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Enantioselective organocatalytic oxa-Michael addition of oximes to β-CF_3-β-disubstituted nitroalkenes: efficient synthesis of β-amino-α-trifluoromethyl alcohol

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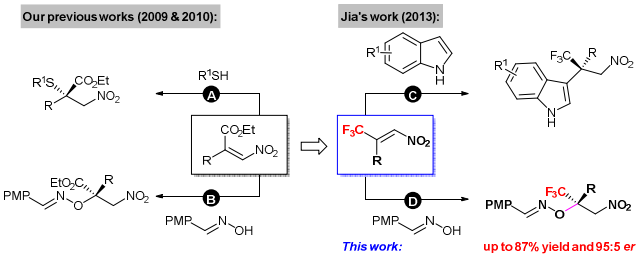
An enantioselective oxa-Michael addition of oxime to β-CF_3-β-disubstituted nitroalkenes catalyzed by a chiral bifunctional cinchona alkaloid-based thiourea has been developed. A variety of trifluoromethylated oxime ethers possessing a tetrasubstituted carbon stereocenter were obtained in good yields with high enantioselectivities.

Trifluoromethylated (CF_3) organic molecules play a primordial role in pharmaceuticals, agrochemicals, and functional materials due to the enhanced metabolic stability, bioavailability, lipophilicity, and binding selectivity upon incorporation of CF_3 group into the parent scaffolds.[1] Accordingly, the development of highly effective methods for the construction of structurally diverse organic molecules bearing a CF_3 moiety has attracted extensive research interest from the synthetic community.[2] In this context, many elegant examples have been established over the past few decades. Typically, there are two types of strategic construction of trifluoromethylated compounds. One is the use CF_3-transfer reagents for introduction of CF_3 into organic chemicals,[2a,3] while the other method is based on the direct functionalization of CF_3-bearing precursors.[4]

Compared with the transition metal-promoted trifluoromethylation reaction, the organocatalytic variants of direct functionalization of CF_3-bearing precursors remain largely unexplored. Recently, Shibata and co-workers have nicely disclosed an enantioselective trifluoromethylation of azamethine imines[5] and an epoxidation of β-CF_3-β-disubstituted enones[6] by phase-transfer catalysis, respectively. The Deng group in 2012 reported an unprecedented 9-OH cinchona alkaloid derivatives-catalyzed highly enantioselective isomerization of aryl and alkyl trifluoromethyl imines, affording the corresponding trifluoromethylated amines with high yields and excellent enantiomeric excesses.[7] Despite these impressive advances, however, the development of efficient organocatalytic methods for the construction of trifluoromethylated quaternary stereogenic centers in a highly enantioselective manner remains a intriguing but challenging task for the organic and medicinal chemists.[8] Recently, Jia and co-workers documented an elegant nickel-catalyzed asymmetric Friedel-Crafts alkylation reaction between indoles and β-CF_3-β-disubstituted nitroalkenes, leading to the formation of diversely functionalized C-3 substituted indoles with trifluoromethylated all-carbon quaternary stereocenters with high yields and excellent enantioselectivities (Scheme 1C).[9]

On the other hand, organocatalytic oxa-Michael addition reactions have been recently established as one of the most straightforward tools for the formation of carbon-oxygen bonds with wide application in the synthesis of natural products.[10] For instance, You and co-workers developed a chiral phosphoric acid-catalyzed asymmetric intramolecular oxa-Michael reaction for desymmetrization of cyclohexadienones, providing the corresponding optically active 1,4-dioxane derivatives with excellent yields and enantioselectivities.[11] Shortly after, the Ye group has achieved an asymmetric intramolecular oxa-Michael reaction of cyclohexadienones by using primary amine salt as the catalyst.[12] As a class of valuable "soft" oxygen nucleophiles, oximes have proved to be a new type of suitable oxygen-centered nucleophiles in the asymmetric intermolecular conjugate addition.[13] In this context, our group have developed two types of organocatalytic asymmetric Micheal addition reactions of thiols[14] and oximes[15] to trisubstituted nitroacrylates using chiral bifunctional cinchona alkaloid-based thiourea (Scheme 1A and 1B). To our knowledge, however, the enantioselective oxa-conjugate addition reaction with β-CF_3-β-disubstituted nitroalkenes as Michael acceptors has never been explored probably due to their low reactivity and steric encumbrance. Inspired on the development of bifunctional thiourea catalysts in conjugate additions,[16] we have recently achieved an organocatalytic asymmetric intermolecular Michael addition of oximes to β-CF_3-β-disubstituted nitroalkenes. The reaction afforded the corresponding synthetically and biologically significant chiral CF_3-bearing oxime ethers in high yield with good enantioselectivities (Scheme 1D). Herein, we wish to communicate our detailed results.

