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The organocatalytic enantiodivergent fluorination of β-ketodiaryl-phosphine oxides for the construction of carbon-fluorine quaternary stereocenters†

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Commercially available cinchona alkaloids that can catalyze the enantiodivergent fluorination of β-ketodiarylphosphine oxides were developed to construct carbon-fluorine quaternary stereocenters. This protocol features a wide scope of substrates and excellent enantioselectivities, and it is scalable.

The fluorine atom has unique properties, such as high electronegativity, a similar atomic radius to that of the hydrogen atom, and especially its switchable lipophilicity, bioavailability and metabolic stability of the corresponding parent compound. Hence, chiral fluorine-containing molecules have attracted attention from synthetic chemists, medicinal chemists, biochemists, and material scientists.[1] Naturally available chiral organic fluorine-containing molecules are scarce.[2] Hence, enantioselective introduction of the fluorine atom into organic molecules is an indispensable approach to efficiently access fluorine-containing compounds. Consequently, numerous asymmetric fluorination methodologies[3] and some chiral fluorinating reagents[4] have been developed from synthetic communities. Despite the significant achievements made in the past decade, enantiodivergent preparation of two chiral compounds with enantiotopic fluorine-containing stereocenters has not been perfectly solved. This is especially true for the production of two enantioisomers bearing a chiral fluorine-containing quaternary stereocenter for further investigation of their characteristics in various fields of fluorine chemistry.[5] Therefore, exploration of enantiodivergent construction of chiral fluorine-containing quaternary stereocenters is needed urgently, but is synthetically challenging.

α-Substituted β-keto phosphine oxide is an important structural moiety,[6] and it could be applied in different disciplines.[7] Preparation of this moiety has been an exciting research area in recent years,[8] and the corresponding transformations have also been investigated.[9] However, the asymmetric variant involving this motif has been underexplored until now. Its analogue β-keto phosphonate has been investigated in some asymmetric transformations, and the transition metal-catalyzed asymmetric fluorination has been developed independently by Sodeoka, Kim, and Jørgensen (Scheme 1a).[10] Unfortunately, the organocatalytic asymmetric fluorination of β-keto phosphine oxide or β-keto phosphonate has not been explored, especially in enantiodivergent transformations.[11] Therefore, development of asymmetric transformations involving β-keto phosphine oxide are necessary and important.

As privileged chiral organocatalysts, cinchona alkaloid (CA) derivatives have unique properties. In particular, they are readily available chiral pseudoenantiomeric catalysts found in nature. Hence, an outstanding array of CA-catalyzed asymmetric reactions with excellent enantioselectivity have been developed.[12] Considering the unique catalytic abilities of CA derivatives, we

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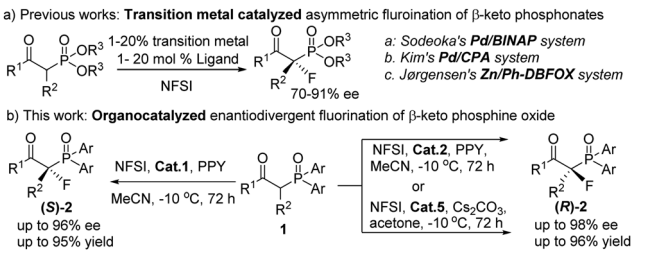


Scheme 1 The construction of carbon-fluorine quaternary stereocenters from α-substituted β-keto phosphonates and phosphine oxides.

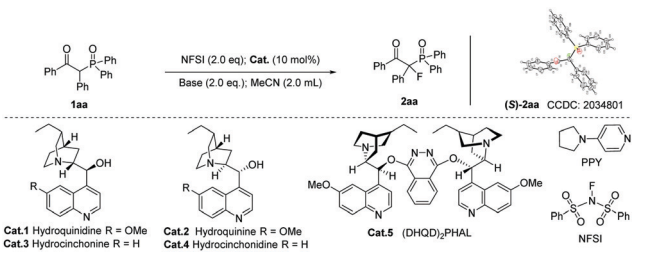
wished to further expand the asymmetric reactions of β-keto phosphine oxide. We also wished to continue with our research into the efficient construction of aza-quaternary C–X bonds.[13] Hence, we report here an enantiodivergent fluorination of α-substituted β-keto phosphine oxide catalyzed by CA-derived catalysts. This reaction resulted in two enantio-enriched isomers with excellent enantiomeric excess (ee) from the same starting materials (Scheme 1b).

