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Water-Enabled Catalytic Asymmetric Michael Reactions of Unreactive Nitroalkenes: One-Pot Synthesis of Chiral GABA-Analogs with All-Carbon Quaternary Stereogenic Centers

*Jae Hun Sim and Choong Eui Song**

Abstract: *Water enables new catalytic reactions for otherwise unreactive substrate systems. Under the "on water" reaction conditions, extremely unreactive β,β-disubstituted nitroalkenes smoothly underwent enantioselective Michael addition reactions with dithiomalonates using a chiral squaramide catalyst, affording both enantiomers of highly enantioenriched Michael adducts with all-carbon-substituted quaternary centers. The developed "on water" protocol was successfully applied for the scalable one-pot syntheses of chiral GABA analogs with all-carbon quaternary stereogenic centers at the β-position, which might show highly interesting pharmaceutical properties.*

The simplest γ-amino acid, γ-aminobutyric acid (GABA), is the major inhibitory neurotransmitter in the central nervous system (CNS) of mammals. GABA deficiency is associated with several important neurological disorders such as Huntington and Parkinson disease, epilepsy, as well as psychiatric disorders, such as anxiety and pain.[1] Thus, synthesis of many structurally diverse GABA analogs has attracted a great deal of interest in the pharmaceutical field, especially with the aim to increase their lipophilicity, thus allowing them to gain access to the central nervous system.[1] In particular, a number of GABA analogs bearing a tertiary chiral carbon center at the β-position such as phenibut,[2] baclofen,[3] pregabalin[4] and rolipram[5] have been developed as important therapeutic agents for a range of CNS-disorders (Figure 1). Moreover, radioactive isotope-labelled β-substituted γ-lactams such as [^{11}C]-labeled UCB-J was shown to have excellent PET (positron emission tomography) imaging properties for in vivo quantification of synaptic density with several potential applications in diagnosis and therapeutic monitoring of neurological and psychiatric disorders (Figure 1).[6]

In this regard, more lipophilic, chiral acyclic β,β-disubstituted γ-aminoacids and their lactam analogs with all-carbon quaternary stereogenic centers are expected to expand the pharmaceutical library with potential bioactivities. However, synthetic difficulties with creating all-carbon quaternary stereogenic centers[7] at the β-position of γ-aminoacids have prevented their implementation in drug discovery. For example, there is only one reported catalytic enantioselective synthesis[8] of β,β-disubstituted γ-amino acids

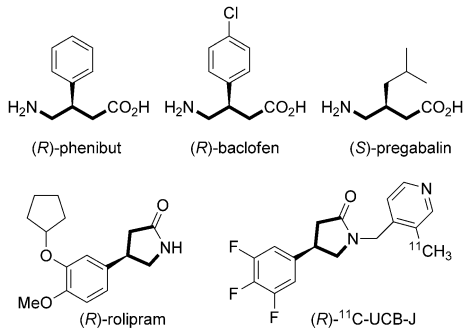
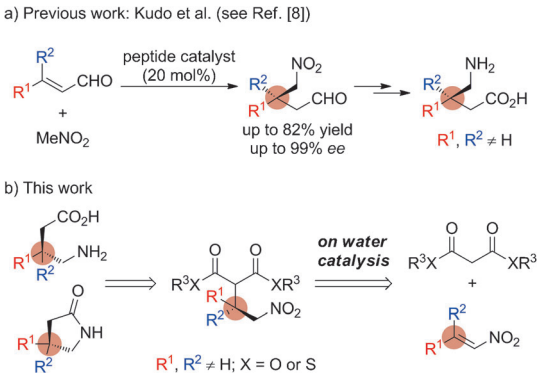


Figure 1. Pharmaceutically important GABA analogs.

without an introduction of activating groups.[9] In this report, the authors developed a catalytic reaction for the synthesis of chiral β,β-disubstituted γ-amino acids via peptide-catalyzed asymmetric Michael addition of nitromethane to β-disubstituted α,β-unsaturated aldehydes (Scheme 1a).[8] Alternatively, a γ-aminobutyric acid precursor with an all-carbon quaternary stereogenic center, in principle, could be directly accessed through a catalytic asymmetric Michael addition of malonates **2** to β,β-disubstituted nitroalkenes **1** (Scheme 1b). However, to the best of our knowledge, Michael addition of β,β-disubstituted nitroalkenes **1** with malonate derivatives have so far not been realized, presumably due to the lack of reactivity associated with the steric and electronic nature of β-carbon.[10]



Scheme 1. a) Previous work for the synthesis of γ-amino acids with an all-carbon quaternary center. b) Proposal for the synthesis of chiral GABA analogs with all-carbon quaternary center at β-position by employing "on water" catalytic conditions.

