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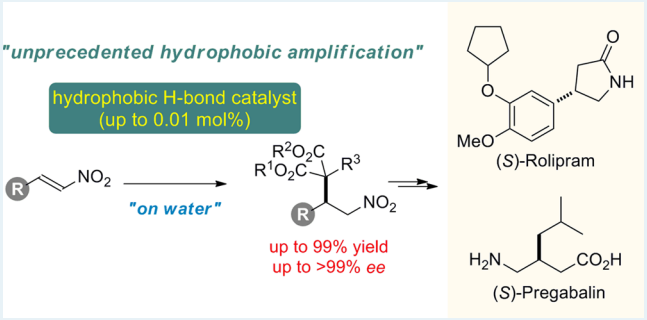
Unprecedented Hydrophobic Amplification in Noncovalent Organocatalysis "on Water": Hydrophobic Chiral Squaramide Catalyzed Michael Addition of Malonates to Nitroalkenes

Han Yong Bae and Choong Eui Song*

Department of Chemistry, Sungkyunkwan University, Gyeonggi, 440-746, Korea

Supporting Information

ABSTRACT: In this study, water was demonstrated to be an exceptionally efficient reaction medium for the noncovalent, hydrogen-bonding-promoted enantioselective Michael addition of malonates to diverse nitroolefins using cinchona-based squaramide catalysts. A significant increase in the reaction rate was observed when the reaction was performed "on water" rather than in the conventional organic solvents, because of the hydrophobic hydration effect. This hydrophobic amplification was significantly dependent upon the hydrophobicity of the C3-substituent (vinyl or ethyl) of cinchona-based catalysts. Thus, the use of more hydrophobic catalyst with an ethyl group at the C3-position, even a highly challenging Michael donor such as dimethyl methylmalonate was also smoothly converted to the desired adduct. Furthermore, because of the remarkable rate acceleration under "on water" conditions, the catalyst loading also significantly decreased. Thus, in the case of β-ketoesters, even 0.01 mol % of catalyst loading was enough to complete the reaction at room temperature, affording the corresponding Michael adducts with perfect diastereo- and enantioselectivity (up to >99:1 d.r., up to 99% ee). The developed "on water" protocol was successfully applied for the scalable syntheses of an antidepressant (*S*)-rolipram and an anticonvulsant (*S*)-pregabalin.



KEYWORDS: *noncovalent organocatalysis "on water", malonates as Michael donors, hydrophobic hydration, hydrophobic substituent effect, Log P*

INTRODUCTION

Organic solvents are obviously the most used materials in the manufacture of active pharmaceutical ingredients (APIs). In general, they make up >80% of the total material usage, giving rise to considerable energy usage, expense, and industrial pollution.[1] To reduce or prevent the use of organic solvents as the reaction medium, water is supposed to be an ideal alternative for industrial processes. Water is inexpensive, nontoxic, inflammable, and nonexplosive. Moreover, its high heat capacity makes it ideally suited for exothermic reactions on an industrial scale.[2] In nature, water is the only medium used for biosynthetic reactions to sustain life. The "hydrophobic effect" is one of the key elements in such enzyme catalysis.[3]

From the perspective of green chemistry as well as increased scientific effort to mimic nature, significant attention has recently been directed to the development of asymmetric catalytic reactions in aqueous environments.[4] There have been a number of successful reports of metal-catalyzed asymmetric reactions[4,5] and asymmetric organocatalytic reactions involving covalent bonding activation (using primary or secondary amine catalysts) in aqueous media.[4,6] However, the introduction of water as a solvent in the noncovalent, hydrogen-bonding promoted asymmetric catalysis has not yet been extensively reported, as it was believed that water can interfere with the catalysis, because of its capacity for disrupting hydrogen bonds. Recently, the Schreiner[7a] and Rueping[7b] groups independently reported in their pioneering works that noncovalent organocatalysis under aqueous environment is not unachievable and can even be amplified by "hydrophobic hydration".[8,9] Soon after, we[7c] also observed the remarkable hydrophobic amplification of enantioselective hydrogen bonding promoted organocatalysis in aqueous medium. More recently, Armas and García-Tellado also reported a successful result of hydrogen bonding promoted asymmetric Aza-Henry reaction in aqueous medium.[7d]

In recent years, the transition-metal free stereoselective preparation of γ-aminobutyric acid (GABA) analogues, which are widely used for inhibitory neurotransmitters such as the antidepressants (*R*)-phenibut and (*R*)-baclofen, and an anticonvulsant (*S*)-pregabalin (marketed by Pfizer, brand name Lyrika), have been intensively studied by several research groups.[10] Moreover, organocatalytic routes for the production

