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Enantioselective Organocatalytic Michael Addition of Nitroalkanes and Other Nucleophiles to β-Trifluoromethylated Acrylamides

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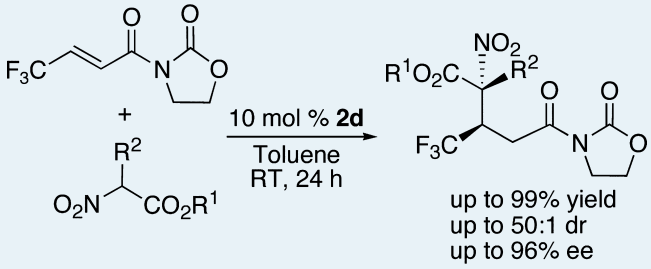
Supporting Information

ABSTRACT: An organocatalytic asymmetric Michael addition of nitroalkanes to trifluoromethylated acrylamides in good yields and with good to excellent diastereoselectivities and excellent enantioselectivities is described. The Michael adducts could be readily transformed into optically pure trifluoromethylated γ-aminobutyric acid 7 in high yields without loss in enantioselectivities.



KEYWORDS: *trifluoromethyl, organocatalyst, Michael addition, fluorine, asymmetric*

INTRODUCTION

In recent years, the stereoselective introduction of fluorine into druglike molecules has attracted great attention in the field of medicinal and agricultural chemistry because of the unique physical properties of organofluorine compounds and the huge demands for chiral drugs.[1] Consequently, development of catalytic enantioselective methods for the construction of trifluoromethyl-containing stereogenicity has become a synthetic challenge.[2,3] More specifically, incorporation of fluorine into γ-aminobutyric acid and its derivatives is of great interest because of their important role in the central nervous system.[4] For example, Pregabalin, Baclofen, and Gabapentin are important medicines for relieving neuropathic pain.[5] One general route for the preparation of optically pure γ-aminobutyric acid is direct asymmetric Michael addition of nitroalkanes to α,β-unsaturated carbonyl compounds, followed by reduction of the nitro group.[6] In the past 10 years, various catalysts, including chiral Lewis acids,[7] phase-transfer catalysts,[8] and organocatalysts[9] based on thiourea, have been shown to be efficient for these reactions. In contrast, Michael additions of nitroalkanes to electron-deficient alkenes bearing a trifluoromethyl group as a Michael acceptor have rarely been reported.[4] We recently reported trifluoroethylidene malonate is a good Michael receptor when it is reacted with aldehydes using prolinol silyl ether as a catalyst to give the addition products with high enantioselectivity.[10] As part of our ongoing programs with the aim to develop high regio- and enantioselective methods for the construction of a chiral center containing a trifluoromethyl group,[11] we wondered if it could be possible to realize highly enantioselective Michael additions of nitroalkanes to trifluoroethylidene malonate, trifluoromethylated acrylates, or acrylamides to give trifluoromethylated γ-nitrobutyric acid derivatives that are precursors of trifluoromethylated γ-aminobutyric acid, a potential drug candidate. Herein, we report a Cinchona-alkaloid-thiourea-catalyzed enantioselective conjugated addition of nitroalkanes to β-trifluoromethylated acrylamides in good to excellent yields with high enantioselectivities up to 96% ee.

