

# A general copper-catalysed enantioconvergent radical Michaelis–Becker-type C(*sp*<sup>3</sup>)–P cross-coupling

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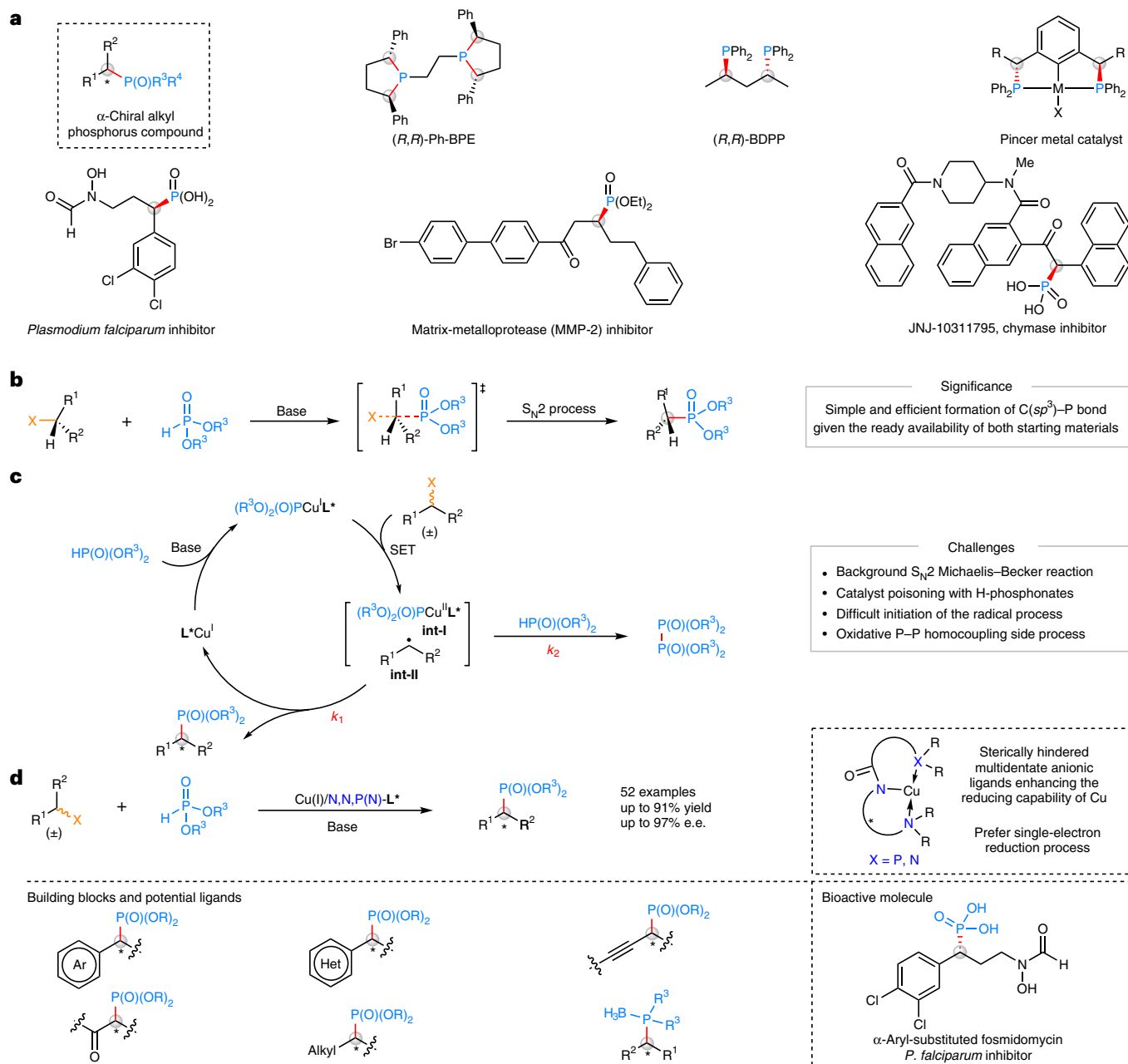
The Michaelis–Becker reaction of H-phosphonates with alkyl halides represents an ideal means for synthesizing alkyl phosphorous compounds. However, the enantioconvergent conversion of racemic alkyl halides into  $\alpha$ -chiral alkyl phosphorous compounds in this reaction is an insurmountable challenge because of the inherent S<sub>N</sub>2 mechanism. Here we disclose a copper-catalysed enantioconvergent radical Michaelis–Becker-type C(*sp*<sup>3</sup>)–P cross-coupling. Key to the success of this reaction is the use of multidentate chiral anionic ligands for enhancing the reducing capability of the copper catalyst to favour a stereoablative radical pathway over a stereospecific S<sub>N</sub>2-type process. Moreover, the ligand architecture is also able to assist the robust association of copper species with alkyl radicals over H-phosphonates, therefore exerting remarkable chemo- and enantioselectivity. This protocol covers a range of (hetero)benzyl-, propargyl- and  $\alpha$ -aminocarbonyl alkyl bromides and chlorides. When allied with follow-up transformations, this method provides a versatile platform for valuable  $\alpha$ -chiral alkyl phosphorous building blocks and drug leads.

