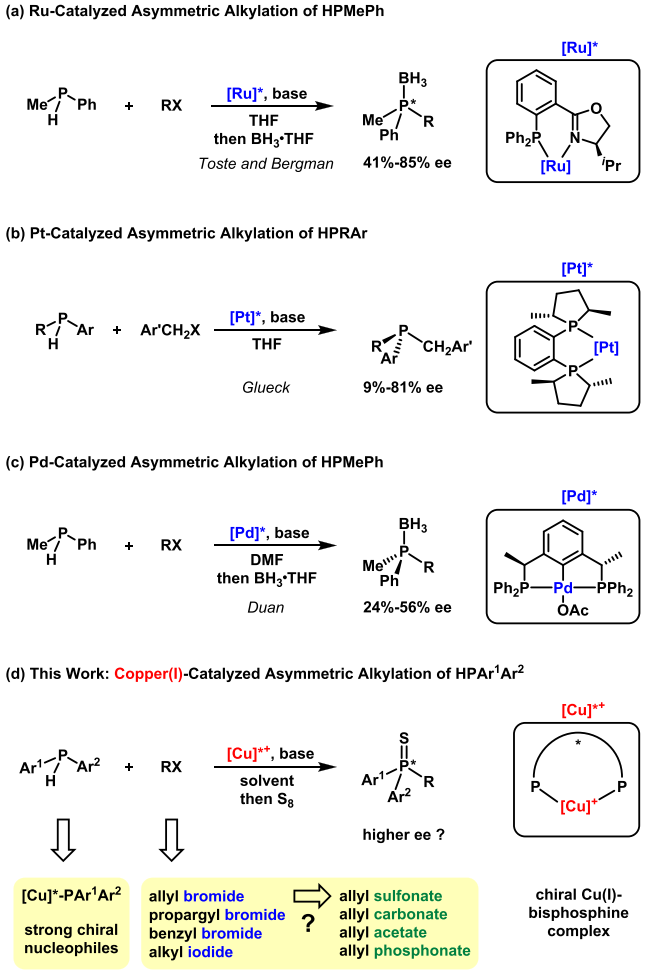
rhodium-catalyzed asymmetric arylation of phospholene oxides,[58] and Pd-catalyzed asymmetric allylic *O*-alkylation of phosphinic acids.[59]

Among these powerful methods, catalytic asymmetric alkylation of secondary phosphines serves as a straightforward method to access *P*-stereogenic phosphines. However, both the starting materials and the products, which contain free phosphine moieties, could serve as competitive ligands to the transition metals. Thus, the desired metal catalysts may decompose partially or even completely. Furthermore, new but undesired metal complexes may be generated, which would catalyze the nonenantioselective reaction to erode the asymmetric induction. In spite of these concerns, transition-metal-catalyzed asymmetric alkylation of secondary phosphines achieved some progress with the continuing efforts from the chemical community.[46−54] In 2006, Toste and Bergman disclosed a Ru-$^i$Pr-PHOX complex-catalyzed asymmetric alkylation of HPMePh with benzyl chlorides and ethyl chloride in moderate enantioselectivity (Scheme 1a).[46] Later, they developed a mixed-ligand catalytic system of Ru to achieve the asymmetric alkylation with benzyl chlorides and alkyl bromides, which furnished various tertiary phosphines in moderate enantioselectivity.[47] Simultaneously in 2006, Glueck and co-workers uncovered a platinum-catalyzed asymmetric alkylation in moderate enantioselectivity (Scheme 1b) and extended the catalytic system to double alkylation later.[48−53]

**Scheme 1. Introduction to Catalytic Asymmetric Alkylation of Unsymmetrical Secondary Phosphines and Our Work**




Moreover, the Duan group applied a pincer palladium catalyst in the asymmetric alkylation of HPMePh and achieved moderate enantioselectivity in 2013 (Scheme 1c).[54] Recently, we have achieved copper(I)-catalyzed asymmetric conjugate addition of diarylphosphines to $\alpha,\beta$-unsaturated phosphine sulfides and $\alpha,\beta$-unsaturated amides with the generation of [Cu]*-$PPh_2$ species.[43,44,60−65] These two reactions were also used to accomplish the dynamic kinetic transformation of unsymmetrical diarylphosphines (HPPhAr). A [Cu]*-PPhAr species was generated as the nucleophile through the deprotonation of HPPhAr in the presence of a copper(I) complex and an organic base. This species would be highly nucleophilic with the assistance of a bisphosphine ligand,[66] which inspires us to envision a catalytic asymmetric $S_N2$-type alkylation of $HPAr^1Ar^2$ with various alkyl halides and even diversified allyl electrophiles (Scheme 1d). Under certain suitable reaction conditions, a Cu(I)-bisphosphine complex-catalyzed asymmetric alkylation with the concurrent dynamic kinetic transformation of $HPAr^1Ar^2$ would be achieved in high yield with satisfactory enantioselecitvity.[67,68]

## RESULTS AND DISCUSSION

**1. Optimization of Reaction Conditions.** The model reaction of HPPhMes (**1a**) and allyl bromide (**2a**) was performed in 1,2-dimethoxyethane (DME) at 0 °C with ($R,R_P$)-TANIAPHOS as the ligand, with Barton's base (10 mol %) as the catalytic base and with $Cs_2CO_3$ (1.2 equiv) as the stoichiometric base to neutralize HBr.[69] Tertiary phosphine sulfide **3aa** was afforded in quantitative yield with 94% ee after quenching the reaction with $CH_3COOH$ and $S_8$ (Table 1, entry 1).[70] The reaction results with varied reaction conditions are shown in entries 2−15. Axially chiral bisphosphine ligands, such as (*R*)-TOL-BINAP and (*R*)-SEGPHOS, showed much worse asymmetric induction but led to a high yield of **3aa** (entries 2 and 3). Bisphosphines containing chiral carbons, such as (*R,R*)-BDPP and (*R,R*)-Ph-BPE, were not effective in the control of the enantioselectivity either (entries 4 and 5). Moreover, a *P*-chiral bisphosphine, such as (*R,R*)-QUINOXP*, was not a suitable ligand as a moderate yield and very low enantioselectivity were observed (entry 6). (*R*)-(*S*)-JOSIPHOS, a very common ferrocene-embedded bisphosphine ligand, did not suit the present reaction either, as very low enantioselectivity was observed (entry 7). A *P,N*-bidentate ligand ((*S,S*)-$^i$Pr-FOXAP) and an *N,N,N*-tridentate ligand ((*S,S*)-Ph-PyBOX) were also tried, which resulted in low enantioselectivity of **3aa** (entries 8 and 9).

The alkylation with ($R,R_P$)-TANIAPHOS in tetrahydrofuran (THF) delivered **3aa** in inferior yield but with maintained high enantioselectivity (entry 10). Moreover, the reaction in more polar solvent (such as dimethylformamide (DMF)) furnished **3aa** in excellent yield but with significantly decreased enantioselectivity (entry 11). The alkylation without 10 mol % Barton's base led to a decreased yield but with high enantioselectivity maintained (entry 12). However, switching $Cs_2CO_3$ to KO$^t$Bu resulted in significantly decreased enantioselectivity, indicating that mainly the background reaction promoted by KO$^t$Bu occurred (entry 13). A weaker potassium base ($K_2CO_3$) led to a very low yield (20%) and attenuated enantioselectivity (75% ee) (entry 14). Finally, decreasing the reaction temperature to −20 °C did not give improved enantioselectivity (entry 15).


