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Access to Chiral GABA Analogues Bearing a Trifluoromethylated All-Carbon Quaternary Stereogenic Center through Water-Promoted Organocatalytic Michael Reactions

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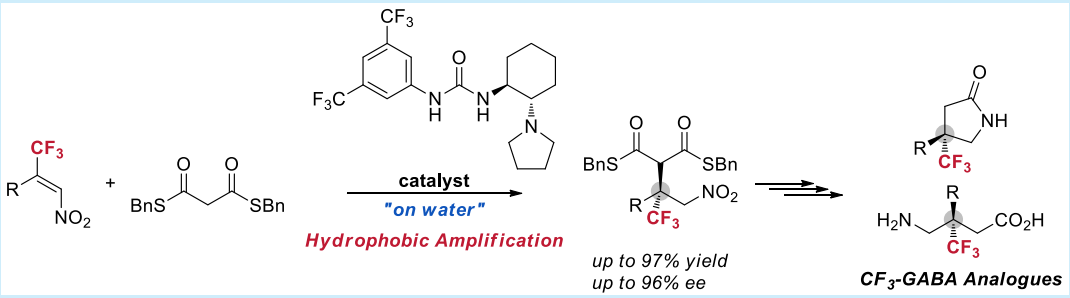
Supporting Information



ABSTRACT: Water enables the highly challenging enantioselective Michael addition of sterically congested β-trifluoromethyl-β-aryl- or -alkyl-substituted nitroolefins with dithiomalonates. Under on-water conditions, the reaction rates were remarkably accelerated as a result of enforced hydrophobic interactions between catalysts and reactants. Takemoto-type thiourea catalysts are very effective for this transformation, affording highly enantioenriched Michael adducts that provide simple access to chiral γ-aminobutyric acid (GABA) analogues with a β-trifluoromethylated quaternary stereocenter.

γ-Aminobutyric acid (GABA) is a major inhibitory neurotransmitter in the human brain.[1] Thus, GABA deficiency is associated with many types of psychiatric and neurological disorders, such as anxiety, depression, pain, epilepsy, Huntington's chorea, Parkinson's disease, and Alzheimer's disease. However, GABA itself is very hydrophilic and thus cannot be used for the treatment of these diseases since it cannot penetrate the blood−brain barrier (BBB). Thus, the synthesis of many structurally modified GABA analogues that show greater lipophilicity and permeability to cross the BBB has drawn a lot of interest in the pharmaceutical field.[2] In particular, structural modification of GABA at the β-position has been the subject of extensive surveys because the potential activity of the resulting derivatives. For example, β-substituted GABA derivatives such as pregabalin,[3] phenibut,[4] baclofen,[5] and rolipram[6] have been developed as novel therapeutic drugs for a wide range of central nervous system diseases (Figure 1).

The enantioselective incorporation of fluorine atoms into therapeutic or diagnostic organic molecules has received considerable attention in medicinal chemistry since it can productively influence the pharmacological properties of a bioactive molecule by enhancing its lipophilicity, metabolic stability, or even permeability compared with the non-fluorinated parent compound.[7] In particular, the trifluoromethyl ($-CF_3$) group is commonly used as the fluorinated bioisostere of an ethyl[7l] or isopropyl[8] group.

In this regard, the development of new facile synthetic protocols to access chiral GABA analogues bearing a trifluoromethylated quaternary stereogenic center[9] at the β-position would be one outstanding challenge, since the introduction of the CF_3 group might enhance the metabolic stability and increase the lipophilicity and membrane permeability.[10] However, only very few reports have accomplished the synthesis of GABA derivatives bearing a trifluoromethylated quaternary stereocenter at the β-position that might be of biological interest.[11]

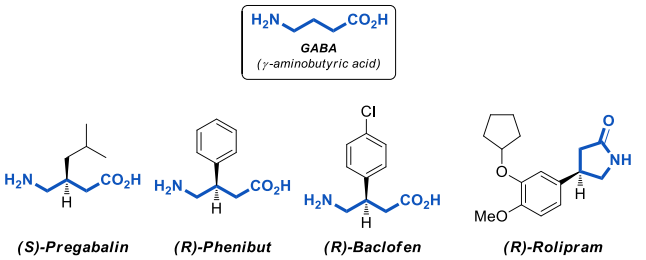


Figure 1. GABA and some of its pharmaceutically important analogues.