$\alpha$ -Chiral alkyl phosphorous compounds are important building blocks in organic synthesis and key structural motifs in biologically active molecules, agricultural chemicals and functional materials (Fig. 1a)<sup>1</sup>. They are widely utilized as chiral organocatalysts and ligands for asymmetric transformations in organic synthesis<sup>2–8</sup>. Moreover, phosphonic acids have also been harnessed as potentially interesting acid bioisosteres and are valuable in structure–activity relationship studies in medicinal chemistry<sup>9–12</sup>. Consequently, the development of catalytic enantioselective methods for constructing chiral C(*sp*<sup>3</sup>)–P bonds is of paramount importance<sup>13–28</sup>. The Michaelis–Becker reaction of H-phosphonates with alkyl halides is one of the most efficient approaches for expedited access to C(*sp*<sup>3</sup>)–P bonds given the ready availability of both starting materials (Fig. 1b)<sup>29</sup>. Discovered in 1897, it has been used extensively for more than a century together with the related Michaelis–Arbuzov reaction<sup>30,31</sup>. However, the reaction

has been seldom used in the synthesis of  $\alpha$ -chiral alkyl phosphorous compounds because its enantiospecific S<sub>N</sub>2 nature<sup>29,32,33</sup> necessitates the utilization of chiral alkyl halides or the easy epimerization of the alkyl halide racemates. However, earth-abundant 3*d* transition metal catalysis provides a suitable mechanism for enantioconvergence by converting a pair of racemic alkyl halides to the prochiral alkyl radical via a single-electron reduction process, a strategy pioneered by Fu and others<sup>34–53</sup>. In this context, the development of 3*d*-transition-metal-catalysed enantioconvergent radical Michaelis–Becker-type C(*sp*<sup>3</sup>)–P cross-coupling would provide a general method toward  $\alpha$ -chiral alkyl phosphorous compounds.

As part of our ongoing interest in asymmetric radical reactions<sup>54–56</sup>, we have found that multidentate chiral anionic ligands can remarkably enhance the reducing capability of Cu(I) catalysts for facile generation of prochiral alkyl radicals from racemic alkyl halides. Accordingly,

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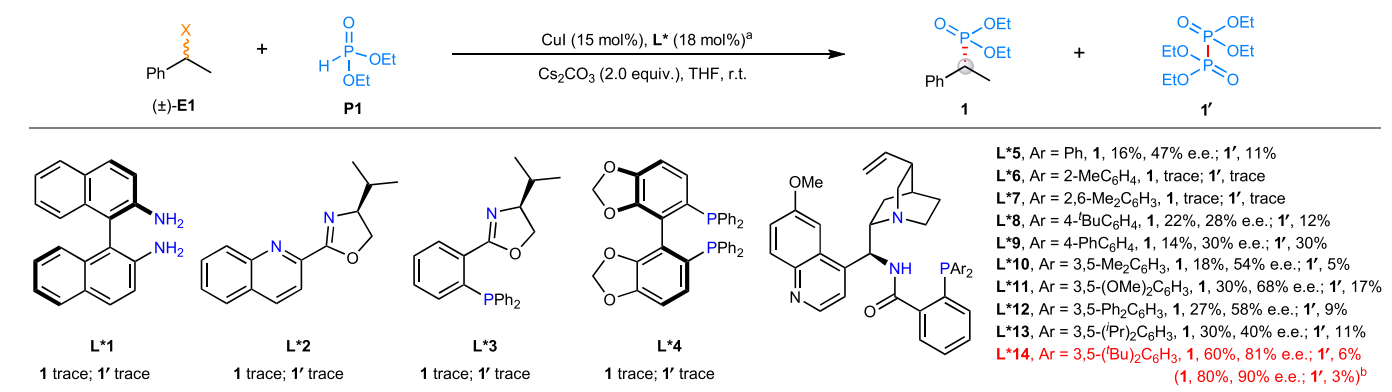


**Fig. 1 | Motivation and design of copper-catalysed enantioconvergent radical Michaelis–Becker-type C( $sp^3$ )-P cross-coupling. a**, Importance of  $\alpha$ -chiral alkyl phosphorus compounds. **b**, Significance of the Michaelis–Becker reaction. **c**, Proposal and challenges for copper-catalysed enantioconvergent radical

C( $sp^3$ )-P coupling. **d**, This work on enantioconvergent radical Michaelis–Becker-type C( $sp^3$ )-P coupling. X, halogen; SET, single-electron transfer; \*, chirality; **L\***, chiral ligand; Het, heteroarene; BPE, 1,2-bis(phospholano)ethane; BDPP, 2,4-bis(diphenylphosphino)pentane.