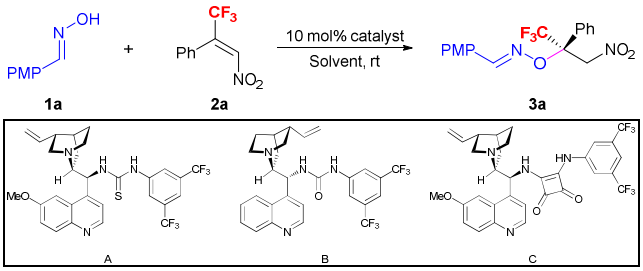


Scheme 1 Enantioselective conjugate addition of β, β-disubstituted nitroalkenes.

At the outset of our studies, we investigated the feasibility of the reaction by choosing 4-methoxybenzaldehyde oxime **1a** and

β-CF_3-β-disubstituted nitroalkene **2a** as the model substrates in the presence of various bifunctional organocatalysts in toluene at room temperature (please see ESI for more details). As shown in Table 1, cinchona alkaloid-based thiourea **A** was identified to be the best catalysts for this reaction, affording the desired product **3a** with moderate yield and enantioselectivity (Table 1, entry 1). With catalyst **A**, we then continued to screen the reaction media and temperature to further improve the efficiency and enantioselectivity. A brief survey of common solvents demonstrated that the reaction in nonpolar solvents provided somewhat superior results (Table 1, entry 1 vs entries 4-8). Further examination of various aromatic solvents showed that mesitylene was the optimal reaction medium and the desired product **3a** was obtained in 91% yield with 92:8 er value (Table 1, entry 10). The enantioselectivity could be slightly improved upon lowering the reaction temperature to 0 °C (Table 1, entry 11).

Table 1 Optimization of the reaction conditions[a]

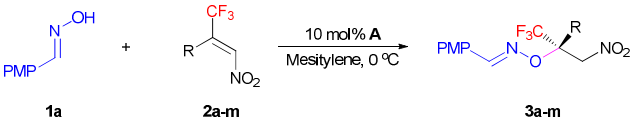


Entry	Solvent	Catalyst	*t* (h)	Yield[b] (%)	e.r.[c]
1	toluene	**A**	72	75	88:12
2	toluene	**B**	96	71	30:70
3	toluene	**C**	105	54	84:16
4	DCE	**A**	91	88	54:46
5	Et_2O	**A**	104	54	83:17
6	THF	**A**	115	8	60:40
7	CH_3CN	**A**	120	46	40:60
8	*n*-hexane	**A**	62	69	76:24
9	chlorobenzene	**A**	50	88	83:17
10	mesitylene	**A**	50	91	92:8
11[d]	**mesitylene**	**A**	**72**	**75**	**93:7**

[a] Unless noted, reactions were carried out with **1** (0.40 mmol), **2a** (0.20 mmol) and catalyst (10 mol%) in solvent (1.0 mL) at rt. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Conducted at 0 °C.