In principle, a catalytic asymmetric Michael addition of malonate derivatives to β-CF_3-β,β-disubstituted nitroalkenes would enable efficient access to GABA analogues with a trifluoromethylated quaternary stereogenic center at the β-position (Scheme 1). However, β-CF_3-β,β-disubstituted nitro-

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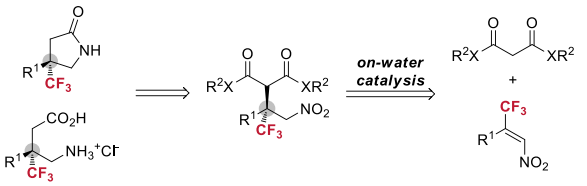
Scheme 1. Proposal for the Synthesis of Chiral GABA Derivatives with a Trifluoromethylated Quaternary Stereogenic Center

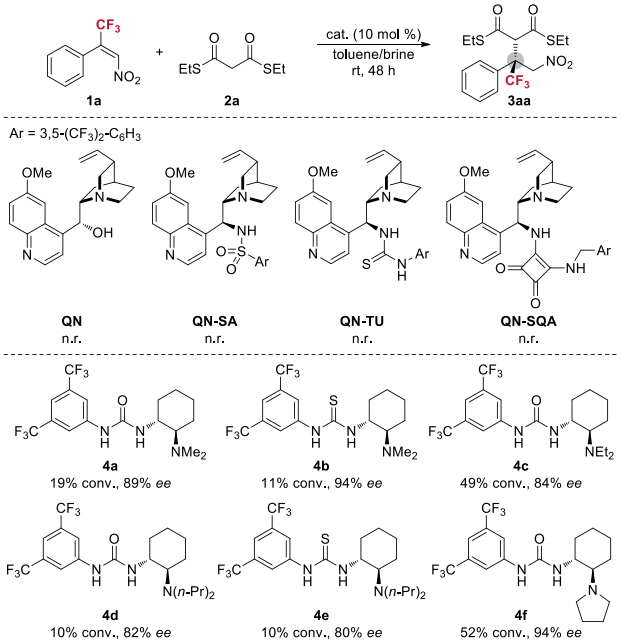


alkenes are sterically highly congested and thus are regarded as poor substrates for Michael addition.[12] We recently demonstrated that the "hydrophobic amplification"[13] achieved under "on-water" conditions[14,15] makes it possible to achieve new catalytic reactions of otherwise completely unreactive substrates.[16,17] On-water catalysis usually enables enforced hydrophobic interactions between catalysts and substrates as a result of hydrophobic hydration effects.[18] Thus, we presumed that the reactivity limitation of this type of substrate could be addressed by employing on-water conditions. Herein we report a practical and versatile synthetic access to chiral GABA analogues with a trifluoromethylated quaternary stereogenic center at the β-position via water-promoted organocatalytic Michael reactions.

In 2017, as mentioned previously, our group demonstrated that the hydrophobic amplification achieved under on-water conditions enabled the enantioselective addition of dithiomalonates (DTMs)[19] to otherwise completely unreactive β,β-disubstituted nitroalkenes using cinchona-derived organocatalysts.[16] Thus, we initiated our study by performing the enantioselective Michael addition of (*E*)-β-CF_3-α-nitrostyrene (**1a**) and diethyl dithiomalonate (**2a**) using different types of cinchona-derived bifunctional organocatalysts under on-water conditions as a model reaction (Scheme 2). However, this class of organocatalysts failed in this model reaction. With quinine (**QN**), quinine−sulfonamide (**QN-SA**), quinine−thiourea (**QN-TU**), or quinine−squaramide (**QN-SQA**) catalysts, the reaction did not proceed at all. In cinchona-type catalysts, steric congestion at the bifunctional active site might hinder the entrance of substrates possessing a sterically demanding CF_3 group to the active site. The van der Waals volume of the trifluoromethyl group ($-CF_3$) is relatively large, similar to that of the ethyl group.[71] We therefore hypothesized that the use of catalysts having a larger active-site cavity might address this low reactivity issue.