a series of enantioconvergent radical C( $sp^3$ )-C/N coupling reactions have been established by our group<sup>57–62</sup>. Motivated by these exciting precedents, we questioned whether a chiral copper catalyst could realize the enantioconvergent Michaelis–Becker-type C( $sp^3$ )-P cross-coupling. Nonetheless, a number of factors would impede the development of such a process (Fig. 1c): (1) the aforementioned background  $S_N2$  reactions due to the strong nucleophilicity of H-phosphonates; (2) catalyst poisoning and/or chiral ligand displacement with H-phosphonates due to the strong coordination properties<sup>31,63–67</sup>; (3) the difficult initiation of the radical process due to the weak reducing capability of Cu(I) catalyst; and (4) the easily occurring copper-catalysed oxidative P–P homocoupling ( $k_2$ )<sup>68</sup>. Therefore, identifying an appropriate ligand that is capable of selectively promoting the desired enantioconvergent

cross-coupling of CuP(O)(OR $_3$ )**int-I** with alkyl radical **int-II** ( $k_1$ ) amidst other competing processes is important. Here we describe a copper-catalysed enantioconvergent radical Michaelis–Becker-type C( $sp^3$ )-P cross-coupling with remarkable chemo- and enantioselectivities. This reaction covers a range of benzyl-, heterobenzyl-, propargyl- and  $\alpha$ -aminocarbonyl alkyl halides and readily available H-phosphonates with high functional group tolerance. It also provides a highly flexible platform to rapidly access diverse synthetically valuable  $\alpha$ -chiral alkyl phosphorous building blocks and drug leads when allied with follow-up transformations (Fig. 1d). Given the ready availability of both coupling partners, this strategy would provide an appealing complementary approach to the known methods to synthesize these compounds<sup>13–28,69–71</sup>.

**Table 1 | The effect of different ligands on the model reaction and the optimal results**

<sup>a</sup>Standard reaction conditions: racemic 1-phenylethyl bromide **E1** (1.5 equiv.), diethyl phosphonate **P1** (0.1 mmol), CuI (15 mol%), ligand (18 mol%) and Cs<sub>2</sub>CO<sub>3</sub> (2.0 equiv.) in THF (1 ml) at r.t. for 5 days under argon. Yields were based on <sup>1</sup>H NMR spectroscopic analysis of the crude product using CH<sub>2</sub>Br<sub>2</sub> as an internal standard. e.e. values were based on HPLC analysis. <sup>b</sup>The reaction was conducted at -15 °C for 5 days. The red text indicates the result with the best ligand. <sup>t</sup>Bu, *tert*-butyl; <sup>i</sup>Pr, *isopropyl*.