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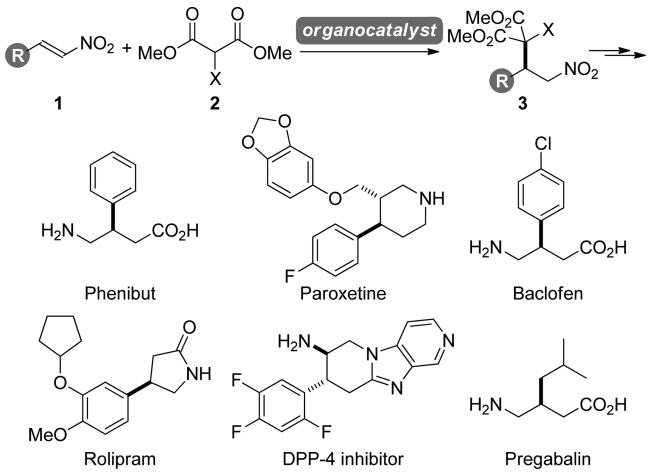
of the antidepressants (*R*)-rolipram and paroxetine,[11] and an aminopiperidine-fused imidazopyridine dipeptidyl peptidase IV (DPP-4) inhibitor[12] were also investigated. To access the aforementioned valuable bioactive chiral compounds, the metal-free asymmetric organocatalytic Michael addition of malonates **2** to nitroolefins **1** was shown to be a powerful approach from a green chemistry perspective (Scheme 1).

Scheme 1. Strategy to Bioactive Compounds via Noncovalent Asymmetric Organocatalytic Michael Addition of Malonates to Nitroalkenes



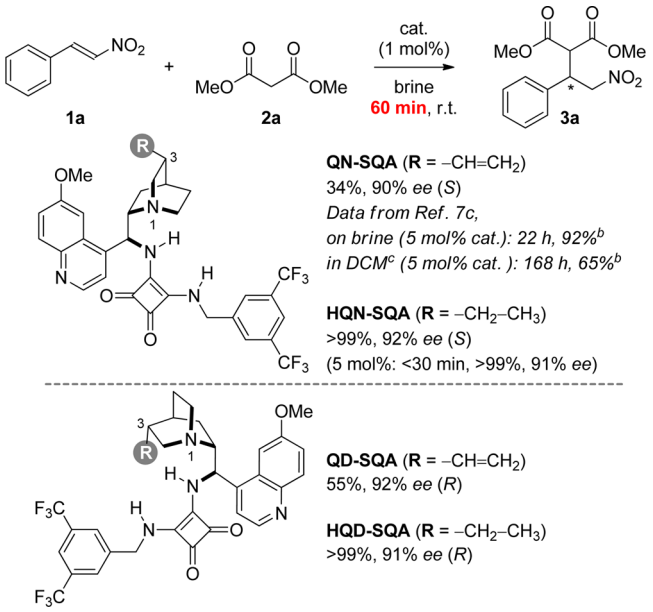
Although impressive progress has been made in terms of organocatalytic synthesis of the optically active Michael adducts **3**,[13] a more environmentally benign as well as scalable synthetic protocol is still truly required.

In our previous communication, we reported that the enantioselective Michael addition of 1,3-diketones or *β*-ketoesters to nitroolefins using quinine-based squaramide (**QN-SQA**) catalyst was dramatically accelerated on brine compared to the reaction in organic solvents, because of the hydrophobic hydration effect.[7c,14] However, under the same conditions, malonates as the Michael donors proved to be very poor substrates (Scheme 2), because of their 10^4 to 10^2 times lower pK_a values than those of 1,3-diketones and *β*-ketoesters, respectively.[15]

We presumed that this limitation of substrate scope could be addressed simply by increasing catalyst hydrophobicity, which might result in enforced hydrophobic interactions and, consequently, more significant rate acceleration under heterogeneous aqueous conditions. The common approach to increase the catalyst's hydrophobicity is installing more hydrophobic substituents (e.g., long alkyl chain, fluoroalkyl chain, and bulky aromatic moiety) on the catalyst structure.[16]