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In nature, water is used for biosynthetic reactions to sustain life in enzymatic processes, inducing hydrophobic interactions between enzyme and substrates.[11] From the perspective of green chemistry as well as increased scientific efforts to mimic nature, tremendous effort has recently been applied to develop asymmetric catalytic reactions in aqueous environments.[12] Recently, the Schreiner[13] and Rueping[14] research groups independently reported that hydrogen-bond-promoted organocatalysis could remarkably be amplified in aqueous environments by the "hydrophobic hydration effect".[15] Soon after, we[16] and Armas research group[17] also reported successful hydrogen bonding promoted asymmetric catalytic reactions in aqueous medium. In particular, we observed that the hydrophobic amplification[13] was significantly dependent upon the hydrophobicity of the catalysts.[16b] For example, in the Michael addition reactions of simple nitroalkenes with malonates, using a hydrophobic cinchona catalyst, even a highly challenging Michael donor such as dimethyl methyl malonate could be smoothly converted to the desired adduct. Thus, we envisioned that hydrophobic amplification "on water"[18,19] conditions would enable unprecedented Michael addition of challenging β,β-disubstituted nitroalkenes with malonate derivatives (Scheme 1 b).

Here, we report the highly enantioselective organocatalytic Michael addition of dithiomalonates to β,β-disubstituted nitroalkenes in water. The obtained Michael adducts could smoothly be converted into diverse chiral GABA analogs with all-carbon quaternary stereogenic centers at the β-position, which might show interesting pharmaceutical properties.

Initially, we examined Michael addition reactions of highly unreactive (*E*)-α-methyl-β-nitrostyrene (**1a**) with dibenzyl malonate (**2a**), dibenzyl monothiomalonate (**2b**) or dibenzyl dithiomalonate (**2c**) in the presence of triethyl amine as a catalyst at ambient temperature. As shown in Figure 2, when malonate **2a** or monothiomalonate **2b** was employed as a Michael donor, no obvious conversion was detected both in organic solvents and "on water" system. However, dithiomalonate **2c**—a reactivity-enhanced malonate surrogate[20]—led to a striking rate difference in the Michael addition between the reactions in an organic solvent and "on water" (Figure 2). When the reactions were performed in toluene, CH_2Cl_2, or THF, no conversion was observed. However, with the "on water" condition (on brine[21]), the reaction was completed after 48 h, presumably due to the hydrophobic hydration effect. Evidence for the hydrophobic hydration effect on rate acceleration was obtained using an antihydrophobic $LiClO_4$.[15a] In the aqueous $LiClO_4$ solution, less than 5% of conversion was observed after 96 h.

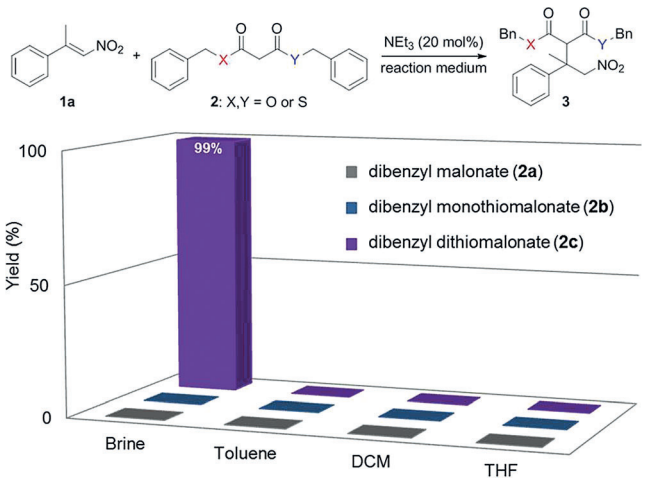
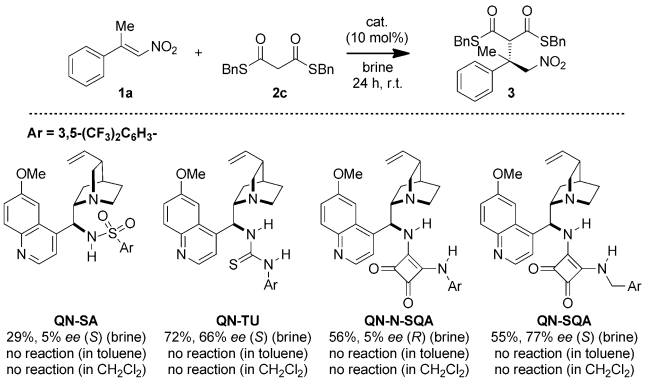


