Organocatalysis

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Phosphine-Catalyzed Asymmetric Umpolung Addition of Trifluoromethyl Ketimines to Morita–Baylis–Hillman Carbonates

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Abstract: *A novel phosphine-catalyzed, highly enantioselective umpolung addition of trifluoromethyl ketimines to Morita–Baylis–Hillman carbonates was developed and it provides facile access to optically active trifluoromethyl amines with a chiral tertiary stereocenter under mild reaction conditions. The salient features of this reaction include general substrate scope, mild reaction conditions, good yields, high enantioselectivity, ease of scale-up to gram scale, and further transformations of the products.*

The presence of fluorine in organic molecules of pharmaceutical and agrochemical importance has had a beneficial yet unique impact on the bioactivities of the molecules, and led to a rapidly increasing demand for developing novel methodology to efficiently synthesize organofluorine compounds.[1] Among fluorinated compounds, chiral trifluoromethyl amines were widely found as the key structural subunits in many biologically interesting compounds, and were recognized to improve lipophilicity and metabolic stability over that of the corresponding methyl amines (Figure 1).[2]

In light of their importance, various powerful strategies for the synthesis of chiral trifluoromethyl amines have been developed in the past years. The strategy which takes advantage of the inherent electrophilicity of prochiral trifluoromethyl imines and their reaction with various nucleophiles has received much attention and several elegant reactions have been reported (Scheme 1 a, left-hand side).[3] For example, the groups of Hoveyda,[3b] Ye,[3c] and Huang,[3d] disclosed highly enantioselective nucleophilic additions to trifluoromethyl ketimines catalyzed by chiral metal or organic catalysts. Although these methods are effective, they are often hampered by the multistep preparation of the reactants as well as the narrow range of products, that is, only aromatic trifluoromethyl amines could be obtained. Consequently, the development of novel and general method for enantioenriched trifluoromethyl amines bearing a chiral tertiary stereocenter is still highly desirable.

In contrast, umpolung of trifluoromethyl imines, that is, inverting the polarization of imines as a nucleophile, may provide alternative access to structures and addition patterns

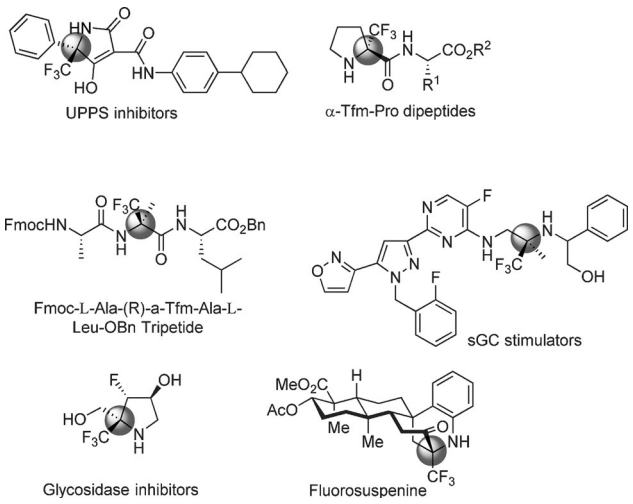
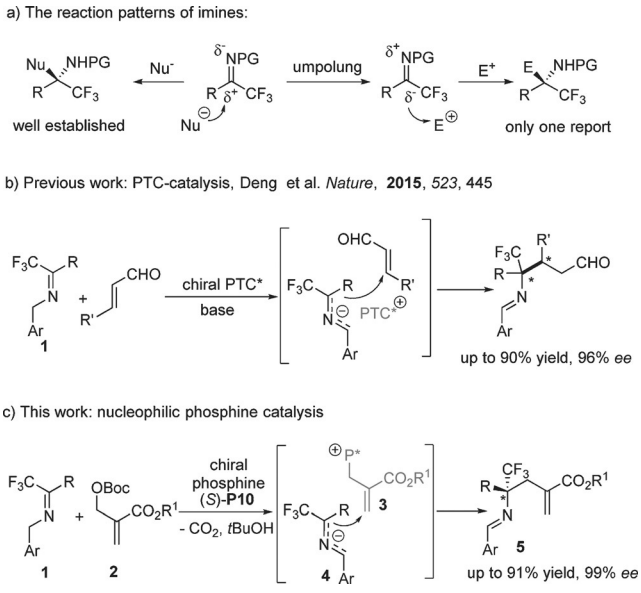


Figure 1. Biologically active natural products containing pyrrolidine and azepine skeletons. Fmoc = 9-fluorenylmethyloxycarbonyl.



