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Synthesis of chiral phosphine derivatives through a copper(I)-catalyzed desymmetric S_NAr reaction

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Axially chiral phosphines are a class of extremely important ligands in asymmetric catalysis. Herein, an unprecedented copper (I)-catalyzed asymmetric S_NAr reaction with $HP(S)R_2$ is uncovered, which delivers a series of axially chiral phosphine derivatives in high yields with excellent enantioselectivity. Furthermore, the diastereoselective reaction with the kinetic resolution of racemic HP(S)ArR proceeds smoothly, providing the products with moderate diastereoselectivity and excellent enantioselectivity. Control experiments indicate that $HP(S)Ph_2$ is much more active than $HPPh_2$ and $HP(O)Ph_2$ as the pronucleophile in the present reaction. It is found that the S_NAr reaction (the first S_NAr) proceeds in a desymmetric manner, providing the desired chiral products while a continued S_NAr reaction (the second S_NAr) slightly occurs in a kinetic resolution manner in the present catalytic system, which enhances the ee of the desired chiral products. DFT calculations support a concerted reaction pathway rather than a step-wise mechanism. Finally, axially chiral olefin-phosphines produced by the present method work as suitable ligands in Pd-catalyzed asymmetric allylic substitution with *C*-, *N*-, and *O*-nucleophiles and Rh-catalyzed asymmetric addition of arylboronic acid to benzil.

asymmetric catalysis, S_NAr reaction, copper catalysis, axially chiral phosphine, desymmetrization

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1 Introduction

Chiral phosphines are indispensable compounds in organic synthesis as phosphine-based ligands serve as one of the most important ancillary weapons in asymmetric transition-metal catalysis [1]. Moreover, chiral phosphines and their oxides are identified as powerful catalysts in asymmetric organocatalysis [2]. Therefore, significant efforts have been devoted to developing efficient synthetic methods for diversified chiral phosphines. Aside from the traditional methods that rely on the stoichiometric amount of chiral auxiliaries or the optical resolution of pre-formed racemates, asymmetric catalysis with the formation of C–P bond has been emerging as an important complementary tool for the synthesis of chiral phosphines and their close derivatives [3]. However, reported methods mainly focus on the synthesis of phosphines or their derivatives bearing carbon or phosphorus, or both stereogenic centers (Scheme 1a) [3].

Among chiral phosphines, axially chiral ones, such as

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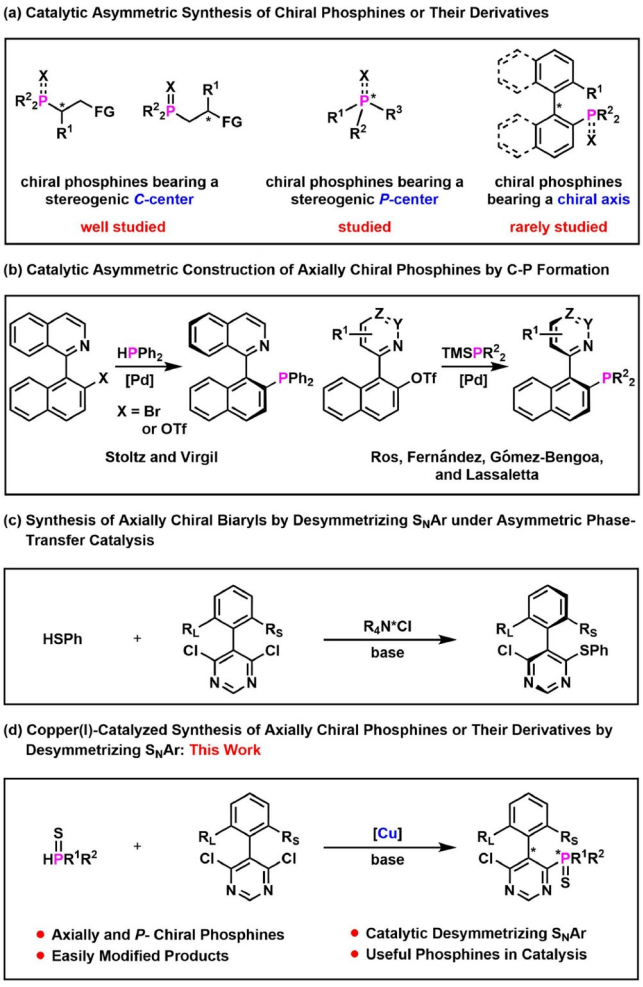


Scheme 1 (Color online) Introduction and our catalytic desymmetric S_NAr reaction.

QUINAP, TOL-BINAP, and DTBM-SEGPHOS are extremely important due to their excellent performances in asymmetric transition-metal catalysis partly caused by the rigid axial skeletons. Recently, there has been considerable research interest in the catalytic asymmetric synthesis of axially chiral compounds, especially biaryl-type compounds [4]. Four strategies have been employed for the synthesis of axially chiral biaryls, including atroposelective transformation of pre-formed biaryls, atroposelective coupling, aromatic ring construction, and central-to-axial chirality transfer [5]. The first strategy comprises desymmetrization, kinetic resolution (KR), dynamic kinetic resolution (DKR), and dynamic kinetic asymmetric transformation (DYKAT) [5].