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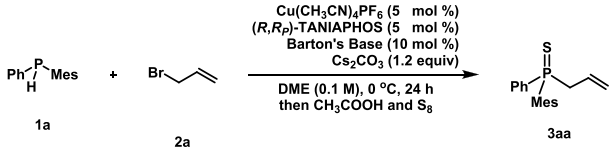
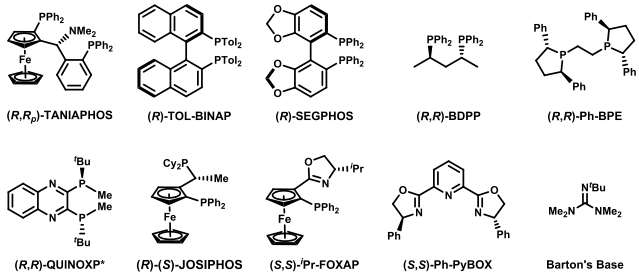
**Table 1. Optimization of the Reaction Conditions**[a]



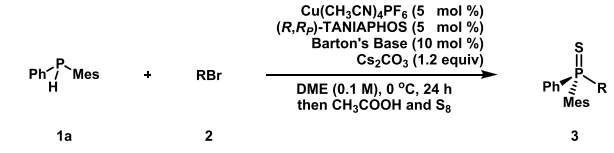

| entry | variations | yield (%)[b] | ee (%)[c] |
|---|---|---|---|
| 1 | - | 100 | 94 |
| 2 | (*R*)-TOL-BINAP in THF | 90 | 5 |
| 3 | (*R*)-SEGPHOS in THF | 92 | 13 |
| 4 | (*R*,*R*)-BDPP in THF | 87 | 14 |
| 5 | (*R*,*R*)-Ph-BPE in THF | 96 | 48 |
| 6 | (*R*,*R*)-QUINOXP* in THF | 45 | −3 |
| 7 | (*R*)-(*S*)-JOSIPHOS in THF | 97 | −18 |
| 8 | (*S*,*S*)-$^i$Pr-FOXAP in THF | 100 | −36 |
| 9 | (*S*,*S*)-Ph-PyBOX in THF | 100 | −23 |
| 10 | THF instead of DME | 75 | 93 |
| 11 | DMF instead of DME | 100 | 9 |
| 12 | without 10 mol % Barton's base in THF | 60 | 93 |
| 13 | without 10 mol % Barton's base, 1.5 KO$^t$Bu in THF | 93 | <5 |
| 14 | without 10 mol % Barton's base, 1.5 $K_2CO_3$ in THF | 20 | 75 |
| 15 | −20 °C instead of 0 °C | 46 | 83 |

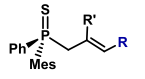
[a]**1a**: 0.1 mmol, **2a**: 0.15 mmol. [b]Determined by $^1$H NMR analysis of the reaction crude mixture using $CH_2Br_2$ as an internal standard. [c]Determined by chiral-stationary-phase HPLC analysis. DME = 1,2-dimethoxyethane.



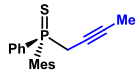

**2. Investigation of the Substrate Scope.** Under the optimized reaction conditions, the substrate scope of alkyl bromides including allyl bromides, propargyl bromide, and benzyl bromides was investigated as shown in Table 2. Compared to the reaction with allyl bromide **2a** (95%, 94% ee), the reaction with **2b** and **2c**, bearing a terminal substituent, generated the corresponding products in lower yields and enantioselectivity (**3ab**, 85%, 85% ee; **3ac**, 60%, 78% ee). The allyl bromide bearing 2-methyl (**2d**) was a suitable substrate to afford tertiary phosphine sulfide **3ad** in 88% yield with 86% ee. 1-Bromobut-2-yne (**2e**) was a competent substrate too, which was transformed to product **3ae** in 88% yield with 94% ee. In this case, Barton's base was removed from the reaction mixture to get higher enantioselectivity and 2 equiv of $Cs_2CO_3$ was used to get higher yield. Subsequently, various benzyl bromides (**2f**−**2z**) were studied. The reaction results were not significantly affected by the electronic nature of a substituent on the *para*-position of the phenyl group (**3af**−**3ap**, 85−95%, 82−90% ee). Moreover, both yield and enantioselectivity were not very sensitive to the substituent on the *meta*-position of the phenyl group (**3aq**−**3au**, 90−96%, 84−87% ee). However, the reaction with benzyl bromide **2v** containing *ortho*-methyl resulted in lower asymmetric

**Table 2. Substrate Scope of RBr**[a]

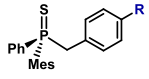


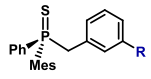
R = R' = H, **3aa**, 95%, 94% ee
R = Me, R' = H, **3ab**, 85%, 85% ee
R = Ph, R' = H, **3ac**, 60%, 78% ee
R = H, R' = Me, **3ad**, 88%, 86% ee



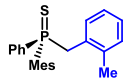
**3ae**, 88%, 94% ee[b]



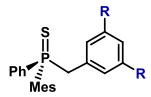
R = H, **3af**, 95%, 87% ee
R = Me, **3ag**, 92%, 90% ee
R = Et, **3ah**, 95%, 87% ee
R = $^i$Pr, **3ai**, 95%, 87% ee
R = $^t$Bu, **3aj**, 95%, 85% ee
R = Ph, **3ak**, 95%, 84% ee
R = F, **3al**, 91%, 88% ee
R = Cl, **3am**, 95%, 87% ee
R = $OCF_3$, **3an**, 95%, 88% ee
R = $CF_3$, **3ao**, 85%, 85% ee
R = $CO_2$Me, **3ap**, 90%, 82% ee



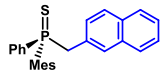
R = Me, **3aq**, 96%, 87% ee
R = OMe, **3ar**, 96%, 85% ee
R = F, **3as**, 96%, 86% ee
R = Cl, **3at**, 95%, 84% ee
R = Br, **3au**, 90%, 85% ee



**3av**, 98%, 77% ee



R = Me, **3aw**, 95%, 82% ee
R = F, **3ax**, 95%, 82% ee



**3ay**, 98%, 83% ee

**3az**, 85%, 90% ee

[a]**1a**: 0.2 mmol, **2**: 0.3 mmol. Isolated yield. Enantioselectivity was determined by chiral-stationary-phase HPLC analysis. [b]With 2 equiv of $Cs_2CO_3$ but without 10 mol % Barton's base.

induction (**3av**, 98%, 77% ee). Fortunately, the substrates with a 3,5-disubstituted phenyl group also successfully reacted with **1a** to deliver the corresponding products in good results (**3aw**−**3ax**, 95%, 82% ee). Moreover, both 2-(bromomethyl)-naphthalene (**2y**) and 3-(bromomethyl)thiophene (**2z**) were well tolerated in the present reaction, providing the desired products in high yields with high enantioselectivity (**3ay**−**3az**, 85−98%, 83−90% ee). The absolute configuration of **3af** was determined to be *S* by X-ray analysis of its single crystals (for the details, see the SI). The stereochemistry in other products (**3**) was assigned by analogy.

In the alkylation with alkyl iodide, both 3.0 equiv of alkyl iodide and 3.0 equiv of $Cs_2CO_3$ were required to achieve the full conversion of **1a**, as shown in Table 3. Short alkyls, including ethyl, *n*-propyl, *n*-butyl, and isobutyl were well tolerated with the corresponding products isolated in high enantioselectivity (**5aa**−**5ad**, 78−95%, 90−92% ee). As for the yield, **5ad** was generated in lower yield possibly due to the steric hindrance of the bulkier isobutyl group. Moreover, the reaction with long linear alkyl iodides afforded consistently good results (**5ae**−**5af**, 93−95%, 89−90% ee). The alkyl iodides containing a functional group were also investigated. Methyl ether, benzyl ether, TBS-ether, ester, trifluoromethyl, and alkyl chloride were acceptable with the corresponding products generated in high yields and high enantioselectivity (**5ag**−**5ao**, 80−98%, 82−90% ee). Noticeably, the wonderful chemoselectivity between the alkyl iodide moiety and alkyl


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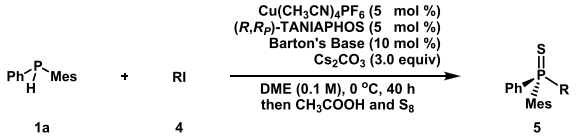
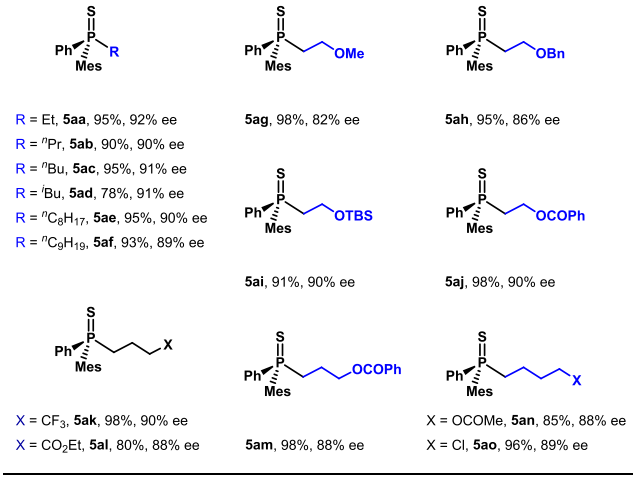
**Table 3. Substrate Scope of RI**[a]