Scheme 1. Asymmetric synthesis trifluoromethylamine bearing a tertiary stereocenter through an umpolung strategy. Boc = *tert*-butoxycarbonyl, PG = protecting group.

which are not (or hardly) accessible by previous methods (Scheme 1 a, right-hand side).[4,5] However, this strategy poses considerable challenges because of the unavoidable reversal of the inherent electrophilicity of imines. Only one example of

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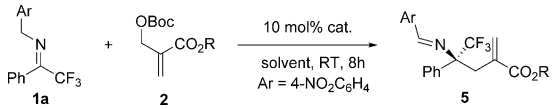
the asymmetric umpolung addition of trifluoromethyl ketimines to electrophiles has been documented so far.[6] Very recently, Deng and co-workers successfully applied this umpolung strategy to the synthesis of optically active trifluoromethyl amines, with a chiral tertiary stereocenter, from readily available trifluoromethyl ketimines (**1**) and enals by the employing a chiral phase-transfer catalyst (PTC; Scheme 1b). Inspired by Deng's work and our continual interest in asymmetric phosphine catalysis,[7,8] we envisaged that the Morita–Baylis–Hillman (MBH) carbonates **2**, another very readily available and widely used compounds in organocatalytic reactions,[9] would generate the chiral quaternary phosphonium salts **3** in the presence of chiral phosphine catalyst (Scheme 1c). Subsequent S_N2' reaction with the in situ generated 2-azaallyl anions **4** would deliver the corresponding enantioenriched triflormethyl amines **5** with a chiral tertiary stereocenter. Herein, we report a novel phosphine-catalyzed and highly enantioselective umpolung addition of trifluoromethyl ketimines to MBH carbonates under mild reaction conditions, and it provides facile access to optically active trifluoromethyl amines with a chiral tertiary stereocenter. Moreover, synthetically valuable α-methylene γ-lactams could be achieved through further transformations of the products by the use of a simple protocol.

With this hypothesis in mind, we chose the phenyl trifluoromethyl ketamine **1a** with the MBH carbonate **2a** as model substrates (Table 1). A wide variety of chiral phosphine

Table 1: Reaction optimization.[a]



Entry	**2**, R =	Cat.	Solvent	Yield [%][b] (*ee* [%])[c]
1	**2a**, Me	(S,R_S)-**X1**	PhMe	**5aa**, 61 (62)
2	**2a**	(S,R_S)-**X10**	PhMe	**5aa**, 67 (63)
3	**2a**	(S,R_S)-**W1**	PhMe	**5aa**, 64 (42)
4	**2a**	(S,R_S)-**P1**	PhMe	**5aa**, 67 (60)
5	**2a**	(S,R_S)-**P2**	PhMe	**5aa**, 62 (57)
6	**2a**	(S,R_S)-**P3**	PhMe	**5aa**, 65 (62)
7	**2a**	(S,R_S)-**P4**	PhMe	**5aa**, 68 (58)
8	**2a**	(S,R_S)-**P5**	PhMe	**5aa**, 72 (75)
9	**2a**	(S,R_S)-**P6**	PhMe	**5aa**, 67 (55)
10	**2a**	(S,R_S)-**P7**	PhMe	**5aa**, 66 (66)
11	**2a**	(S,R_S)-**P8**	PhMe	**5aa**, 71 (60)
12	**2a**	(*S*)-**P9**	PhMe	**5aa**, 70 (42)
13	**2a**	(*S*)-**P10**	PhMe	**5aa**, 78 (81)
14	**2b**, Et	(*S*)-**P10**	PhMe	**5ab**, 74 (92)
15	**2c**, Bn	(*S*)-**P10**	PhMe	**5ac**, 77 (80)
16	**2d**, *i*Pr	(*S*)-**P10**	PhMe	**5ad**, 75 (96)
17	**2e**, *t*Bu	(*S*)-**P10**	PhMe	**5ae**, 85 (98)
18	**2e**	(*S*)-**P10**	THF	**5ae**, 78 (95)
19	**2e**	(*S*)-**P10**	DCM	**5ae**, 84 (95)
20	**2e**	(*S*)-**P10**	Et_2O	**5ae**, 79 (94)
21[d]	**2e**	(*S*)-**P10**	PhMe	**5ae**, 82 (99)
22[e]	**2e**	(*S*)-**P10**	PhMe	**5ae**, 73 (97)
22[f]	**2e**	(*S*)-**P10**	PhMe	**5ae**, 52 (94)