Among these methods, catalytic atroposelective synthesis of chiral phosphines bearing a biaryl skeleton through the construction C–P bond is particularly noteworthy. In 2013, Stoltz, Virgil, and co-workers [6a] prepared chiral QUINAP *via* KR by a Pd-catalyzed atroposelective C–P coupling reaction. Meanwhile, they synthesized chiral QUINAP *via* DKR in both high yield and high enantioselectivity (Scheme 1b) [6a]. Later, the method was nicely extended to the atroposelective synthesis of chiral PINAP [6b]. In 2016, based on their previous research on Pd-catalyzed dynamic kinetic C–C and C–N cross-couplings [7], Ros, Fernández, Gómez-Bengoa, Lassaletta, and co-workers [8] investigated a Pd-catalyzed atroposelective C–P coupling reaction in detail and disclosed a DYKAT pathway rather than a DKR pathway (Scheme 1b). Except for these notable examples [6,8], the catalytic asymmetric construction of axially chiral phosphines by C–P formation through atroposelective transformation of pre-installed biaryls is rarely achieved [9].

Nucleophilic aromatic substitutions (S_NAr) are a class of reactions of fundamental importance in organic synthesis, which is known for the proposed simple two-step addition-elimination mechanism [10]. Although significant research efforts have been put into this field, catalytic asymmetric variants of S_NAr were much less explored. It was not until recently that some catalytic asymmetric S_NAr reactions were disclosed based on asymmetric organocatalysis with limited nucleophiles [11–15]. Among these achievements, a catalytic enantioselective synthesis of atropisomeric biaryls through desymmetric S_NAr was particularly noteworthy, which was disclosed by Smith and co-workers [17] (Scheme 1c). However, transition metal-catalyzed asymmetric S_NAr remains elusive, which would significantly broaden the scope of nucleophiles. Herein, by means of the desymmetrization method [16,17], an unprecedented copper(I)-catalyzed asymmetric S_NAr with $HP(S)R^1R^2$ is uncovered, which affords either axially chiral or both axially-chiral and *P*-chiral phosphine derivatives in excellent enantioselectivity (Scheme 1d). More importantly, the produced atropisomeric phosphine has proved to be an appropriate chiral ligand in transition-metal catalysis.

2 Experimental

General information, optimization results, general procedures, mechanism studies, characterization data, nuclear magnetic resonance (NMR) spectra and high resolution mass spectrometer (HRMS) data are listed in the Supporting Information online.

3 Results and discussion

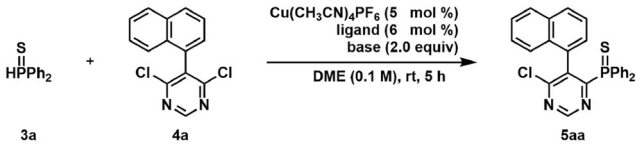
3.1 Optimization of the reaction conditions

Based on our previous experiences on copper(I)-catalyzed asymmetric synthesis of chiral phosphines and aminophosphinites with $HPAr^1Ar^2$ [3g,18], the S_NAr reaction of $HPPh_2$ (**1a**) and biaryl **4a** [14a] was set up initially in the presence of 5 mol% copper(I)-bisphosphine complex and 2 equiv. Cs_2CO_3 at room temperature. However, screening of com-

mercially available bisphosphine ligands was unfruitful as the highest ee was less than 20%. It was possibly due to the decomposition of the catalytically active copper(I)-bisphosphine complex caused by the stoichiometric $HPPh_2$ or the semi-stoichiometric product through competitive complexation in the present catalytic system. Then both $HP(O)Ph_2$ (**2a**) and $HP(S)Ph_2$ (**3a**) were supposed to be candidates for $HPPh_2$. Considering the potential "soft-soft" interaction between the sulfur atom and copper(I)-bisphosphine complex [18a,19], which might result in the decrease of the pK_a, $HP(S)Ph_2$ was employed as the pronucleophile for further optimization.

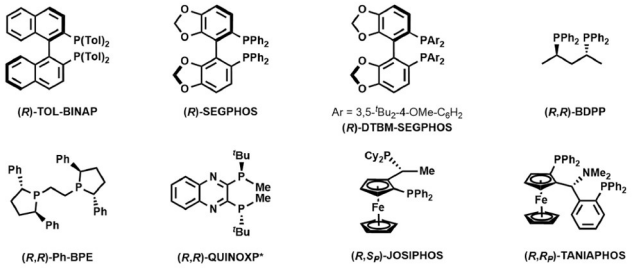
As shown in Table 1, in the presence of 5 mol% $Cu(CH_3CN)_4PF_6$, 6 mol% (*R*)-TOL-BINAP, and 2.0 equiv. K_2CO_3, the desired S_NAr product **5aa** was obtained in 49% yield with 32% ee at room temperature in dimethoxyethane (DME) in 5 h (entry 1). A second S_NAr reaction also occurred to give double S_NAr product in a 30% yield. Moreover, 18% **4a** was recovered. Screening of several common bisphosphines identified (*R*,*R*)-Ph-BPE and (*R*,R_P)-TANIAPHOS as suitable ligands in terms of enantioselectivity (entries 2–8). In view of the slightly superior performance of asymmetric induction, (*R*,R_P)-TANIAPHOS was employed for further optimization. Then several common bases were investigated (entries 9–11). Cs_2CO_3 was proved to be unsuitable due to the significantly decreased enantioselectivity (14% ee, entry 9). Evidently, the background reaction occurred significantly, which was caused by the superior basicity of Cs_2CO_3. Moreover, the second S_NAr reaction occurred to give the undesired product in 51% yield. K_3PO_4 was less basic than Cs_2CO_3 and the reaction with K_3PO_4 afforded **5aa** in 56% yield with 88% ee (entry 10). Et_3N was found to be as good as K_2CO_3 as the base (entry 11). As shown in entry 12, the reaction quenched in 3.5 h led to **5aa** in 84% yield with 98% ee. Evidently, the yield is higher than the reaction in entry 8 while the enantioselectivity is slightly lower. The reaction quenched in 4.5 h furnished **5aa** in 79% yield with >99% ee (entry 13). It is concluded that a longer reaction time is beneficial for the second S_NAr reaction, which is a kinetic resolution process. Fortunately, the second S_NAr reaction is helpful for getting higher ee for **5aa**. Clearly, excessive **3a** would benefit the second S_NAr reaction. Therefore, the amount of **3a** was reduced from 1.5 equiv. to 1.1 equiv. As given in entry 14, **5aa** was generated in 94% yield with >99% ee. Then the catalyst loading was successfully decreased to 3 mol% with constant reaction results (entry 15).

