Chinese Chemical Letters 35 (2024) 109294

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Copper(I)-catalyzed diastereodivergent construction of vicinal *P*-chiral and *C*-chiral centers facilitated by dual “soft-soft” interaction

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ARTICLE INFO

Article history:
Received 8 July 2023
Revised 4 November 2023
Accepted 9 November 2023
Available online 11 November 2023

Keywords:
Copper catalysis
Asymmetric catalysis
Diastereodivergent synthesis
P-Chirality
“Soft-soft” interaction

ABSTRACT

A copper(I)-catalyzed diastereodivergent addition of phosphinothioates (HP(S)ROR’) to α,β-unsaturated thioamides is disclosed, which constructs vicinal *P*-chiral and *C*-chiral centers in generally high diastereo- and enantioselectivities. In this reaction, the kinetic resolution of HP(S)ROR’ occurs, which affords (*R*)-HP(S)PhOMe in high enantioselectivity in the addition with (*R,R*)-Ph-BPE as the ligand. It is found through control experiment that dual “soft-soft” interaction, indicated by both ^{1}H and ^{31}P NMR experiments, is indispensable in the present reaction. The first “soft-soft” interaction between copper(I) catalyst and HP(S)ROR’ enables facile deprotonation to generate nucleophilic [Cu]-SPROR’ species. The second one between the [Cu]-SPROR’ species and α,β-unsaturated thioamides facilitated the nucleophilic addition. Finally, both Michael adducts and (*R*)-HP(S)PhOMe are easily converted to synthetically useful compounds.

Recently, there has been a considerable interest in the asymmetric synthesis of *P*-chiral compounds as *P*-chiral stereogenic centers appear as key structural features not only in bioactive molecules [1,2] but also in chiral ligands [3–6]. Besides the classical methods based on transformations from chiral pool or auxiliary-assisted diastereoselective synthesis [7,8], new methods focusing on asymmetric catalysis contribute to the efficient asymmetric synthesis of *P*-chiral compounds [9–12]. Among *P*-chiral compounds, phosphinates are a class of important compounds in both medicinal and synthetic chemistry. For example, several chiral phosphinates exhibit strong anti-proliferative activity against a large panel of NCI cancer cell lines [13]. Furthermore, it is well known that chiral phosphinates serve as starting materials for the preparation of *P*-chiral tertiary phosphine oxides [14]. However, there are only limited methods available for the catalytic asymmetric preparation of *P*-chiral phosphinates.

Three strategies have been employed for the catalytic asymmetric synthesis of *P*-chiral phosphinates. The first one is the catalytic desymmetrization. Both transition metal catalysis and organocatalysis enabled the facile synthesis of *P*-chiral phosphinates *via* desymmetrization [15–18]. The second one is the catalytic kinetic resolution (KR) (Scheme 1a). In 2020, both Wang and Zhang studied the construction of *P*-chiral phosphinates by means of palladium-catalyzed asymmetric hydrophosphorylation of alkynes *via* KR [19,20]. Zhang’s method was particularly efficient for secondary phosphine oxides but not very suitable for *H*-phosphinate. Moreover, Zhang and co-workers developed a Ni-catalyzed enantioselective allylic alkylation of *H*-phosphinates *via* KR based on their previous work with secondary phosphine oxides [21–23]. The third one is catalytic dynamic kinetic asymmetric transformation (DyKAT) (Scheme 1b). In 2022, Yang and co-workers disclosed a copper(I)-catalyzed dynamic kinetic intramolecular C-P cross-coupling reaction, which delivered *P*-chiral cyclic phosphinates in high enantioselectivity [24]. Despite the above achievements *via* three strategies, new methods towards the catalytic asymmetric synthesis of more diversified *P*-chiral phosphinates remain elusive. Conjugate addition has been identifed as a powerful tool to access *P*-chiral phosphine derivatives [25–34]. However, its application in the synthesis of *P*-chiral phosphinates *via* KR has never been disclosed largely due to the weak nucleophilicity of *H*-phosphinates [21].

The catalytic asymmetric construction of vicinal tertiary and quaternary stereogenic centers is a challenging issue as there are limited strateties available in literature. The possbile reasons inlcude difficult diastereo- and enantio-discrimination caused by the rotational freedom of acyclic molecules and steric repulsion caused by the two multi-substituted stereogenic centers [35–38]. It would be more challenging to achieve the construction of vicinal *P*-chiral center and *C*-chiral center through asymmetric catalysis, which is reflected by the very limited methodologies [25–30,39–41]. In such reported reactions, the pronucle-