[a] Unless otherwise specified, **1a** (0.2 mmol), **2** (0.3 mmol), catalyst (0.02 mmol), solvent (2 mL), RT. [b] Yield of isolated product. [c] Determined by HPLC analysis using a chiral stationary phase. [d] 0 °C. [e] 5.0 mol% catalyst, 24 h. [f] 2.5 mol% catalyst, 48 h.

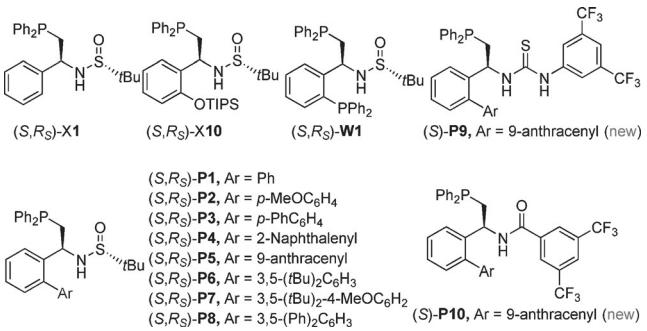
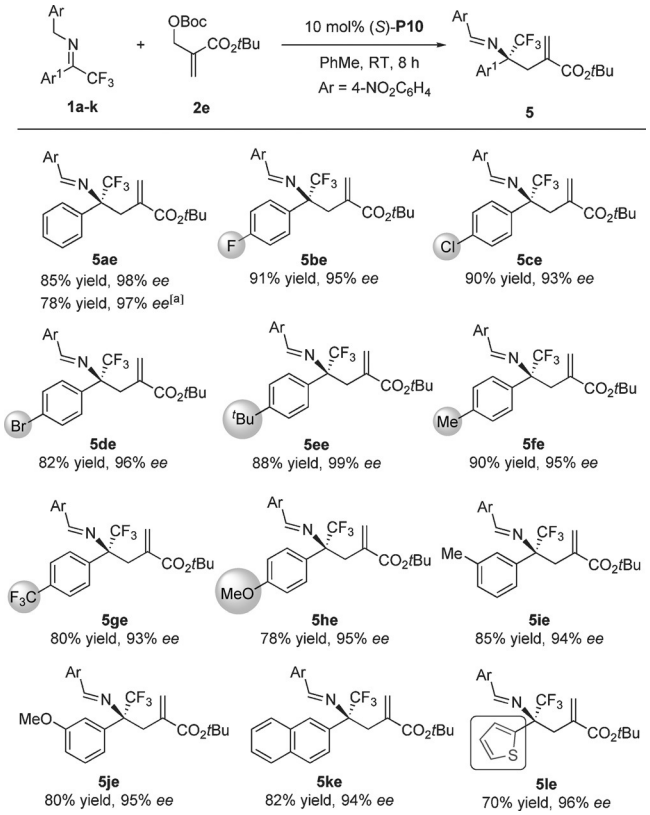


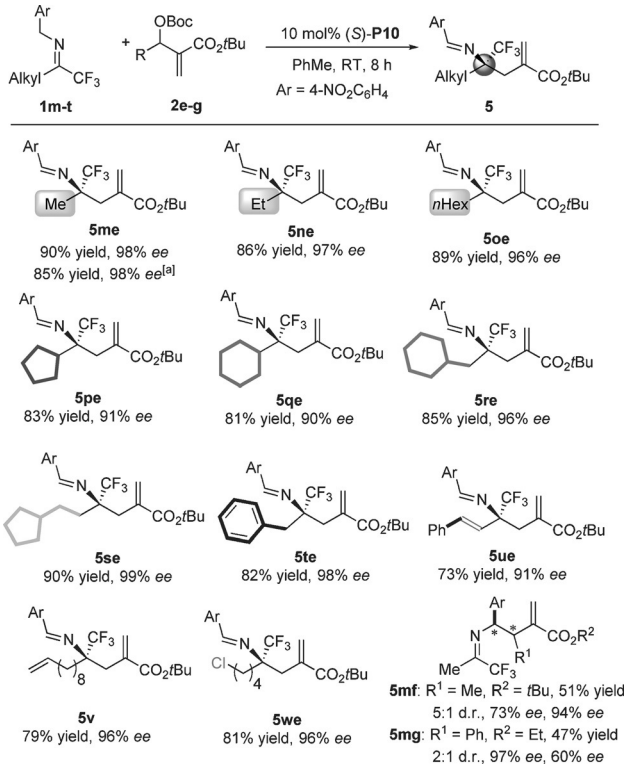
Figure 2. The screened chiral phosphine catalysts.