Herein, we report our findings on the remarkable hydrophobic amplification derived from the catalyst substituent effect in the noncovalent asymmetric Michael addition reaction of malonates to nitroalkenes "on water";[17,18] that is, the hydrophobic amplification was highly dependent upon the hydrophobicity of the catalysts. Thus, using more hydrophobic catalyst, the substrate scope was not limited to the *α*-unsubstituted malonates. Even highly unreactive *α*-substituted malonates such as dimethyl methylmalonate also showed good reactivity. The obtained Michael adducts were smoothly transformed into diverse bioactive compounds, which was highlighted by synthesis of the anticonvulsant drug (*S*)-

Scheme 2. Dramatic Effect of the Catalyst Hydrophobicity on the Reactivity in the Enantioselective Michael Addition "on Water"[a]



[a]Reactions were performed with **1a** (1.0 mmol), **2a** (2.0 equiv), and catalyst (1 mol %) on brine (3.0 mL) at room temperature (r.t.). The conversion was determined by ^{1}H NMR integration, and the % ee was determined by HPLC analysis on a chiral stationary phase. [b]Isolated yield. [c]DCM = dichloromethane

pregabalin on a multiten gram scale. The key step of this protocol needs no chromatography to obtain the desired product and to recover the catalyst.

RESULT AND DISCUSSION

Our studies commenced with performing enantioselective Michael addition on brine[19] using 1 mol % of differently

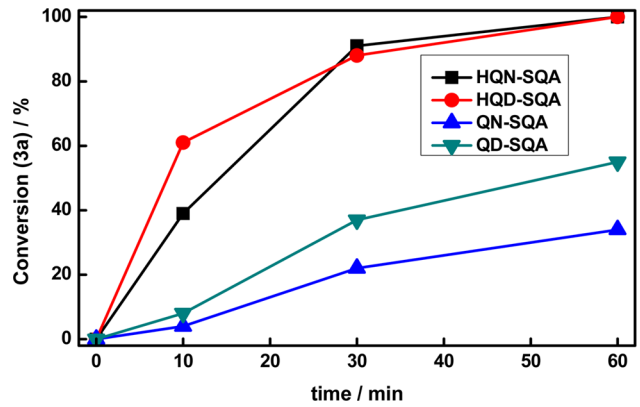


Figure 1. Reaction progress of the Michael addition of **2a** to **1a** on brine catalyzed by the squaramide catalysts: reactions were performed with **1a** (1.0 mmol), **2a** (2.0 mmol), and catalyst (1 mol %) on brine (3.0 mL) at r.t. The conversion was determined by ^{1}H NMR integration. See the Supporting Information for details.

substituted cinchona-derived squaramide organocatalysts to investigate the effect of the substituent at carbon C3 (cinchona numbering) on the catalytic efficiency.[20] The conversion and the ee value were measured after 1 h of the reaction time

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Table 1. Computational Calculation Data of Log *P* Values of Squaramide Catalysts

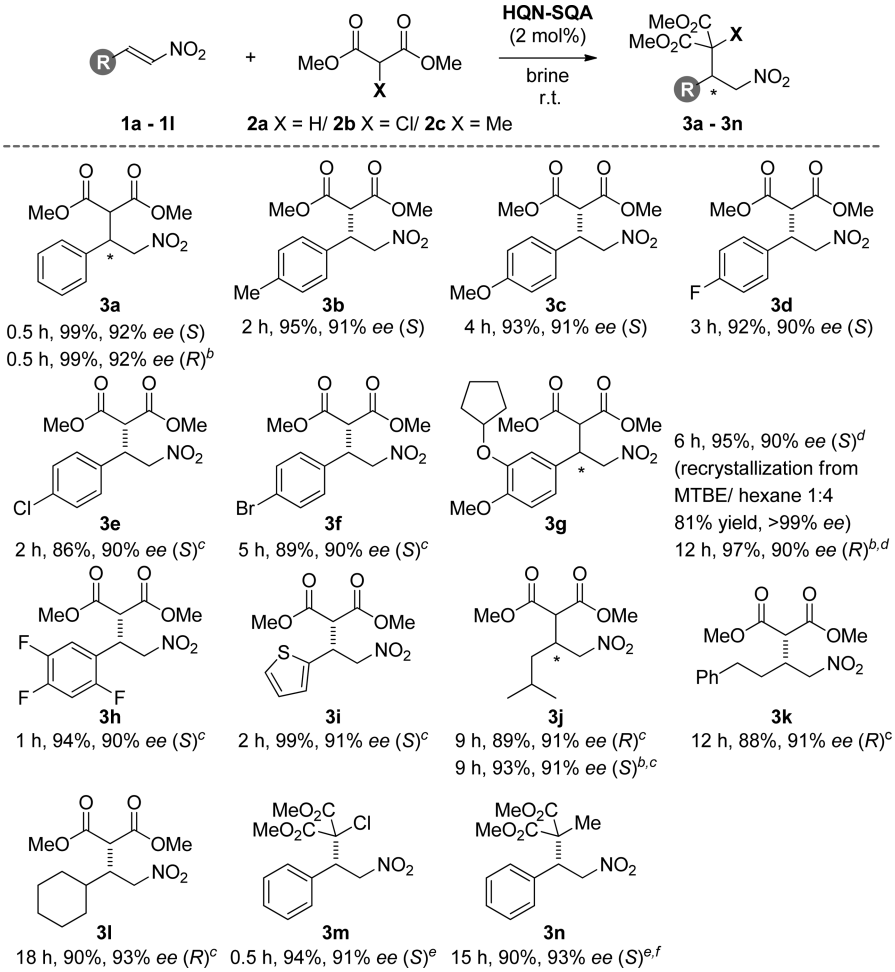
catalyst	HQN-SQA	QN-SQA	HQD-SQA	QD-SQA
Log *P*	2.68	2.41	5.29	5.02

