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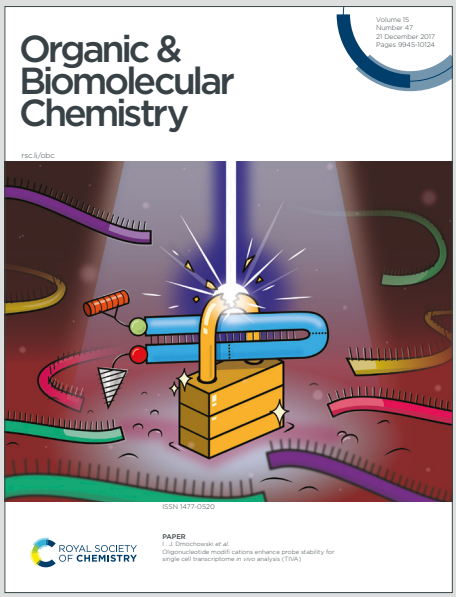

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COMMUNICATION

Enantioselective vinylogous aldol/lactonization cascade reaction between β,γ-unsaturated amides and trifluoromethyl ketones: facile access to chiral trifluoromethyl dihydropyranones

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An efficient asymmetric vinylogous aldol/lactonization cascade reaction between β,γ-unsaturated amides and trifluoromethyl ketones has been developed. Using chiral cyclohexanediamine-based tertiary amine-thiourea catalyst, optically active trifluoromethyl dihydropyranones have been constructed in moderate-to-excellent yields (up to 99%) and excellent stereoselectivities (96->99.5% ee).

Fluorinated compounds are ubiquitous in pharmaceuticals and agrochemicals.[1] In particular, trifluoromethyl-containing compounds are important because the CF_3 group can improve the metabolic stability, lipophilicity and selectivity of bioactive molecules.[2] Therefore, the development of efficient and flexible methods to construct trifluoromethyl-substituted compounds has received much attention from academia.[3,4] Among these compounds, α-trifluoromethyl alcohols have proven to be increasingly popular as chiral building blocks for pharmaceuticals and drug candidates (Figure 1).[5] Asymmetric additions to trifluoromethyl aldehydes and ketones are straightforward and convenient approaches to obtain chiral α-trifluoromethyl alcohols and their derivatives.[5] With the success in asymmetric vinylogous aldol (AVA) reaction,[6] trifluoromethyl ketones as electrophiles have been explored in AVA reactions to produce a variety of products with CF_3 group. However, the use of γ-nucleophiles are limited to highly reactive compounds such as α,β-unsaturated acyl chlorides, α,β-unsaturated aldehydes, alkylidene oxindoles and α,β- or β,γ-unsaturated ketones (Figure 2).[7] In 2011, Ye and co-workers[7a] reported a cascade reaction involving an AVA process between α,β-unsaturated acyl chlorides and trifluoromethyl ketones, producing trifluoromethyl-containing 5,6-dihydropyran-2-ones, which are building blocks of bioactive compounds.[8] Chi and co-workers[7b] developed another approach to afford these products *via* an enantioselective formal oxa-Diels-Alder reaction between α,β-unsaturated aldehydes and trifluoromethyl ketones. Subsequently, cascade reactions between cyclic nucleophiles and trifluoromethyl ketones were reported by Chi's,[7c] Connon's[7e] and Bencivenni's group.[7f] In addition, direct AVA reaction of trifluoromethyl ketones has been developed by Jiang, Bencivenni and Han.[7d,g,h]