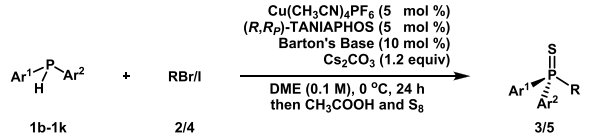



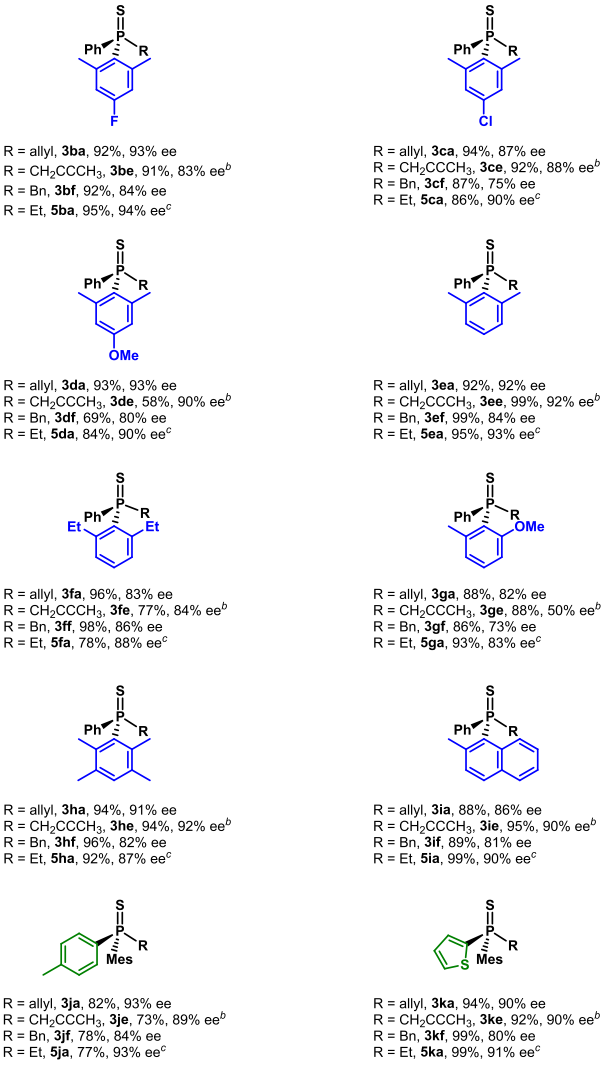

[a]**1a**: 0.2 mmol, **4**: 0.6 mmol. Isolated yield. Enantioselectivity was determined by chiral-stationary-phase HPLC analysis.

chloride moiety was achieved in the synthesis of **5ao**, which allowed further functionalization with the alkyl chloride unit.

Several secondary phosphines ($HPAr^1Ar^2$) other than HPPhMes (**1b**−**1k**)[71] were also tried (Table 4). When $Ar^1$ = Ph, the $Ar^2$ group was changed to other 2,4,6-trisubstituted aryls, such as 4-F-2,6-$Me_2$-$C_6H_2$ (**1b**), 4-Cl-2,6-$Me_2$-$C_6H_2$ (**1c**), and 4-MeO-2,6-$Me_2$-$C_6H_2$ (**1d**). To our joy, four representative alkylation reactions (allylation, propargylation, benzylation, and ethylation) proceeded smoothly to furnish the corresponding products in moderate to high yields with moderate to high enantioselectivity (**3ba**−**3da**, 92−94%, 87−93% ee; **3be**−**3de**, 58−92%, 83−90% ee; **3bf**−**3df**, 69−92%, 75−84% ee; **5ba**−**5da**, 84−95%, 90−94% ee). It was noted that moderate yields were observed in the propargylation and the benzylation of **1d** (**3de**, 58%; **3df**, 69%), and moderate enantioselectivity was obtained in the benzylation of **1c** (**3cf**, 75% ee). Moreover, it was found that the benzylation generally led to inferior enantioselectivity to the allylation, the propargylation, and the ethylation. The $Ar^2$ group could also be extended to 2,6-disubstituted aryls, including 2,6-$Me_2$-$C_6H_3$ (**1e**), 2,6-$Et_2$-$C_6H_3$ (**1f**), and 2-methoxyl-6-methyl-$C_6H_3$ (**1g**) (**3ea**−**3ga**, 88−96%, 82−92% ee; **3ee**−**3ge**, 77−99%, 50−92% ee; **3ef**−**3gf**, 86−99%, 73−86% ee; **5ea**−**5ea**, 78−95%, 83−93% ee). As for **1e** and **1f**, the four alkylation reactions occurred with satisfactory results. Although satisfying results were obtained in the allylation and the ethylation of **1g**, propargylation and benzylation delivered the products in moderate enantioselectivity (**3ge**, 50% ee; **3gf**, 73% ee). Furthermore, 2,3,5,6-$Me_4$-$C_6H$ (**1h**) served as a competent $Ar^2$ substituent. The four alkylation reactions proceeded in high yields with high enantioselectivity (**3ha**, 94%, 91% ee; **3he**, 94%, 92% ee; **3hf**, 96%, 82% ee; **5ha**, 92%, 87% ee). Remarkably, 2-Me-1-naphthyl (**1i**) was also an appropriate $Ar^2$ group with the corresponding products of the four alkylation reactions obtained in good results (**3ia**, 88%, 86% ee; **3ie**, 95%, 90% ee; **3if**, 89%, 81% ee; **5ia**, 99%, 90% ee). Finally, 4-

**Table 4. Substrate Scope of $HPAr^1Ar^2$**[a]




[a]**1b**−**1k**: 0.2 mmol, **2**: 0.3 mmol, **4**: 0.6 mmol. Isolated yield. Enantioselectivity was determined by chiral-stationary-phase HPLC analysis. [b]With 2 equiv of $Cs_2CO_3$ but without 10 mol % Barton's base. [c]With 3 equiv of $Cs_2CO_3$, 40 h.

methylphenylmesityl phosphine (**1j**) and 2-thienylmesityl phosphine (**1k**) were investigated, and competent results were obtained (**3ja**, 82%, 93% ee; **3je**, 73%, 89% ee; **3jf**, 78%, 84% ee; **5ja**, 77%, 93% ee; **3ka**, 94%, 90% ee; **3ke**, 92%, 90% ee; **3kf**, 99%, 80% ee; **5ka**, 99%, 91% ee). Evidently, higher enantioselectivity was obtained in the alkylation with a larger steric difference between the two aryl groups ($Ar^1$ = $Ar^S$ vs $Ar^2$ = $Ar^L$).

The present methodology was applied to double and triple asymmetric alkylation with substrates bearing two or three alkyl halide units (Table 5). Both (*E*)-1,4-dibromobut-2-ene (**6a**) and 1,4-dichlorobut-2-yne (**6b**) underwent double alkylation smoothly to give the desired bisphosphine sulfides



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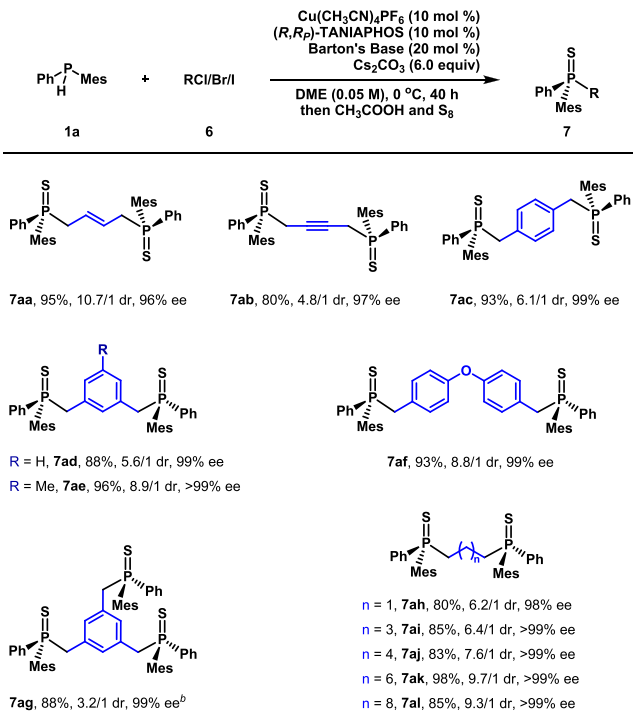
**Table 5. Catalytic Asymmetric Double and Triple Alkylation**[a]

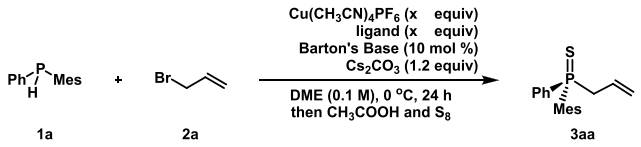



[a]**1a**: 0.2 mmol for double alkylation and 0.3 mmol for triple alkylation, **6**: 0.1 mmol. Isolated yield. Both diastereoselectivity and enantioselectivity were determined by chiral-stationary-phase HPLC analysis. [b]15 mol % $Cu(CH_3CN)_4PF_6$, 15 mol % $(R,R_P)$-TANIAPHOS, 30 mol % Barton's base, and 9.0 equiv of $Cs_2CO_3$ were used.