Initially, we selected 2-(diphenylphosphoryl)-1,2-diphenylethanone (**1aa**) as a model substrate, *N*-fluorodibenzene-sulfonimide (NFSI) as the fluoride source, and commercially available CA derivatives as catalysts to investigate the reaction conditions for fluorination (Table 1).[14] Screening of various reaction parameters showed that when 4-pyrrolidinopyridine (PPY)[15] was used as a base and 10% hydroquinidine (HQD, **Cat. 1**) was used as a catalyst, the expected product **2aa** was isolated in 91% yield with 87% ee (entry 1). Pleasingly, lowering the reaction temperature resulted in excellent enantioselectivity (94% ee) and good chemical yield (86%) (entry 2).[14,16] A further decrease in the reaction temperature led to low conversion, and the starting material **1aa** was recovered. Finally, NFSI was replaced by other fluorine sources to further optimize the reaction conditions. However, better results were not obtained.[14] Therefore, the reaction parameters listed in entry 2 were selected as the optimal reaction conditions.

Using these optimal conditions, we explored the scope of substrates for the (*S*)-selective procedure (Method I), and the reaction results are shown in Scheme 2. For aryl ketones moieties, various substrates bearing electron-donating groups (EDGs) or electron-withdrawing groups (EWGs) on the aryl ring at *ortho*, *meta*, or *para* positions were first evaluated, which all afforded the corresponding products (*S*)-**2ab**-(*S*)-**2ai** in good-to-excellent yields (54–92%) with excellent enantioselectivities (≤96% ee).[16] Moreover, substrate **1aj** with α-naphthyl group was tolerated, and generated the desired product (*S*)-**2aj** (96% ee and 77% yield). For aryl moieties at the α-position of the carbonyl group, most substrates with EWGs (*e.g.*, F, Cl, Br, and even CF_3) or EDGs (*e.g.*, Me and OMe) reacted well, producing the desired products (*S*)-**2ak**-(*S*)-**2as** in good-to-excellent yields (50–94%) with 90–95% ee.[16] It seems that the *meta*-position substituent at the aryl ring had a marginal effect in product yields (low conversion) but slightly influenced the enantioselectivity, and the products (*S*)-**2am** and (*S*)-**2ar** were isolated in 32% and 30% yields, respectively. 2-Naphthyl, 3-thienyl, and different functionalized diaryl-substituted substrates were well tolerated, and yielded the corresponding products (*S*)-**2at**-(*S*)-**2av** in moderate yields with excellent enantioselectivities. Then, diaryl oxide moieties were examined, and various EDGs (Me, OMe) and EWGs (Cl, CF_3) substituents at the aryl ring had a slight influence on the reaction outcomes, and delivered the expected products (*S*)-**2aw**-(*S*)-**2az** in good yields with high enantioselectivies. Subsequently, replacement of aryl substituents with aliphatic substituents in the α-branched position of the carbonyl group was investigated. Results showed that asymmetric fluorination was also compatible with the alkyl-substituted substrates, and the expected products (*S*)-**2ba**-(*S*)-**2be** were isolated in good-to-excellent yields with good-to-excellent enantioselectivity. Finally, a cyclic substrate **1ca** also produced the desired fluorinating product (*S*)-**2ca** (95% yield and 90% ee),[16] whereas the linear substrate **1cb** gave good enantioselectivity with a low yield.[14] Hence, this methodology for asymmetric fluorination featured a wide scope of substrates in terms of substituents at carbonyl α positions (cyclic or linear alkyl substituents or aryl substituents), with each case yielding the expected α-fluorinated product.