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https://doi.org/10.1016/j.cclet.2023.109294
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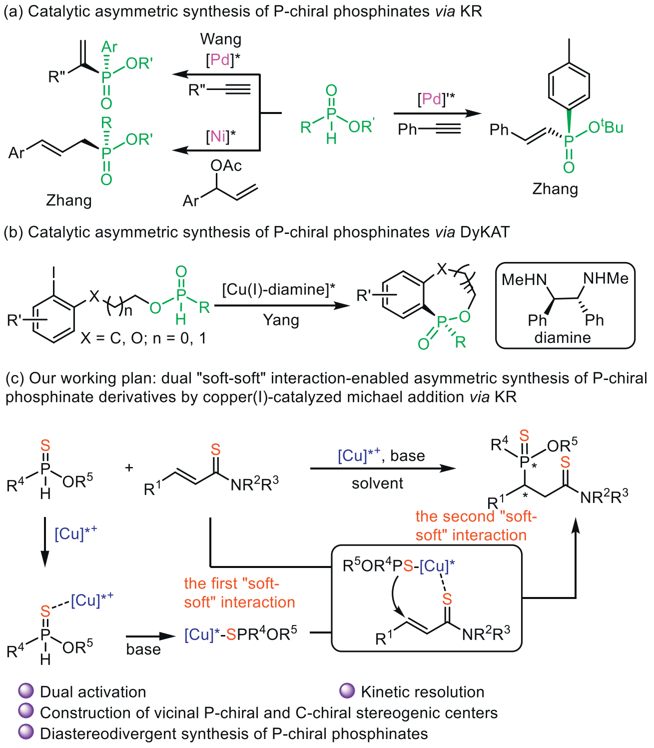
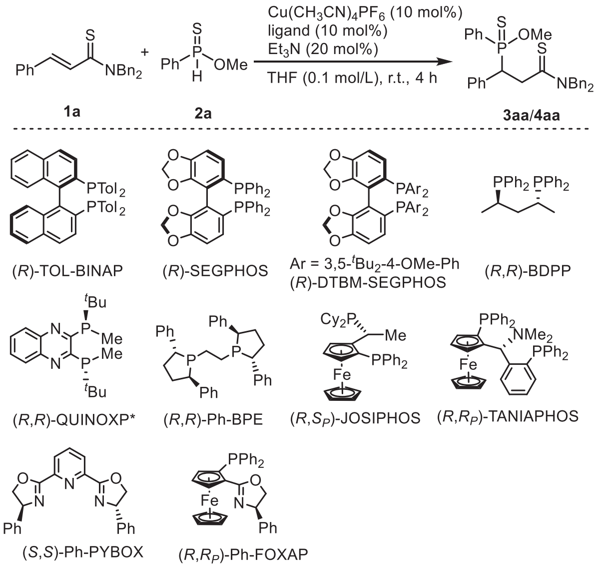


Scheme 1. Catalytic asymmetric synthesis of *P*-chiral phosphinates *via* KR or DyKAT and our working hypothesis.

ophiles were limited to racemic secondary phosphines, which led to a DyKAT process. Moreover, the diastereodivergent synthesis [42,43] of each diastereoisomer has never been achieved. Herein, by means of the dual "soft-soft" interaction [44], a copper(I)-catalyzed diastereodivergent construction of vicinal *P*-chiral center and *C*-chiral center was accomplished, providing new chiral phosphinate derivatives in generally high to excellent diastereo- and enantioselectivities (Scheme 1c). Interestingly, a kinetic resolution process accompanies the catalytic asymmetric Michael addition. Moreover, the dual "soft-soft" interaction between copper(I) and sulfur-containing nucleophiles (phosphinothioates), as well as electrophiles (α,β-unsaturated thioamides [45–48]), was carefully studied through NMR analysis.

The reaction of α,β-unsaturated thioamide **1a** and *O*-methyl phenylphosphinothioate (**2a**) was studied for the optimization of reaction conditions (Table 1). In the presence of 10 mol% $Cu(CH_3CN)_4PF_6$, 10 mol% (*R*)-TOL-BINAP, and 20 mol% Et_3N, the conjugate addition with 1.0 equiv. **1a** and 2.0 equiv. **2a** occurred smoothly to deliver the product **3aa** in moderate yield with unsatisfied diastereo- and enantioselectivities in 4 h (entry 1). Then, a series of bisphosphine ligands were further evaluated (entry 2-7). The highest diastereoselectivity was observed in the reaction with (*R*,*R*)-Ph-BPE (entry 6). Fortunately, the enantioselectivity for the major diastereoisomer **3aa** was high. Interestingly, in the reaction with (R,R_P)-TANIAPHOS, the diastereoselectivity was reversed (entry 8). Instead of **3aa**, its diastereoisomer (**4aa**) was observed in 4/1 *dr* with 85%/71% *ee*. Except for the bisphosphine ligands, (R,R_P)-^{i}Pr-FOXAP and (*S*,*S*)-Ph-PYBOX were also tested. However, no superior results were obtained (entries 9 and 10). By setting up the reaction with (*R*,*R*)-Ph-BPE at 10 °C and increasing the amount of **2a** to 3.0 equiv., **3aa** was afforded in enhanced both diastereo- and enantioselectivities in 12 h (entry 12). As for the reaction with (R,R_P)-TANIAPHOS, **4aa** was generated in 10/1 *dr* with 92% *ee* at –20 °C in the presence of 3.0 equiv. **2a** with a concentration of 0.05 mol/L for **1a** (entry 14).

Table 1
Optimization of reaction conditions. [a]



Entry	Ligand	Yield (%)[b]	*dr*[b]	*ee* (%)[c]
1	(*R*)-TOL-BINAP	78	3/1	78/28
2	(*R*)-SEGPHOS	98	3/1	84/34
3	(*R*)-DTBM-SEGPHOS	92	4/1	99/98
4	(*R*,*R*)-BDPP	96	2/1	22/40
5	(*R*,*R*)-QUINOXP*	98	4/1	89/83
6	(*R*,*R*)-Ph-BPE	91	8/1	-92/-75
7	(*R*)-(*S*)-JOSIPHOS	91	2/1	10/33
8	(R,R_P)-TANIAPHOS	96	1/4	71/85
9	(R,R_P)-^{i}Pr-FOXAP	72	1.5/1	-28/-7
10	(*S*,*S*)-Ph-PYBOX	94	2/1	0/0
11[d]	(*R*,*R*)-Ph-BPE	92	12/1	-97/-89
12[d,e]	(*R*,*R*)-Ph-BPE	94	14/1	-97[f]
13[g]	(R,R_P)-TANIAPHOS	92	1/6	74/87
14[e,g,h]	(R,R_P)-TANIAPHOS	96	1/10	92 [f]

[a] **1a**: 0.1 mmol, **2a**: 0.2 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] 10 °C.