in high yields with excellent enantioselectivity (**7aa**−**7ab**, 80−95%, 96−97% ee). However, the diastereoselectivity in the case of **6b** was lower than that in the case of **6a** (4.8/1 vs 10.7/1). In the double alkylation of 1,4- and 1,3-bis(bromomethyl)-benzenes (**6c**−**6e**) and 4,4′-oxybis((bromomethyl)benzene) (**6f**), the reaction proceeded smoothly with the corresponding products furnished in high yields with moderate diastereo- and excellent enantioselectivities (**7ac**−**7af**, 88−96%, 5.6/1 to 8.9/1 dr, 99%−>99% ee). Remarkably, the triple alkylation of 1,3,5-tris(bromomethyl)benzene (**6g**) was accomplished with uncompromising yield and enantioselectivity (**7ag**, 88%, 99% ee). However, the diastereoselectivity dropped down to 3.2/1 dr. Moreover, by using a series of alkyl diiodides (**6h**−**6l**) as the electrophiles, the double alkylation was successfully carried out to provide the target bisphosphine sulfides in high yields with moderate diastereo- and excellent enantioselectivities (**7ah**−**7al**, 80−98%, 6.2/1 to 9.7/1 dr, 98%−>99% ee). Obviously, the diastereoselectivity increased with the increase of the alkyl chain length. The absolute configuration of **7ah** was determined by X-ray crystallography. Analogously, the absolute configurations of **5** and **7ah**−**7al** were assigned tentatively. The absolute configurations of **7aa**−**7ag** were assigned by their analogy to the exact structure of **3af**.

**3. Insights into the Reaction Mechanism and Proposed Reaction Pathway.** Previously, in the copper(I)-catalyzed asymmetric addition of $HPPh_2$ to $\alpha,\beta$-unsaturated amides, we demonstrated that the Cu(I)-(*R*)-BINAP complex was not stable in the presence of 5 equiv of $HPPh_2$ and the ligand exchange of (*R*)-BINAP by $HPPh_2$ occurred completely to deliver some undesired Cu(I)-$(HPPh_2)_x$ species.[44] Thus, although the asymmetric reaction with stoichiometric Cu(I)-(*R*)-BINAP complex delivered the target product in moderate enantioselectivity, the catalytic version afforded the racemic product. In view of the above interesting phenomenon, both the stoichiometric version and the catalytic version with several Cu(I)-bisphosphine complexes (Cu(I)-(*R*)-BINAP, Cu(I)-(*R*)-TOL-BINAP, Cu(I)-(*R*,*R*)-Ph-BPE, Cu(I)-(*R*)-(*S*)-JOSIPHOS, and Cu(I)-$(R,R_P)$-TANIAPHOS) were investigated in the present asymmetric alkylation as shown in Scheme 2. Surprisingly, the two versions provided

**Scheme 2. Asymmetric Alkylation with both Catalytic and Stoichiometric Cu(I)-Bisphosphine Complexes ($^1$H NMR Yields Are Given)**




x = 0.05, (*R*)-BINAP, 96%, 1% ee; x = 1.0, (*R*)-BINAP, 100%, 8% ee;
x = 0.05, (*R*)-TOL-BINAP, 96%, 8% ee; x = 1.0, (*R*)-TOL-BINAP, 100%, 10% ee;
x = 0.05, (*R*,*R*)-Ph-BPE, 96%, 52% ee; x = 1.0, (*R*,*R*)-Ph-BPE, 100%, 51% ee;
x = 0.05, (*R*)-(*S*)-JOSIPHOS, 93%, -10% ee; x = 1.0, (*R*)-(*S*)-JOSIPHOS, 100%, -18% ee;
x = 0.05, $(R,R_P)$-TANIAPHOS, 100%, 94% ee x = 1.0, $(R,R_P)$-TANIAPHOS, 100%, 95% ee

the desired products in similar enantioselectivity. From these results, it was speculated that the catalytically active Cu(I)-bisphosphine complexes remain relatively stable in the presence of stoichiometric HPPhMes. Thus, stoichiometric HPPhMes had a weaker effect on the stability of the Cu(I)-bisphosphine complexes than stoichiometric $HPPh_2$. Moreover, the produced P(allyl)PhMes did not disturb the catalytic asymmetric induction significantly. Lastly, the low enantioselectivity was attributed to the poor performances of these Cu(I)-bisphosphine complexes in asymmetric induction except for the Cu(I)-$(R,R_P)$-TANIAPHOS complex.

In order to get some insights on the difference of $HPPh_2$ and HPPhMes, the $^{31}$P NMR experiments of $Cu(CH_3CN)_4PF_6$ and (*R*)-BINAP were performed as shown in Figure 1. The $^{31}$P

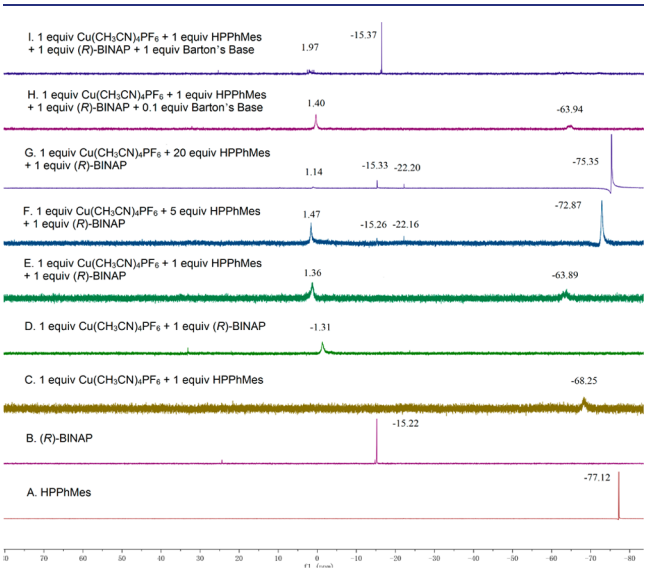



**Figure 1.** $^{31}$P NMR studies with (*R*)-BINAP



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NMR signals of HPPhMes and (*R*)-BINAP appeared at $\delta$ −77.12 and $\delta$ −15.22 ppm, respectively (Figure 1A and B). A certain complex formed from $Cu(CH_3CN)_4PF_6$ and HPPhMes gave a broad peak at $\delta$ −68.25 ppm (Figure 1C). The signal of Cu(I)-(*R*)-BINAP was recorded as $\delta$ −1.31 ppm (Figure 1D). When 1 equiv of HPPhMes was added to the solution of Cu(I)-(*R*)-BINAP in THF, one new sharp peak ($\delta$ 1.36 ppm) and one new broad peak ($\delta$ −63.89 ppm) were observed, indicating the formation of the Cu(I)-(*R*)-BINAP-HPPhMes complex (Figure 1E). When 5 equiv of HPPhMes was added, the signal at $\delta$ −15.26 ppm indicated that some amount of (*R*)-BINAP was liberated from the Cu(I) complex (Figure 1F). However, a substantial amount of Cu(I)-(*R*)-BINAP complex remained, which was indicated by the signal at $\delta$ 1.47 ppm. When 20 equiv of HPPhMes was added, although a significant amount of free (*R*)-BINAP was detected, a certain Cu(I)-(*R*)-BINAP complex still remained ($\delta$ 1.14 ppm) (Figure 1G). These $^{31}$P NMR experiments suggested that HPPhMes has a much weaker competitive coordinating ability toward the Cu(I)-(*R*)-BINAP complex than $HPPh_2$ possibly due to its larger steric hindrance. Previously, it was realized that the Cu(I)-(*R*,*R*$_P$)-TANIAPHOS complex was relatively stable in the presence of stoichiometric $HPPh_2$.[44] Thus, it was conjectured that the Cu(I)-(*R*,*R*$_P$)-TANIAPHOS complex would be more stable in the presence of stoichiometric HPPhMes. The high enantioselectivity in the present catalytic asymmetric alkylation could be attributed to the high performance of the Cu(I)-(*R*,*R*$_P$)-TANIAPHOS complex in asymmetric induction. Moreover, the $^{31}$P NMR experiment of the mixture of $Cu(CH_3CN)_4PF_6$ (1 equiv), (*R*)-BINAP (1 equiv), HPPhMes (1 equiv), and Barton's base (0.1 equiv) was performed, which gave the same signals as the mixture without Barton's base (0.1 equiv) (Figure 1H vs E). When 1 equiv of Barton's base was added, the mixture gave unidentified multiple signals, suggesting the formation of many copper(I) complexes (Figure 1I). Definitely, a certain catalytically active Cu(I)-PPhMes-(*R*)-BINAP complex existed. However, its $^{31}$P NMR signal was not unambiguously identified. Furthermore, it should be pointed out that Barton's base not only worked as an organic base but also served as a ligand to copper(I), which was revealed by the presence of a significant amount of free (*R*)-BINAP ($\delta$ −15.37 ppm).

