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Bifunctional Thiourea Catalyzed Asymmetric Mannich Reaction Using Trifluoromethyl Aldimine as Trifluoromethyl Building Blocks

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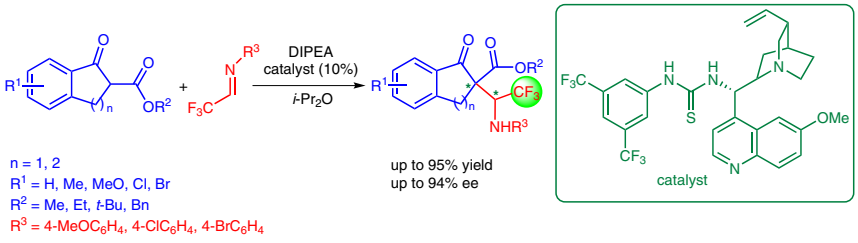

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Abstract An efficient bifunctional thiourea catalyzed asymmetric Mannich reaction with trifluoromethyl aldimine as trifluoromethyl building block was achieved to give the products in good diastereoselectivity and enantioselectivity.

Key words thiourea catalysts, trifluoromethyl aldimine, β-keto esters, Mannich reaction, bifunctional organocatalyst

In recent years, trifluoromethyl compounds have received much attention in pharmaceuticals and agrochemicals because of the unique impact of the CF_3 group on the enhancement and modification of their original biological activities.[1–3] Among these useful fluorine-containing organic compounds, the trifluoromethylated organic compounds have played increasing important roles in the pharmaceutical area.[1,2,4] In particular, some of the trifluoromethylated drugs bear chiral trifluoromethyl stereocenters (Figure 1).[1,5] Consequently, numerous methodologies have been developed in the area of trifluoromethylation using nucleophilic,[6,7] electrophilic,[8–10] and radical[6,9,11] trifluoromethylation reagents as well as transformations of prochiral trifluoromethylated substrates.[12] Furthermore, enantioselective introduction of a CF_3 group into organic molecules was also achieved with the traditional trifluoromethylation reagents[13] such as Umemoto,[14] Togni,[10,15] and Ruppert–Prakash[16] reagents. Trifluoromethyl building blocks were another useful tool for enantioselective construction of CF_3-containing stereocenters because of their easy availability and low cost.[17]

On the other hand, organocatalysis has developed into an essential asymmetric catalysis that complements the fields of metal and enzyme catalysis in the last decade.[18] It has also been used in enantioselective fluorination and trifluoromethylation reactions.[19,20] Our research group also engaged in enantioselective fluorination and trifluoromethylation reactions, and firstly demonstrated that thiourea-based bifunctional organocatalysts have been successfully applied in the enantioselective fluorination reactions of β-keto esters using NFSI as fluorination reagents with the enantiomeric excess of the products up to 99%.[20] Herein, we wish to report the bifunctional thiourea cata-

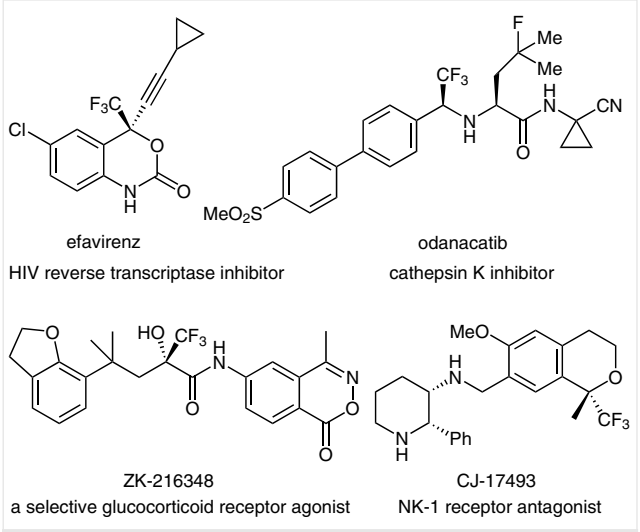


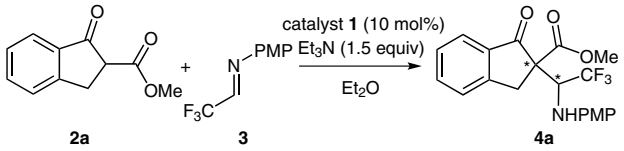
Figure 1 Examples of trifluoromethylated drugs

lyzed Mannich reaction for enantioselective trifluoromethylation of β-keto esters using trifluoromethyl aldimine as trifluoromethyl building blocks.