Under the optimized conditions, the generality of this reaction was then evaluated using a variety of β-CF_3-β-disubstituted nitroalkenes, and representative results are highlighted in Table 2. In addition to **2a**, the oxa-Michael reaction tolerated a wide range of β-CF_3-β-disubstituted nitroalkenes bearing Me, Cl, Br, and CF_3 at *meta* or *para* positions on the benzene ring, giving the corresponding products with good yields (67-87%) with er values (87:13 to 95:5, Table 2, entries 2-9). Surprisingly, the reaction with nitroalkene **2f** bearing a Cl at *ortho* position of the phenyl ring led to no formation of the corresponding product **3f**, which was also observed by Jia in asymmetric Friedel-Crafts alkylation reaction of indoles with β-CF_3-β-disubstituted nitroalkenes (Table 2, entry 6). Moreover, β-naphthyl, heteroaryl and alkyl substituted β-CF_3-disubstituted nitroalkenes also reacted well with 4-methoxybenzaldehyde oxime **1a** under the optimal conditions (Table 2, entries 11-13), while the relatively less sterically hindered alkyl substituted substrate **2m** resulted in a significant decrease of enantioselectivity (Table 2, entry 13). Fortunately, the use of cinchonidine-derived thiourea catalyst increased the enantiomeric ratio from 73:27 to 85:15 (Table 2, entry 14).

Table 2 Substrate scope of β-CF_3-β-disubstituted nitroalkenes[a]



Entry	R	Product	Yield[b] (%)	e.r.[c]
1	Ph (**2a**)	**3a**	75	93:7
2	3-MePh (**2b**)	**3b**	74	93:7
3	4-MePh (**2c**)	**3c**	70	90.5:9.5
4	3,5-Me_2Ph (**2d**)	**3d**	77	95:5
5[d]	4-MeOPh (**2e**)	**3e**	71	92:8
6	2-ClPh (**2f**)	**3f**	n.d.[e]	-
7	3-ClPh (**2g**)	**3g**	87	93.5:6.5
8	4-ClPh (**2h**)	**3h**	67	89:11
9	4-BrPh (**2i**)	**3i**	86	87:13
10	4-CF_3 (**2j**)	**3j**	80	79:21
11	2-naphthyl (**2k**)	**3k**	83	91:9
12	3-thienyl (**2l**)	**3l**	69	90.5:9.5
13	2-phenylethyl (**2m**)	**3m**	71	73:27
14[f]	2-phenylethyl (**2m**)	**3m**	52	85:15

[a] Unless noted, reactions were carried out with **1** (0.40mmol), **2** (0.20 mmol) and **A** (10mol %) in mesitylene (1.0 mL) at 0 °C for 3 d. [b] Isolated yield. [c] Determined by chiral HPLC. [d] For 4 d. [e] Not detected. [f] With the use of cinchonidine-derived thiourea as the catalyst, see Table S3 in ESI for more details.

The absolute configuration of the product was unambiguously established to be *S* by X-ray crystallographic analysis of **3e**. Based on the experimental results and previous studies,[14,16c] we proposed a plausible transition state model to account for the stereochemistry of the product. As shown in Fig. 1, catalyst **A** serves as bifunctional catalyst by activating both reaction partners, wherein the tertiary amine deprotonates the oxime while the thiourea moiety coordinates with the nitro group of β-CF_3-β-disubstituted nitroalkene through H-bond interaction, thus leading to the preferential attack of oxygen to the *Si* face of β-CF_3-β-disubstituted nitroalkene.

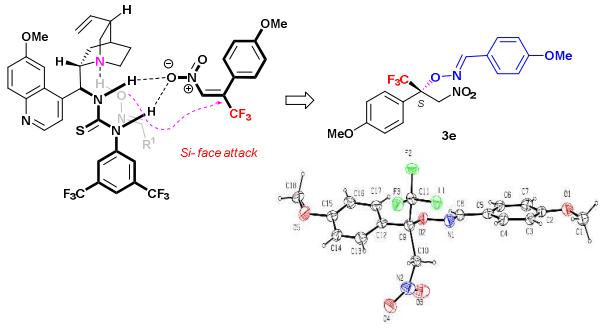
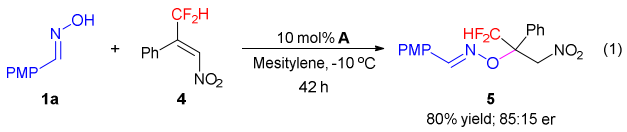


Fig. 1 X-ray crystal structure of product (*S*)-**3e** (thermal ellipsoids are set at 30% probability, Flack parameter = -0.6 (8) and the proposed transition state.