catalysts were examined at room temperature. Our recently developed chiral phosphine catalysts Xiao-Phos (S,R_S)-**X1** and (S,R_S)-**X10** (Figure 2), as well as Wei-Phos (S,R_S)-**W1** gave the adduct **5aa** in moderate enantioselectivities (Table 1, entries 1–3). The substituent effect at the *ortho*-position of the phenyl ring, such as in (S,R_S)-**P1**–**P8**, was then investigated. (S,R_S)-**P5**, with the rigid 9-anthracenyl substituent gives better results (entry 8). To further enhance the capability of hydrogen-bonding or proton donation, two new catalysts, (*S*)-**P9** with 3,5-bistrifluoromethylphenyl thiourea and (*S*)-**P10** with 3,5-bistrifluoromethyl benzoyl, were prepared from **P5** in two steps (entries 12 and 13). To our delight, 78% yield and 81% *ee* could be obtained for the product when using (*S*)-**P10** as the catalyst. Further studies showed that the *ee* values and yields could be further improved with increasing the size of the ester group of the MBH carbonate from methyl to ethyl, isopropyl, and *tert*-butyl (entries 14–17), and the adduct **5ae** was obtained in 85% yield with 98% *ee* from **2e**. The evaluation of the solvents showed that toluene was the best reaction medium in terms of reactivity and enantioselectivity (entries 17–19). And an 82% yield with 99% *ee* could be furnished when running the reaction of **1a** with **2e** at −10 °C instead of room temperature. Remarkably, the catalyst loading could be further reduced to 2.5 mol%, thus delivering 52% yield and 94% *ee*.

With the optimized reaction conditions in hand, the scope with respect to the aryl trifluoromethyl ketimines **1** was investigated by reaction with **2e** (Scheme 2). To our delight, the aryl trifluoromethyl ketimines bearing diverse functional groups, such as the halogens (F, Cl, Br), an electron-withdrawing group (CF_3), and electron-donating groups (*t*Bu, Me, OMe) at the *para*-position of the phenyl ring generally react well, thus delivering the corresponding products **5de**–**he** in good yields with 93–99% *ee* values under the optimal reaction conditions. Further substrate scope investigation demonstrated that the *meta*-substituent of the aryl trifluoromethyl ketimines is also compatible and delivers the desired products **5ie**–**je** in good yields and high enantioselectivities. High *ee* values and good yields could be also obtained when phenyl was replaced by other aryl groups such as naphthyl (**5ke**) and thienyl (**5le**). For example, the thienyl-derived **1l** delivered the corresponding amine **5le** in 70% yield with 96% *ee*. Finally, it is noteworthy that this reaction is amenable to gram scale without obvious loss of the efficiency and enantioselectivity, even with a lower catalyst loading. **5ae** could be



Scheme 2. Asymmetric umpolung reaction of aryl trifluoromethyl imines with MBH carbonates. [a] The gram-scale experiment was carried out with 5 mmol of **3a** and 6 mmol of **2e** and (*S*)-**P10** (5 mol%) at RT.

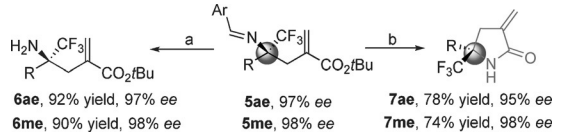


Scheme 3. Asymmetric umpolung reaction of alkyl trifluoromethyl imines with MBH carbonate. [a] The gram-scale experiment was carried out with 5 mmol of **1m** and 6 mmol of **2e** and (*S*)-**P10** (5 mol%).

obtained in 78% yield with 97% *ee* for a 5 mmol scale reaction with the use of 5 mol% (*S*)-**P10**.