Table 1 Optimization of the reaction conditions[a]



entry	ligand	base	yield[b]	ee[c]	double S_NAr[b]	Remaining 4a[b]
1	(*R*)-TOL-BINAP	K_2CO_3	49%	-32%	30%	18%
2	(*R*)-SEGPHOS	K_2CO_3	48%	-65%	36%	13%
3	(*R*)-DTBM-SEGPHOS	K_2CO_3	43%	-22%	27%	25%
4	(*R*,*R*)-BDPP	K_2CO_3	54%	56%	29%	16%
5	(*R*,*R*)-Ph-BPE	K_2CO_3	74%	99%	23%	2%
6	(*R*,*R*)-QUINOXP*	K_2CO_3	41%	8%	16%	34%
7	(*R*,S_P)-JOSIPHOS	K_2CO_3	53%	62%	25%	21%
8	(*R*,R_P)-TANIAPHOS	K_2CO_3	72%	>99%	28%	0%
9	(*R*,R_P)-TANIAPHOS	Cs_2CO_3	38%	14%	51%	10%
10	(*R*,R_P)-TANIAPHOS	K_3PO_4	56%	88%	36%	6%
11	(*R*,R_P)-TANIAPHOS	Et_3N	77%	99%	20%	3%
12[d]	(*R*,R_P)-TANIAPHOS	K_2CO_3	84%	98%	6%	10%
13[e]	(*R*,R_P)-TANIAPHOS	K_2CO_3	79%	>99%	21%	0%
14[f]	(*R*,R_P)-TANIAPHOS	K_2CO_3	94%	>99%	6%	0%
15[f,g]	(*R*,R_P)-TANIAPHOS	K_2CO_3	94%	>99%	5%	1%

[a]**3a**: 0.15 mmol, **4a**: 0.10 mmol. [b]Determined by ^1H NMR analysis of reaction crude mixture using CH_2Br_2 as an internal standard. [c]Determined by chiral-stationary-phase HPLC analysis. [d]3.5 h. [e]4.5 h. [f]**3a**: 0.11 mmol. [g]3.0 mol % $Cu(CH_3CN)_4PF_6$ and 3.6 mol % ligand were used.