Moreover, the ligand-accelerating effect[72] in this reaction was roughly investigated with HPPhMes and allyl bromide as shown in Figure 2. Without an external ligand, the copper(I)-catalyzed nonenantioselective reaction proceeded slowly and provided the product in 40% yield in 24 h. In this reaction, HPPhMes itself might serve as a ligand to Cu(I). In the reaction with (*R*)-TOL-BINAP, the yield in 24 h increased to 73%, indicating that the reaction catalyzed by Cu(I)-(*R*)-TOL-BINAP complex was not accelerated significantly. However, the reactions with (*R*,*R*)-Ph-BPE and (*R*,*R*$_P$)-TANIAPHOS were much faster than the background reaction. Evidently, the moderate enantioselectivity in the reaction with (*R*,*R*)-Ph-BPE was largely due to its unsatisfactory performance in asymmetric induction. Such an interesting ligand-accelerating effect was the key to achieve high enantioselectivity.

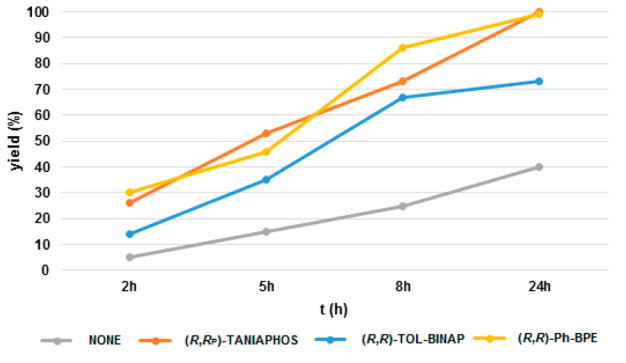
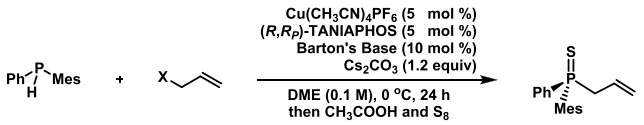



**Figure 2.** Ligand-accelerating effect in the catalytic asymmetric allylation of HPPhMes with allyl bromide ($^1$H NMR yields are given).

Except for allyl bromide **2a**, a series of other electrophiles with an allyl group (**8**−**15**) was studied as described in Scheme 3. Obviously, allyl chloride **8** was a much less efficient

**Scheme 3. Trials with Various Allyl Electrophiles ($^1$H NMR Yields Are Given)**




1a | 2a/8-15 | 3aa

| | |
|---|---|
| X = Br, **2a** | 100%, 94% ee |
| X = Cl, **8** | 24%, 85% ee |
| X = $OSO_2Me$, **9** | 22%, 60% ee |
| X = OTs, **10** | 100%, 85% ee |
| X = $OSO_2Mes$, **11** | 100%, 80% ee |
| X = $OCO_2Me$, **12** | no reaction |
| X = OTroc, **13** | no reaction |
| X = OAc, **14** | no reaction |
| X = OP(O)$(OEt)_2$, **15** | trace |

electrophile under the present reaction conditions, as **3aa** was generated in 24% yield with 85% ee. As for allyl sulfonate, less bulky allyl mesylate **9** was transformed to **3aa** in 22% yield with 60% ee. Bulky allyl tosylate (**10**) was an appropriate substrate, and **3aa** was produced in quantitative yield with 85% ee. Unfortunately, the reaction with much bulkier allyl 2,4,6-trimethylbenzenesulfonate (**11**) provided **3aa** in slightly decreased enantioselectivity (80% ee). Subsequently, allyl methyl carbonate (**12**), allyl 2,2,2-trichloroethyl carbonate (**13**), and allyl acetate (**14**) were tried, which were widely used in palladium- or iridium-catalyzed asymmetric allylic alkylation.[73] However, no reaction occurred. Furthermore, allyl diethyl phosphate (**15**) frequently used in copper-catalyzed asymmetric allylic alkylation[73−78] was employed. Nevertheless, only trace **3aa** was observed. Therefore, we believe that the present alkylation proceeds through a simple $S_N2$ substitution mechanism.

With the assistance of the above control experiments and our previous realization toward the [Cu]*-$PPh_2$ species,[43,44] a plausible mechanism for the copper(I)-catalyzed asymmetric alkylation is proposed in Scheme 4. As previously reported, the coordination of $HPAr^1Ar^2$ to Cu(I)-(*R*,*R*$_P$)-TANIAPHOS complex (**U**) results in complex **V** and thus activates $HPAr^1Ar^2$, which enables its facile deprotonation to afford two diastereoisomers, Cu(I)-$PAr^1Ar^2$-(*R*,*R*$_P$)-TANIAPHOS complexes **W** and **W′**. Then in the presence of RBr, the asymmetric $S_N2$ substitution of **W** occurs fast to afford the desired chiral $RPAr^1Ar^2$ as the product and the complex **U** is regenerated as the catalyst. The asymmetric $S_N2$ substitution of **W′** is very slow, which finally leads to high asymmetric induction in the present reaction. It should be pointed out that the bromide anion was finally transformed to CsBr in the presence of stoichiometric $Cs_2CO_3$.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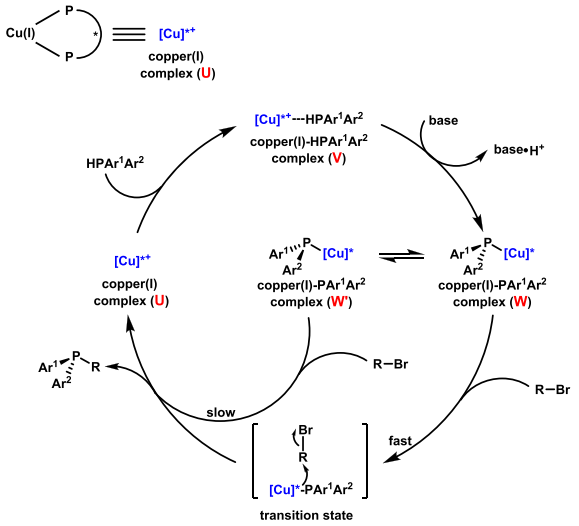
**Scheme 4. Proposed Mechanism for the Copper(I)-Catalyzed Asymmetric Alkylation**




**4. Application of the Present Methodology.** Under the inert atmosphere (Ar), the free phosphines could be obtained directly in high yields. For example, **3af′**, **7ab′**, and **7ah′** were isolated in 97%, 94%, and 97% yields, respectively (for the details, see the SI). Chiral phosphines are supposed to be suitable ligands for transition metals.[1−7] Here, by using copper(I) as the metal species, several chiral complexes were prepared as shown in Figure 3 (for details, see the SI). Treating monophosphine **3af′** with 1 equiv of CuI in $CH_3CN$ at room temperature in 12 h resulted in chiral complex **16** in 89% yield after recrystallization with $CH_3CN$ and *n*-pentane, whose structure was determined by single-crystal X-ray diffraction. **16** was a dimer and iodide worked as a bridged ligand in this case. Moreover, the solution of chiral bisphosphine **7ab′** and CuCl (2 equiv) in toluene was stirred at room temperature for 12 h to give complex **17**, which was recrystallized with $CH_2Cl_2$/petroleum ether to afford its crystals in 61% yield. **17** was identified as a self-assembled coordination cage compound by X-ray analysis of its single crystals. Interestingly, the classical interaction between copper(I) and the alkyne group was not observed, and bisphosphine **7ab′** served as a monodentate ligand to each copper(I) center. Finally, CuCl (1 equiv) was subjected to the toluene solution of chiral bisphosphine **7ah′** at room temperature, and the resulting mixture was stirred at room temperature for 12 h. Then complex **18** was obtained in 81% yield after recrystallization with $CH_2Cl_2$/petroleum ether, and its exact structure was determined by X-ray diffraction crystallography. In this complex, bisphosphine **7ah′** worked as a bidentate ligand. The facile preparation of these copper(I) complexes demonstrated that the synthesized chiral phosphines were versatile ligands toward transition metals.