Our initial investigation started with the trifluoromethylation of β-keto ester **2a** with *N*-(2,2,2-trifluoromethylidene)anisidine (**3**) in Et_2O at room temperature. Various thioureas (Figure 2) were screened, and the results are summarized in Table 1. It is shown that the catalysts **1a**–**g** derived from (+)-quinidine gave the products in low to moderate yields with moderate diastereomeric ratio and low to moderate enantiomeric excess (Table 1, entries 1–7). However, the catalysts **1h**,**i**,**j**,**k** gave racemic products or the products with poor enantiomeric excess (Table 1, entries 8–11). Furthermore, we examined the catalysts **1l**–**n** derived from the chiral amino acids, which still provided the racemic products (Table 1, entries 12–14). Thus, the catalyst **1g** (Table 1, entry 7) was regarded as the best catalyst and used for further optimization of other reaction conditions.

The solvent effects were checked next (Table 2). The results showed that the diastereoselectivities of the reactions were almost the same in different solvents when **1g** was used as the catalyst for the reaction between **2a** and **3**. However, the solvents influenced the enantioselectivity greatly. For example, the enantiomeric excess of the product can reach to 84% when *i*-Pr_2O was used as solvent (Table 2, entry 7). However, when the protic solvent such as methanol was used, the product was obtained in low enantioselectivity (Table 2, entry 1). There were no improvement in the yield and enantioselectivity when the THF or dioxane was used as solvent (Table 2, entries 2 and 3). The reaction

Table 1 Screening of Thiourea Catalysts for Asymmetric Mannich Reaction[a]



2a **3** **4a**

Entry	Cat.	Yield (%)	dr[b]	Major ee (%)[b]	Minor ee (%)[b]
1	**1a**	41	80:20	17	19
2	**1b**	26	70:30	0	0
3	**1c**	66	81:19	13	14
4	**1d**	48	82:18	5	17
5	**1e**	39	77:23	24	24
6	**1f**	30	65:35	16	48
7	**1g**	85	77:23	70	69
8	**1h**	26	70:30	0	0
9	**1i**	30	79:21	0	0
10	**1j**	30	85:15	27	23
11	**1k**	39	84:16	0	0
12	**1l**	26	78:22	0	0
13	**1m**	47	82:18	60	2
14	**1n**	68	83:17	0	0

[a] The reactions were carried out under argon atmosphere by addition of a solution of **2a** (0.158 mmol) to a mixture of **3** (1.2 equiv), catalyst (10 mol%), and Et_3N (1.5 equiv) in Et_2O (3 mL) at r.t. for 72 h.
[b] The enantiomeric excesses and diastereomeric ratios of **4a** were determined by HPLC analysis with a Chiralcel AD-H column, 2-PrOH–hexane (1:9), 1.0 mL/min, λ = 254 nm.

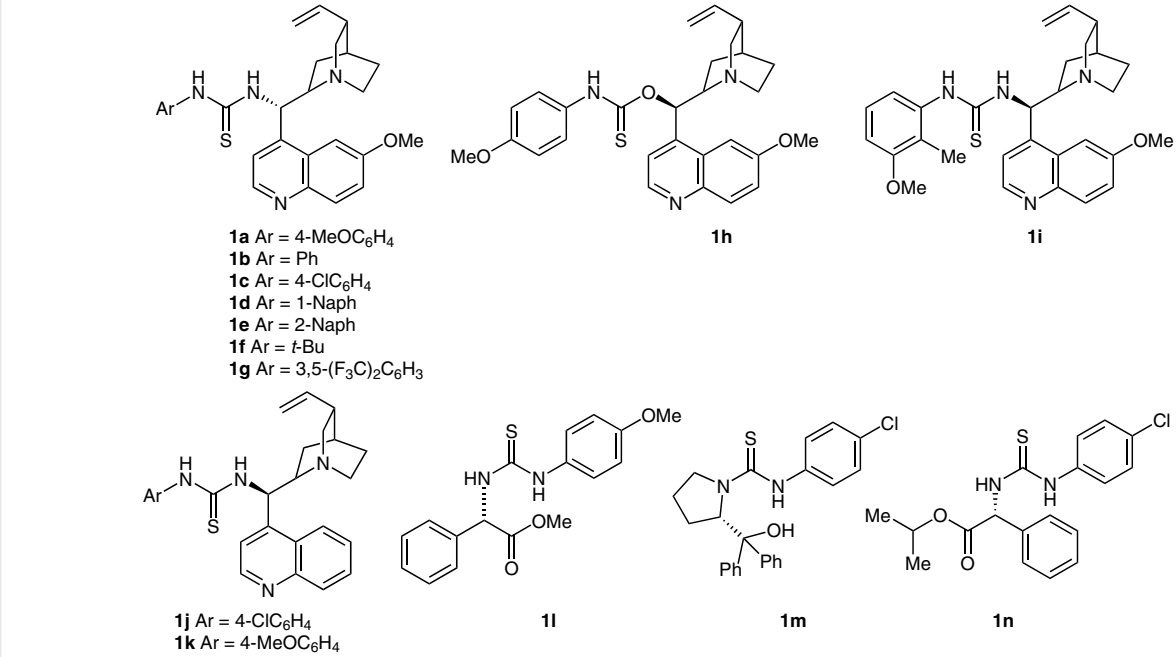
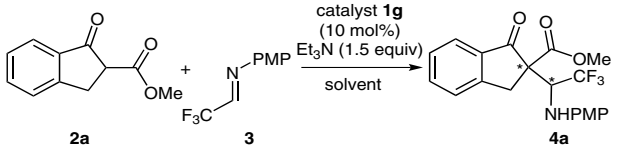