[e] 5 mol% copper catalyst, 3 equiv. **2a**, 12 h.

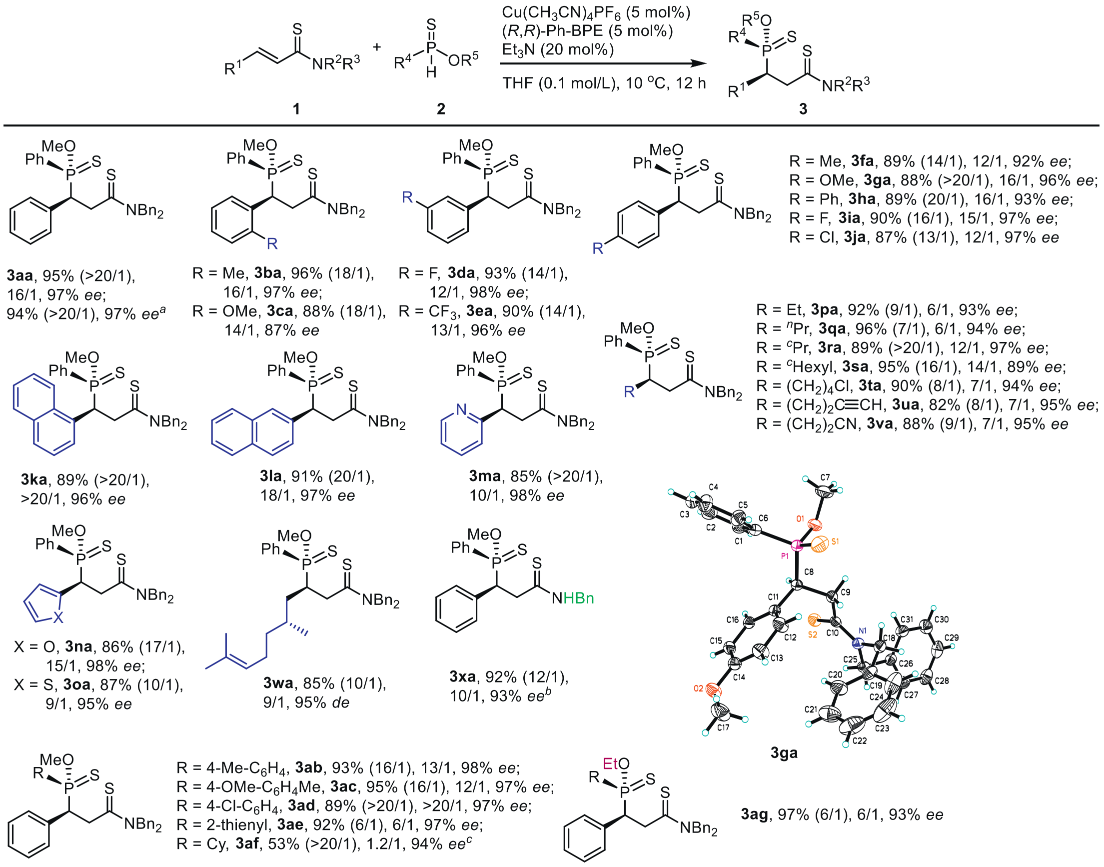
[f] *ee* for the major diastereoisomer.

[g] -20 °C.

[h] 0.05 mol/L.

By using the reaction conditions in entry 12 in Table 1, the substrate scopes for synthesizing **3** were evaluated as given in Scheme 2. It should be noticed that the *dr* values were generally enhanced in the isolation process. As for R^1, various mono-substituted phenyls were applied. The excellent reaction results (**3ba-3ja**, 87%-96%, 13/1∼>20/1 *dr*, 87%-98% *ee*) were not affected by the substitution pattern on the phenyl ring, including the *ortho*-, *meta*-, and *para*-substitution. Both electron-donating groups and electron-withdrawing groups were also well tolerated on the phenyl group. Moreover, both 1-naphthyl and 2-naphthyl were nicely accepted at the R^1 position with satisfactory results obtained (**3ka-3la**, 89%-91%, 20/1 ∼ >20/1 *dr*, 96%-97% *ee*). Some heteroaryl groups, such as 2-pyridinyl, 2-furanyl, and 2-thienyl were also appropriate for R^1 (**3ma-3oa**, 85%-87%, 10/1 ∼ >20/1 *dr*, 95%-98% *ee*).

Then several alkyl groups for R^1 were tested. It was found that simple linear alkyls, simple cyclic alkyls, and functionalized alkyls were well applicable (**3pa-3va**, 82%-96%, 7/1 ∼ >20/1 *dr*, 89%-97% *ee*). It was notable that alkyl chloride was not touched by the pronucleophile **2a**. Furthermore, the terminal alkyne group did not