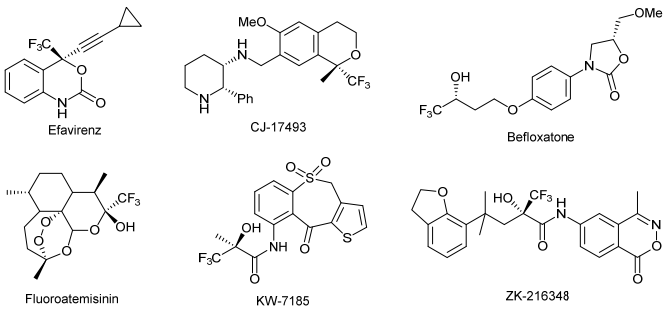

Figure 1. Examples of bioactive structures containing CF_3 group

Due to their relatively low reactivity comparing to aldehydes, ketones and acyl chlorides, the enantioselective vinylogous aldol reactions between acyclic unsaturated amides and trifluoromethyl ketones has been much less developed.[9-11] With our continuing interest in the AVA-based tandem reaction,[9a-c] herein, we report an asymmetric vinylogous aldol/lactonization cascade reaction of β,γ-unsaturated amides and trifluoromethyl ketones to construct chiral 5,6-dihydropyran-2-ones bearing CF_3 groups.

Our study began with the model reaction between β,γ-unsaturated amide **1a** and trifluoromethyl acetophenone **2a**. The reaction was carried out in toluene at 25 °C with 10 mol%

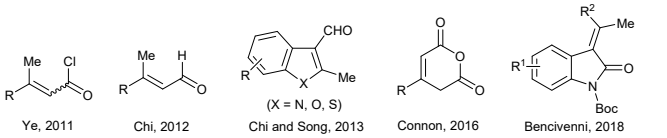

Figure 2. Nucleophiles using for asymmetric vinylogous aldol/lactonization cascade reactions of trifluoromethyl ketones in literatures

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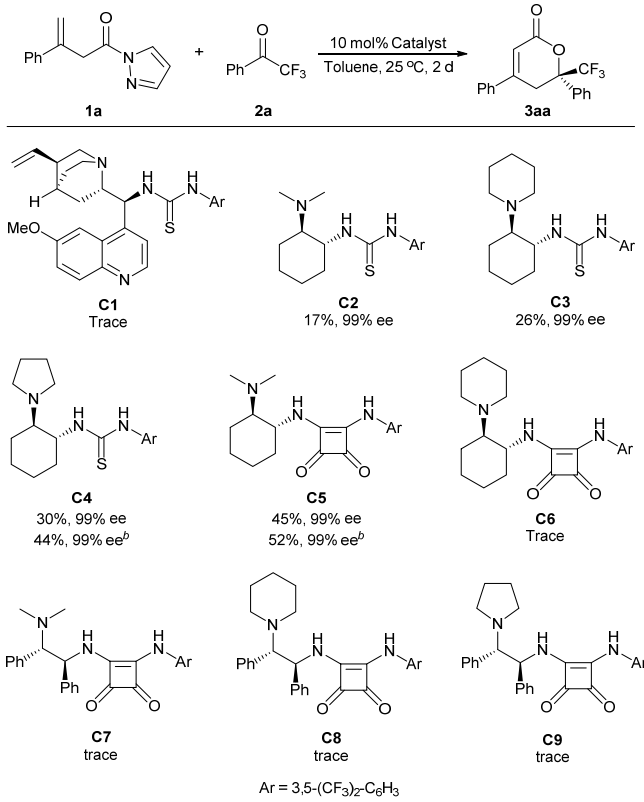
of chiral bifunctional organocatalyst (Table 1). It was observed that β,γ-unsaturated amide **1a** was easily transformed to the corresponding α,β-unsaturated amide in the presence of the tertiary amine catalysts used. As described previously,[9a,9b] α,β-unsaturated amides are unreactive under the vinylogous aldol condition. To improve the chemical yield, we sought to decrease the reaction temperature in order to prevent the generation of α,β-unsaturated amide. When the reaction was carried out with **C4** and **C5** in toluene at 0 °C, product **3aa** was obtained with an improved yield and retained enantioselectivity (entry 4 vs entry 10, entry 5 vs entry 11).