Figure 2. Relative reactivity of malonate types in various reaction media.[a] [a] Reaction was carried out using **1a** (0.1 mmol), **2** (1.2 equiv) and NEt_3 (20 mol%) in the indicated reaction medium (2.0 mL) at RT for 48 h. The yield was determined by ^{1}H NMR integration.

With the promising preliminary results in hand, we next explored the enantioselective Michael reaction of (*E*)-α-methyl-β-nitrostyrene (**1a**) with dithiomalonate **2c** on brine using a variety of cinchona-based bifunctional organocatalysts. However, the use of readily available cinchona-based bifunctional catalysts, quinine-based sulfonamide **QN-SA**, thiourea **QN-TU** and *N*-squaramide **QN-N-SQA** led to unsatisfactory enantioselectivities (5–66% *ee*) (Scheme 2).

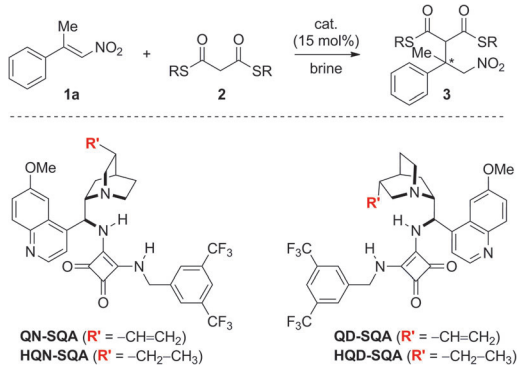


Scheme 2. Preliminary catalyst screening.

Gratifyingly, the squaramide catalyst **QN-SQA** was found to be a promising catalyst, showing remarkably higher enantioselectivity (77% *ee*) than those obtained with other catalysts (Scheme 2, for more results for catalyst screening, see the Supporting Information). Note that, all catalysts examined in this study showed no activity in pure organic solvents such as toluene and CH_2Cl_2.

Although "on water" reaction conditions enabled the unprecedented catalytic reaction, *ee* values achieved with **QN-SQA** catalyst and its derivatives were still unsatisfactory. However, to our delight, the addition of hydrophobic co-solvents such as, for example, toluene, *o*-, *m*- and *p*-xylene, mesitylene, hexane, and cyclohexane, yielded enhanced enantioselectivity (Table 1, see the Supporting Information for details). For example, the enantioselectivity was increased from 77% *ee* to 86% *ee* by adding 7 equiv of *o*-xylene (entry 3 in Table 1). However, the reverse mixing of solvents (i.e., brine as an additive (7 equiv) in *o*-xylene) did not promote the reaction, which is a further evidence of the hydrophobic hydration effect on the rate acceleration. To further improve the yields and enantioselectivity, the effect of the substituents (R) of dithiomalonates **2** in our reaction system was also

Table 1: Reaction condition optimization with squamide-based catalysts.[a]