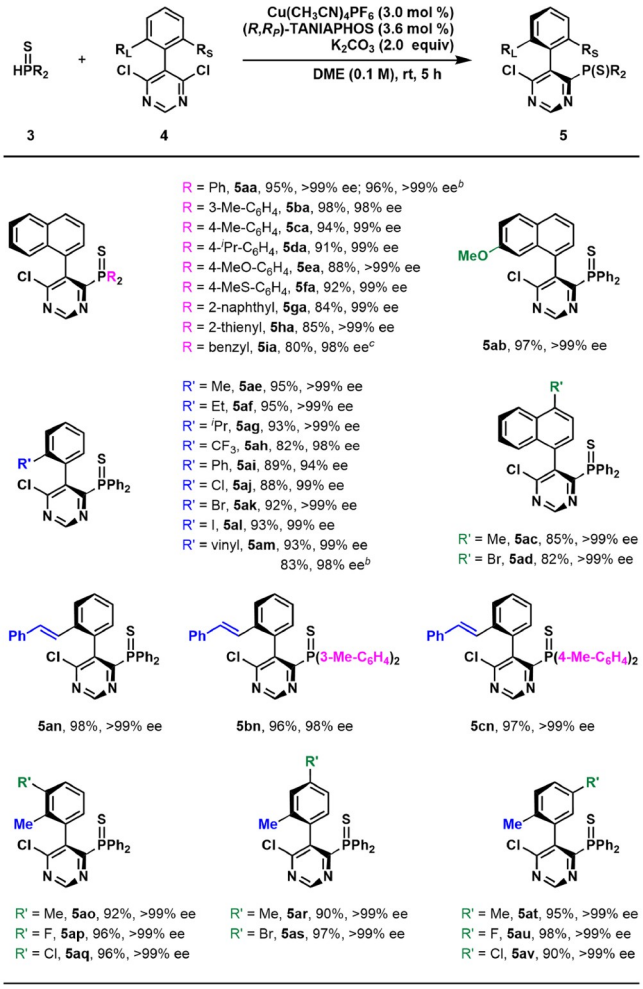


electron-rich aryls were well accepted as the corresponding products were isolated in high yields and excellent enantioselectivity (**5ba**–**5fa**, 88%–98%, 98%–>99% ee). Moreover, both the *meta*- and the *para*-substitution patterns were well tolerated in the aryl group. However, the reaction with $HP(S)(o\text{-Me-}C_6H_4)_2$ did not occur at all possibly due to the bulkiness. Unfortunately, electron-poor aryls were not suitable because of the low nucleophilicity of the generated [Cu]-$SPAr_2$ species. To our joy, both 2-naphthyl and 2-thienyl were appropriate aryl groups in diarylphosphine sulfides (**5ga**–**5ha**, 84%–85%, 99%–>99% ee). It should be noted that the adduct of di(2-thienyl)phosphine sulfide to acetone (**3h**) was used as the precursor of di(2-thienyl)phosphine sulfide as the former was easily obtained. As for dialkylphosphine sulfides, $HP(S)Cy_2$ was completely inert under the present catalytic system possibly owing to the bulky cyclohexyl group. Fortunately, the reaction of dibenzylphosphine sulfide (**3i**) occurred smoothly to deliver the product **5ia** in

3.2 Investigation of substrate scope

Under the optimized reaction conditions, the substrate scopes of both secondary phosphine sulfides (**3**) and biaryls (**4**) were investigated (Table 2). As for diarylphosphine sulfides,

Table 2 Substrate scopes[a]



[a]**3**: 0.22 mmol, **4**: 0.20 mmol. Isolated yield. Ee was determined by chiral-stationary-phase HPLC analysis. [b]Gram-scale preparation. [c]24 h.

80% yield with 98% ee in 24 h.

As for the starting biaryls (**4**), 1-naphthyls with an additional substituent, such as MeO, Me, and Br were well tolerated, which is reflected by the high yields and wonderful enantioselectivity (**5ab**–**5ad**, 82%–97%, >99% ee). Phenyls with an additional C_2-substitutent were also evaluated. Both electron-donating and electron-withdrawing substituents were acceptable in the phenyl group (**5ae**–**5an**, 82%–98%, 94%–>99% ee). Evidently, both the halogen and the alkenyl substituents on the phenyl group allow facile further functionalization of the products. Furthermore, with biaryl **4n** as the electrophile, diphenylphosphine sulfide (**3a**) was successfully varied to substituted ones (**3b** and **3c**) with decent reaction results (**5bn**–**5cn**, 96%–97%, 98%–>99% ee). Besides C_2-subsituted phenyls, $C_{2,3}$-disubstitued, $C_{2,4}$-disbustituted, and $C_{2,5}$-disbustituted phenyls served as wonderful aryl groups in the starting biaryls (**5ao**–**5av**, 90%–98%, >99% ee). Strikingly, the gram-scale preparations of both **5aa** and **5am** proceeded with almost the same reaction efficiency as the ones on a small scale. It should be noted that the dibromo-analogue of **4a′** worked equally well under the present reaction conditions to give **5aa′** in 97% yield with 99% ee (for the details, see Supporting Information online). Furthermore, the reaction of 1-(4,6-dichloropyrimidin-5-yl) isoquinoline with **3a** also proceeded, providing the corresponding product in 90% yield with 60% ee (for the details, see Supporting Information online). The absolute configuration of **5aa** was determined by X-ray crystallography and the stereochemistry of other products was assigned tentatively [20].

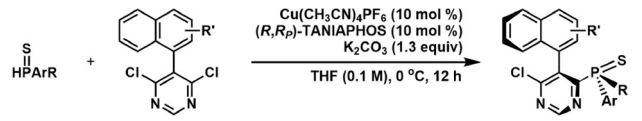
Next, the desymmetric S_NAr reaction with racemic secondary phosphine sulfides was investigated as shown in Table 3. Several reactions with HP(S)Ph^{i}Pr (**3j**) proceeded smoothly, providing the corresponding products in high yields with moderate diastereoselectivity and excellent enantioselectivity (**5ja** and **5jc**–**5jd**, 84%–89%, 5/1–7/1 dr, 97%–>99% ee), which contained both a chiral axis and a chiral phosphorus stereocenter. **3j** was successfully varied to **3k**, **3l**, and **3m** with decent results obtained (**5ka**–**5ma**, 72%–92%, 3/1–11/1 dr, 98%–99% ee). HP(S)Ph^{t}Bu was also tested. However, no reaction occurred. The moderate diastereoselectivity might be due to the less efficient resolution of racemic secondary phosphine sulfides by the chiral copper catalyst. The stereochemistry of **5jd** was determined unambiguously by means of single-crystal X-ray diffraction of its derivative **5jd′** (for the details, see Supporting Information online) [21]. The absolute configurations of other products were deduced by the structural analogy.