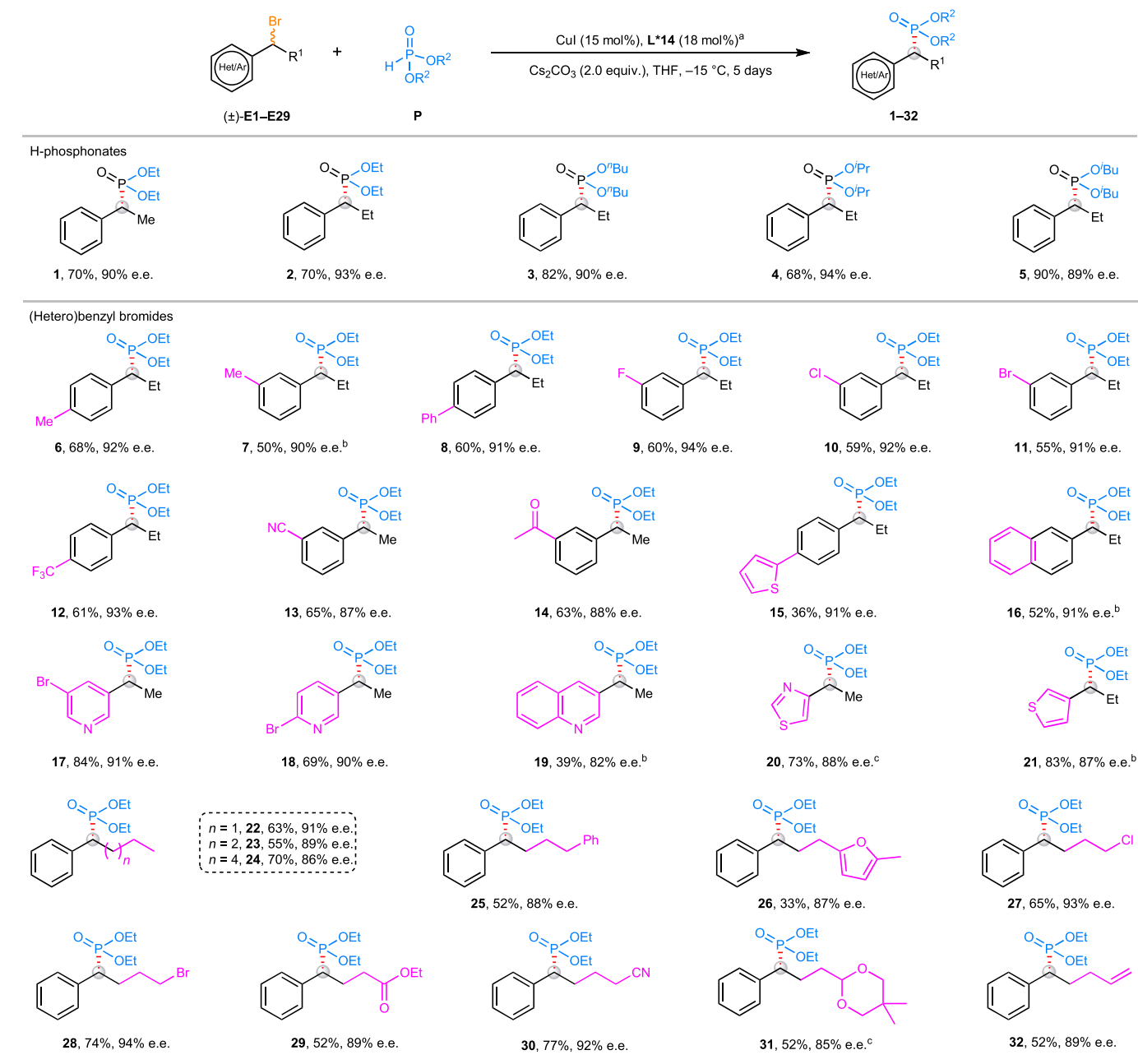
## Results and discussion

At the outset, we investigated the reaction of racemic 1-phenylethyl bromide **E1** and diethyl phosphonate **P1** (Table 1). To avoid the S<sub>N</sub>2-type Michaelis–Becker background reaction, we first tested the reaction with Cs<sub>2</sub>CO<sub>3</sub> in different solvents and found that no strong background reaction was observed in low polar solvents (Supplementary Table 1). To verify the ligand effect in the proposed enantioconvergent radical process, various types of ligands were subsequently screened with CuI as the catalyst in tetrahydrofuran (THF) (Table 1). The bidentate ligands, such as N,N-ligands **L\*1** and **L\*2**, N,P-ligand **L\*3**, and P,P-ligand **L\*4**, failed to initiate the single-electron reduction of **E1**. In sharp contrast, Dixon's PPh<sub>3</sub>-based cinchona-derived tridentate anionic N,N,P-ligand<sup>72</sup> **L\*5** could initiate this reaction to deliver the desired product **1** in 16% yield with 47% enantiomeric excess (e.e.), along with the P–P homocoupling side product **1'**. Considering the substantial role that the phosphine motif might play in improving reaction efficiency and enantioselectivity, we then screened a series of N,N,P-ligands with different steric and electronic substituents at the P-aryl ring. While *ortho*-substituted N,N,P-ligands **L\*6** and **L\*7** did not work, *para*-substituted ones **L\*8** and **L\*9** gave rise to **1** with low chemo- and enantioselectivity. It is noteworthy that 3,5-disubstituted ligands **L\*10**–**L\*14** showed remarkably good efficiency and enantioselectivity. The N,N,P-ligand **L\*14** bearing a steric bulky *tert*-butyl P-substituent gave the best result (60% yield, 81% e.e.) and the P–P homocoupling process could be greatly inhibited (6% yield of **1'**). These results collectively indicated that the use of a sterically bulky N,N,P-ligand is crucial for the robust association of CuP(O)(OR)<sub>2</sub> **int-I** with in-situ-generated alkyl radical **int-II** over H-phosphonate, which would exert effective radical C(sp<sup>3</sup>)–P coupling while inhibiting oxidative P–P homocoupling (Fig. 1c). After further optimization of reaction parameters, including the copper catalysts, catalyst loading, bases, the molar ratio of the reactants and the reaction temperature (Supplementary Tables 2–6), we identified the optimal conditions as follows: 1.0 equiv. **P1**, 1.5 equiv. **E1**, 15 mol% CuI, 18 mol% **L\*14** and 2.0 equiv. Cs<sub>2</sub>CO<sub>3</sub> in THF at -15 °C. Under the optimal conditions, the desired product **1** was obtained in 80% yield with 90% e.e. (Table 1).

With the optimized reaction conditions in hand, we examined the generality of the enantioconvergent radical C(sp<sup>3</sup>)–P coupling reaction (Table 2). With regard to the H-phosphonate scope, a series of H-phosphonate diesters, including diethyl, dibutyl, diisopropyl and diisobutyl groups, can be utilized in this reaction to deliver **1**–**5** in 68–90% yields with 89–94% e.e. However, diphenylphosphine oxide (H(O)PPh<sub>2</sub>) is not applicable to the reaction, possibly due to the large steric congestion in the formation of the C(sp<sup>3</sup>)–P bond with this phosphorus reagent (Supplementary Fig. 1).

We next evaluated the scope of racemic (hetero)benzyl halides using diethyl phosphonate **P1** as a coupling partner. As for the phenyl ring of alkyl bromides, a series of electron-donating and electron-withdrawing substituents at different (*meta* or *para*) positions and bicyclic naphthalene rings were all compatible with the reaction conditions to afford **6**–**16** with 87–94% e.e. Heterobenzyl bromides featuring different types of medicinally relevant heterocycles including pyridine, quinoline, thiazole and thiophene were well accommodated, providing the desired products **17**–**21** in moderate to good yields with excellent enantioselectivity. With respect to the alkyl side chain of benzyl bromides, simple unfunctionalized aliphatic and phenyl groups were suitable for this reaction to access **22**–**25** with good results. More importantly, a gamut of potentially reactive functional groups, such as furan (**26**), primary chloride (**27**) and bromide (**28**), ester (**29**), nitrile (**30**), acetal (**31**) and terminal olefin (**32**) on the side chain of benzyl bromides, were all well tolerated under the reaction conditions. It is noteworthy that excellent chemoselectivity was also observed for the secondary benzyl bromide over primary bromide and chloride (**27** and **28**). The absolute configuration of **1** was determined to be *R* by comparing its HPLC spectrum and optical rotation with those reported in the literature<sup>73</sup> and those of other products were assigned in reference to **1**.