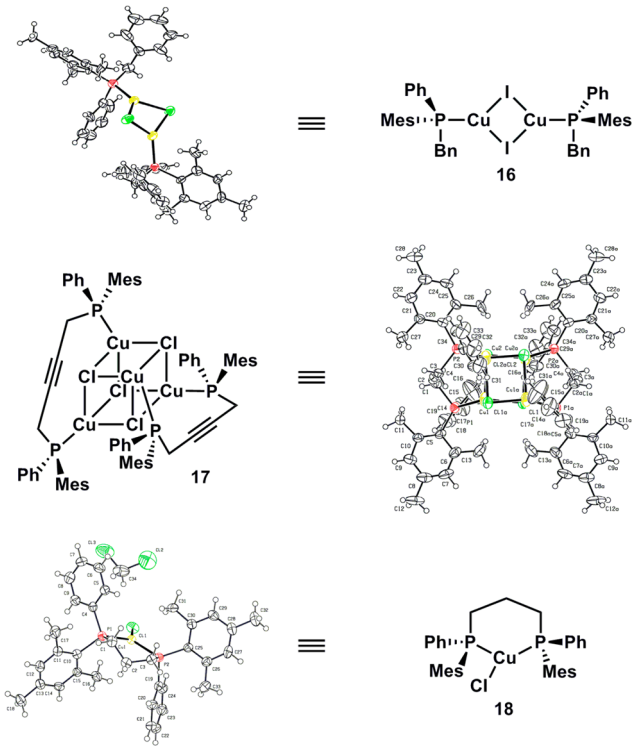



**Figure 3.** Three copper(I) complexes prepared with the produced *P*-chiral phosphines.

## CONCLUSION

In summary, by means of the dynamic kinetic transformation of $HPAr^1Ar^2$, a catalytic asymmetric alkylation was achieved, which furnished a variety of *P*-chiral phosphines in moderate to high yields with moderate to high enantioselectivity. Various electrophiles, such as allyl bromides, propargyl bromide, benzyl bromides, and alkyl iodides, served as appropriate substrates, and 11 secondary phosphines were found as suitable pronucleophiles. Moreover, the present reaction was successfully extended to double alkylation and triple alkylation with the corresponding products generated in moderate diastereoselectivity and excellent enantioselectivity. Control experiments suggested that bulky HPPhMes exhibited weak competitive coordinating ability toward the Cu(I)-bisphosphine complex and thus stoichiometric $HPAr^1Ar^2$ did not have a significant disturbing effect on the asymmetric induction in the present alkylation. Lastly, several produced chiral phosphines worked as wonderful ligands to copper(I) salts, which provided three structurally diversified chiral copper(I) complexes. Further efforts on the development of catalytic asymmetric alkylation of HPRAr (R = alkyl) and the application of the produced *P*-chiral phosphines in asymmetric catalysis with transition metals are in progress.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c04112.

Experimental procedures, characterizations, and analytical data of new compounds, X-ray diffraction data for **3af**, **7ah**, **16**, **17**, and **18**, and spectra of NMR and HPLC for new compounds (PDF)

### Accession Codes

CCDC 2020486, 2020488, 2020490, 2021216, and 2025208 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, UK; fax: +44 1223 336033.



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### Notes

The authors declare no competing financial interest.

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## REFERENCES


(1) Grabulosa, A. *P-Stereogenic Ligands in Enantioselective Catalysis*; RSC Publishing: Cambridge, 2011.

(2) Dutartre, M.; Bayardon, J.; Jugé, S. Applications and Stereoselective Synthesis of P-Chirogenic Phosphorus Compounds. *Chem. Soc. Rev.* **2016**, *45*, 5771−5794.

(3) Cui, Y.-M.; Lin, Y.; Xu, L.-W. Catalytic Synthesis of Chiral Organoheteroatom Compounds of Silicon, Phosphorus, and Sulfur via Asymmetric Transition Metal-Catalyzed C−H Functionalization. *Coord. Chem. Rev.* **2017**, *330*, 37−52.

(4) Xu, G.; Senanayake, C. H.; Tang, W. P-Chiral Phosphorus Ligands Based on a 2,3-Dihydrobenzo[*d*][1,3]oxaphosphole Motif for Asymmetric Catalysis. *Acc. Chem. Res.* **2019**, *52*, 1101−1112.

(5) Lemouzy, S.; Giordano, L.; Hérault, D.; Buono, G. Introducing Chirality at Phosphorus Atoms: An Update on the Recent Synthetic Strategies for the Preparation of Optically Pure P-Stereogenic Molecules. *Eur. J. Org. Chem.* **2020**, *2020*, 3351−3366.

(6) Zhu, R.-Y.; Liao, K.; Yu, J.-S.; Zhou, J. Recent Advances in Catalytic Asymmetric Synthesis of *P*-Chiral Phosphine Oxides. *Huaxue Xuebao* **2020**, *78*, 193−216.

(7) Glueck, D. S. Catalytic Asymmetric Synthesis of P-Stereogenic Phosphines: Beyond Precious Metals. *Synlett* **2021**, *32*, 875−884.

(8) Nishida, G.; Noguchi, K.; Hirano, M.; Tanaka, K. Enantioselective Synthesis of P-Stereogenic Alkynylphosphine Oxides by Rh-Catalyzed [2 + 2+2] Cycloaddition. *Angew. Chem., Int. Ed.* **2008**, *47*, 3410−3413.

(9) Harvey, J. S.; Malcolmson, S. J.; Dunne, K. S.; Meek, S. J.; Thompson, A. L.; Schrock, R. R.; Hoveyda, A. H.; Gouverneur, V. Enantioselective Synthesis of P-Stereogenic Phosphinates and Phosphine Oxides by Molybdenum-Catalyzed Asymmetric Ring-Closing Metathesis. *Angew. Chem., Int. Ed.* **2009**, *48*, 762−766.

(10) Du, Z.-J.; Guan, J.; Wu, G.-J.; Xu, P.; Gao, L.-X.; Han, F.-S. Pd(II)-Catalyzed Enantioselective Synthesis of P-Stereogenic Phosphinamides via Desymmetric C-H Arylation. *J. Am. Chem. Soc.* **2015**, *137*, 632−635.

(11) Lin, Z.-Q.; Wang, W.-Z.; Yan, S.-B.; Duan, W.-L. Palladium-Catalyzed Enantioselective C-H Arylation for the Synthesis of P-Stereogenic Compounds. *Angew. Chem., Int. Ed.* **2015**, *54*, 6265−6269.

(12) Xu, G.; Li, M.; Wang, S.; Tang, W. Efficient Synthesis of *P*-Chiral Biaryl Phosphonates by Stereoselective Intramolecular Cyclization. *Org. Chem. Front.* **2015**, *2*, 1342−1345.

(13) Sun, Y.; Cramer, N. Rhodium(III)-Catalyzed Enantiotopic C−H Activation Enables Access to *P*-Chiral Cyclic Phosphinamides. *Angew. Chem., Int. Ed.* **2017**, *56*, 364−367.

(14) Jang, Y.-S.; Dieckmann, M.; Cramer, N. Cooperative Effects between Chiral $Cp^x$−Iridium(III) Catalysts and Chiral Carboxylic Acids in Enantioselective C−H Amidations of Phosphine Oxides. *Angew. Chem., Int. Ed.* **2017**, *56*, 15088−15092.

(15) Wang, Z.; Hayashi, T. Rhodium-Catalyzed Enantioposition-Selective Hydroarylation of Divinylphosphine Oxides with Aryl Boroxines. *Angew. Chem., Int. Ed.* **2018**, *57*, 1702−1706.

(16) Jang, Y.-S.; Woźniak, Ł.; Pedroni, J.; Cramer, N. Access to *P*- and Axially Chiral Biaryl Phosphine Oxides by Enantioselective $Cp^xIr^{III}$-Catalyzed C−H Arylations. *Angew. Chem., Int. Ed.* **2018**, *57*, 12901−12905.

(17) Sun, Y.; Cramer, N. Tailored Trisubstituted Chiral $Cp^xRh^{III}$ Catalysts for Kinetic Resolutions of Phosphinic Amides. *Chem. Sci.* **2018**, *9*, 2981−2985.

(18) Zheng, Y.; Guo, L.; Zi, W. Enantioselective and Regioselective Hydroetherification of Alkynes by Gold-Catalyzed Desymmetrization of Prochiral Phenols with P-Stereogenic Centers. *Org. Lett.* **2018**, *20*, 7039−7043.

(19) Zhang, Y.; Zhang, F.; Chen, L.; Xu, J.; Liu, X.; Feng, X. Asymmetric Synthesis of *P*-Stereogenic Compounds via Thulium-(III)-Catalyzed Desymmetrization of Dialkynylphosphine Oxides. *ACS Catal.* **2019**, *9*, 4834−4840.

(20) Fernández-Pérez, H.; Vidal-Ferran, A. Stereoselective Catalytic Synthesis of *P*-Stereogenic Oxides via Hydrogenative Kinetic Resolution. *Org. Lett.* **2019**, *21*, 7019−7023.

(21) Li, Z.; Lin, Z.-Q.; Yan, C.-G.; Duan, W.-L. Pd-Catalyzed Asymmetric C−H Bond Activation for the Synthesis of P-Stereogenic Dibenzophospholes. *Organometallics* **2019**, *38*, 3916−3920.

(22) Zhu, R.-Y.; Chen, L.; Hu, X.-S.; Zhou, F.; Zhou, J. Enantioselective Synthesis of *P*-Chiral Tertiary Phosphine Oxides with an Ethynyl Group *via* Cu(I)-Catalyzed Azide−Alkyne Cycloaddition. *Chem. Sci.* **2020**, *11*, 97−106.