Figure 2 Catalysts used in this research work

in toluene or Et_2O gave better yield and enantioselectivity (Table 2, entries 4–8). Thus, mixed solvents of toluene and ether were tested in order to improve the yield and enantioselectivity further (Table 2, entries 9–11), but there were no improvements in yield and enantioselectivity. Thus, *i*-Pr_2O was determined as the best solvent finally.

Table 2 Effects of Solvents on the Reaction Using **1g** as Catalysts[a]



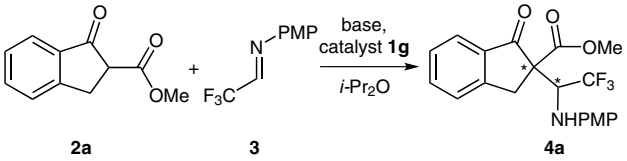
2a **3** **4a**

Entry	Solvent	Yield (%)	dr[b]	Major ee (%)[b]	Minor ee (%)[b]
1	MeOH	20	71:29	34	25
2	THF	40	76:24	44	49
3	dioxane	15	76:24	19	29
4	toluene	65	72:28	65	84
5	CH_2Cl_2	70	76:24	71	70
6	Et_2O	85	77:23	70	69
7	*i*-Pr_2O	80	78:22	79	84
8	TBME	20	78:22	77	82
9	*i*-Pr_2O–Et_2O (1:1)	60	75:25	70	75
10	Et_2O–toluene(1:1)	70	78:22	53	70
11	*i*-Pr_2O–toluene (1:1)	85	75:25	67	82

[a] The reactions were carried out under argon atmosphere by addition of a solution of **2a** (0.158 mmol) to a mixture of **3** (1.2 equiv), **1g** (10 mol%), and Et_3N (1.5 equiv) in solvent (3 mL) at r.t. for 72 h.
[b] The enantiomeric excesses and diastereomeric ratios of **4a** were determined by HPLC analysis with a Chiralcel AD-H column, 2-PrOH–hexane (1:9), 1.0 mL/min, λ = 254 nm.

In our previous study, we found that the base used in the reaction played an important role in bifunctional thiourea catalyzed asymmetric fluorination of β-keto esters.[20] Thus, different bases were examined again based on the above optimized catalyst and solvent (Table 3, entries 1–7). After carefully screening, it was found that the best base for the reaction was DIPEA, which afforded the product in 80:20 diastereomeric ratio, up to 84% enantiomeric excess for the major product and 88% enantiomeric excess for the minor product (Table 3, entry 2). The amount of DIPEA also had influence on the reaction. The yield and enantioselectivity of the reaction would increase when the amount of DIPEA increased. However, the yield and enantioselectivity were almost the same when DIPEA was used above 1.5 equivalents (Table 3, entries 2, 9 and 10). Investigation of catalyst loading also showed that 10 mol% of catalyst was suitable for the reaction (Table 3, entries 2 and 11 and 12). Moreover, the reaction temperature was confirmed as 10 °C (Table 3, entries 2 and 13–15). Therefore, the optimized reaction conditions were 10 mol% **1g** and 1.5 equivalents Hünig's base in *i*-Pr_2O at 10 °C.