Entry	Catalyst	R	Additive (equiv)[b]	*T* [°C]	*t* [h]	Yield [%][c]	*ee* [%][d]
1	**QN-SQA**	Bn	–	20	48	61	77
2	**QN-SQA**	Bn	toluene	20	48	47	84
3	**QN-SQA**	Bn	*o*-xylene	20	48	44	86
4	**QN-SQA**	Et	*o*-xylene	20	48	36	87
5	**QN-SQA**	Et	*o*-xylene	20	96	49	87
6	**HQN-SQA**	Et	*o*-xylene	20	96	99	84
7	**QD-SQA**	Et	*o*-xylene	20	96	47	85[e]
8	**HQD-SQA**	Et	*o*-xylene	20	96	99	86[e]
9	**HQN-SQA**	Et	*o*-xylene	0	96	98	92
10	**HQD-SQA**	Et	*o*-xylene	0	96	97	93[e]

[a] Reactions were performed with **1a** (0.1 mmol), **2** (3 equiv) and catalyst (15 mol%) on brine (2.0 mL). [b] 7 equivalents of additive were used. [c] The yield was determined by ^{1}H NMR integration. [d] The *ee* values were determined by HPLC analysis using a chiral stationary phase. [e] Using the pseudo-enantiomeric **QD-SQA** and **HQD-SQA**, the opposite enantiomer was obtained.

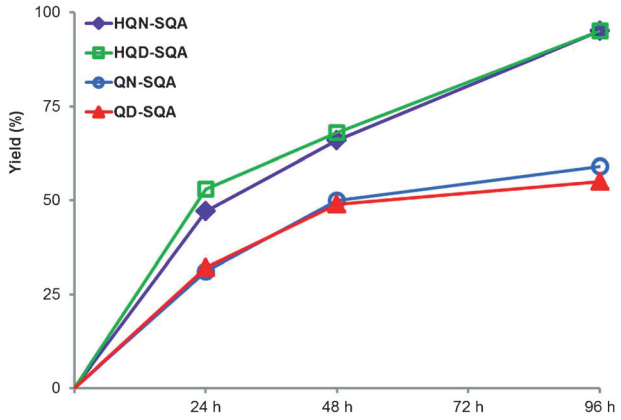
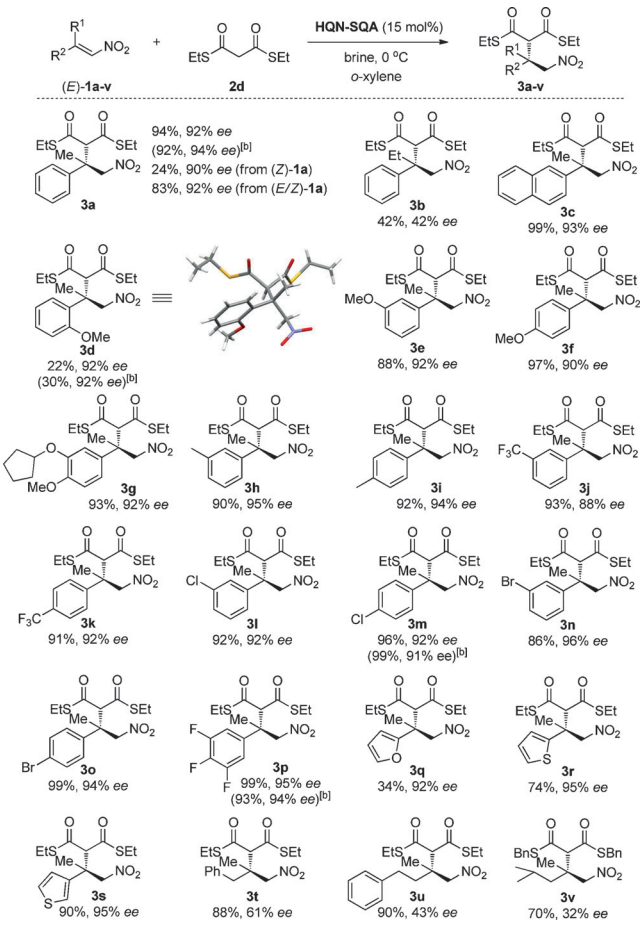


Figure 3. Reaction progress of the Michael addition of **2d** to **1a** on brine.[a] a) using squaramide catalysts.[a] The reactions were performed with **1a** (0.1 mmol), **2d** (1.2 equiv), catalyst (10 mol%) and *o*-xylene (5 equiv) on brine (3.0 mL) at RT.