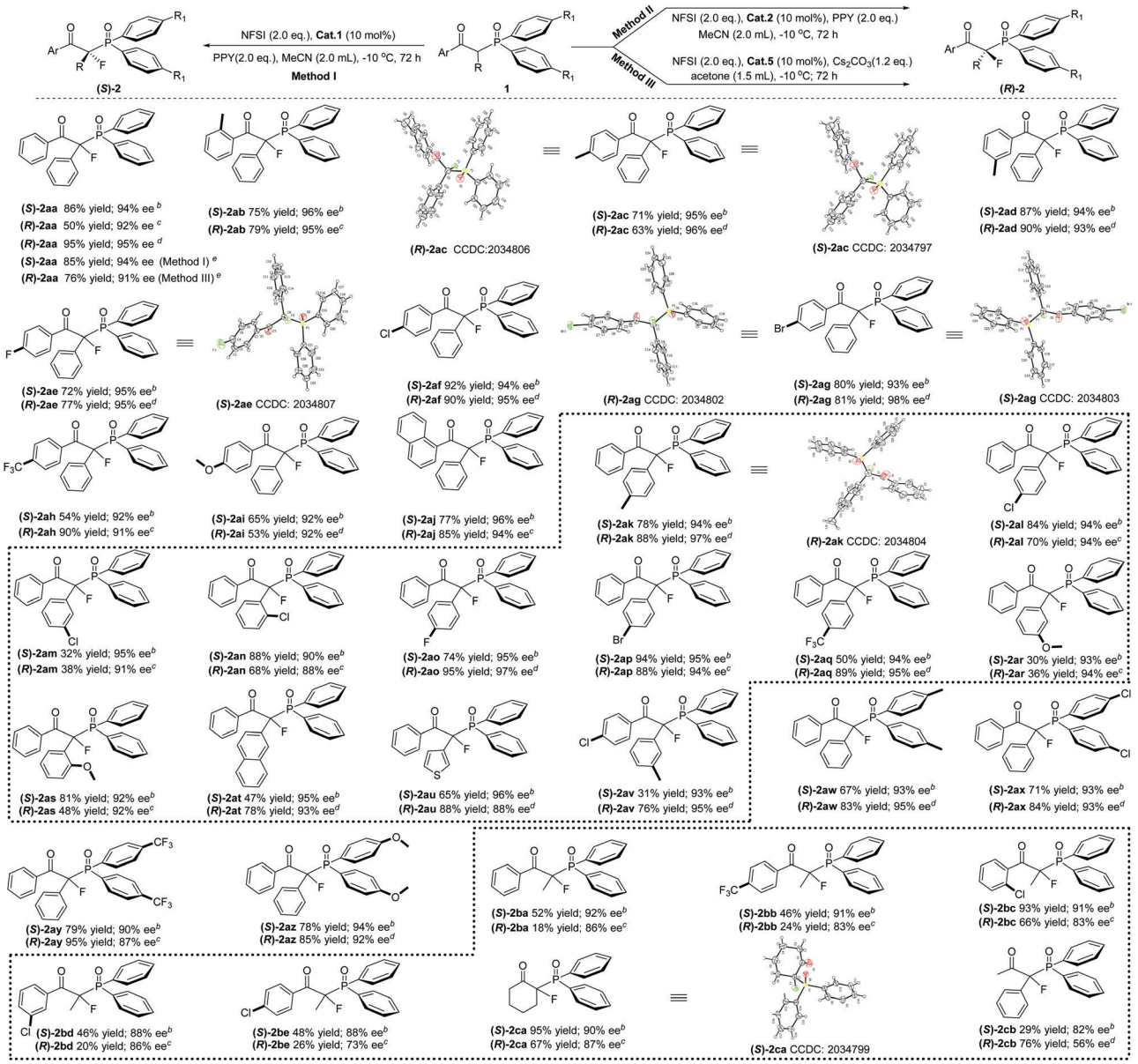
Two enantioisomers with chiral fluorine-containing stereocenters, in general, showed very distinct properties in organic functional molecules. Therefore, after completing expansion of the substrate scope of (*S*)-products, we turned our attention to enantiodivergent transformation. The pseudo-enantiomeric catalyst hydroquinine (HQ, **Cat. 2**) was used to replace **Cat. 1** under the optimal reaction conditions (entry 3, Table 1, Method II) to prepare the corresponding (*R*)-configuration products starting from the same materials. To our pleasure, almost all expected (*R*)-products were synthesized readily merely by varying the catalyst (Scheme 2).[14] Various substrates bearing EDGs or EWGs at different positions of three aryl rings or alkyl substituents at the α-position of carbonyl group were also compatible, and resulted in the desired products (***R***)-**2** obtained in good-to-excellent yields with excellent enantioselectivity, in most cases.[16] These results demonstrated that enantiodivergent fluorinated products could be obtained concisely by varying commercially available catalysts. However, in comparison with the reaction results from its isomer **Cat. 1**, the yield and ee value of (***R***)-**2** products catalyzed by **Cat. 2** were relatively lower in some cases. To improve these unsatisfactory results, we screened other commercially available cinchona catalysts (entries 4–6).[14] Pleasingly, when the dimetric catalyst **Cat. 5** was used, the **(*R*)-2aa** product was obtained in 95% yield with 95% ee through changing the base to Cs_2CO_3 and the solvent to acetone (entry 6, Table 1, Method III).[14] Therefore, these slightly changed reaction conditions were used to improve some low yields and enantioselectivities of (*R*)-selective