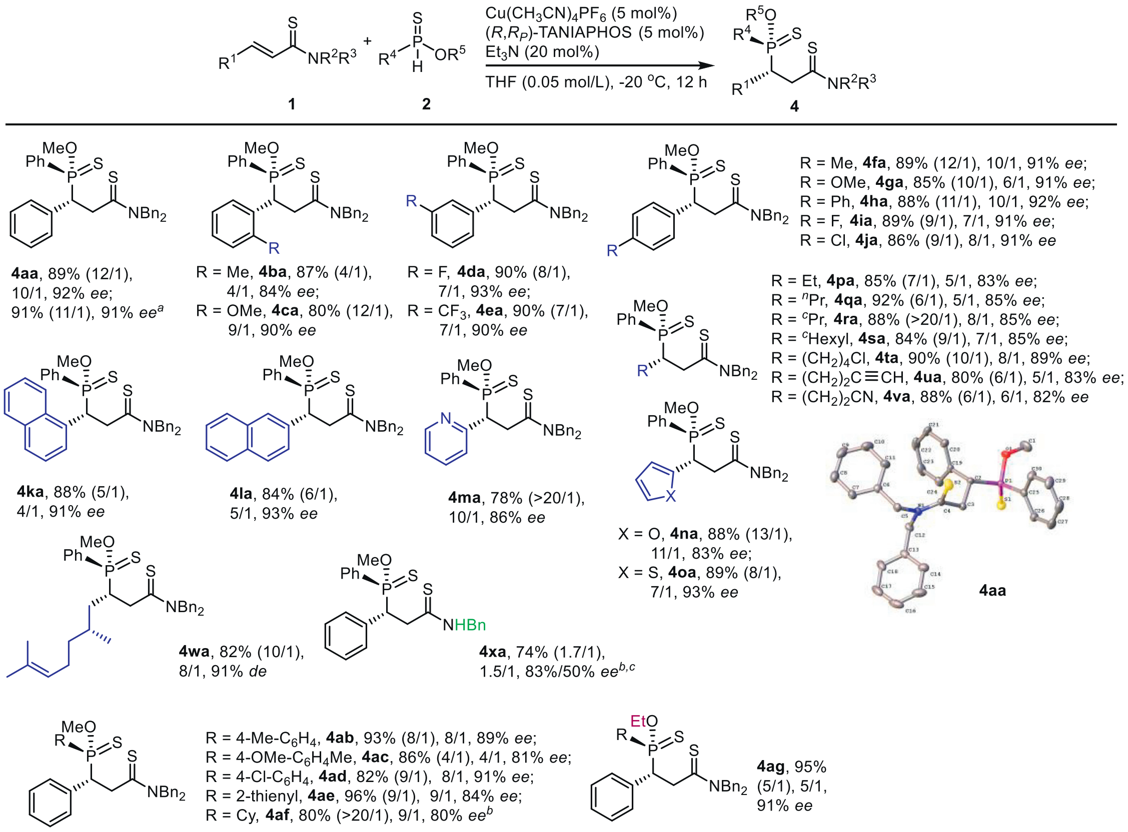
Scheme 2. Substrate scope I of the catalytic asymmetric reaction. **1**: 0.2 mmol, **2**: 0.6 mmol. Isolated yields. *ee* of the major diastereoisomer was determined by chiral-stationary-phase HPLC analysis. *dr* was determined by ^{1}H NMR analysis of crude mixture. *dr* in parenthesis was determined by ^{1}H NMR analysis of an isolated sample. [a] Gram-scale reaction. [b] 10 mol% copper(I) catalyst used. [c] 10 mol% Cu(CH$_3$CN)$_4$PF$_6$ and 10 mol% (*R*)-DTBM-SEGPHOS used at room temperature.

disturb the addition although alkynyl copper(I) species was often formed, which might undergo a conjugate addition to unsaturated amide **1a** [42]. The reaction results were not disturbed by the presence of a nearby chiral center (**3wa**, 85%, 10/1 *dr*, 95% *de*). Interestingly, an *α,β*-unsaturated *N*-H thioamide served as a wonderful electrophile (**3xa**, 92%, 12/1 *dr*, 93% *ee*).

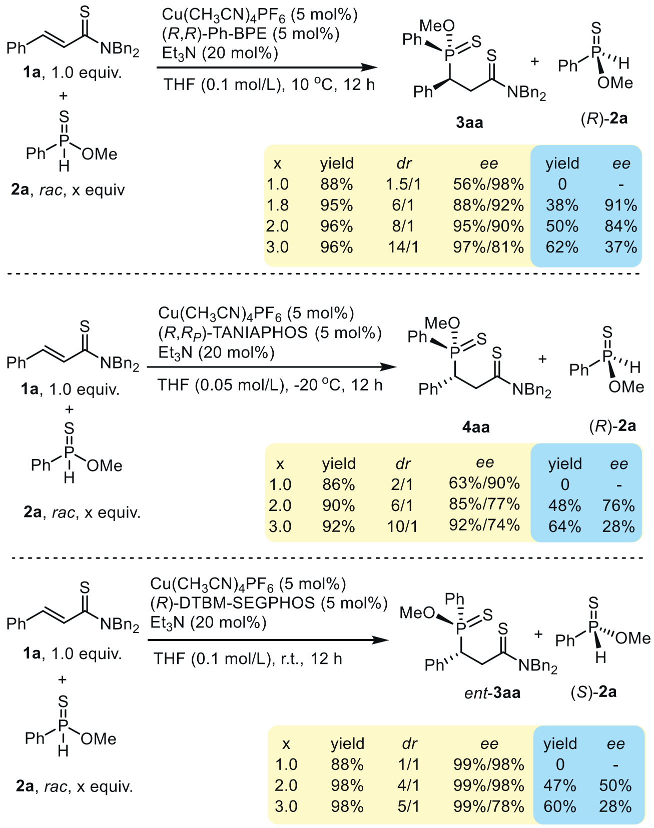
The phenylphosphinothioate **2a** was then varied. 4-Methylphenyl, 4-OMe-phenyl, 4-Cl-phenyl, and 2-thienyl were introduced into R^4. The corresponding products were isolated in good results (**3ab**-**3ae**, 89%-95%, 6/1 ∼ >20/1 *dr*, 97%-98% *ee*). However, the phosphinothioate with cyclohexyl at R^4 position worked in the present conditions with low diastereoselectivity (**3af**, 1.2/1 *dr*). Fortunately, **3af** was isolated in moderate yield with excellent *dr* (53%, >20/1 *dr*, 94% *ee*). *O*-Ethyl phenylphosphinothioate (**2g**) was also a good substrate (**3ag**, 97%, 6/1 *dr*, 94% *ee*). The absolute configuration of **3ga** was determined by X-ray analysis and the stereochemistry of other products (**3**) was deduced by the structural analogy.