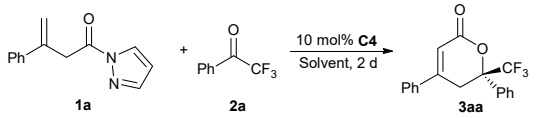
A survey of solvents indicated that CH_2Cl_2 and EtOAc were not suitable for this cascade reaction, and the β,γ-unsaturated amide **1a** isomerized to the corresponding α,β-unsaturated amide completely (Table 2, entries 2 and 3). Therefore, we turned our attention to aromatic solvents. Although isomerization still existed, a moderate conversion rate of the raw material to final product was observed. Among the toluene homologues screened, tert-butylbenzene provided the highest chemical yield, and a 99% ee was achieved for all the aromatic solvents used (Entries 4-11).

Table 1. Screening of the chiral organocatalysts for the vinylogous aldol/cyclization cascade reaction [a]



[a]Unless stated otherwise, the reactions were performed with 0.3 mmol β,γ-unsaturated amide **1a**, 0.2 mmol trifluoromethyl acetophenone **2a** and 0.02 mmol of the organocatalyst in 1 mL toluene at 25 °C. The yields refer to isolated yields, and the ee values were determined by HPLC analysis using chiral stationary phase. [b]The reaction was performed at 0 °C.

Table 2. Optimization of reaction conditions [a]



Entry	Solvent	Additive	Temp. (°C)	Yield (%)[b]	Ee (%)[c]
1	Toluene	-	0	44	99
2	CH_2Cl_2	-	0	trace	nd[d]
3	EtOAc	-	0	trace	nd
4	*p*-xylene	-	0	56	99
5	*o*-xylene	-	0	52	99
6	*m*-xylene	-	0	57	99
7	mesitylene	-	0	52	99
8	^{t}BuPh	-	0	64	99
9	EtPh	-	0	44	99
10	^{i}PrPh	-	0	51	99
11	CF_3Ph	-	0	36	99
12	^{t}BuPh	-	-15	65	99
13	^{t}BuPh	-	-30	60	99
14	^{t}BuPh	10 mg 4Å MS	-15	83	99
15	^{t}BuPh	20 mg 4Å MS	-15	90	99
16	^{t}BuPh	30 mg 4Å MS	-15	88	99
17	^{t}BuPh	20 mg 3Å MS	-15	85	99
18	^{t}BuPh	20 mg 5Å MS	-15	88	99
19[e]	^{t}BuPh	20 mg 4Å MS	-15	80	99
20[f]	^{t}BuPh	20 mg 4Å MS	-15	65	99
21[g]	^{t}BuPh	20 mg 4Å MS	-15	67	99
22[h]	^{t}BuPh	20 mg 4Å MS	-15	40	99
23[i]	^{t}BuPh	20 mg 4Å MS	-15	72	99

[a]Unless stated otherwise, the reactions were performed with 0.3 mmol β,γ-unsaturated amide **1a**, 0.2 mmol trifluoromethyl acetophenone **2a** and catalyst **C4** in 1 mL solvent, the reaction time was 2 days. [b]Isolated yields. [c]Determined by HPLC analysis using chiral stationary phase. [d]Not determined. [e]The amount of *t*-BuPh was 0.67 mL (0.3 M). [f]The amount of *t*-BuPh was 2 mL (0.1 M). [g]The catalyst loading was 5 mol%. [h]The catalyst loading was 2 mol%. [i]0.2 mmol H_2O was added.

Next, the substrate concentration, reaction temperature, catalyst loading and additive concentration were optimized to further improve the chemical yield of the cascade reaction (Table 2, entries 12-23). When the temperature was lowered from 0 °C to -15 °C, similar results were obtained (entry 12 vs entry 8). However, a decreased yield was obtained at -30 °C (entry 13). To our delight, the chemical yield could be remarkably improved to 90% with 99% ee in the presence of 4Å molecular sieves (entry 15). The concentration of substrate **2a** influenced the reaction. When the concentration of **2a** was changed from 0.2 M to 0.1 M or 0.3 M, the yield substantially decreased (entries 19 and 20 vs entry 15). The reduction of the catalyst loading led to a decrease of yield (entries 21 and 22 vs entry 15). The results suggest that the catalyst loading has a significant impact on the reaction rate of the vinylogous aldol/lactonization cascade reaction. To test the role of 4Å molecular sieves in the cascade reaction, 1 equivalent of water was added to the reaction system. As a result, the yield decreased dramatically probably due to the water absorption of 4Å molecular sieves, thereby lowering their catalytic activity. The optimal result was achieved by using 10 mol% tertiary amine-thiourea **C4** as chiral catalyst, *tert*-butylbenzene as