Table 1 Optimization of the reaction conditions[a]



Entry	Cat.	Base	Temp. (°C)	Time (h)	Yield[b] (%)	ee[c] (%)
1	**Cat. 1**	PPY	r.t.	24	91	−87[d]
2	**Cat. 1**	PPY	−10	72	86	−94
3	**Cat. 2**	PPY	−10	72	50	+92[e]
4	**Cat. 3**	PPY	−10	72	36	−94
5	**Cat. 4**	PPY	−10	72	43	+93
6	**Cat. 5**	Cs_2CO_3	−10	72	95	+95[f]

[a] Reaction was undertaken using substrate **1aa** (0.1 mmol). [b] Isolated yield. [c] ee was determined *via* UPC[2]. [d] The **(*S*)-2aa** product was obtained. [e] The **(*R*)-2aa** product was obtained. [f] 1.2 eq. Cs_2CO_3 was used in 1.5 mL of acetone.



Scheme 2 The substrate scope of the enantiodivergent fluorination of β-keto diarylphosphine oxides. [a] The reaction was undertaken on a 0.1 mmol scale, and isolated yield and ee values were determined *via* UPC^2; [b] Method I was applied; [c] Method II was applied; [d] Method III was applied; [e] the reaction was undertaken on a 1 g scale.

transformation, and some representative results are listed in Scheme 2.[14]

Furthermore, two gram-scale model reactions were carried out, and **(*S*)-2aa** was isolated in 94% ee with 85% yield, whereas **(*R*)-2aa** was isolated in 91% ee with 76% yield (Scheme 2). Remarkably, a single recrystallization of two resulting products could increase the ee value to 99%. These results indicated that our methodology was practical for the preparation of fluorinated β-keto diarylphosphine oxide.

In conclusion, we developed, for the first time, the enantiodivergent fluorination of α-substituted β-keto diarylphosphine oxides catalyzed by commercially available CA derivatives. Two desired enantioisomers with a fluorine-containing quaternary stereocenter were obtained conveniently at ≤98% ee with moderate-to-excellent yields (≤95%). This transformation features a wide scope of substrates, switchable enantioselectivity, and a scalable procedure.

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Conflicts of interest

There are no conflicts to declare.

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16 CCDC numbers: 2034801 ((***S***)-**2aa**), 2034797 ((***S***)-**2ac**), 2034806 ((***R***)-**2ac**), 2034807 ((***S***)-**2ae**), 2034803 ((***S***)-**2ag**), 2034802 ((***R***)-**2ag**), 2034804 ((***R***)-**2ak**) and 2034799 ((***S***)-**2ca**)†.