RESULTS AND DISCUSSIONS

We initially examined quinine (**2a**), quinidine (**2b**), 9-amino-9-deoxyquinidine (**2c**), Cinchona-alkaloid-thiourea[9b] (**2d**) and Takemoto's catalyst[12] (**2e**) (5−15 mol %) as potential catalysts for reaction of nitromethane and diethyl 2,2,2-trifluoroethylidene malonate **1a**, (*E*)-ethyl-4,4,4-trifluorobut-2-enoate **1b**, or β-trifluoromethylated acrylamide **1c** (Table 1). Reactions of nitromethane and diethyl 2,2,2-trifluoroethylidene malonate **1a** using quinine **2a** or quinidine **2b** as the catalyst occurred with over 90% conversion after 7 h at room temperature; however, these reactions formed the desired products in 3−5% ee (Table 1, entries 1 and 2). Reactions in the presence of quinidine derivatives **2c** occurred much more slowly, and only 31% conversion was observed after 72 h at room temperature (Table 1, entry 3). When Cinchona-alkaloid-thiourea **2d** was used as the catalyst, the enantioselectivity was improved to 43% ee (Table 1, entry 4). When Takemoto's catalyst **2e** was used as the catalyst, reaction was much faster. Only 5 mol % of the catalyst was required for the reaction to occur to full conversion after 12 h at room temperature. However, only 44% ee was observed (Table 1, entry 5). Lowering the reaction temperature to 0 °C resulted in only slightly improved enantioselectivity (Table 1, entry 6). Switching the substrate to the less reactive (*E*)-ethyl-4,4,4-trifluorobut-2-enoate **1b** led to much slower reactions. Less then 10% conversion of the starting material was observed after 24 h at room temperature (Table 1, entry 7). When β-trifluoromethy-

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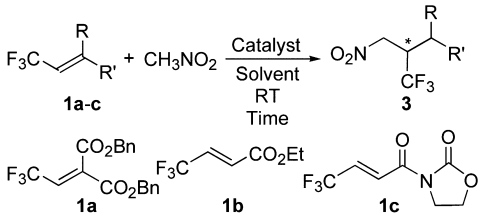
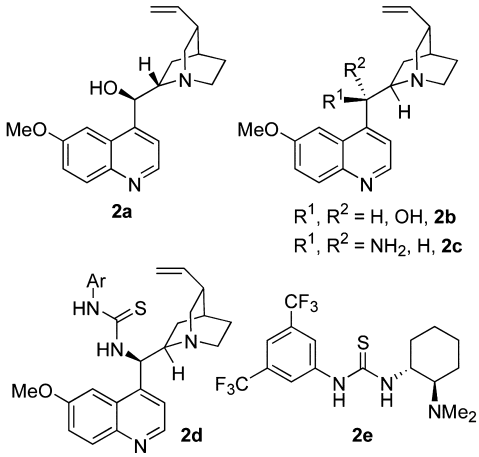
Table 1. Optimization of Reaction Conditions[a]



entry	subs	cat. (mol%)	solvent	time	conv. (%)[b]	ee (%)[c]
1	**1a**	**2a** (15)	toluene	7	99	3
2	**1a**	**2b** (15)	toluene	7	90	5
3	**1a**	**2c** (15)	toluene	72	31	0
4	**1a**	**2d** (15)	toluene	12	99	44
5	**1a**	**2e** (5)	toluene	12	99	43
6	**1a**	**2e** (5)	toluene	12	48[d]	50
7	**1b**	**2d** (10)	toluene	24	<10	-
8	**1c**	**2d** (10)	toluene	24	99	94
9	**1c**	**2e** (10)	toluene	24	99	-91
10	**1c**	**2d** (10)	CH_2Cl_2	24	99	87
11	**1c**	**2d** (10)	CH_3CN	48	51	85
12	**1c**	**2d** (10)	EtOAc	48	42	93
13	**1c**	**2d** (10)	THF	48	<10	-



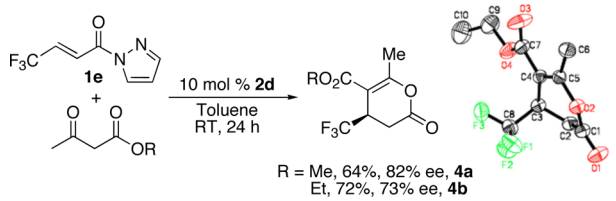
[a]Reaction conditions: **1a**−**c** (0.1 mmol), nitromethane (0.5 mmol), and catalyst (5−15 mol %) in solvent (0.5 mL) at indicated temperature. [b]The conversion of starting material was determined by ^{19}F NMR analysis of the crude reaction mixture. [c]The ee value was determined by chiral-phase HPLC analysis. [d]The reaction was conducted at 0 °C.