Table 3 The Effect of Base and Temperature on the Reaction[a]



2a **3** **4a**

Entry	Base (equiv)	Yield (%)	Cat. (mol%)	Temp (°C)	dr[b]	Major ee (%)[b]	Minor ee (%)[b]
1	Et_3N (1.5)	72	10	20	78:22	79	84
2	DIPEA (1.5)	80	10	10	80:20	84	88
3	sparteine (1.5)	60	10	20	80:20	64	66
4	DABCO (1.5)	50	10	20	77:23	58	59
5	DMAP (1.5)	47	10	20	67:33	34	38
6	DBU (1.5)	80	10	20	37:63	15	0
7	K_2CO_3 (1.5)	56	10	20	78:22	36	46
8	DIPEA (1.0)	50	10	20	61:39	41	62
9	DIPEA (2.0)	77	10	20	77:23	87	88
10	DIPEA (3.0)	82	10	20	78:22	79	82
11	DIPEA (1.5)	62	5	20	74:26	51	67
12	DIPEA (1.5)	82	25	20	76:24	86	89
13	DIPEA (1.5)	90	10	20	77:23	73	80
14	DIPEA (1.5)	70	10	0	73:27	70	51
15	DIPEA (1.5)	50	10	–10	77:23	58	45

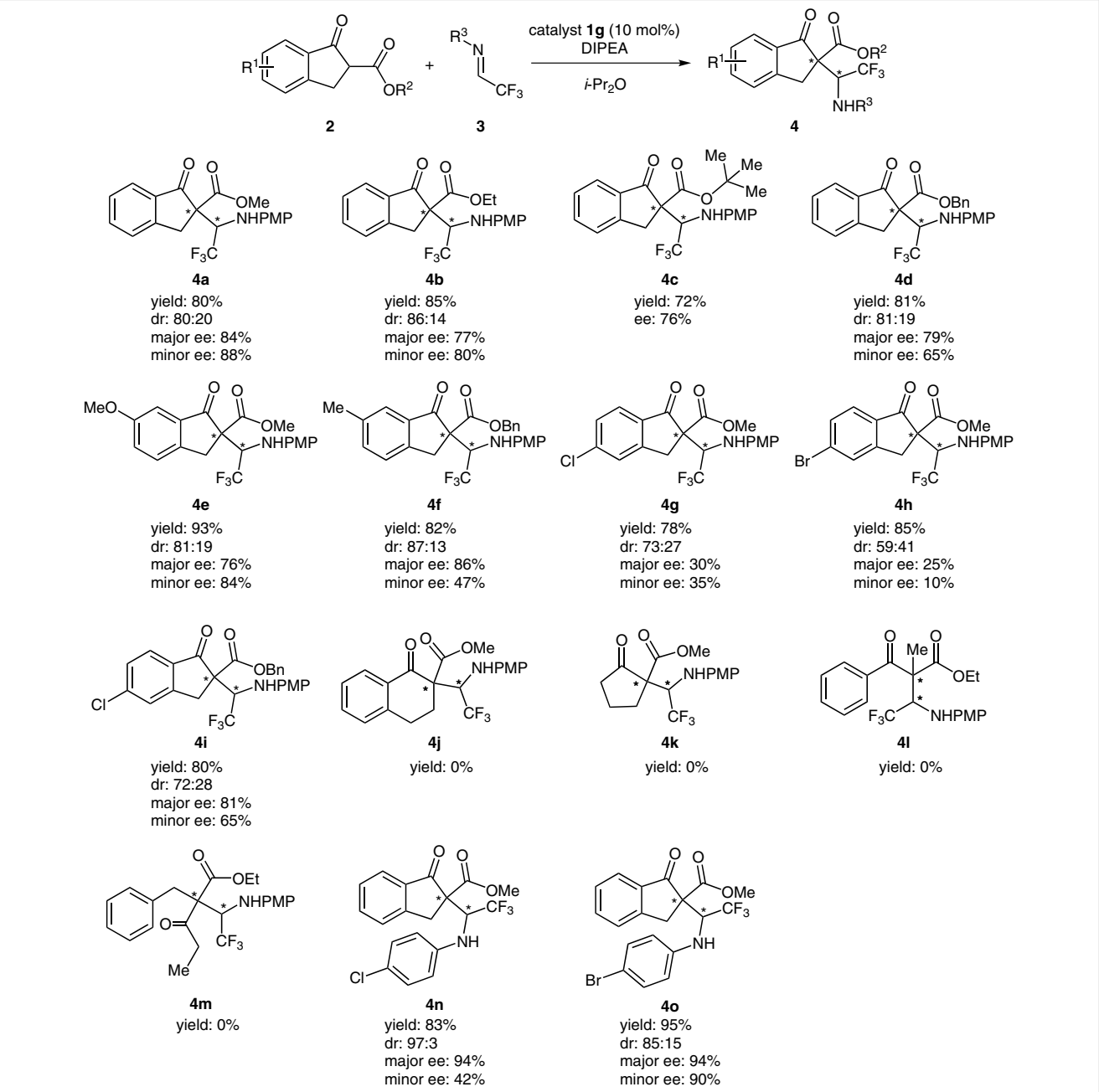
[a] The reactions were carried out under argon atmosphere by addition of a solution of **2a** (0.158 mmol) to a mixture of **3** (1.2 equiv) and **1g** for 72 h.
[b] The enantiomeric excesses and diastereomeric ratios of **4a** were determined by HPLC analysis with a Chiralcel AD-H column, 2-PrOH–hexane (1:9), 1.0 mL/min, λ = 254 nm.