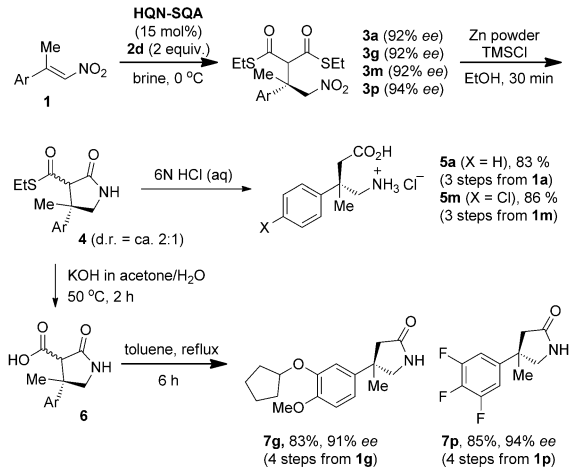
investigated. Among the tested substrates (R = benzyl, ethyl, *n*-butyl, *t*-butyl, phenyl etc.), the diethyl dithiomalonate **2d** was found to be the most suitable Michael donor (87% *ee*, entry 4) (For more results obtained from thiomalonates screening, see the Supporting Information). However, in spite of our intensive optimization efforts, we could not obtain higher than 49% yield even with prolonged reaction times (entry 5 in Table 1). Recently, we reported that the catalyst hydrophobicity, which can result in enforced hydrophobic interactions between catalysts and substrates, is critical for the reaction rate in some "on water" reactions.[16b] As shown in Table 1 (entries 5 and 7 vs. entries 6 and 8) and Figure 3, the reaction rate issue of the present reaction was also addressed by using more hydrophobic catalysts. When more hydrophobic dihydroquinine-derived squaramide **HQN-SQA** (Log*P*; 2.41 for **QN-SQA**, 2.68 for **HQN-SQA**)[16b] was used, an enormous rate acceleration (>99% conversion) was observed (entries 6 and 8 in Table 1 and Figure 3). Further improvement of enantioselectivity was achieved by lowering the reaction temperature to 0°C [92% *ee* using **HQN-SQA** (entry 9) and 93% *ee* using the **HQD-SQA** (entry 10)]. The same trends highlighting the remarkable effect of catalyst hydrophobicity on the reactivity was also observed with racemic tertiary amine catalysts. The more hydrophobic tri-*n*-butyl amine (Log*P*; 3.97) and tri-*n*-hexyl amine (Log*P*; 6.47) exhibited much higher catalytic activity than the less hydrophobic triethyl amine (Log*P*; 1.26) (see the Supporting Information).

With the optimal catalytic conditions in hand, the substrate scope of our protocol was investigated, and the results are shown in Scheme 3. Excellent enantioselectivities (up to 96% *ee*) and isolated chemical yields (up to 99%) were obtained with diverse aryl and heteroaryl substituted nitroalkenes **1**. In particular, substituents in *meta*-, or *para*-positions were all found to be excellent substrates for the reaction. Regardless of the electronic nature of the aromatic substituent, high enantioselectivity was achieved. Although the sterically demanding *ortho*-substituted substrate **3d** also gave excellent enantioselectivity, a significantly lower reaction rate was observed, due to steric limitations. Heteroaromatic substrates such as 2-furanyl (**1q**), 2-thienyl (**1r**) and 3-thienyl (**1s**) also gave excellent enantioselectivities (92% *ee*, 95% *ee* and 95% *ee*, respectively). In addition, aliphatic substrates **1t**–**1v** were also smoothly converted to the corresponding adducts in moderate to high yields, however with lower *ee*s. The absolute configuration of **3d** was determined to be (*S*) by a single crystal X-ray structure analysis.[22] The absolute configuration of other Michael adducts **3** were assigned by analogy. It is also noteworthy that this process is stereoconvergent, a highly desirable feature for a catalytic asymmetric reaction.[23] *E* or *Z* isomer of **1a** afforded the same (*S*)-enantiomer of the Michael adduct **3a**. Thus, the mixture of *E*/*Z*-isomers of **1** can be used without a purification step.