3.3 Control experiments

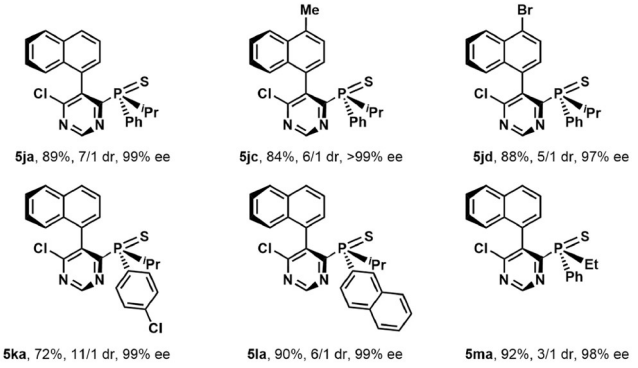
With *rac*-**5aa** as the substrate, the kinetic resolution through the second S_NAr was studied by using 0.5 equiv. **3a**. As shown in Table 4, the reaction with (R,R_P)-TANIAPHOS afforded double S_NAr product **8** in 46% conversion of *rac*-**5aa** in 5 h (entry 1). Meanwhile, **5aa** was recovered in 54% yield with 74% ee. Clearly, the kinetic resolution process was not very efficient. Several other phosphine ligands were also evaluated (entries 2–4). However, no better results were observed. It is noted that (R,R)-Ph-BPE was found to be as good as (R,R_P)-TANIAPHOS in Table 1. However, it showed inferior asymmetric induction ability for the kinetic resolution. Then by using 3.0 mol% $Cu(CH_3CN)_4PF_6$ and 3.6 mol% (R,R_P)-TANIAPHOS, the kinetic resolution provided **8** in 50% conversion of *rac*-**5aa**. 48% **5aa** was recovered in 82% ee in 12 h (entry 5). Evidently, the second S_NAr enhanced the enantioselectivity of **5aa**, which was generated in the first catalytic asymmetric S_NAr. This fact might be the reason for the excellent enantioselectivity (>99% ee) in most cases in Table 2. When 1.0 equiv. **3a** was used, the complete conversion of *rac*-**5aa** to **8** was observed in 12 h (entry 6).

Subsequently, under the optimized reaction conditions, the

Table 3 Preliminary substrate scopes on the kinetic resolution of HP(S)ArR[a]



3 4 5

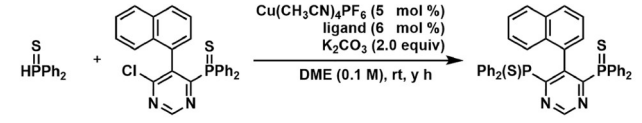


5ja, 89%, 7/1 dr, 99% ee; **5jc**, 84%, 6/1 dr, >99% ee; **5jd**, 88%, 5/1 dr, 97% ee

5ka, 72%, 11/1 dr, 99% ee; **5la**, 90%, 6/1 dr, 99% ee; **5ma**, 92%, 3/1 dr, 98% ee

[a]**3**: 0.60 mmol, **4**: 0.20 mmol. Isolated yield. Ee was determined by chiral-stationary-phase HPLC analysis.

Table 4 Kinetic resolution of *rac*-**5aa**[a]



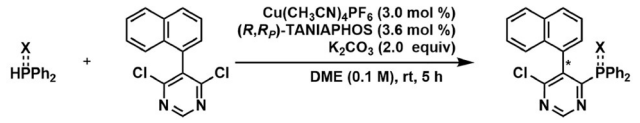
3a, x equiv *rac*-**5aa**, 1.0 equiv **8**

entry	x	y	ligand	coversion of *rac*-5aa[b]	remaining 5aa[b]
1	0.5	5	(*R*,*R*$_P$)-TANIAPHOS	46%	54% (74% ee)[c]
2	0.5	5	(*R*,*R*)-Ph-BPE	42%	53% (66% ee)[c]
3	0.5	5	(*R*,*R*)-BDPP	32%	66% (16% ee)[c]
4	0.5	5	(*R*)-SEGPHOS	48%	42% (-34% ee)[c]
5[d]	0.5	12	(*R*,*R*$_P$)-TANIAPHOS	50%	48% (82% ee)[c]
6[d]	1.0	12	(*R*,*R*$_P$)-TANIAPHOS	100%	0%

[a]*rac*-**5aa**: 0.05 mmol. [b]Determined by ^{1}H NMR analysis of reaction crude mixture using CH_2Br_2 as an internal standard. [c]Determined by chiral-stationary-phase HPLC analysis. [d]3 mol % $Cu(CH_3CN)_4PF_6$ and 3.6 mol % ligand were used.

reactions of $HPPh_2$ (**1a**) and $HP(O)Ph_2$ (**2a**) were studied (Table 5). As previously mentioned, the enantioselectivity was very low in the reaction with **1a** (entry 1). Although the enantioselectivity was moderate in the reaction with **2a** (entry 2), the yield was very low, possibly owing to the inferior nucleophilicity of the [Cu]-$OPPh_2$ species to the [Cu]-$SPPh_2$ species. A competitive experiment was more straightforward to see the performances of these phosphine reagents. As shown in Scheme 2, both **6aa** and **7aa** were not observed. Only the reactions with **3a** occurred, providing **5aa** in 78% with 96% ee and **8** in 12% yield. Furthermore, the ^{31}P NMR studies of some mixtures indicated the complexation of $Cu(CH_3CN)_4PF_6$ and $HP(S)Ph_2$ and the formation of the complex $Cu(CH_3CN)_4PF_6$-(*R*)-BINAP-$HP(S)Ph_2$ (for the details, see Supporting Information online), confirming the "soft-soft" interaction between Cu(I) and the sulfur atom. These experimental facts demonstrated the uniqueness of $HP(S)R_2$ in the present reaction.