lated acrylamide **1c** was used as the substrate and **2d** was used as the catalyst, to our delight, excellent conversion (99%) and enantioselectivity (94%) were observed (Table 1, entry 8). Interestingly, when **2e** was used as the catalyst for the same transformation, slightly lower enantioselectivity (91%) but in opposite rotation was observed (Table 1, entry 9). Different solvents were then examined to improve the yield and enantioselectivity. It was found that reactions in dichloromethane occurred with full conversion after 24 h at room temperature to give the desired product **3a** in slightly lower enentioselectivity, whereas reactions in acetonitrile or ethyl acetate occurred much more slowly (Table 1, entries 10−12). Less than 10% conversion was observed when the reaction was conducted in THF at room temprature (Table 1, entry 13).

On the basis of the results summarized in Table 1, the reaction conditions of entry 8 were chosen to study the scope of the Michael reactions of nitroalkanes or other nucheophiles with trifluoromethylated acrylamides, and the results are summarized in Table 2. Reaction of nitromethane with trifluoromethylated acrylamide **1c** was faster than pentafluoroethyl-substituted acrylamide **1c**′, which required 48 h to result in full conversion. Both of them afforded the desired Michael adducts in excellent enentioselectivities (Table 2, **3a** and **3b**). Both methyl and ethyl nitropropanoate or nitrobutanoate reacted with trifluoromethylated acrylamide **1c** or **1c**′ with excellent diastereo- and enantioselectivities (Table 2, **3c**−**f**). The diastereoselectivity was determined by ^{19}F NMR spectroscopy of the crude reaction mixture. Excellent diastereoselectivity in a ratio of 31:1 was achieved for the reaction of trifluoromethylated acrylamide derived from Evan's auxiliary catalyzed by Cinchona-alkaloid-thiourea **2d**, whereas reaction using triethylamine as the base gave the corresponding product in a 1.1:1 ratio of diastereoselectivity (Table 2, **3g**). Reaction of malononitrile with trifluoromethylated acrylamide **1c** occurred with excellent yield but moderate enantioselectivity (Table 2, **3h**).

Reactions of other nucleophiles such as malonate or β-ketoester occurred much more slowly and in low enantioselectivity. For example, reaction of β-ketoester required 96 h to reach full conversion to give the desired product in 54% ee with a 1.4/1 ratio of diastereoselectivity, but reaction of malonate was much slower and required 8 days to reach full conversion to give the product in 39% yield in 77% ee (Table 2, **3i**, **j**). In general, reactions of trifluoromethylated acrylamide **1c** were much faster than those of trifluoromethylated acrylamide **1d** and **1d**′ derived from imidazolidin-2-one, which occurred with good enantioselectivity but typically required being heated to 60 °C for 24 h for full conversion (Table 2, **3k** and **3l**).

Reactions of trifluoromethylated acrylamide **1e** derived from imidazole were only slightly slower, but occurred with lower diastereo- and enantioselectivity than those of trifluoromethylated acrylamide **1c** (Table **3m**-**r**). For example, reaction of methyl nitro-2-propanoate with trifluoromethylated acrylamide **1e** afforded the Michael adduct in 75% yield in 88% ee and 4.4/1 diastereoselectivity after 48 h at room temperature (Table 2, **3n**). Interestingly, when methyl or ethyl acetyl acetate was used as the nucleophile, a cascade Michael addition, followed by intramolecular cyclization, proceeded to give trifluoromethylated lactone **4a**, **b** in good yields and with moderate enantioselectivity (eq 1). The absolute configuration of the product was determined by X-ray crystallographic analysis of a single crystal of **4b.**



(1)

The absolute configuration of the stereogenic center (R) in compound **3** was determined by X-ray crystallographic analysis of a single crystal of **3c** (Figure 1). The absolute configurations of the Michael adducts **3p** and **3q** obtained from reaction of methyl and ethyl nitropropanoate or nitrobutanoate with trifluoromethylated acrylamide **1e** derived from imidazole were determined by their reduced derivatives **5a** and **5b** (eq 2). The configurations of the rest of the products were assigned on the assumption of a uniform mechanistic pathway.