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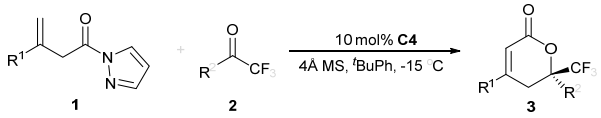
Table 3. Substrate scope of the enantioselective vinylogous aldol/lactonization cascade reaction[a]



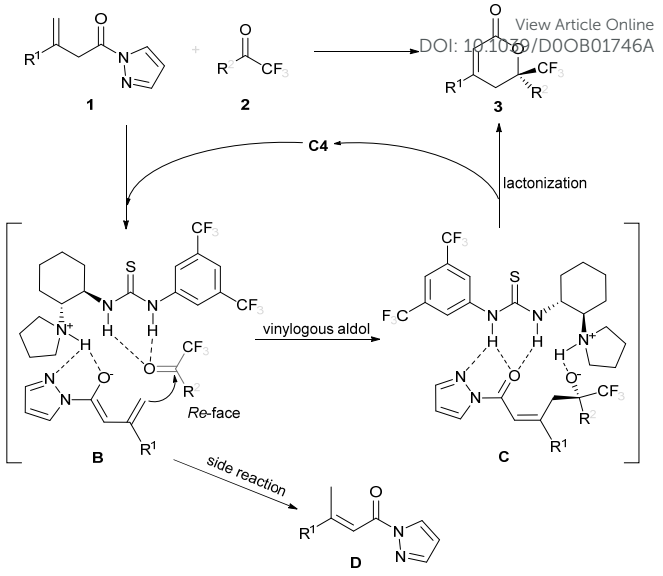
Entry	R^1	R^2	Time (d)	Yield (%)[b]	Ee (%)[c]
1	C_6H_5	C_6H_5	2	90 (**3aa**)	99
2	C_6H_5	4-FC_6H_4	3	82 (**3ab**)	>99.5
3	C_6H_5	4-ClC_6H_4	2	99 (**3ac**)	99
4	C_6H_5	3-ClC_6H_4	2	99 (**3ad**)	98
5	C_6H_5	2-ClC_6H_4	3	28 (**3ae**)	>99.5
6	C_6H_5	4-BrC_6H_4	2	95 (**3af**)	99
7	C_6H_5	4-MeC_6H_4	3	60 (**3ag**)	>99.5
8	C_6H_5	(*E*)-C_6H_5CH=CH	2	88 (**3ah**)	99
9	C_6H_5	Et	4	22 (**3ai**)	99
10	4-MeC_6H_4	C_6H_5	3	61 (**3ba**)	99
11	4-FC_6H_4	C_6H_5	2	84 (**3ca**)	>99.5
12	3-ClC_6H_4	C_6H_5	3	80 (**3da**)	99
13	4-ClC_6H_4	C_6H_5	3	79 (**3ea**)	>99.5
14	4-$CF_3C_6H_4$	C_6H_5	3	92 (**3fa**)	>99.5
15	3,4-$Cl_2C_6H_3$	C_6H_5	3	99 (**3ga**)	>99.5
16	2-thienyl	C_6H_5	3	83 (**3ha**)	>99.5
17	1-naphthyl	C_6H_5	3	51 (**3ia**)	96
18[d]	^{n}Bu	C_6H_5	7	57 (**3ja**)	99

[a]Unless stated otherwise, the reactions were performed with 0.3 mmol β,γ-unsaturated amides **1**, 0.2 mmol trifluoromethyl ketones **2** and 0.02 mmol chiral catalyst **C4** in 1 mL *t*-BuPh at -15 °C. [b]Isolated yields. [c]Determined by HPLC analysis using chiral stationary phase. [d]The loading of catalyst **C4** was 20 mol%.

solvent, and 4Å molecular sieves as an additive (20 mg for 0.2 mmol scale) at -15 °C.