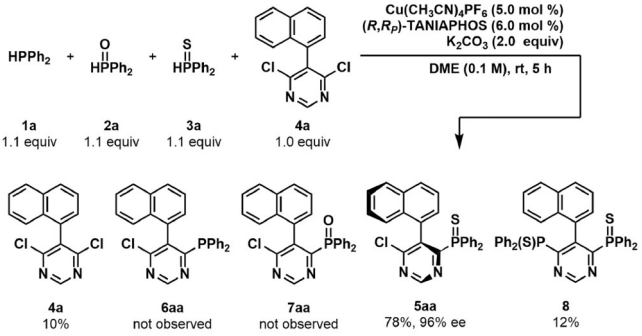
Table 5 Control experiments[a]



1a/2a/3a **4a** **6aa/7aa/5aa**

entry	X	yield[b]	ee[c]	double S_NAr[b]	Remaining 4a
1	- (1a)	12% (6aa)	4%	-	66%
2	O (2a)	8% (7aa)	48%	-	92%
3	S (3a)	94% (5aa)	>99%	5%	1%

[a]**1a**/**2a**/**3a**: 0.11 mmol, **4a**: 0.10 mmol. [b]Determined by ^{1}H NMR analysis of reaction crude mixture using CH_2Br_2 as an internal standard. [c]Determined by chiral-stationary-phase HPLC analysis.



1a 1.1 equiv; 2a 1.1 equiv; 3a 1.1 equiv; 4a 1.0 equiv

4a 10%; 6aa not observed; 7aa not observed; 5aa 78%, 96% ee; 8 12%

Scheme 2 Competitive experiment.

3.4 Investigation of the reaction mechanism by DFT calculations

The proposed mechanism is illustrated in Figure 1a. The chiral cavity in the [Cu-(*R*,*R*$_P$)-TANIAPHOS]$^+$ (**complex A**) was previously disclosed by us [22]. The coordination of **3a** and **4a** to **complex A** delivered **complex B**, which would occur deprotonation by K_2CO_3 affording **complex C** to enhance the nucleophilic attacking in the S_NAr step. In **complex C**, the Ph_2P-S-group must be on the below sites of the chiral Cu-P-P plane (the coordination modes, see Figure S1, Supporting Information online). Subsequently, an intramolecular S_NAr substitution reaction occurred in **transition state D** to furnish the major enantio-product (S_a) and regenerate the catalyst **complex A**. As the mechanism of S_NAr reaction is generally controversial [10], DFT calculations using the SMD(DME)-M06-D3/Def2tzvpp focus on the stereo-determined S_NAr process. It was found that the S_NAr process, involving the formation of the C–P bond and

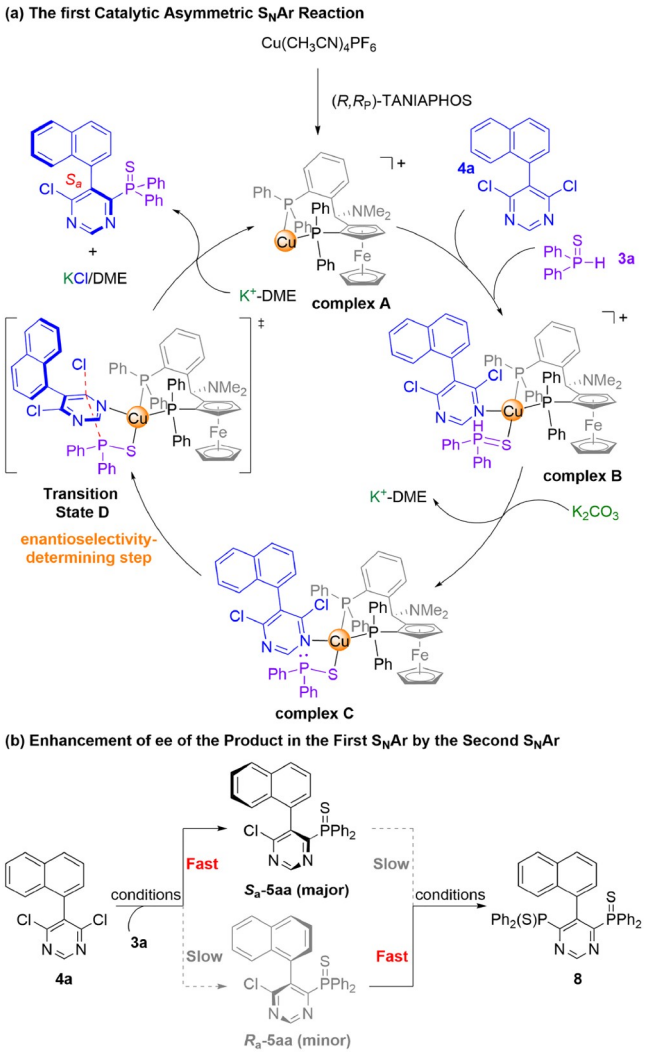


Figure 1 (Color online) Proposed reaction pathways.