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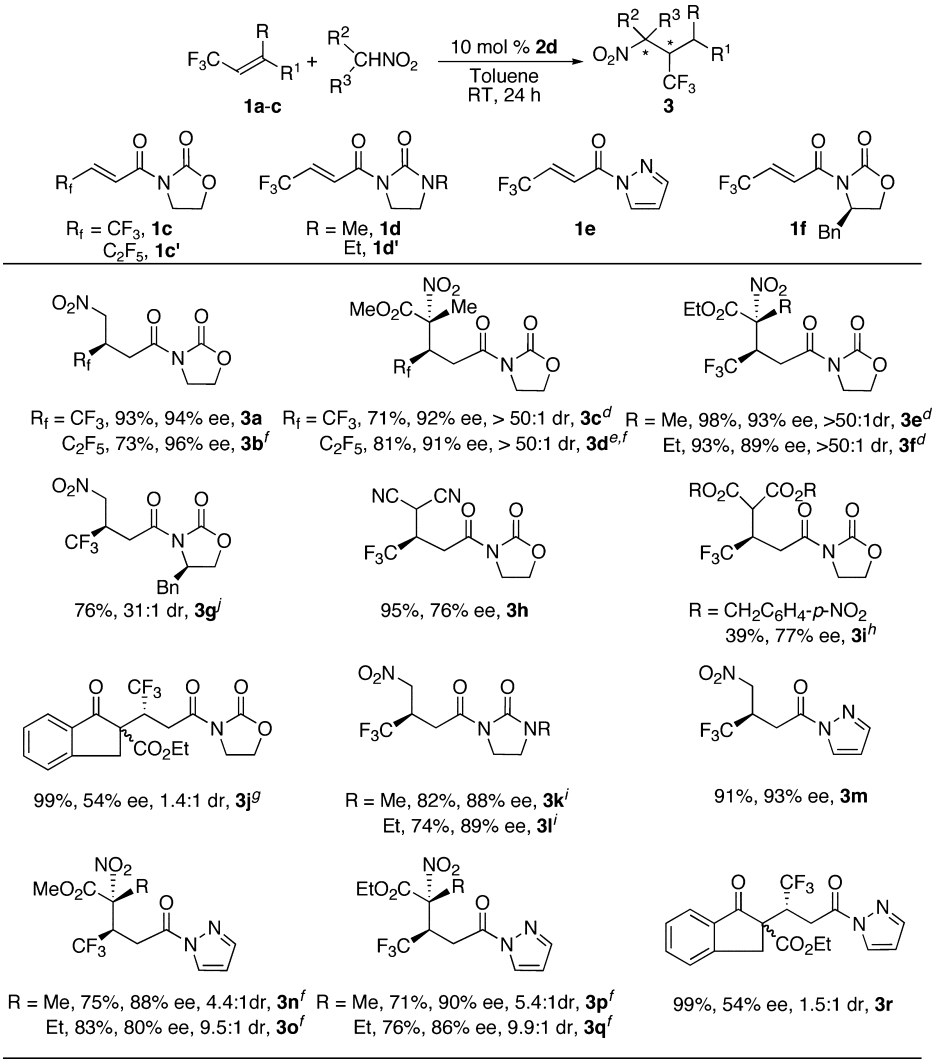
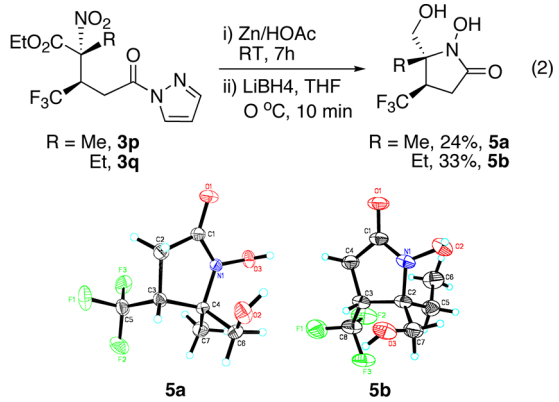
Table 2. Enantioselective Michael Addition of Nitroalkanes and Other Nucleophiles to Trifluoromethylated Acrylamides[a,b,c]



[a]Isolated yield. [b]Diastereoselectivity was determined by ^{19}F NMR of the crude adducts. [c]The ee value was determined by chiral-phase HPLC analysis. [d]5 mol % catalyst was used. [e]15 mol % catalyst was used. [f]48 h. [g]96 h. [h]8 days. [i]60 °C. [j]1.1/1 dr for reaction using Et_3N as the base.