Encouraged by the above results, we extended the scope of aryl trifluoromethyl ketimines to alkyl trifluoromethyl ketimines (Scheme 3). To our delight, a broad range of either linear or α,β-branched alkyl trifluoromethyl ketimines worked well with **2e** to furnish the desired products **5me**–**te** in 81–90% yields with 90–99% *ee* values. It is noteworthy that even the pretty challenging substrate, the methyl trifluoromethyl ketimine **1m**, with two similarly bulky groups, delivered the desired adduct **5me** in 90% yield with 98% *ee*, and again this reaction was amenable to gram scale, with a lower catalyst loading (5 mol%), without loss of the efficiency and enantioselectivity. Moreover, the trifluoromethyl ketimines **1u**, **1v**, and **1w** with diverse functional groups gave the desired products **5ue**–**we** in good yields and excellent *ee* values.[10] When the substituted MBH adducts **2f** and **2g** were used, the direct substitution without polarity inversion (umpolung) of the imine[3n] instead of the umpolung addition was observed, thus delivering moderate yields of **5mf** and **5mg**, having two contiguous stereocenters, in moderate to good stereoselectivities.

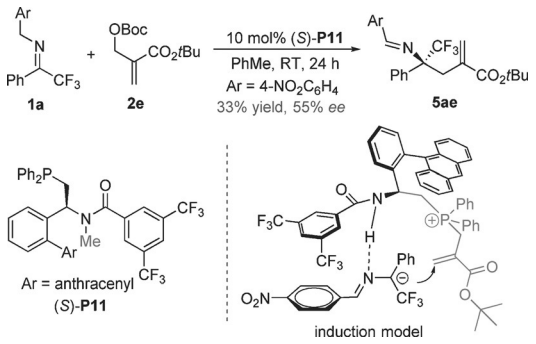
To illustrate the synthetic utility of the present transformation, two representative transformations of the products were performed as shown in Scheme 4. Upon subjection of **5ae** and **5me** to 1M HCl at room temperature, the imine moiety readily underwent hydrolysis to give the desired chiral



Scheme 4. Further transformations of the products **5ae** and **5me**. Reaction conditions: a) 1M HCl, THF, RT; b) 1. CF_3CO_2H, 2. EDC, DCM, RT. DCM = dichloromethane, EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride.

trifluoromethyl amines **6ae** (92%) and **6me** (90%), respectively, without loss of the chiral information. Further transformations of **5ae** and **5me** were realized by treatment with CF_3CO_2H and then EDC, thus providing the synthetically valuable α-methylene γ-lactams **7ae** and **7me**, respectively, in good yields with the excellent *ee* values. They could serve as valuable synthetic building blocks, and are often found in many anticancer drugs because of its cytotoxic properties.[11] The structures and absolute configurations of **7ae** and **7me** were established by X-ray crystallographic analysis and other products were assigned by analogy.[12]

It appears that the enantioselectivity is primarily influenced by the MBH carbonate moiety, and might provide a certain rationale for the stereochemical outcome. A plausible chirality induction model is proposed in Scheme 5, where the hydrogen bonding between the amide NH with the imine might play a crucial role in chirality induction. Indeed, the N-methylated chiral phosphine catalyst (*S*)-**P11**[13] deliv-



Scheme 5. The NH-effect study and the chirality induction model.

ered **5ae** in only 33% yield with 51% *ee* after 24 hours, thus indicating that the hydrogen-bonding interaction might indeed contribute significantly to the catalytic activity and enantioselectivity control.

In summary, we have developed a new method for asymmetric synthesis of enantioenriched trifluoromethyl amines with a chiral tertiary stereocenter by a highly effective and enantioselective phosphine-catalyzed umpolung addition of trifluoromethyl imines to MBH carbonates under mild reaction conditions. The salient features for this transformation include general substrate scope, mild reaction conditions, good yields, high enantioselectivity, ease of scale-up to gram scale, and easy conversion into valuable chiral γ-trifluoromethyl amines, α-methylene esters, and α-methylene γ-lactams. Further studies, including the application of this new type of chiral phosphine to other related reactions, and the metal-catalyzed asymmetric umpolung coupling reaction of trifluoromethyl ketimines are underway, and will be reported in due course.

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Keywords: asymmetric catalysis · enantioselectivity · fluorine · organocatalysis · umpolung

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[12] CCDC 1474183 (**7ae**) and 1474183 (**7me**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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