Gratifyingly, Takamoto-type catalysts **4** showed some promising catalytic results. When the model reaction was carried out using Takemoto catalyst **4a**, the desired product **3aa** was obtained in 19% yield with 89% *ee*. Further catalyst screening revealed Takemoto-type catalyst **4f** to be the optimal catalyst. The presence of the pyrrolidine moiety in **4f** provoked a dramatic change in the reactivity (52% yield) and enantioselectivity (94% *ee*). Thus, with **4f** as the optimal catalyst, further optimization studies were performed (Table 1). Further improvements in the conversion and enantioselectivity were simply achieved by increasing the catalyst loading (15 mol %), lowering the reaction temperature (0 °C), and prolonging the reaction time (96 h) (entry 3). Furthermore, screening of different dithiomalonates **2** (see the Supporting Information) showed that dibenzyl dithiomalonate (**2b**) was also a suitable Michael donor (entries 4−11). In particular, the use of 2.0 equiv of **2b** in the presence of **4f** (15 mol %) and

Scheme 2. Catalyst Screening[a]



[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), catalyst (0.01 mmol), toluene (0.5 mmol), brine (2.0 mL), rt, 48 h. Conversions were calculated by ^{19}F NMR integration, and *ee* values were determined by HPLC analysis. n.r. = no reaction.

toluene (5.0 equiv) as a hydrophobic cosolvent at 0 °C for 96 h was the most effective protocol for this model reaction (>99% conversion with 96% *ee*) (entry 5).[20] Here it should also be noted that in the absence of a hydrophobic cosolvent, a slightly lower enantioselectivity was obtained (entry 5 vs entry 11). It is probable that some water molecules around the transition state can interfere with this hydrogen-bonding catalysis, consequently lowering the enantioselectivity. The hydrophobic cosolvent can suppress the interaction of water molecules with transition state by sequestering the transition state away from water.[16,17] Thus, the addition of each of the hydrophobic cosolvents tested in this study yielded slightly enhanced enantioselectivity (entries 5−10 vs entry 11). In addition, to highlight the on-water effect, control experiments in organic solvents (toluene and DCM) were performed, and only poor yields were obtained (see the Supporting Information for experimental details).

With the optimal reaction conditions in hand, the scope of the enantioselective Michael addition of a variety of β-CF_3-β,β-disubstituted nitroalkenes **1a−w** in the presence of a catalytic amount of **4f** was explored to establish the generality of the process (Scheme 3). A series of trifluoromethylated nitroalkene derivatives **1a−o** having a variety of different *ortho*-, *meta*-, and *para*-substituted phenyl groups at the β-position, including a 2-naphthyl group, were successfully converted into the corresponding products **3a−o** in excellent yields with 93−96% *ee*. This reaction also works very well for a range of trifluoromethylated nitroalkenes with different heteroaryl (products **3p−r**) and alkyl (products **3s** and **3t**) substituents at the β-position. Nitroalkene **1u** with a CF_2H group was also examined. To our delight, the Michael adduct **3u** possessing a CF_2H group at the β-position was also attainable under the same conditions. However, nitroalkenes **1v** and **1w** having sterically more demanding perfluoroalkyl groups (e.g., $-C_2F_5$,