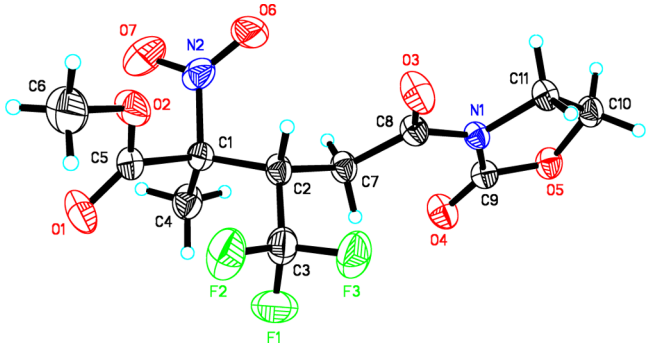


Figure 1. The ORTEP view of compound **3c**.

As a demonstration of the synthetic utility of this catalytic approach, the adduct **3a** was further converted into trifluoromethylated γ-aminobutyric acid **7** (Scheme 1). Hydrogenation of compound **3a** using Raney Ni as the catalyst in a mixed EtOH/EtOAc solvent at room temparature gave an inseparable mixture of trifluoromethylated γ-lactam and 2-oxazolidone, which was further reacted with TsCl or $(Boc)_2O$ to give compound **6a** and **6b** in 57% and 82% yield, respectively. The structure of the compound **6a** was characterized by ^1H, ^{13}C, ^{19}F NMR spectroscopies and further confirmed by X-ray diffraction analysis of its single crystal. Compound **6b** can be easily converted to trifluoromethylated γ-aminobutyric acid **7** in refluxed 6 N hydrochloric acid in quantitative yield.

CONCLUSION

In summary, we have developed a new protocol for the asymmetric Michael addition of nitroalkanes to trifluoromethy-

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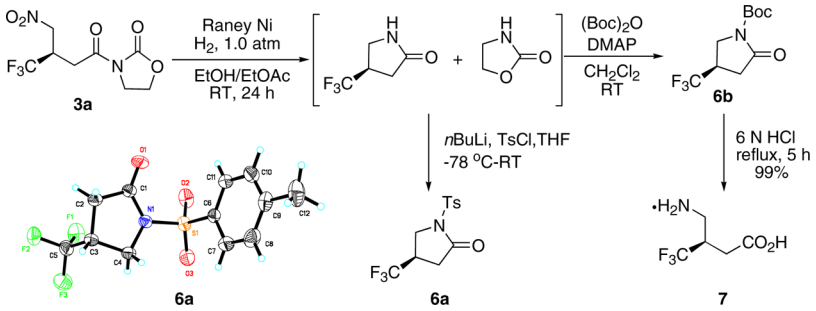
Scheme 1. Preparation of Trifluoromethylated γ-Aminobutyric Acid 7 from Compound 3a



lated acrylamides in good yields and with good to excellent diastereoselectivities and excellent enantioselectivities. The Michael adducts could be readily transformed into optically pure trifluoromethylated γ-aminobutyric acid **7** in high yields without loss in enantioselectivities. Mechanistic studies, synthetic applications of these transformations, and development of other organocatalytic enantioselective conjugate addition reactions are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Proton and carbon NMR as well as HPLC spectra of novel reported compounds **3a−r**, **4a−b**, **5a−b**, **6a−b**, and **7**; cif files of single crystals **3c**, **4b**, **5a−b**, and **6a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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