(23) Huang, Z.; Huang, X.; Li, B.; Mou, C.; Yang, S.; Song, B.-A.; Chi, Y. R. Access to P-Stereogenic Phosphinates via N-Heterocyclic Carbene-Catalyzed Desymmetrization of Bisphenols. *J. Am. Chem. Soc.* **2016**, *138*, 7524−7527.

(24) Yang, G.-H.; Li, Y.; Li, X.; Cheng, J.-P. Access to P-Chiral Phosphine Oxides by Enantioselective Allylic Alkylation of Bisphenols. *Chem. Sci.* **2019**, *10*, 4322−4327.

(25) Zhang, Y.; He, H.; Wang, Q.; Cai, Q. Asymmetric Synthesis of Chiral P-Stereogenic Triaryl Phosphine Oxides via Pd-Catalyzed

Kinetic Arylation of Diaryl Phosphine Oxides. *Tetrahedron Lett.* **2016**, *57*, 5308−5311.
(26) Dai, Q.; Li, W.; Li, Z.; Zhang, J. P-Chiral Phosphines Enabled by Palladium/Xiao-Phos-Catalyzed Asymmetric P-C Cross-Coupling of Secondary Phosphine Oxides and Aryl Bromides. *J. Am. Chem. Soc.* **2019**, *141*, 20556−20564.
(27) Qiu, H.; Dai, Q.; He, J.; Li, W.; Zhang, J. Access to *P*-Chiral *sec*- and *tert*-Phosphine Oxides Enabled by Le-Phos-Catalyzed Asymmetric Kinetic Resolution. *Chem. Sci.* **2020**, *11*, 9983−9988.
(28) Dai, Q.; Liu, L.; Qian, Y.; Li, W.; Zhang, J. Construction of P-Chiral Alkenylphosphine Oxides through Highly Chemo-, Regio-, and Enantioselective Hydrophosphinylation of Alkynes. *Angew. Chem., Int. Ed.* **2020**, *59*, 20645−20650.
(29) For a catalytic asymmetric kinetic resolution of ethyl phenylphosphinate, see: Yang, Z.; Gu, X.; Han, L.-B.; Wang, J. Palladium-Catalyzed Asymmetric Hydrophosphorylation of Alkynes: Facile Access to *P*-Stereogenic Phosphinates. *Chem. Sci.* **2020**, *11*, 7451−7455.
(30) Liu, X.-T.; Zhang, Y.-Q.; Han, X.-Y.; Sun, S.-P.; Zhang, Q.-W. Ni-Catalyzed Asymmetric Allylation of Secondary Phosphine Oxides. *J. Am. Chem. Soc.* **2019**, *141*, 16584−16589.
(31) Moncarz, J. R.; Laritcheva, N. F.; Glueck, D. S. Palladium-Catalyzed Asymmetric Phosphination: Enantioselectivie Synthesis of a P-Chirogenic Phosphine. *J. Am. Chem. Soc.* **2002**, *124*, 13356−13357.
(32) Korff, C.; Helmchen, G. Preparation of Chiral Triarylphosphines by Pd-Catalysed Asymmetric P−C Cross-Coupling. *Chem. Commun.* **2004**, 530−531.
(33) Blank, N. F.; Moncarz, J. R.; Brunker, T. J.; Scriban, C.; Anderson, B. J.; Amir, O.; Glueck, D. S.; Zakharov, L. N.; Golen, J. A.; Incarvito, C. D.; Rheingold, A. L. Palladium-Catalyzed Asymmetric Phosphination. Scope, Mechanism, and Origin of Enantioselectivity. *J. Am. Chem. Soc.* **2007**, *129*, 6847−6858.
(34) Chan, V. S.; Bergman, R. G.; Toste, F. D. Pd-Catalyzed Dynamic Kinetic Enantioselective Arylation of Silylphosphines. *J. Am. Chem. Soc.* **2007**, *129*, 15122−15123.
(35) Brunker, T. J.; Anderson, B. J.; Blank, N. F.; Glueck, D. S.; Rheingold, A. L. Enantioselective Synthesis of P-Stereogenic Benzophospholanes via Palladium-Catalyzed Intramolecular Cyclization. *Org. Lett.* **2007**, *9*, 1109−1112.
(36) Anderson, B. J.; Guino-o, M. A.; Glueck, D. S.; Golen, J. A.; DiPasquale, A. G.; Liable-Sands, L. M.; Rheingold, A. L. Platinum-Catalyzed Enantioselective Tandem Alkylation/Arylation Phosphines. Asymmetric Synthesis of Primary P-Stereogenic 1-Phosphaacenaphthenes. *Org. Lett.* **2008**, *10*, 4425−4428.
(37) Beaud, R.; Phipps, R. J.; Gaunt, M. J. Enantioselective Cu-Catalyzed Arylation of Secondary Phosphine Oxides with Diaryliodonium Salts toward the Synthesis of P-Chiral Phosphines. *J. Am. Chem. Soc.* **2016**, *138*, 13183−13186.
(38) Scriban, C.; Kovacik, I.; Glueck, D. S. A Protic Additive Suppresses Formation of Byproducts in Platinum-Catalyzed Hydrophosphination of Activated Olefins. Evidence for P-C and C-C Bond Formation by Michael Addition. *Organometallics* **2005**, *24*, 4871−4874.
(39) Huang, Y.; Pullarkat, S. A.; Li, Y.; Leung, P.-H. Palladacycle-Catalyzed Asymmetric Hydrophosphination of Enones for Synthesis of C*- and P*-Chiral Tertiary Phosphines. *Inorg. Chem.* **2012**, *51*, 2533−2540.
(40) Li, C.; Bian, Q.-L.; Xu, S.; Duan, W.-L. Palladium-Catalyzed 1,4-Addition of Secondary Alkylphenylphosphines to $\alpha,\beta$-Unsaturated Carbonyl Compounds for the Synthesis of Phosphorus- and Carbon-Stereogenic Compounds. *Org. Chem. Front.* **2014**, *1*, 541−545.
(41) Song, Y.-C.; Dai, G.-F.; Xiao, F.; Duan, W.-L. Palladium-Catalyzed Enantioselective Hydrophosphination of Enones for the Synthesis of Chiral P,N-Compounds. *Tetrahedron Lett.* **2016**, *57*, 2990−2993.
(42) Teo, R. H. X.; Chen, H. J.; Li, Y.; Pullarkat, S. A.; Leung, P.-H. Asymmetric Catalytic 1,2-Dihydrophosphination of Secondary 1,2-Diphosphines − Direct Access to Free *P**- and *P*,*C*-Diphosphines. *Adv. Synth. Catal.* **2020**, *362*, 2373−2378.
(43) Yue, W.-J.; Xiao, J.-Z.; Zhang, S.; Yin, L. Rapid Synthesis of Chiral 1,2-Bisphosphine Derivatives through Copper(I)-Catalyzed Asymmetric Conjugate Hydrophosphination. *Angew. Chem., Int. Ed.* **2020**, *59*, 7057−7062.
(44) Li, Y.-B.; Tian, H.; Yin, L. Copper(I)-Catalyzed Asymmetric 1,4-Conjugate Hydrophosphination of $\alpha,\beta$-Unsaturated Amides. *J. Am. Chem. Soc.* **2020**, *142*, 20098−20106.
(45) Huang, Y.; Li, Y.; Leung, P.-H.; Hayashi, T. Asymmetric Synthesis of *P*-Stereogenic Diarylphosphinites by Palladium-Catalyzed Enantioselective Addition of Diarylphosphines to Benzoquinones. *J. Am. Chem. Soc.* **2014**, *136*, 4865−4868.
(46) Chan, V. S.; Stewart, I. C.; Bergman, R. G.; Toste, F. D. Asymmetric Catalytic Synthesis of *P*-Stereogenic Phosphines via a Nucleophilic Ruthenium Phosphide Complex. *J. Am. Chem. Soc.* **2006**, *128*, 2786−2787.
(47) Chan, V. S.; Chiu, M.; Bergman, R. G.; Toste, F. D. Development of Ruthenium Catalysts for the Enantioselective Synthesis of P-Stereogenic Phosphines via Nucleophilic Phosphido Intermediates. *J. Am. Chem. Soc.* **2009**, *131*, 6021−6032.
(48) Scriban, C.; Glueck, D. S. Platinum-Catalyzed Asymmetric Alkylation of Secondary Phosphines: Enantioselective Synthesis of P-Stereogenic Phosphines. *J. Am. Chem. Soc.* **2006**, *128*, 2788−2789.
(49) Scriban, C.; Glueck, D. S.; Golen, J. A.; Rheingold, A. L. Platinum-Catalyzed Asymmetric Alkylation of a Secondary Phosphine: Mechanism and Origin of Enantioselectivity. *Organometallics* **2007**, *26*, 1788−1800.
(50) Anderson, B. J.; Glueck, D. S.; DiPasquale, A. G.; Rheingold, A. L. Substrate and Catalyst Screening in Platinum-Catalyzed Asymmetric Alkylation of Bis(secondary) Phosphines. Synthesis of an Enantiomerically Pure $C_2$-Symmetric Diphosphine. *Organometallics* **2008**, *27*, 4992−5001.
(51) Chapp, T. W.; Glueck, D. S.; Golen, J. A.; Moore, C. E.; Rheingold, A. L. Platinum-Catalyzed Asymmetric Alkylation of Bis(isitylphosphino)ethane: Stereoselectivity Reversal in Successive Formation of Two P−C Bonds. *Organometallics* **2010**, *29*, 378−388.
(52) Chapp, T. W.; Schoenfeld, A. J.; Glueck, D. S. Effects of Linker Length on the Rate and Selectivity of Platinum-Catalyzed Asymmetric Alkylation of the Bis(isitylphosphino)alkanes IsHP$(CH_2)_n$PHIs (Is = 2,4,6-($i$-Pr)$_3$C$_6$H$_2$, $n$ = 1−5). *Organometallics* **2010**, *29*, 2465−2473.
(53) Anderson, B. J.; Reynolds, S. C.; Guino-o, M. A.; Xu, Z.; Glueck, D. S. Effect of Linker Length on Selectivity and Cooperative Reactivity in Platinum-Catalyzed Asymmetric Alkylation of Bis(phenylphosphino)alkanes. *ACS Catal.* **2016**, *6*, 8106−8114.
(54) Li, C.; Li, W.; Xu, S.; Duan, W. Pd-Catalyzed Asymmetric Alkylation of Methylphenylphosphine with Alkyl Halides for the Synthesis of P-Stereogenic Compounds. *Youji Huaxue* **2013**, *33*, 799−802.
(55) Wang, C.; Huang, K.; Ye, J.; Duan, W.-L. Asymmetric Synthesis of P-Stereogenic Secondary Phosphine-Boranes by an Unsymmetric Bisphosphine Pincer-Nickel Complex. *J. Am. Chem. Soc.* **2021**, *143*, 5685−5690.
(56) Lebel, H.; Morin, S.; Paquet, V. Alkylation of Phosphine Boranes by Phase-Transfer Catalysis. *Org. Lett.* **2003**, *5*, 2347−2349.
(57) Toda, Y.; Pink, M.; Johnston, J. N. Brønsted Acid Catalyzed Phosphoramidic Acid Additions to Alkenes: Diastereo- and Enantioselective Halogenative Cyclizations for the Synthesis of *C*- and *P*-Chiral Phosphoramidates. *J. Am. Chem. Soc.* **2014**, *136*, 14734−14737.
(58) Lim, K. M.-H.; Hayashi, T. Dynamic Kinetic Resolution in Rhodium-Catalyzed Asymmetric Arylation of Phospholene Oxides. *J. Am. Chem. Soc.* **2017**, *139*, 8122−8125.
(59) Trost, B. M.; Spohr, S. M.; Rolka, A. B.; Kalnmals, C. A. Desymmetrization of Phosphinic Acids via Pd-Catalyzed Asymmetric Allylic Alkylation: Rapid Access to *P*-Chiral Phosphinates. *J. Am. Chem. Soc.* **2019**, *141*, 14098−14103.
(60) Laitar, D. S. Synthetic and Catalytic Studies of Group 11 N-Heterocyclic carbene complexes. Ph.D. Thesis, MIT, 2006.
(61) Fortman, G. C.; Slawin, A. M. Z.; Nolan, S. P. A Versatile Cuprous Synthon: [Cu(IPr)(OH)] (IPr = 1,3 bis-