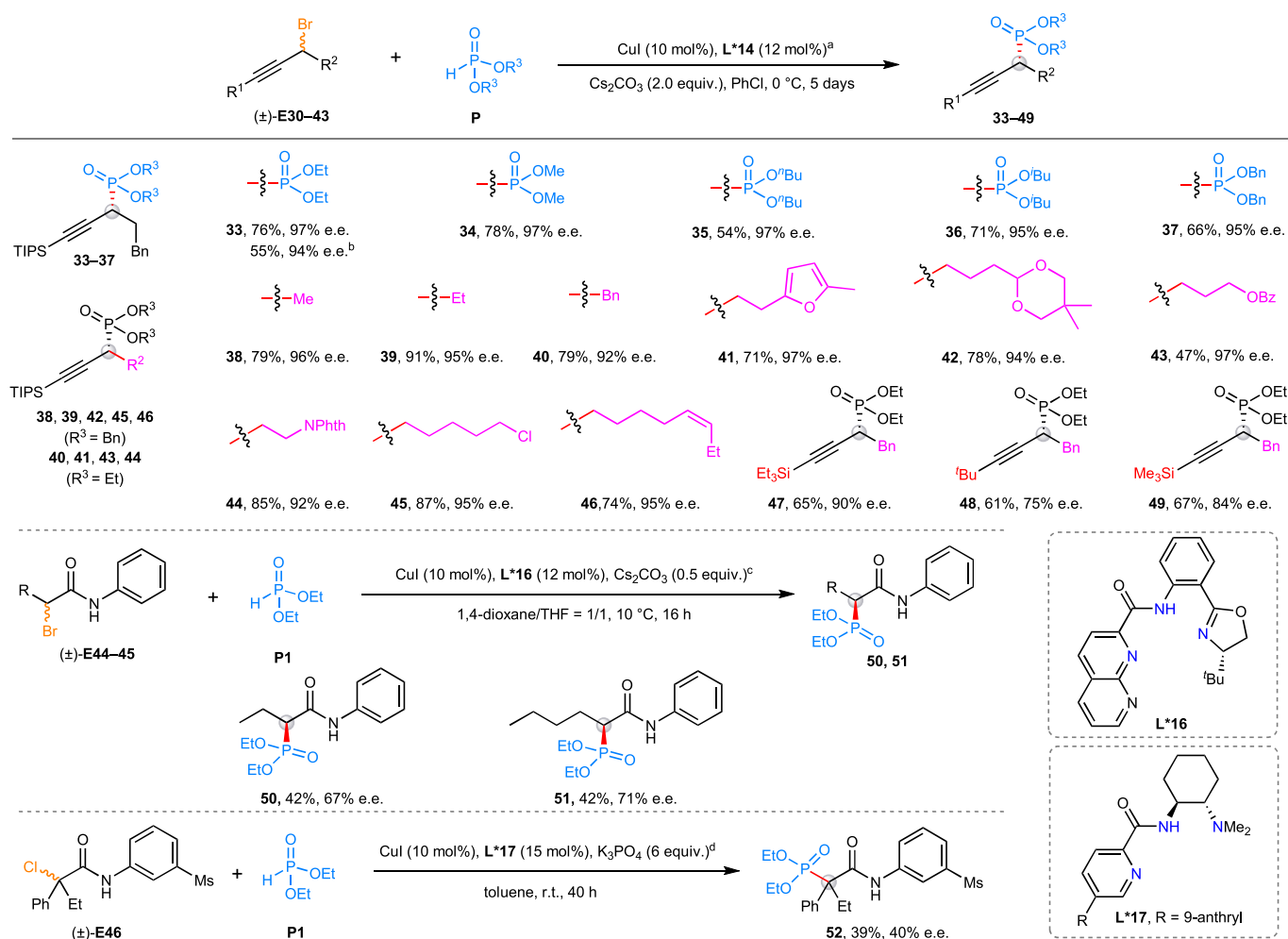
To further explore the generality of this process, more alkyl halides were evaluated (Table 3). Racemic propargyl bromides were first selected as the coupling partner because the easy modification of the alkynyl group renders the corresponding chiral propargyl phosphorous compounds useful as building blocks<sup>74,75</sup>. As expected, a series of H-phosphonate diesters were successfully coupled with propargyl bromide **E30** to give **33**–**37** in moderate to good yields with excellent enantioselectivity under simply modified reaction conditions (see Supplementary Table 7 for reaction condition optimization). With regard to the propargyl bromide scope, a range of substituents bearing both simple alkyl and functional groups at the aliphatic chain were compatible with the reaction conditions to afford **38**–**46** in 47–91% yields with 92–97% e.e. A gamut of functional groups, such as phenyl ring (**40**), furan (**41**), acetal (**42**), ester (**43**), amide (**44**), primary chloride (**45**) and internal alkene (**46**), were well tolerated under the standard conditions. Additionally, the substrates bearing triethylsilyl (**47**), *tert*-butyl (**48**) and trimethylsilyl (**49**) on the alkynyl moiety were also amenable to the reaction conditions. Further, the less reactive propargyl chloride **E43** was also a suitable substrate for the cross-coupling to provide **33** with slightly low efficiency and similar enantioselectivity. It should be noted that the formation of P–P homocoupling side product **1'** and the slight decomposition of **P1** led to the low yield for substrates that had low reactivities.