By using the reaction conditions in entry 14 in Table 1, both unsaturated amides **1** and phosphinothioates **2** evaluated in Scheme 2 were examined again to assemble **4** (Scheme 3). As for *α,β*-unsaturated amides **1**, both aryls and heteroaryls were suitable substituents for R$_1$ as the corresponding products were isolated in high yields with moderate to high diastereo- and high enantioselectivity (**4aa**-**4oa**, 78%-90%, 4/1 ∼ >20/1 *dr*, 83%-93% *ee*). Various alkyls served as proper substituents at R^1 too (**4pa**-**4va**, 80%-92%, 6/1 ∼ >20/1 *dr*, 82%-89% *ee*). The *α,β*-unsaturated thioamide bearing a chiral center (**1w**) worked also as a suitable electrophile (**4wa**, 82%, 10/1 *dr*, 91% *de*). However, the reaction of *α,β*-unsaturated N-H thioamide **2x** occurred in moderate yield with 1.7/1 *dr* and 83%/50% *ee* (**4xa**, 74%). The bad *dr* was attributed to the decreased steric hindrance of N-H thioamide. As for phosphinothioates **2**, both aryls and heteroaryl were well accepted at R^4 (**4ab**-**4ae**, 82%-96%, 4/1-9/1 *dr*, 81%-91% *ee*). Remarkably, *O*-methyl cyclohexylphosphinothioate (**2f**) underwent the Michael addition to give **4af** in satisfactory results (**4af**, 80%, >20/1 *dr*, 80% *ee*). Although the enantioselectivity was lower than the one in Scheme 2, the diastereoselectivity in the crude mixture was significantly increased (9/1 *vs.* 1.2/1). The reaction with *O*-ethyl phenylphosphinothioate (**2g**) also worked nicely to deliver the desired product (**4ag**, 95%, 5/1 *dr*, 91% *ee*). Generally speaking, both the diastereo- and the enantioselectivities obtained in Scheme 3 were lower than the ones acquired in Scheme 2. The absolute configuration of **4aa** was determined unambiguously with the assistance of X-ray crystallography. The stereochemistry in other products (**4**) was tentatively assigned.

After the studies on the substrate scope, the kinetic resolution of **2a** was investigated. As shown in Scheme 4, with (*R*,*R*)-Ph-BPE as the ligand, the reaction with 1.0 equiv. **1a** and 1.0 equiv. *rac*-**2a** afforded **3aa** in 88% yield with 1.5/1 *dr* and 56%/98% *ee*. By increasing to 1.8 equiv. *rac*-**2a**, the reaction furnished **3aa** in 95% yield with 6/1 *dr* and 88%/92% *ee*. Meanwhile, (*R*)-**2a** was obtained in 38% yield with 91% *ee*. With 2.0 equiv. *rac*-**2a**, both the *dr* and the *ee* of the major diastereoisomer increased (8/1 *dr*, 95%/90% *ee*). (*R*)-**2a** was generated in 50% yield with 84% *ee*. When 3.0 equiv. *rac*-**2a** was employed, **3aa** was generated in 96% yield with 14/1 *dr* and 97%/81% *ee* and (*R*)-**2a** was recovered in 62% yield with 37% *ee*. Then, the kinetic resolution of **2a** with (*R*,*R$_P$*)-TANIAPHOS was probed. The reaction with 1.0 equiv. **1a** and 1.0 equiv. *rac*-**2a** afforded **4aa** in 86% yield with 2/1 *dr* and 63%/90% *ee*. In the reaction with 1.0 equiv. **1a** and 2.0 equiv. *rac*-**2a**, (*R*)-**2a** was af-



Scheme 3. Substrate scope II of the catalytic asymmetric reaction. **1**: 0.2 mmol, **2**: 0.6 mmol. Isolated yields. *ee* of the major diastereoisomer was determined by chiral-stationary-phase HPLC analysis. *dr* was determined by ^{1}H NMR analysis of crude mixture (in parenthesis of an isolated sample). [a] Gram-scale reaction. [b] 10 mol% catalyst loading. [c] 24 h.



x	yield	*dr*	*ee*	yield	*ee*
1.0	88%	1.5/1	56%/98%	0	-
1.8	95%	6/1	88%/92%	38%	91%
2.0	96%	8/1	95%/90%	50%	84%
3.0	96%	14/1	97%/81%	62%	37%