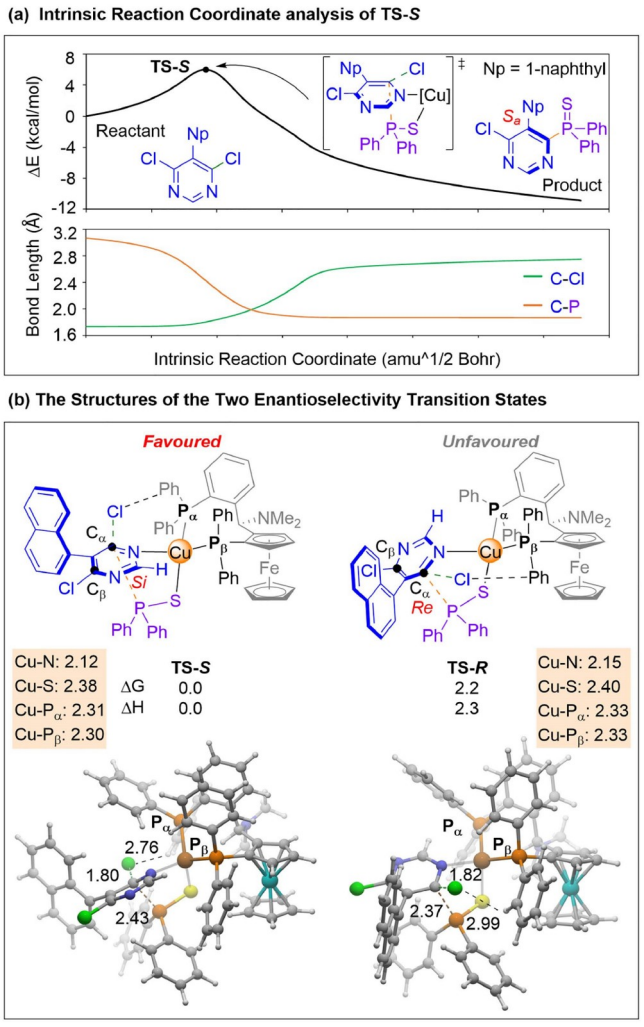


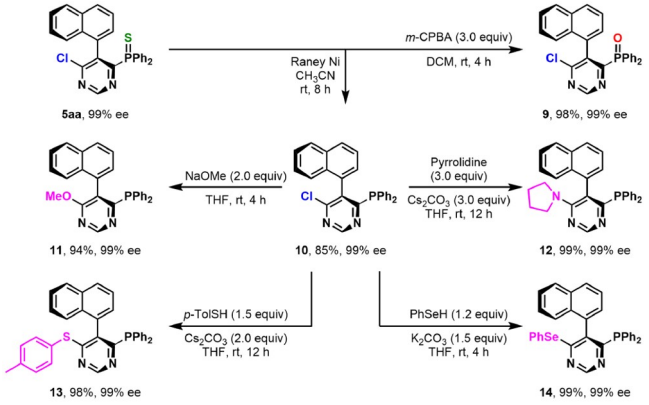
Figure 2 (Color online) (a) Potential energy (top) and bond length change (bottom) along the intrinsic reaction coordinate of TS-*S*. (b) Insights of the stereocontrols by DFT calculations. The energy and the bond length were given in kcal/mol and Å, respectively.

cleavage of the C–Cl bond, proceeded with a concerted mechanism [23–25]. Both the intrinsic reaction coordinate (IRC) curve and the potential energy surface scan confirmed that there was no stepwise process in terms of the most favored transition state **TS-*S*** (see Figure 2a and Figure S2 for details). The concerted nature of this S_NAr was also supported by continuous changes of C–P and C–Cl bond lengths along the reaction coordinate, indicating the unlikely formation of a Meisenheimer intermediate after the transition state (Figure 2a).

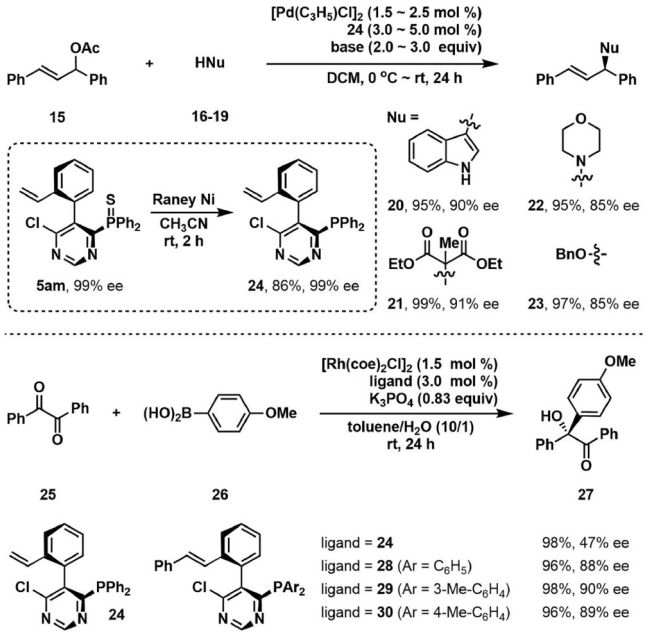
The stereo-control of the concerted S_NAr process was ascribed to the face selectivity of dichloropyrimidine and axial chirality of naphthyl orientation (Figure 2b). *Si*-face nucleophilic attacking with the Ph_2P-S- group would be favored in **TS-*S*** because of the strong coordination of copper(I) and pyrimidine, which activated the C–Cl bond and formed an early transition state with a relatively long C–P distance. Moreover, the developing Cl anion of breaking C–Cl bond was stabilized by a non-classical hydrogen bond with the phenyl group on the P_α atom (H···Cl = 2.76 Å). The naphthyl orientation was restricted by entropic effect under certain face-selectivity of pyrimidine (Figure S3). As for the regioselectivity of the defined *Si*-face, the C_α site rather than the C_β site was more accessible for the nucleophilic attack due to the activated C_α–Cl bonds by Cu(I)-pyrimidine coordination (see Figure S4 for details). Extra six transition states had also been evaluated for the flexible conformations (Figure S3), and the calculated enantioselectivity (94% ee) was in good agreement with the experimental result (98% ee) based on the Boltzmann distributions of all calculated transition states at 298.15 K. The secondary S_NAr reaction was also stereoselective as shown in Figure 2b, which led to enhanced ee of the product in the first S_NAr reaction. This was the key to successfully achieving so many >99% ee as shown in Table 2.