**Table 2 | Substrate scope for H-phosphonates and (hetero)benzyl bromides**

<sup>a</sup>Standard reaction conditions: racemic (hetero)benzyl bromide **E1-E29** (1.5 equiv.), H-phosphonate **P** (0.2 mmol), CuI (15 mol%), ligand (18 mol%) and Cs<sub>2</sub>CO<sub>3</sub> (2.0 equiv.) in THF (2 ml) at -15 °C for 5 days under argon. Isolated yields are shown. e.e. values were based on HPLC analysis. <sup>b</sup>The reaction was conducted at -15 °C for 4 days and then at -5 °C for 1 day. <sup>c</sup>The reaction was conducted at -15 °C for 4 days and then at 0 °C for 1 day. <sup>n</sup>Bu, *n*-Butyl; <sup>i</sup>Bu, isobutyl.

We next investigated the coupling of  $\alpha$ -aminocarbonyl alkyl bromides with H-phosphate (Table 3), given the importance of enantioenriched  $\beta$ -carbonylphosphorous compounds as key motifs in potent inhibitors of human mast cell chymase (Fig. 1a)<sup>76</sup>. Nonetheless,  $\alpha$ -aminocarbonyl- $\alpha$ -phenyl alkyl bromide **E44** afforded the desired product **50** in poor efficiency and enantioselectivity in the presence of **L\*14** or **L\*15** (see Supplementary Table 8 for reaction condition optimization), possibly due to the high reactivity of such a substrate. This prompted us to examine less electron-rich N,N,N-ligands and carry out additional systematic optimization of reaction parameters. We identified oxazoline-derived tridentate anionic N,N,N-ligand **L\*16** as the best one for the coupling of  $\alpha$ -aminocarbonyl alkyl bromides

with good enantioselectivity. In addition, we also tested the reaction of tertiary alkyl chloride **E46** but found that neither **L\*14** nor **L\*16** gave a good result. We further optimized the reaction conditions of **E46** and identified that N,N,N-ligand (**L\*17**) was suitable for the coupling of tertiary alkyl halides<sup>62</sup> and gave the desired product **52** in 39% yield with 40% e.e. (Table 3 and Supplementary Table 9). These reactions are currently undergoing further optimization in our laboratory. Unfortunately, unactivated alkyl bromides or iodides failed to afford the desired coupling products due to their inertness, and the electrophiles are recovered (Supplementary Fig. 2). Collectively, the broad scope and easy availability of alkyl halides and H-phosphonates enable the coupling reactions to be an important complementary approach to

**Table 3 | Substrate scope for propargyl halides and  $\alpha$ -carbonyl alkyl halides**

<sup>a</sup>Standard reaction conditions: racemic **E30–E43** (0.3 mmol), **P** (0.2 mmol), **CuI** (10 mol%), **L\*14** (12 mol%) and  $\text{Cs}_2\text{CO}_3$  (2.0 equiv.) in **PhCl** (2 ml) at 0 °C for 5 days under argon. <sup>b</sup>Alkyl chloride **E43** was used and the reaction was conducted at r.t. <sup>c</sup>Reaction conditions: racemic **E44** or **E45** (0.2 mmol), **P1** (0.2 mmol), **CuI** (10 mol%), **L\*16** (12 mol%) and  $\text{Cs}_2\text{CO}_3$  (0.5 equiv.) in 1,4-dioxane and **THF** (2 ml, 1,4-dioxane/THF=1/1) at 10 °C for 16 h under argon. <sup>d</sup>Reaction conditions: racemic **E46** (0.2 mmol), **P1** (0.3 mmol), **CuI** (10 mol%), **L\*17** (15 mol%) and  $\text{K}_3\text{PO}_4$  (6 equiv.) in toluene at r.t. for 40 h under argon. Isolated yields are shown. e.e. values were based on HPLC analysis. Bn, benzyl; TIPS, triisopropylsilyl; Bz, benzoyl; NPhth, phthalimidyl; Ms, methylsulfonyl.

the reported catalytic methods in the synthesis of  $\alpha$ -chiral alkyl phosphorous compounds<sup>13–28,69–71</sup>.

To demonstrate the synthetic potential of this strategy, facile transformations were performed to convert them to other enantioenriched building blocks (Fig. 2a). For example, we transformed the alkynyl motif of **33** to an alkyl group and obtained **54** through a sequential deprotection and hydrogenation process, which could provide an alternative approach for the  $\text{C}(\text{sp}^3)\text{-P}$  cross-coupling of unfunctionalized alkyl halides. In addition, we converted the phosphonate moiety of **2** to chiral phospholane borane **55** using a sequential reduction/alkylation process without remarkable loss of enantiopurity, thereby demonstrating its potential for the synthesis of chiral organocatalysts and ligands. Another interesting application would be the expedient access to a biologically interesting compound (Fig. 2b). Racemic  $\alpha$ -aryl-substituted fosmidomycin analogues have shown more favourable physicochemical properties and higher activity than fosmidomycin in inhibiting malaria parasite growth<sup>11–13</sup>. However, catalytic asymmetric processes for the synthesis of the enantioenriched substituted fosmidomycin analogues have remained rare<sup>77–79</sup>. To illustrate this, we evaluated the enantioconvergent  $\text{C}(\text{sp}^3)\text{-P}$  coupling of racemic **E47** and dibenzyl phosphonate **P6**, and the reaction delivered the chiral phosphonate **56** in 64% yield with 93% e.e. Then, **56** could be easily