https://doi.org/10.1021/jacs.1c04112
J. Am. Chem. Soc. 2021, 143, 9912−9921

(diisopropylphenyl)imidazol-2-ylidene). *Organometallics* **2010**, *29*, 3966−3972.
(62) Najafabadi, B. K.; Corrigan, J. F. Enhanced Thermal Stability of Cu-Silylphosphido Complexes via NHC Ligation. *Dalton Trans.* **2015**, *44*, 14235−14241.
(63) Wang, G.; Gibbons, S. K.; Glueck, D. S.; Sibbald, C.; Fleming, J. T.; Higham, L. J.; Rheingold, A. L. Copper−Phosphido Intermediates in Cu(IPr)-Catalyzed Synthesis of 1-Phosphapyracenes via Tandem Alkylation/Arylation of Primary Phosphines. *Organometallics* **2018**, *37*, 1760−1772.
(64) Gibbons, S. K.; Valleau, C. R. D.; Peltier, J. L.; Cain, M. F.; Hughes, R. P.; Glueck, D. S.; Golen, J. A.; Rheingold, A. L. Diastereoselective Coordination of P-Stereogenic Secondary Phosphines in Copper(I) Chiral Bis(phosphine) Complexes: Structure, Dynamics, and Generation of Phosphido Complexes. *Inorg. Chem.* **2019**, *58*, 8854−8865.
(65) Horsley Downie, T. M.; Hall, J. W.; Collier Finn, T. P.; Liptrot, D. J.; Lowe, J. P.; Mahon, M. F.; McMullin, C. L.; Whittlesey, M. K. The First Ring-Expanded NHC−Copper(I) Phosphides as Catalysts in the Highly Selective Hydrophosphination of Isocyanates. *Chem. Commun.* **2020**, *56*, 13359−13362.
(66) Glueck, D. S. Metal-Catalyzed Nucleophilic Carbon−Heteroatom (C−X) Bond Formation: the Role of M−X Intermediates. *Dalton Trans.* **2008**, 5276−5286.
(67) For a nonenantioselective reaction, see: Cain, M. F.; Hughes, R. P.; Glueck, D. S.; Golen, J. A.; Moore, C. E.; Rheingold, A. L. Synthesis and Structure of Intermediates in Copper-Catalyzed Alkylation of Diphenylphosphine. *Inorg. Chem.* **2010**, *49*, 7650−7662.
(68) As far as we know, the Glueck group is also working on the copper(I)-catalyzed asymmeric alkylation of HPPhR, and some very preliminary results were described in a Ph.D. Thesis. See: Gibbons, S. K. Catalytic Asymmetric P−C Bond Formation Via Chiral Copper(I)- or Nickel(II)-Phosphido Complexes. Ph.D. Thesis, Dartmouth College, 2019.
(69) Due to Barton's base's excellent performance in our previous two reactions (copper(I)-catalyzed asymmetric additions of diarylphosphines to $\alpha,\beta$-unsaturated phosphine sulfides and to $\alpha,\beta$-unsaturated amides), it was used as the catalytic base in the present reaction.
(70) For the ease of manipulation in purification and analysis, tertiary phosphines were oxidized by $S_8$ to the corresponding phosphine sulfides.
(71) Secondary phosphines, such as HPMePh and HP$^i$PrPh, were studied in the present allylation with allyl bromide (**2a**). However, racemic products were afforded in high yields, indicating that a new catalytic system is required.
(72) Berrisford, D. J.; Bolm, C.; Sharpless, K. B. Ligand-Accelerated Catalysis. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1059−1070.
(73) Kazmaier, U. Transition Metal Catalyzed Enantioselective Allylic Substitution in Organic Synthesis. *Top. Organomet. Chem.* **2012**, *38*, 1−340.
(74) Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pàmies, O.; Diéguez, M. Enantioselective Copper-Catalyzed Conjugate Addition and Allylic Substitution Reactions. *Chem. Rev.* **2008**, *108*, 2796−2823.
(75) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. Catalytic Asymmetric Conjugate Addition and Allylic Alkylation with Grignard Reagents. *Chem. Rev.* **2008**, *108*, 2824−2852.
(76) Falciola, C. A.; Alexakis, A. Copper-Catalyzed Asymmetric Allylic Alkylation. *Eur. J. Org. Chem.* **2008**, *2008*, 3765−3780.
(77) Geurts, K.; Fletcher, S. P.; van Zijl, A. W.; Minnaard, A. J.; Feringa, B. L. Copper-Catalyzed Asymmetric Allylic Substitution Reactions with Organozinc and Grignard Reagents. *Pure Appl. Chem.* **2008**, *80*, 1025−1037.
(78) Alexakis, A.; Krause, N.; Woodward, S. *Copper-Catalyzed Asymmetric Synthesis*; Wiley-VCH: Weinheim, 2014.


https://doi.org/10.1021/jacs.1c04112
*J. Am. Chem. Soc.* 2021, 143, 9912−9921