(Scheme 2). As aforementioned, the quinine-based squaramide **QN-SQA** bearing a vinyl group at C3 carbon[21] showed poor activity in the Michael addition of dimethyl malonate (**2a**) to *β*-nitrostyrene (**1a**), yielding the adduct (*S*)-**3a** in only 34% of conversion with 90% ee.[7c] However, surprisingly, when more hydrophobic dihydroquinine-derived squaramide **HQN-SQA** was used, an enormous rate acceleration was observed with excellent enantioselectivity (>99% conv., 92% ee). Moreover, by increasing the catalyst loading to 5 mol %, the reaction completed within 30 min and retained the enantioselectivity (91% ee). As expected, this substituent effect on the catalytic results can be simply ascribed to the difference in the hydrophobicity of the catalysts (i.e., C3-ethyl group incorporated **HQN-SQA** is more hydrophobic than the C3-vinyl group incorporated **QN-SQA**). The same trends for the catalytic efficiency were also observed using the pseudoenantiomeric catalysts (quinidine-based squaramide catalyst **QD-SQA**: 55% conv., 90% ee; dihydroquinidine-based squaramide catalyst **HQD-SQA**: >99% conv., 91% ee). The remarkable effect of the C3 substituent of the catalyst on the reactivity is shown in Figure 1.[22] Notably, Liu and co-workers quite recently reported that heterogeneous cinchona-based squaramide catalyst bearing a hydrophobic C3 substituent ($-CH_2CH_2SCH_2CH_2CH_2-$) also displayed excellent catalytic activity and enantioselectivity in asymmetric Michael addition of 1,3-dicarbonyl compounds to nitroalkenes in brine.[14f]

To investigate the relationship between the catalyst structure and hydrophobicity, computational calculation of Log *P* values was performed using SPARTAN 14 software (Table 1).[23] As expected, the Log *P* values of **HQN-SQA** and **HQD-SQA** were higher (2.68 and 5.29) than those of **QN-SQA** and **QD-SQA** (2.41 and 5.02), respectively (see the Supporting Information for details).

Evidence of the hydrophobic hydration effect on the remarkable rate acceleration was obtained by performing **HQN-SQA** catalyzed Michael addition of **1a** with **2** under different aqueous conditions (see refs 24, 25 and the Supporting Information for details). The rate of the reaction dramatically decreased by the addition of typically antihydrophobic $LiClO_4$ (r.t., 60 min, 14% conv.).[8] Moreover, the

Scheme 3. Substrate Scope of the Reaction[a]



[a]General reaction conditions: **1** (1.0 mmol), **2** (2.0 mmol), and **HQN-SQA** (2 mol %) on 3.0 mL of brine at r.t. The yield was determined after the chromatographic purification, and the % ee was determined by HPLC analysis on a chiral stationary phase. [b]Using **HQD-SQA** as the catalyst. [c]Using 5 mol % of catalyst at 0 °C. [d]Using 10 mol % of catalyst at r.t. [e]Using 5 mol % of catalyst at r.t. [f]Using 5.0 equiv of **2c**.