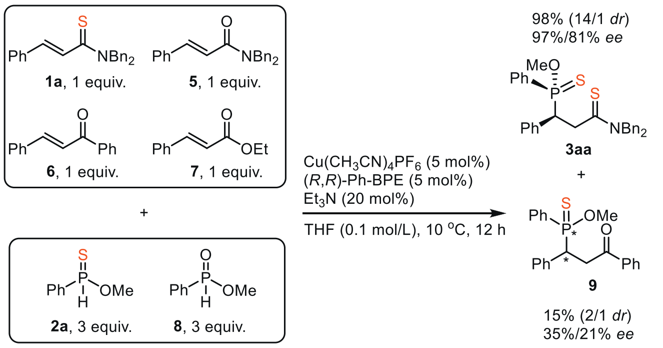
x	yield	*dr*	*ee*	yield	*ee*
1.0	86%	2/1	63%/90%	0	-
2.0	90%	6/1	85%/77%	48%	76%
3.0	92%	10/1	92%/74%	64%	28%

x	yield	*dr*	*ee*	yield	*ee*
1.0	88%	1/1	99%/98%	0	-
2.0	98%	4/1	99%/98%	47%	50%
3.0	98%	5/1	99%/78%	60%	28%

Scheme 4. Control experiments on kinetic resolution of **2a**.

forded in 48% yield with 76% *ee*. The reaction with 3.0 equiv. *rac*-**2a** gave **4aa** in 92% yield with 10/1 *dr* and 92%/74% *ee* and 64% (*R*)-**2a** was obtained in 28% *ee*. Evidently, the resolution of **2a** with (*R*,*R*)-Ph-BPE is more efficient than the one with (*R*,R_P)-TANIAPHOS. It was noted that the reaction with (*R*)-DTBM-SEGPHOS gave the corresponding adduct in excellent enantioselectivity for both diastereoisomers (Table 1, entry 3). Therefore, the dynamic resolution with (*R*)-DTBM-SEGPHOS was also tested. In the reaction with 1.0 equiv. **1a** and 1.0 equiv. *rac*-**2a**, two diastereoisomers with 1/1 ratio were obtained in a total yield of 88%. By using 2.0 equiv. **2a**, the reaction provided both *ent*-**3aa** in 98% yield with 4/1 *dr* and 99%/98% *ee* and (*S*)-**2a** in 47% yield with 50% *ee*. It is deduced that *ent*-**3aa** and the major enantiomer in its diastereoisomers had reversed *P*-chiral centers, which would rationalize the above experimental facts.

The power of dual “soft-soft” interaction was demonstrated by a competitive experiment (Scheme 5). A test tube was charged with 5 mol% $Cu(CH_3CN)_4PF_6$, 5 mol% (*R*,*R*)-Ph-BPE, 20 mol% Et_3N, and THF ahead. Then four electrophiles (1.0 equiv. for each), including unsaturated thioamide **1a**, unsaturated amide **5**, unsaturated ketone **6**, and unsaturated ester **7**, and two nucleophiles (3.0 equiv. for each), including methyl phenylphosphinate **8** and *O*-methyl phenylphosphinothioate **2a** were added to the test tube. After stirring the reaction mixture at 10 °C for 12 h, **3aa** was obtained in 98% yield with 14/1 *dr* and 97% *ee* together with **9** in 15% yield. It should be noted that **9** was generated in low yield, low *dr*, and low enantioselectivity. Obviously, under the “soft-soft” interaction, α,β-unsaturated thioamide exhibited even higher electrophilicity than unsaturated ketone. Furthermore, *O*-methyl phenylphosphinothioate showed much higher reactivity than methyl phenylphosphinate. Evidently, this experimental fact demonstrated the unique



Scheme 5. Competitive experiment (^{1}H NMR yields based on **1a** and **6** are given).

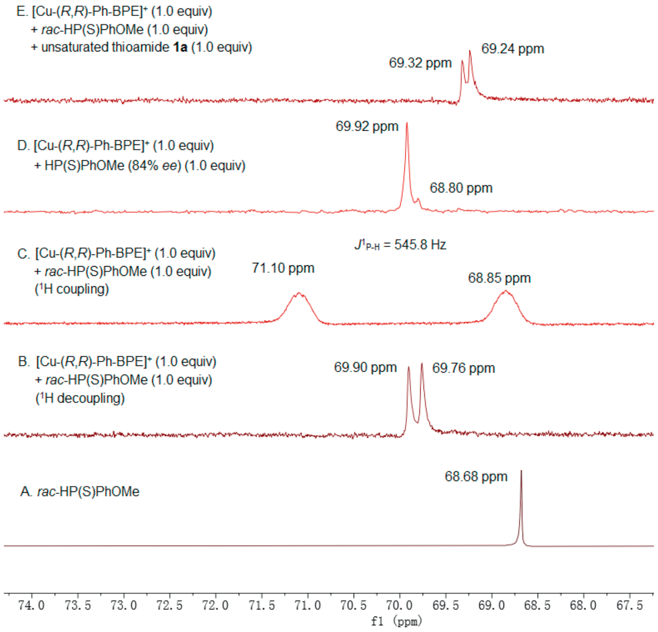


Fig. 1. ^{31}P NMR studies on some mixtures.

advantage of the dual “soft-soft” interaction in transition-metal catalysis.