With the optimized reaction conditions in hand, the asymmetric trifluoromethylation via a Mannich reaction was exploited with various 1,3-dicarbonyl compounds (Scheme 1).[21] The different kinds of alkoxy groups in indanonecarboxylates were tested (Scheme 1, **4a**–**d**). It was found that the alkoxy groups such as MeO, EtO, *t*-BuO, or BnO in indanonecarboxylates had little influence on the enantiomeric excess of the products. What was worth noticed was that tertiary butyl ester **2c** gave single diasteroisomer **4c** in 76% enantiomeric excess and 72% yield. However, tetralone derivatives such as **2j** did not afford the product **4j**. Cyclopentane derivative **4k**, acyclic **4l** and **4m** could not be obtained either under the standard reaction conditions. Then, the scope of different trifluoroalkyl aldimines was examined. Although various anilines were used to prepare the corresponding perfluoroalkyl aldimines with trifluoroacetaldehyde hemiacetal, just 4-Cl and 4-Br anilines gave desired aldimines. 4-Toluidine and aniline as well as ben-

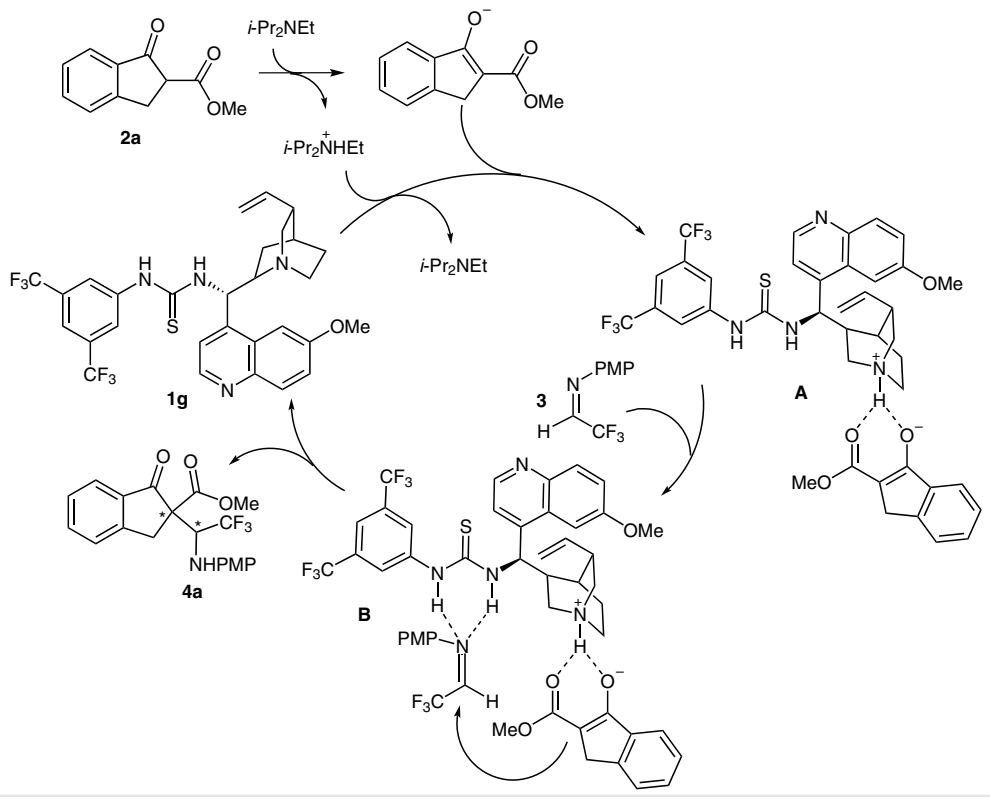
zylamine did not supply the corresponding aldimines. Thus, the aldimines obtained were used for Mannich reaction and provided **4n** and **4o** in excellent enantiomeric excess and diastereomeric ratio with good yield. Furthermore, it was found that, when the product in Table 3, entry 2 was recrystallized from isopropanol, the diastereomeric ratio would increase to 98:2, and the enantiomeric excess would increase to 97% for the major product and 73% for the minor product.