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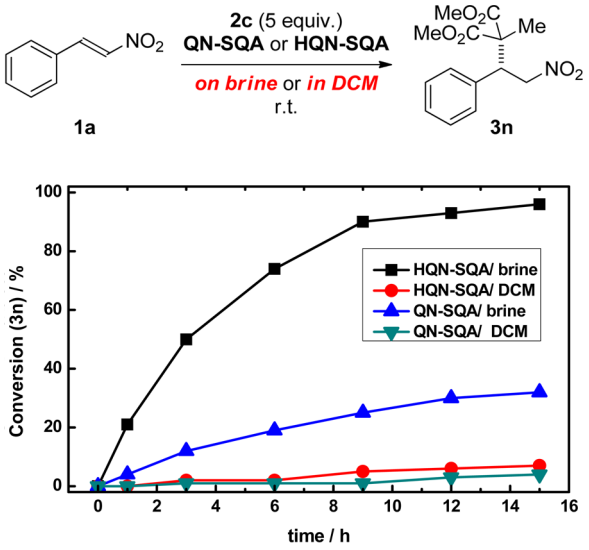


Figure 2. Reaction progress of the Michael addition of **2c** to **1a** catalyzed by the squaramide catalysts. Reactions were performed with **1a** (1.0 mmol), **2c** (5.0 equiv) and catalyst (5 mol %) in DCM (3.0 mL) or on brine (3.0 mL) at r.t. The conversion was determined by ^{1}H NMR integration (see the Supporting Information for details).

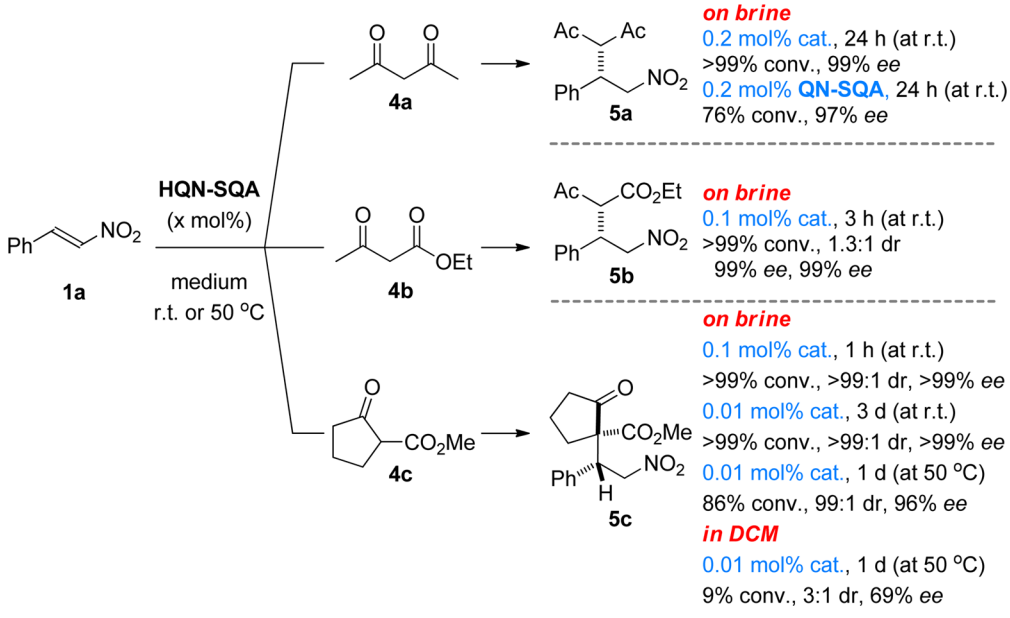
observation of a significant solvent isotope effect provides additional support for the hydrophobic hydration mechanism: the reaction slowed noticeably when NaCl in D_2O was used in the place of brine (r.t., 60 min, 22% conv.).[26]

With the optimized catalysts (**HQN-SQA** and **HQD-SQA**) in hand, the scope of the reaction with diverse nitroolefins (**1a**–**1l**) and malonates (**2a**–**2c**)[27] was investigated using 2–5 mol % of catalyst (Scheme 3). Excellent enantioselectivities (90–93% ee) and yields (86–99%) were observed for diverse aryl (**1a**–**1h**), heteroaryl (**1i**), alkyl (**1j**–**1l**) substituted β-nitroolefins, whereas the less hydrophobic catalyst **QN-SQA** showed significantly lower activity.[28] In all the cases, significant rate acceleration was observed on brine because of the hydrophobic hydration effect.