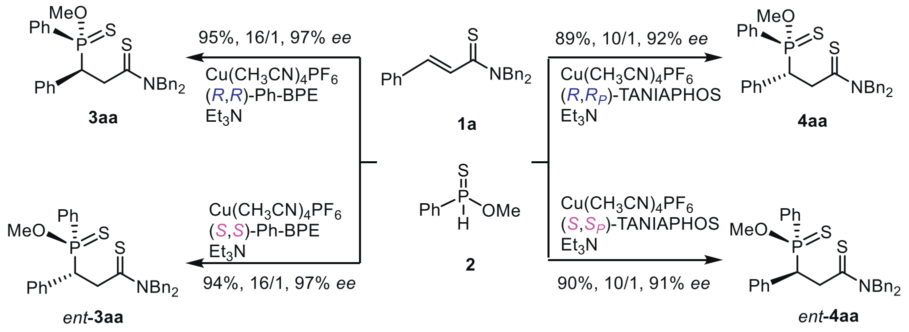
Then, some NMR studies were performed to get insights into the dual “soft-soft” interaction as shown in Fig. 1 (for the full spectra among the range of -5∼100 ppm, see Supporting information). The ^{31}P signal of *rac*-HP(S)PhOMe was recorded as δ 68.68 ppm (Fig. 1A). The 1/1 mixture of [Cu–(*R*,*R*)-Ph-BPE]$^+$ and *rac*-HP(S)PhOMe gave two ^{31}P signals at δ 69.90 and δ 69.76 ppm with 1/1 *dr* ratio in the range of 66-75 ppm (Fig. 1B), which indicated the formation of [Cu–(*R*,*R*)-Ph-BPE]$^+$–*rac*-HP(S)PhOMe species and thus confirmed the “soft-soft” interaction between copper(I) and HP(S)PhOMe. Evidently, the 1/1 *dr* ratio is in accordance with the fact that *rac*-HP(S)PhOMe was employed. In the spectrum without decoupling by ^{1}H (Fig. 1C), two peaks with a $J^1{}_{H\text{-}P} = 545.8$ Hz were observed. The huge H-P coupling constant implied that P(V) was present in the complex rather than HSP(III)PhOMe. By using a sample of (*R*)-HP(S)PhOMe with 84% *ee* (Fig. 1D), the appearances of a big peak at δ 69.92 ppm and a small peak at δ 68.80 ppm further confirmed the formation of the [Cu–(*R*,*R*)-Ph-BPE]$^+$–HP(S)PhOMe complex. Finally, the 1/1/1 mixture of [Cu–(*R*,*R*)-Ph-BPE]$^+$, *rac*-HP(S)PhOMe, unsaturated thioamide **1a** gave two ^{31}P signals at δ 69.32 and δ 69.24 ppm, which might suggest the formation of the [Cu–(*R*,*R*)-BPE]$^+$–*rac*-HP(S)PhOMe–thioamide **1a** complex (Fig. 1E).

In order to further explore the “soft-soft” interaction between copper(I)-bisphosphine complex and α,β-unsaturated thioamide **1a**, the ^{1}H NMR spectrum of the 1/1 mixture of [Cu–(*R*)-BINAP]$^+$ and **1a** was studied (for the details, see Supporting information). Although the chemical shifts of the two benzylic methylenes in the mixture were almost the same as the counterparts in **1a**, the four methylene hydrogens in the mixture gave doublet peaks, which were different from the two single peaks in **1a**. This information indicated that there was a chiral environment around the two hydrogens in the methylenes and thus the [Cu–(*R*)-BINAP]$^+$-**1a** complex was formed, which provided the required chiral environment. Evidently, there is a “soft-soft” interaction between the [Cu–(*R*)-BINAP]$^+$ complex and α,β-unsaturated thioamide **1a**. In the study of the 1/1/1 mixture of [Cu–(*R*)-BINAP]$^+$, **1a**, and **2a**, a similar instructive phenomenon was observed (for the details, see Supporting information), which also indicated the “soft-soft” interaction between the [Cu–(*R*)-BINAP]$^+$-**2a** complex and α,β-unsaturated thioamide **1a**. Evidently, these NMR experiments offered some proof for the double “soft-soft” interaction.

The stereodivergent synthesis of all four stereoisomers was easily achieved by using unsaturated thioamide **1a** and *O*-methyl phenylphosphinothioate (**2a**) as model substrates (Scheme 6). With (*S*,*S*)-Ph-BPE instead of (*R*,*R*)-Ph-BPE, the reaction proceeded in the same reaction efficiency, affording *ent*-**3aa** in 94% yield with 16/1 *dr* and 97% *ee*. By replacing (*R*,*R*$_P$)-TANIAPHOS with (*S*,*S*$_P$)-TANIAPHOS, *ent*-**4aa** was prepared in 90% yield with 10/1 *dr* and 91% *ee*. Evidently, both (*R*,*R*)-Ph-BPE and (*R*,*R*$_P$)-TANIAPHOS led to *P*-stereogenic center with (*S*)-configuration while both (*S*,*S*)-Ph-BPE and (*S*,*S*$_P$)-TANIAPHOS led to *P*-stereogenic center with (*R*)-configuration.

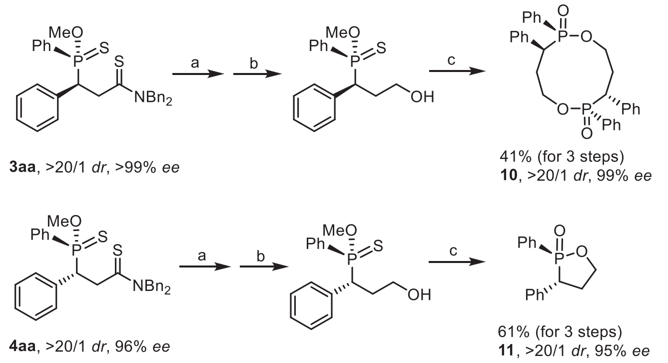
Subsequently, transformations of the products were proved to be straightforward by using **3aa** and **4aa** as model substrates (Scheme 7). By reduction with Schwartz reagent [49] at −78 °C and further reduction with NaBH$_4$, thioamide **3aa** was converted to a chiral alcohol, which was then treated with *m*CPBA. Interestingly, an intermolecular esterification occurred to give cyclic diphosphinate **10** in 41% yield for three steps with uncompromising both diastereo- and enantioselectivities. It should be noted that without the oxidative conversion of phosphinothioate to phosphinate, the intermolecular esterification did not proceed at all. Furthermore, the *P*-chiral centers were reversed in the esterification. On the contrary, the three-step transformation of **4aa** afforded cyclic monophosphinate **11** rather than diphosphinate in 61% yield with unchanged both *dr* and *ee* by an intramolecular esterification. This special phenomenon highlighted the potential different reaction behavior of two diastereoisomers under the same reaction condition. At this stage, the origin for this interesting phenomenon is unclear.