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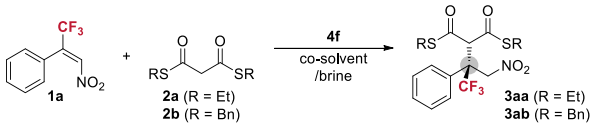
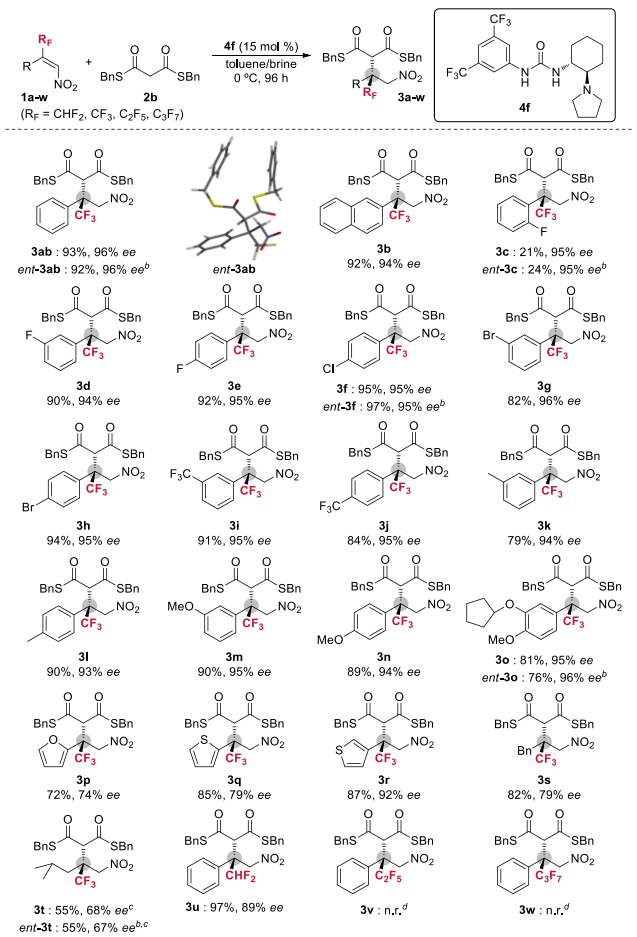
Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst mol %	DTM (equiv)	cosolvent	temp. (°C)	time (h)	conv. (%)[b]	*ee* (%)[c]
1	10	**2a** (1.2)	toluene	rt	48	52	94
2	15	**2a** (2.0)	toluene	rt	48	84	94
3	15	**2a** (2.0)	toluene	0	96	82	96
4	15	**2b** (2.0)	toluene	rt	48	86	94
5	15	**2b** (2.0)	toluene	0	96	>99	96
6	15	**2b** (2.0)	hexane	0	96	86	94
7	15	**2b** (2.0)	cyclohexane	0	96	98	96
8	15	**2b** (2.0)	*o*-xylene	0	96	93	94
9	15	**2b** (2.0)	*p*-xylene	0	96	95	95
10	15	**2b** (2.0)	mesitylene	0	96	89	95
11	15	**2b** (2.0)	–	0	96	87	93

[a]Reaction conditions: **1a** (0.1 mmol), **2a** or **2b**, **4f**, cosolvent (0.5 mmol), brine (2.0 mL). [b]Calculated by ^{19}F NMR integration. [c]Determined by HPLC analysis.

Scheme 3. Substrate Scope[a]

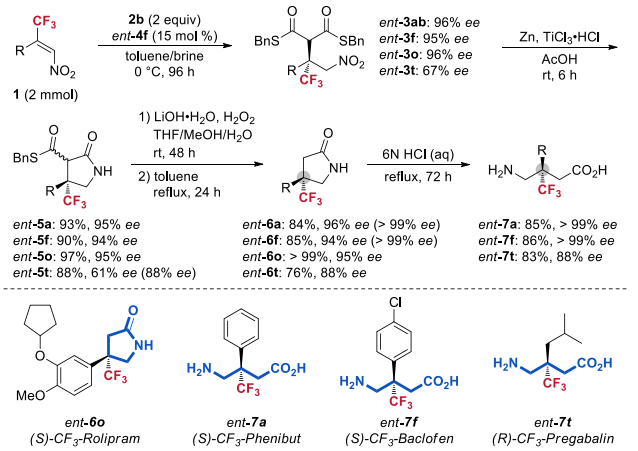


[a]General reaction conditions: **1a**–**v** (0.3 mmol), **2b** (0.6 mmol), **4f** (0.045 mmol), toluene (1.5 mmol), brine (4.0 mL), 0 °C, 96 h. [b]*ent*-**4f** was used as the catalyst. [c]**2b** (0.3 mmol) was used. [d]n.r. = no reaction.