To highlight the significant hydrophobic amplification effect, the Michael addition reaction of a highly challenging substrate such as dimethyl methylmalonate (**2c**), which shows very poor reactivity in the conventional organic solvents,[29] was examined. As shown in Figure 2, the reaction with **2c** proceeded very sluggishly using both **HQN-SQA** and **QN-SQA** in DCM (after 15 h, 7% conv. and 4% conv., respectively). However, "on water", remarkable rate acceleration was observed when a more hydrophobic catalyst **HQN-SQA** was used (15 h, 95% conv.), whereas a less hydrophobic catalyst **QN-SQA** showed significantly lower activity (15 h, 32% conv.).

Although enantioselective organocatalysis has shown significant progress in terms of noble activation modes and excellent selectivity,[30] a development of highly active catalysis is quite reluctant.[31] Thus, developing high turnover organocatalysis is a remarkably challenging task.[32] We anticipated that significantly low catalyst loading can be achievable by taking advantage of the hydrophobic amplification effect. In accordance with our expectation, when more reactive Michael donors such as 1,3-diketone (**4a**) and β-ketoesters (**4b**,**4c**) were used, only very low catalyst loading (up to 0.01 mol %) was enough to complete the reaction at room temperature, affording the corresponding Michael adducts (**5a**–**5c**) with perfect stereoselectivities at r.t. (up to >99:1 dr, up to >99% ee, Scheme 4). Notably, this high level of stereoselectivities could be maintained even at elevated temperature (50 °C, 86% conv., 99:1 dr, 96% ee). In contrast, when the same reaction was performed in DCM at 50 °C, only 9% conversion and much lower stereoselectivity (3:1 dr, 69% ee) were obtained (see the Supporting Information for details).

Scheme 4. Enantioselective Michael Addition Reactions of 2,4-Pentanedione (4a) and β-Ketoesters (4b,4c) to Nitrostyrene (1a)[a]



[a]Reactions were performed with **1a** (10.0 mmol), **4** (2.0 equiv), and **HQN-SQA** catalyst on brine (10.0 mL) or in DCM (10.0 mL). The conversion and the diastereomeric ratio (dr) were determined by ^{1}H NMR integration. The % ee was determined by HPLC analysis on a chiral stationary phase. See the Supporting Information.

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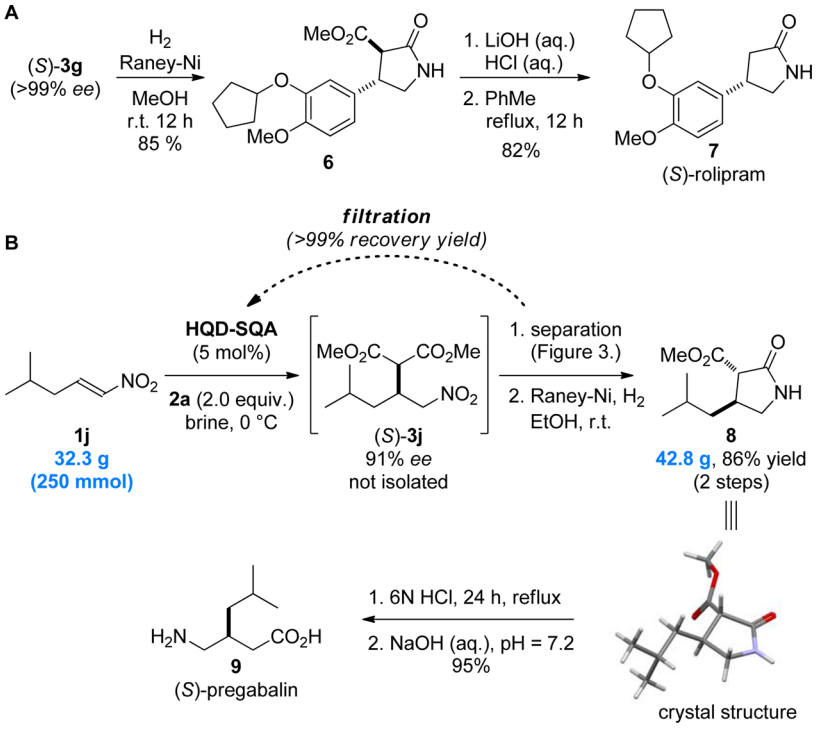
Scheme 5. Synthetic Utilities of Catalytic Michael Addition[a]



[a]Asymmetric syntheses of (*S*)-rolipram **7** (A) and (*S*)-pregabalin **9** (B).