To demonstrate the synthetic utility and potential large-scale applications of the present catalytic protocol, gram-scale one-pot process for the synthesis of chiral GABA analogs bearing chiral quaternary carbon centers was developed. As shown in Scheme 4, the Michael addition reactions of **1a**, **1g**, **1m** and **1p** with diethyl dithiomalonate (**2d**) on a 13 mmol scale afforded multi-gram quantities of the corresponding desired products, (*S*)-**3a** (92% *ee*), (*S*)-**3g** (92% *ee*), (*S*)-**3m**



Scheme 3. Substrate scope of the reaction.[a] [a] Unless otherwise indicated, the reactions were performed with (*E*)-**1** (0.5 mmol), **2d** (3.0 equiv), **HQN-SQA** (15 mol%), and *o*-xylene (7.0 equiv) on brine (4.0 mL) at 0 °C for 96 h. [b] The yields and % *ee*s in parentheses were obtained by using **HQD-SQA** as the catalyst.



Scheme 4. Synthetic applications—one-pot syntheses of chiral beta-disubstituted GABA analogs.

(92 % *ee*) and (*R*)-**3p** (94 % *ee*), respectively. The catalyst was easily recovered by simple filtration from the reaction mixture as a yellowish solid after the addition of methylcyclohexane (see the Supporting Information for experimental details).[16b] After the separation of the organic layer from the biphasic filtrate and evaporation under reduced pressure, the crude products were subjected to reduction (Zn/TMSCl), affording the corresponding chiral γ- lactam thioesters **4a**, **4g**, **4m** and **4p**, respectively. Subsequent hydrolysis of crude γ-lactam thioesters **4a** and **4m** with 6 N HCl provided the HCl salt of the corresponding β,β-disubstituted γ-amino acid **5a** (83 % yield, 3 steps from **1a**) and **5m** (86 % yield, 3 steps from **1m**), which are the respective β-methylated analogs of phenibut and baclofen. On the other hand, the β-methylated analog of rolipram **7g** was prepared by hydrolysis of crude **4g**, followed by a decarboxylation step (83 % yield, 91 % *ee*, 4 steps from **1g**). In a similar manner, the γ-lactam **7p** was also obtained which can be used to synthesize the beta-methylated analog of [^{11}C]-labeled UCB-J (85 % yield, 94 % *ee*, 4 steps from **1p**). The enantioselectivities of the original Michael adducts **3** were maintained in the γ-lactams **7**, indicating the perfect preservation of the stereochemistry during the reduction and decarboxylation steps. The absolute configuration of γ-lactams **7** was also determined by a single crystal X-ray structure analysis.[22]

In summary, we demonstrated here that on-water catalysis enables new catalytic reactions for otherwise unreactive substrate systems. Highly enantioselective organocatalytic Michael addition of dithiomalonates to unreactive β,β-disubstituted nitroalkenes, affording both enantiomers of highly enantioenriched Michael adducts with all-carbon-substituted quaternary centers, has been achieved by employing the "on water condition," which enables enforced hydrophobic interactions between catalysts and substrates due to the hydrophobic hydration effects. The developed "on water" protocol was successfully applied for the scalable one-pot syntheses of chiral GABA analogs with all-carbon quaternary stereogenic centers at the β-position, which might show highly interesting pharmaceutical properties.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: amino acids · asymmetric organocatalysis · Michael addition · stereogenic centers · water

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Communications

Organocatalysis

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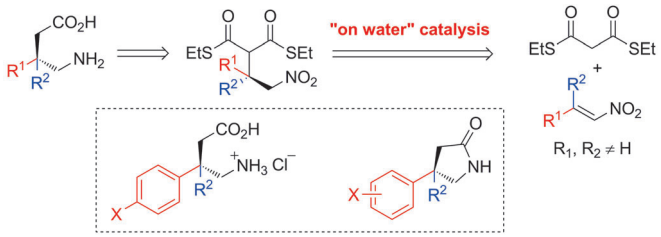

Hydrophobic hydration: Under aqueous reaction conditions, extremely unreactive β,β-disubstituted nitroalkenes smoothly underwent enantioselective Michael addition reactions with dithiomalonates using a chiral squaramide catalyst, affording both enantiomers of the highly enantioenriched Michael adducts with all-carbon-substituted quaternary centers.