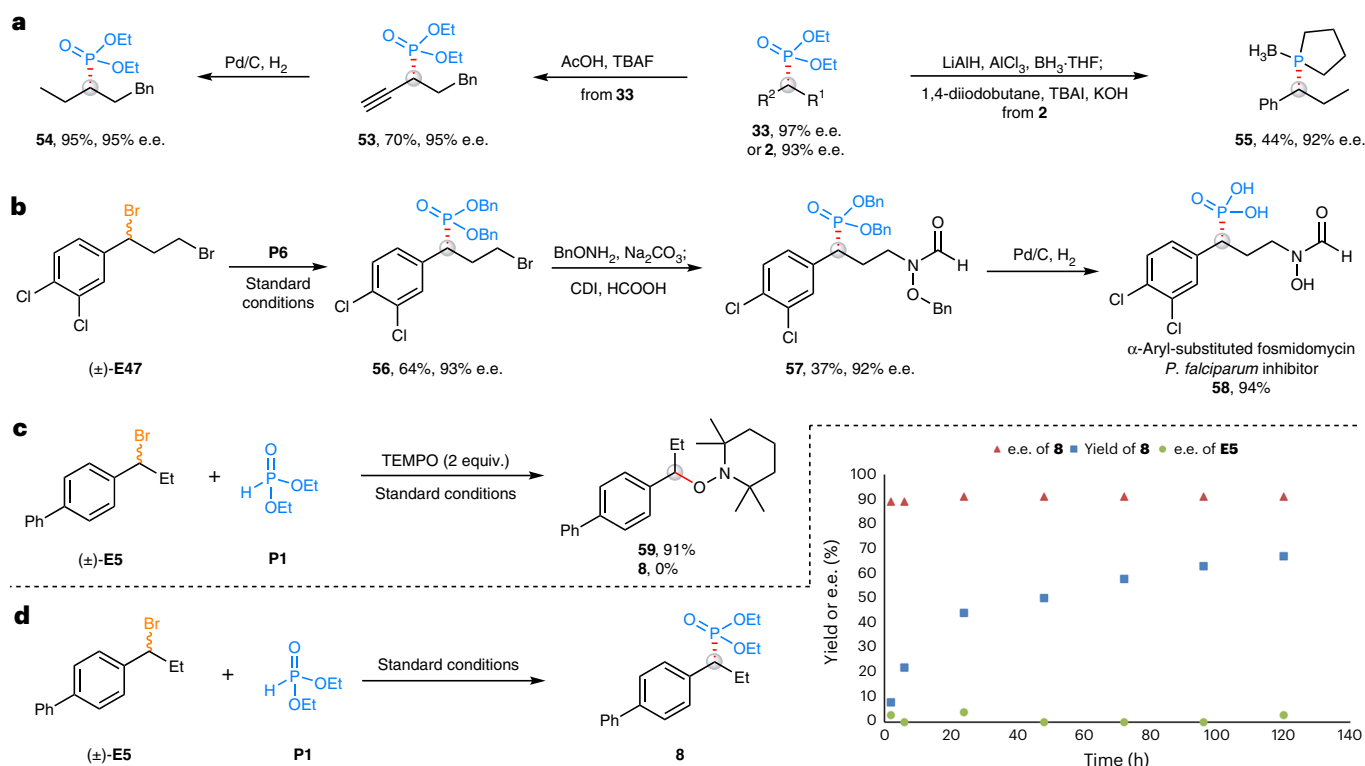
converted into enantioenriched  $\alpha$ -3,4-dichlorophenyl-substituted fosmidomycin **58** through a sequential substitution, acylation and deprotection process. Therefore, the present cross-coupling would provide a versatile platform for the diversity-oriented synthesis of such chiral fosmidomycin-derived library and is beneficial to the discovery of promising drug leads.

Concerning the reaction mechanism, a radical trap experiment with 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) revealed that the coupling was completely inhibited and the TEMPO-trapped product **59** was isolated instead (Fig. 2c). Additionally, no apparent enantioenrichment of the recovered alkyl bromide **E5** was observed under typical conditions (Fig. 2d), disfavoring a possible kinetic resolution of **E5**. Moreover, the observed e.e. values of the product remained nearly constant at different time intervals, favouring the involvement of a uniform mechanism throughout the reaction course. These observations strongly support the formation of alkyl radical species from alkyl halides. Overall, all these preliminary experimental results together with previous mechanistic studies<sup>57–62</sup> support our initial proposal, as shown in Fig. 1c.