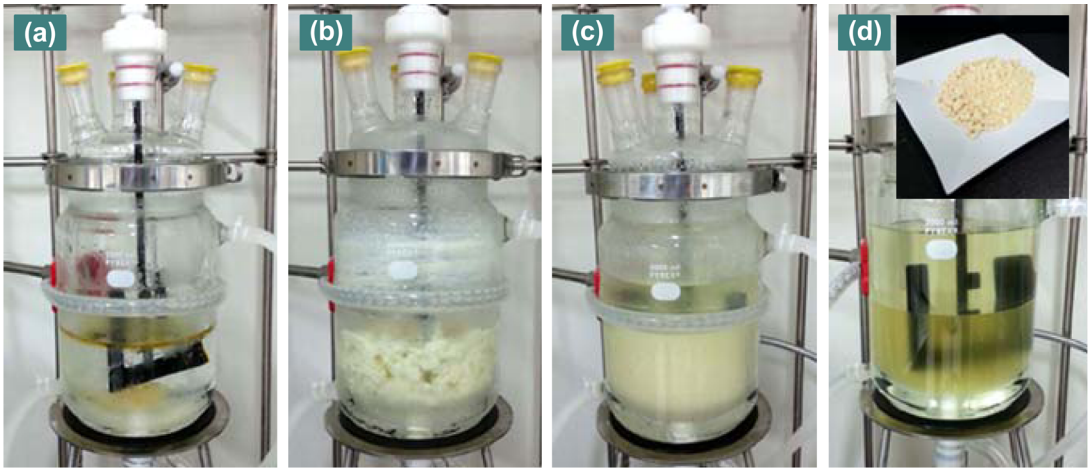


Figure 3. Pictures of the catalyst recovery and product separation procedure from the crude mixture of the Michael addition step appearing in Scheme 5B. (a) Before starting the reaction; (b) after completion of the reaction; (c) after the addition of methylcyclohexane; (d) after filtration, biphasic filtrate (product (org.)/ brine (aq)) and recovered catalyst.

To demonstrate the synthetic utility of our "on water" protocol, the syntheses of pharmaceutically important γ-amino acids such as (*S*)-rolipram **7** and (*S*)-pregabalin **8** were performed. The enantiopure (*S*)-**3g** (obtained by the recrystallization from MTBE/hexane 1:4) was smoothly converted to chiral γ-lactam **6** by the reduction of the nitro group using Raney Ni/H_2 (85% yield). Enantiomerically pure (*S*)-rolipram **7** ($[\alpha]_D^{18}$ = +25.9 (*c* = 0.50, MeOH); lit.[33] $[\alpha]_D^{25}$ = +26.2 (*c* = 0.6, MeOH)) was then obtained in 82% yield by the decarboxylative elimination of methyl ester group of **6** (Scheme 5A). Moreover, multiten gram scale synthesis of an anticonvulsant blockbuster drug (*S*)-pregabalin was also achieved successfully (Scheme 5B, see the Supporting Information for details). The Michael addition reaction of **1j** with dimethyl malonate (**2a**) using 5 mol % of **HQD-SQA** was performed at 250 mmol scale (Figure 3a) to afford the desired product, (*S*)-**3j** (Figure 3b, 24 h, >95% conv., 91% ee). The catalyst **HQD-SQA** was quantitatively recovered by simple filtration from the reaction mixture as a yellowish solid (with recovery yield >99%) after the addition of methylcyclohexane (Figure 3c). After the separation of the organic layer from the biphasic filtrate (Figure 3d) and evaporation under reduced pressure, the crude product was hydrogenated using Raney Ni/H_2, affording chiral γ-lactam **8** in 86% yield (the 3,4-*anti* selectivity was determined by the single crystal X-ray analysis[34]). Consequently, the hydrolysis of γ-lactam **8** with 6 N HCl afforded the (*S*)-pregabalin **9** in 95% yield and 91% ee.

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Enantiomerically pure (*S*)-pregabalin was obtained by simple recrystallization from 2-propanol/water.

CONCLUSIONS

In summary, we successfully developed an efficient and scalable protocol for hydrogen-bonding-promoted asymmetric organocatalytic Michael addition "on water". The Michael addition of malonates and β-ketoesters to diverse nitroolefins using a bifunctional cinchona-based squaramide organocatalyst was remarkably accelerated because of the hydrophobic hydration effect. The hydrophobic amplification could be enforced simply by increasing the hydrophobicity of the catalyst. Thus, using more hydrophobic catalysts such as **HQN-SQA** and **HQD-SQA**, a highly challenging substrate such as dimehtyl methylmalonate was also smoothly converted to the desired Michael adduct. For β-ketoesters as the Michael donors, extremely low catalyst loading (up to 0.01 mol %) was sufficient to complete the reaction, affording the corresponding Michael adducts with perfect stereoselectivities. Modifying catalyst hydrophobicity is the key of this successful catalysis. The developed "on water" protocol was successfully applied for the scalable syntheses of antidepressants, (*S*)-rolipram, and anticonvulsant (*S*)-pregabalin drugs. Further studies of other hydrogen-bonding promoted asymmetric transformations under "on water system" are ongoing in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.5b00685.