$-C_3F_7$) showed no reactivity.[21] The opposite enantiomeric products *ent*-**3ab**, *ent*-**3c**, *ent*-**3f**, *ent*-**3o**, and *ent*-**3t** were also obtained in good yields and stereoselectivities using the enantiomer of **4f** as the catalyst. The absolute configuration of *ent*-**3ab** was established as *S* by X-ray analysis.[22]

Finally, the synthetic utility of our catalytic protocol was showcased by the synthesis of β-CF_3-β-aryl- or -alkyl-functionalized γ-aminobutyric acids (**7**) from Michael adducts **3**. As shown in Scheme 4, the Michael addition reactions of **1a**, **1f**, **1o**, and **1t** with dibenzyl dithiomalonate (**2b**) using *ent*-**4f** (15 mol %) as the catalyst on a 2 mmol scale afforded the corresponding desired Michael products (*S*)-**3ab** (96% *ee*), (*S*)-**3f** (95% *ee*), (*S*)-**3o** (96% *ee*), and (*R*)-**3t** (67% *ee*), respectively. The obtained Michael products were then smoothly converted into the corresponding γ-lactam thioesters *ent*-**5a**, *ent*-**5f**, *ent*-**5o**, and *ent*-**5t**, respectively, under reduction conditions (Zn, $TiCl_3$·HCl in AcOH). The enantiopurity of *ent*-**5t** was increased above 88% *ee* after recrystallization from diethyl ether. Subsequent hydrolysis of γ-lactam thioesters **5** followed by a decarboxylation step provided β-CF_3-substituted

Scheme 4. Synthetic Utility of the Michael Adducts 3 To Obtain β-CF_3-GABA Analogues[ab]



[a]The % *ee* values in parentheses were obtained after recrystallization. [b]The corresponding enantiomers of (*S*)-**7a**, (*S*)-**7f**, (*S*)-**6o**, and (*R*)-**7t** were also prepared with **3ab**, **3f**, **3o**, and **3t**, respectively (see the Supporting Information).

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γ-lactams **6**. Enantiomerically pure *ent*-**6a**[23] and *ent*-**6f** could be obtained by recrystallization from methyl *tert*-butyl ether. Notably, *ent*-**6o** is the β-trifluoromethylated analogue of rolipram. Finally, the HCl salts of *ent*-**7a**, *ent*-**7f**, and *ent*-**7t**, which are the β-trifluoromethylated analogues of phenibut, baclofen, and pregabalin, respectively, were obtained by hydrolysis of the corresponding γ-lactams with 6 N HCl.

In summary, we herein have introduced a practical and versatile synthetic access to CF_3-substituted GABA analogues bearing a quaternary stereogenic center at the β-position via water-promoted Michael reactions. Under on-water conditions, the highly challenging enantioselective Michael addition of sterically congested β-CF_3-β,β-disubstituted nitroalkenes with dithiomalonates as reactivity-enhanced malonate surrogates has been achieved. As a result of enforced hydrophobic interactions between catalysts and reactants, the reaction rates were remarkably accelerated under on-water conditions. Takemoto-type thiourea catalysts are very effective for this transformation, and excellent chemical yields with enantioselectivities of over 90% *ee* were obtained in most cases. Thus, this approach enables the very efficient asymmetric synthesis of enantioenriched Michael adducts containing a quaternary stereogenic center bearing a trifluoromethyl group, which provide simple access to GABA analogues with a β-trifluoromethylated quaternary stereocenter.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02320.

Experimental details and analytical data (PDF)

Accession Codes

CCDC 1920284 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(20) The same reaction with dialkyl malonates or malonic acid half-thioesters did not proceed at all (see the Supporting Information).
(21) The sterically highly congested substrates having an *ortho*-substituted phenyl (e.g., *o*-Me, *o*-OMe) or 1-naphthyl group were not compatible with the same reaction conditions.
(22) The absolute configurations of the other Michael adducts **3** were tentatively assigned by analogy.
(23) The absolute configuration of *ent*-**6a** was further confirmed to be *S* by comparison with the sign of the specific rotation given in the literature data (see ref 11b).

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