3.5 Transformations and applications

With **5aa** as the mode substrate, transformations of the products were performed as shown in Scheme 3. Oxidation with *m*-CPBA at room temperature afforded phosphine oxide **9** in 98% yield with maintained ee. Reduction with Raney Ni provided chiral triarylphosphine **10** in 85% yield with unchanged ee. Further S_NAr reactions with chiral phosphine **10** were straightforward. Ether **11** was prepared from **10** in 94% yield with untouched ee. Amination proceeded smoothly to deliver tertiary amine **12** in 99% yield with uncompromising ee. The preparations of both thioether **13** and selenoether **14** from **10** were easily accomplished and the products were isolated in excellent yields with unaffected ee under similar conditions. It should be noted that all the axially chiral compounds in this study were very stable in axial chirality and did not undergo any racemization in their transformations.



Scheme 3 (Color online) Transformations with product **5aa**.



Scheme 4 Pd-catalyzed asymmetric allylic alkylation and Rh-catalyzed asymmetric arylation with synthesized axially chiral phosphine-olefin ligands (for the detailed reaction conditions, see Supporting Information online).

As shown in Scheme 4, chiral biaryl **5am** was transformed to olefin-phosphine **24** in 86% yield without any eroding in enantioselectivity through reduction with Raney Ni. It has been disclosed that chiral terminal-alkene-phosphine hybrid ligands worked as powerful ligands in Pd-catalyzed asymmetric allylic substitution [18d,26]. Therefore, **24** was tested as a chiral ligand in the Pd-catalyzed asymmetric alkylation with several nucleophiles. Initially, the C_3-alkylaiton with indole occurred smoothly to give **20** in 95% yield with 90% ee at 10 °C. When diethyl 2-methylmalonate was employed as the pronucleophile, the allylic alkylation afforded **21** in 99% yield with 91% ee at room temperature. Moreover, the Pd-catalyzed allylic amination with morpholine and etherification with benzyl alcohol worked very well, providing the chiral tertiary amine **22** in 95% yield with 85% ee at room temperature and the chiral ether **23** in 97% yield with 85% ee at 0 °C, respectively.

Furthermore, by using olefin-phosphines **24** and **28**–**30** as ligands, the Rh-catalyzed asymmetric addition of boronic acid **25** to benzil (**24**) was studied [27]. Obviously, increasing the steric hindrance of the olefin unit was beneficial for higher enantioselectivity (47% ee *vs.* 88% ee). **29** was identified as the best ligand in terms of the highest enantioselectivity. These catalytic reactions with high enantioselectivity demonstrated the application potential of such chiral ligands in transition-metal catalysis.

4 Conclusions

In summary, a copper(I)-catalyzed desymmetric S_NAr reaction was developed by using $HP(S)R_2$ as a superior pronucleophile to HPR_2 and $HP(O)R_2$ [28]. An array of axially chiral phosphine sulfides was produced in high yields with excellent enantioselectivity. Remarkably, >99% ee was observed in more than one-half of the examples. Furthermore, both axial chirality and *P*-chirality were constructed in moderate diastereoselectivity and excellent enantioselectivity through the S_NAr reaction by using racemic HP(S)ArR. It was disclosed that a second S_NAr reaction occurred after the first S_NAr reaction, which proceeded in a kinetic resolution manner and thus enhanced the ee of the products in the first S_NAr reaction. Two gram-scale preparations demonstrated the robustness of the present reaction. DFT calculations supported a concerted reaction pathway rather than a step-wise mechanism and nicely rationalized the enantioselectivity in the reaction. With **5aa** as the model substrate, various transformations including C–O formation, C–N formation, C–S formation, and C–Se formation were successfully carried out. Finally, some terminal alkene-

phosphines produced by simple desulfuration served as efficient chiral ligands in Pd-catalyzed asymmetric allylic substitution with various nucleophiles and Rh-catalyzed asymmetric addition of arylboronic acid to benzil. Developing efficient chiral ligands through the present method and further application of $H(S)PR_2$ in the asymmetric synthesis of new chiral phosphines are currently ongoing in our laboratory.

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Conflict of interest The authors declare no conflict of interest.

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