Based on the experimental results and related literatures,[20,22] a mechanism was proposed for the reaction as shown in Scheme 2.

Firstly, the reaction is initiated by deprotonation of **2a** to form the enolate, which can interact with bifunctional thiourea via the hydrogen bond to furnish the intermediate **A**. Then, intermediate **B** was formed from **A** and trifluoromethyl aldimine by hydrogen bond. Enolate attacked the aldimine in intermediate **B** to produce finally the trifluoromethylated product.



Scheme 1 Scope of substrates



Scheme 2 Plausible reaction mechanism

In conclusion, we have identified an efficient bifunctional thiourea catalyzed asymmetric trifluoromethylation of β-keto esters with trifluoromethyl aldimine as trifluoromethyl building block to provide the products with vicinal chiral centers in good distereoselectivity and enantioselectivity. It proves that bifunctional thiourea catalysts can be successfully used in construction of CF_3-containing stereocenter using trifluoromethyl aldimine as trifluoromethyl building block.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380693.

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(21) **General Procedure for Preparing 4**

To the mixture of **2** (0.158 mmol, 1 equiv) and **3** (0.189 mmol, 1.2 equiv) in *i*-Pr_2O (2 mL), DIPEA (0.237 mmol, 1.5 equiv) and thiourea catalyst **1g** (9.4 mg, 10 mol%) were added successively into a flame-dried flask at 10 °C under Ar atmosphere. The mixture was stirred at 10 °C for 72 h. When the reaction was completed, the mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography using PE–EtOAc–CH_2Cl_2 (7:1:1) as eluent to obtain the desired product **4**.

Data of Compound 4a

Yield 80%; white solid; mp 148–150 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80–7.78 (d, *J* = 7.6 Hz, 1 H), 7.68–7.64 (t, *J* = 7.6 Hz, 1 H), 7.55–7.53 (d, *J* = 8.0 Hz, 1 H), 7.43–7.39 (t, *J* = 7.6 Hz, 1 H), 6.81 (s, 4 H), 5.23–5.15 (m, 1 H), 4.07–4.03 (d, *J* = 17.2 Hz, 1 H), 3.76 (s, 3 H), 3.71–3.68 (d, *J* = 11.6 Hz, 1 H), 3.56 (s, 3 H), 3.43–3.39 (d, *J* = 17.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.7, 167.5, 153.7, 152.3, 139.4, 135.8, 133.9, 129.4–120.9 (q, J_{C-F} = 284.3 Hz), 128.0, 126.4, 125.1, 116.1, 114.7, 63.9, 60.9–60.1 (q, J_{C-F} = 27.8 Hz), 55.5, 53.3, 31.4 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –70.36 to –70.38 (d, *J* = 6.8 Hz) ppm. ESI-HRMS: *m/z* calcd for $C_{20}H_{18}F_3NO_4$ $[M + H]^+$: 394.1261; found: 394.1258. IR (thin film): 3370, 3032, 2961, 1745, 1514, 1465, 1245, 1033, 828, 760 cm^{-1}. HPLC: major ee = 84%; minor ee = 88%; dr = 80:20 [Chiralpak AD-H, *n*-hexane–*i*-PrOH (90:10), 1 mL/min, 254 nm]: t_1 (major isomer) = 17.70 min, t_2 (major isomer) = 29.28 min; t_3 (minor isomer) = 11.97 min, t_4 (minor isomer) = 22.82 min.

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