The synthetic utility of chiral *O*-methyl phenylphosphinothioate ((*R*)-**2a**) was demonstrated by several transformations (Scheme 8). The conjugate addition of (*R*)-**2a** to benzyl acrylate was successfully carried out, furnishing thiophosphinate **12** in 92% yield with uncompromising *ee*. Moreover, the heteroarylation reaction of (*R*)-**2a** through nucleophilic aromatic substitution proceeded smoothly at −40 °C to deliver thiophosphinate **13** in 67% yield with unchanged *ee* [50]. The alkylation with EtI worked well to produce thiophosphinate **14** in 80% yield with slightly decreased *ee*. **14** was easily converted to tertiary phosphine oxide **15** in 69% yield for two steps with slightly eroded *ee* [14]. Notably, **15** is easily reduced to *P*-chiral tertiary phosphine, which may serve as chiral ligands in transition-metal catalysis. Finally, an amination with benzylamine by means of the Atherton-Todd reaction [51] led to phosphonamidothioate **16** in 89% yield with remained *ee*. Ammonia also served as a wonderful substrate in the amination to give phosphonamidothioate **17** in 91% yield with retained *ee*. It should be noted that the *P*-chiral centers were reversed in the Atherton-Todd reaction.

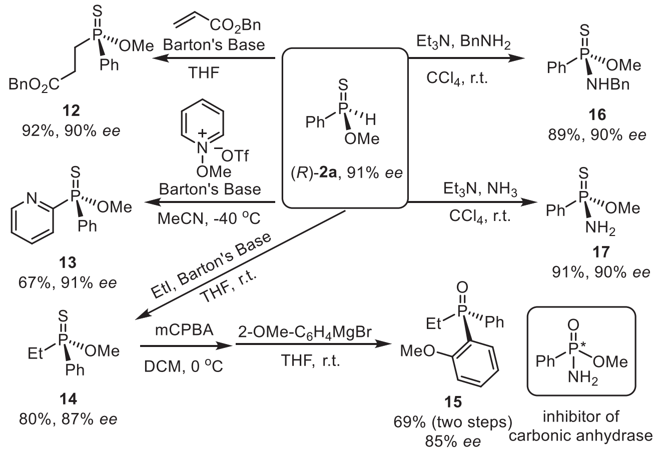


Note: Standard conditions. Isolated yield. *dr* was determined by ^{1}H NMR analysis of crude mixture.

Scheme 6. Stereodivergent synthesis to all four stereoisomers with vicinal *P*-chiral and *C*-chiral centers.



Scheme 7. Transformations of **3aa** and **4aa**. Conditions: (a) Cp_2ZrHCl, toluene, -78 °C to r.t. (b) $NaBH_4$, MeOH, r.t. (c) mCPBA, DCM, 0 °C to r.t.



Scheme 8. Transformations of (*R*)-**2a**.

Moreover, it is interesting to see that the oxide derivative of **17** was identified as an inhibitor of carbonic anhydrase [52,53].

In conclusion, with the assistance of the dual "soft-soft" interaction between copper(I) and the sulfur atoms in substrates, a catalytic asymmetric diastereodivergent addition of phosphinothioates to α,β-unsaturated thioamides was successfully carried out. The diastereodivergent additions were achieved by using (*R*,*R*)-Ph-BPE and (*R*,*R*$_P$)-TANIAPHOS as the ligand, respectively. The Michael addition enjoyed broad substrate scopes on both α,β-unsaturated thioamides and phosphinothioates. In the meanwhile of asymmetric addition, the kinetic resolution of phosphinothioates occurred. With (*R*,*R*)-BPE as the ligand, the resolution proceeded smoothly to afford (*R*)-HP(S)PhOMe in 38% yield with 91% *ee*. A competitive experiment showed that such a dual "soft-soft" interaction was indispensable in the present reaction as the first "soft-soft" interaction activated the phosphinothioates to enable the facile deprotonation and the second "soft-soft" interaction facilitated the addition. Interestingly, both ^{1}H and ^{31}P NMR studies offered some proof for the dual "soft-soft" interaction. Finally, the transformation of the product afforded a cyclic diphosphinate while the reaction of its diastereoisomer delivered a cyclic mono-phosphinate. The recovered (*R*)-*O*-methyl phenylphosphinothioate was smoothly converted to various *P*-chiral compounds without significantly eroded *ee*. Expanding the application of the dual "soft-soft" interaction in transition metal-catalysis is currently on going in our laboratory.

Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We gratefully acknowledge the financial support from the National Natural Science Foundation of China (No. 22271302), the Science and Technology Commission of Shanghai Municipality (Nos. 20JC1417100 and 21XD1424800), CAS Key Laboratory of Synthetic Chemistry of Natural Substances, and Shanghai Institute of Organic Chemistry.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2023.109294.

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