Having established the optimal protocol for the reaction, the substrate scope of the cascade reaction was examined (Table 3). The reaction tolerated all of the trifluoromethyl ketones used, providing excellent enantioselectivities (98->99.5% ee, entries 1-9). The acetophenones bearing electron-withdrawing groups gave a better yield than those with electron-rich substituents (entries 2-4 and 6 vs entry 7). However, 2-chloro substituted trifluoromethyl acetophenone **2e** produced a low yield (28%), probably due to a steric effect (entry 5). The cinnamenyl analogue also provided high yield and excellent enantioselectivity (entry 8). However, the trifluoromethyl alkyl ketones were low reactive. Only 22% yield was obtained for 1,1,1-trifluorobutan-2-one (entry 9), while 1,1,1-trifluoropropan-2-one was unreactive under the typical reaction conditions.

Next, the substrate scope of β,γ-unsaturated amides was investigated (entries 10-18). Both electron-withdrawing and electron-donating substituents on β-phenyl afforded the corresponding products **3** in 99% or >99.5% ee. The electron-deficient substrates provided good-to-excellent yields (79-99%) than those with electron-rich substituents (entries 11-15 vs entry 10). Good yield and high enantioselectivity was also obtained for the heterocyclic substrate (entry 16). However, allyl pyrazoleamide with a fused-ring gave a relatively lower yield (51% with 96% ee, entry 17). The β-butyl β,γ-unsaturated



Scheme 1. Proposed reaction pathway

amide is less reactive, and a 20 mol% catalyst was required to proceed the reaction under the optimal reaction condition (entry 18). Allylic amide provided vinylogous aldol adduct in 57% yield and 73% ee, while and γ-phenyl β,γ-unsaturated amide was unreactive under the typical reaction conditions.

To determine the absolute configuration, we compared the HPLC trace and optical rotation value of product **3aa** with those of the *R*-product described in Chi's report.[7b] As a result, we determined the absolute configuration to be *S*. The absolute configuration of other products was assigned by analogy.

According to our experimental results and the related literatures,[7f,9a,9b,12] a possible mechanism for this cascade reaction is illustrated in Scheme 1. Initially, reaction partners **1** and **2** are synergistically activated by the bifunctional catalyst **C4** to form the hydrogen bonding species **A**, which then undergoes vinylogous aldol reaction through *Re* face attack of dienolates to trifluoromethyl ketone to form *S*-configurated intermediate **B**. Finally, the lactonization of intermediate **B** give the desired product **3** and regenerate catalyst **C4**. The side reaction of intermediate **A** is the formation of α,β-unsaturated amide **D**, which could not act as a prenucleophile to perform the vinylogous reaction.

Conclusions

In conclusion, we have developed a highly enantioselective vinylogous aldol/lactonization cascade reaction between β,γ-unsaturated amides and trifluoromethyl ketones. In the presence of 10 mol% tertiary amine-thiourea **C4**, the cascade reaction was achieved in excellent enantioselectivities (96->99.5% ee) with up to 99% yield. This approach might prove useful for the construction of biologically active trifluoromethyl dihydropyranones.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgment

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Enantioselective vinylogous aldol/lactonization cascade reaction between β,γ-unsaturated amides and trifluoromethyl ketones: facile access to chiral trifluoromethyl dihydropyranones

Jun-Hao Fu, Zhen-Guo Zhang, Xue-Ying Zhou, Chun-Wei Fu, Feng Sha, Xin-Yan Wu*

β,γ-Unsaturated amides have been firstly employed to react with trifluoromethyl ketones, and chiral α,β-unsaturated δ-lactones bearing trifluoromethyl group have been constructed conveniently.