Moreover, the CF_2H moiety is also of key interest in the fields of medicines, agrochemicals, and material chemistry.

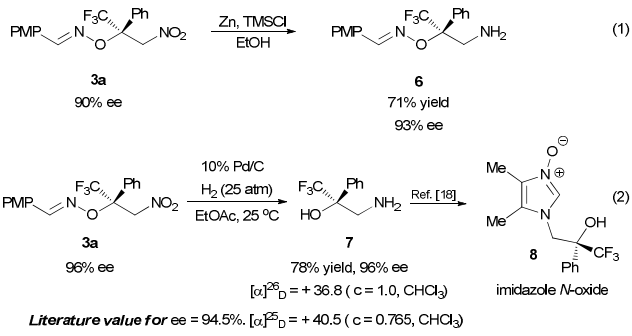
Therefore, we also preliminarily examined β-CF_2H-β-disubstituted nitroalkenes as Michael acceptors. For example, the 4-methoxybenzaldehyde oxime **1a** can also react well with β-CF_2H-β-disubstituted nitroalkene **4**, affording the corresponding product **5** in 80% yield with 85:15 er (eqn (1)).



1a **4** **5**

80% yield; 85:15 er

Finally, the synthetic utility of the addition adducts **3** obtained from this transformation was demonstrated in Scheme 3. For example, the adduct **3a** can be conveniently converted into the amine **6** in 71% yield with 93% ee by the reduction of nitro group in the presence of zinc powder [Scheme 2, eqn (1)]. Moreover, the synthetically useful β-amino-α-trifluoromethyl tertiary alcohol **7** could also be expediently obtained in 78% yield with 96% ee by cleavage of the weak N-O bond and reduction of the nitro group [Scheme 2, eqn (2)]. The absolute configuration of **7** was also confirmed by comparison its optical rotation with literatures ($[\alpha]^{26}_D$ = + 36.8 (c = 1.0, $CHCl_3$)).[17] Importantly, the β-amino-α-trifluoromethyl alcohols of type **7** represent a family of valuable building blocks for the construction of biologically potential chiral CF_3-containg heterocycles. For example, further elaboration of **7** would afford the bioactive imidazole *N*-oxide **8** according to Heimgartner's procedure [Scheme 2, eqn (2)].[18]



Scheme 2 Synthetic transformations of product **3a**.

In conclusion, we have developed the first example of organocatalytic asymmetric intermolecular oxa-Michael addition of oximes to β-CF_3-β-disubstituted nitroalkenes, which allows an efficient synthesis of various structurally diverse CF_3-containing oxime ethers with high yields and enantioselectivities. Notably, the products could be easily transformed into synthetically useful chiral building blocks such as β-amino-α-trifluoromethyl tertiary alcohol.[20] The reaction advantageously enriches and complements the existing strategies for the construction of chiral CF_3- and CF_2H-containing molecules.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures and compound characterisation data, including X-ray crystal structures of **3e**. For ESI and crystallographic data in CIF or other electronic format See DOI: 10.1039/b000000x/

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19 CCDC 963303 (**3e**) contains the supplementarycrystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/daa_request/cif.

20 According to one of refrees' suggestions, we have also tested the asymmetric Michael addition of thiols (ArSH) to β-CF_3-β-alkyl-disubstituted nitroalkenes. At the current stage, however, all the attempts with various chiral bifunctional cinchona alkaloid-based thioureas lead to only moderate enantioselectivity while with good yield. Please see the ESI for more details.