## Conclusions

We have established a general copper-catalysed enantioconvergent radical Michaelis–Becker-type  $\text{C}(\text{sp}^3)\text{-P}$  cross-coupling of racemic





**Fig. 2 | Synthetic utility and mechanistic discussion.** **a**, Conversion of enantioenriched products to valuable chiral building blocks. **b**, Expedient synthesis of highly enantioenriched  $\alpha$ -3,4-dichlorophenyl-substituted fosmidomycin **58**. **c**, Radical trap experiment with TEMPO. **d**, No apparent

kinetic resolution of the alkyl bromide was observed and the nearly constant product enantiopurity suggested a uniform mechanism during the reaction. TBAF, tetrabutylammonium fluoride; TBAI, tetrabutylammonium iodide; CDI, 1,1'-carbonyldiimidazole.

alkyl halides with H-phosphonates. The key to the success is the use of chiral anionic ligands to forge the robust association of copper species with alkyl radical intermediate over the  $S_N2$  Michaelis–Becker process and P–P homocoupling, therefore exerting radical C( $sp^3$ )–P coupling with excellent chemo- and stereoselectivity. The reaction features a remarkably broad scope for alkyl halides and gives rise to a wide array of  $\alpha$ -chiral alkyl phosphorus compounds. The synthetic utility is also demonstrated in the facile transformation of the coupling products to many valuable enantioenriched building blocks and to drug leads. We anticipate that this strategy will open up new avenues for more enantioconvergent carbon–heteroatom cross-coupling reactions of racemic alkyl halides with other heteroatom nucleophiles.

## Methods

### Synthesis of 1–32

An oven-dried resealable Schlenk tube equipped with a magnetic stir bar was charged with CuI (5.7 mg, 0.03 mmol, 15 mol%), **L\*14** (30 mg, 0.036 mmol, 18 mol%) and  $\text{Cs}_2\text{CO}_3$  (130.0 mg, 0.40 mmol, 2.0 equiv.). The tube was evacuated and backfilled with argon three times. THF (2.0 mL) was then added by syringe under argon. (Hetero)benzyl bromides (0.30 mmol, 1.5 equiv.) and H-phosphonate (0.2 mmol, 1.0 equiv.) were sequentially added into the mixture and the reaction mixture was stirred at  $-15^\circ\text{C}$  for 5 days. Upon completion, the precipitate was filtered off and washed with ethyl acetate. The filtrate was evaporated and the residue was purified by flash column chromatography on silica gel to afford the desired product.

### Synthesis of 33–49

An oven-dried resealable Schlenk tube equipped with a magnetic stir bar was charged with CuI (3.8 mg, 0.020 mmol, 10 mol%), **L\*14** (20 mg, 0.024 mmol, 12 mol%) and  $\text{Cs}_2\text{CO}_3$  (130.0 mg, 0.40 mmol, 2.0 equiv.).

The tube was evacuated and backfilled with argon three times. PhCl (2.0 mL) was then added by syringe under argon. Propargyl halide (0.30 mmol, 1.5 equiv.) and H-phosphonate (0.2 mmol, 1.0 equiv.) were sequentially added into the mixture and the reaction mixture was stirred at  $0^\circ\text{C}$  for 5 days. Upon completion, the precipitate was filtered off and washed with ethyl acetate. The filtrate was evaporated and the residue was purified by flash column chromatography on silica gel to afford the desired product.

### Synthesis of 50 and 51

An oven-dried resealable Schlenk tube equipped with a magnetic stir bar was charged with CuI (3.8 mg, 0.020 mmol, 10 mol%), **L\*16** (9.0 mg, 0.024 mmol, 12 mol%),  $\text{Cs}_2\text{CO}_3$  (32.6 mg, 0.10 mmol, 0.5 equiv.) and  $\alpha$ -carbonyl alkyl halide (0.20 mmol, 1 equiv.). The tube was evacuated and backfilled with argon three times. Mixed solvent of 1,4-dioxane and THF (1/1 vol/vol, 2.0 mL) and H-phosphonate (0.20 mmol, 1.0 equiv.) were then sequentially added into the mixture and the reaction mixture was stirred at  $10^\circ\text{C}$  for 16 h. Upon completion, the precipitate was filtered off and washed with ethyl acetate. The filtrate was evaporated and the residue was purified by flash column chromatography on silica gel to afford the desired product.

### Synthesis of 52

An oven-dried resealable Schlenk tube equipped with a magnetic stir bar was charged with CuI (3.8 mg, 0.020 mmol, 10 mol%), **L\*17** (12.7 mg, 0.03 mmol, 15 mol%),  $\text{K}_3\text{PO}_4$  (255 mg, 1.2 mmol, 6 equiv.) and  $\alpha$ -aminocarbonyl- $\alpha$ -aryl alkyl chloride (0.20 mmol, 1 equiv.). The tube was evacuated and backfilled with argon three times. Toluene and H-phosphonate (0.30 mmol, 1.5 equiv.) were then sequentially added into the mixture and the reaction mixture was stirred at room temperature for 40 h. Upon completion, the precipitate was filtered

off and washed with ethyl acetate. The filtrate was evaporated and the residue was purified by column chromatography on silica gel to afford the desired product.

## Data availability

Data relating to the materials and methods, optimization studies, experimental procedures, mechanistic studies, HPLC spectra, NMR spectra and high-resolution mass spectrometry data are available in the Supplementary Information.

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## Author contributions

X.-Y.L. conceived and supervised the project. L.-L.W., H.Z., Y.-X.C., C.Z., Y.-Q.R., Z.-L.L. and Q.-S.G. designed and performed the experiments and analysed the data. X.-Y.L., and L.-L.W. wrote the paper. All authors discussed the results and commented on the manuscript.

## Competing interests

The authors declare no competing interests.

## Additional information

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