Experimental procedures, characterization data, kinetic data, and Log *P* calculation data (PDF)
Crystallographic data (CIF)

AUTHOR INFORMATION

Corresponding Author

*E-mail for C. E. S.: s1673@skku.edu.

Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Constable, D. J. C.; Jimenez-Gonzalez, C.; Henderson, R. K. *Org. Process Res. Dev.* **2007**, *11*, 133−137. (b) Dunn, P. J. *Chem. Soc. Rev.* **2012**, *41*, 1452−1461. (c) Prat, D.; Pardigon, O.; Flemming, H. W.; Letestu, S.; Ducandas, V.; Isnard, P.; Guntrum, E.; Senac, T.; Ruisseau, S.; Cruciani, P.; Hosek, P. *Org. Process Res. Dev.* **2013**, *17*, 1517−1525.

(2) Lindström, U. M. *Chem. Rev.* **2002**, *102*, 2751−2772.

(3) Berne, B. J.; Weeks, J. D.; Zhou, R. H. *Annu. Rev. Phys. Chem.* **2009**, *60*, 85−103 and references therein .

(4) (a) In *Science of Synthesis: Water in Organic Synthesis*; Kobayashi, S., Ed.; Thieme: Stuttgart/New York, 2012; pp 53−851. (b) Manabe, K.; Kobayashi, S. *Chem. - Eur. J.* **2002**, *8*, 4094−4101. (c) Bhowmick, S.; Bhowmick, K. C. *Tetrahedron: Asymmetry* **2011**, *22*, 1945−1979. (d) Simon, M. O.; Li, C. J. *Chem. Soc. Rev.* **2012**, *41*, 1415−1427.

(5) For reviews, see: (a) Dwars, T.; Oehme, G. *Adv. Synth. Catal.* **2002**, *344*, 239−260. (b) Sinou, D. *Adv. Synth. Catal.* **2002**, *344*, 221−237.

(6) For reviews, see: (a) Paradowska, J.; Stodulski, M.; Mlynarski, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 4288−4297. (b) Gruttadauria, M.; Giacalone, F.; Noto, R. *Adv. Synth. Catal.* **2009**, *351*, 33−57. (c) Raj, M.; Singh, V. K. *Chem. Commun.* **2009**, 6687−6703. (d) Mase, N.; Barbas, C. F. *Org. Biomol. Chem.* **2010**, *8*, 4043−4050. For a successful example for the preparation of optically pure warfarin anticoagulant, see: (e) Rogozinska, M.; Adamkiewicz, A.; Mlynarski, J. *Green Chem.* **2011**, *13*, 1155−1157.

(7) (a) Kleiner, C. M.; Schreiner, P. R. *Chem. Commun.* **2006**, 4315−4317. (b) Rueping, M.; Theissmann, T. *Chem. Sci.* **2010**, *1*, 473−476. (c) Bae, H. Y.; Some, S.; Oh, J. S.; Lee, Y. S.; Song, C. E. *Chem. Commun.* **2011**, *47*, 9621−9623. (d) Cruz-Acosta, F.; de Armas, P.; Garcia-Tellado, F. *Chem. - Eur. J.* **2013**, *19*, 16550−16554.

(8) Breslow, R. *Acc. Chem. Res.* **2004**, *37*, 471−478.

(9) (a) Pirrung, M. C.; Das Sarma, K. *Tetrahedron* **2005**, *61*, 11456−11472. (b) Pirrung, M. C. *Chem. - Eur. J.* **2006**, *12*, 1312−1317.

(10) (a) Maltsev, O. V.; Kucherenko, A. S.; Beletskaya, I. P.; Tartakovsky, V. A.; Zlotin, S. G. *Eur. J. Org. Chem.* **2010**, *2010*, 2927−2933. (b) For a review, see: Ordóñez, M.; Cativiela, C. *Tetrahedron: Asymmetry* **2007**, *18*, 3−99. (c) Baran, R.; Veverkova, E.; Skvorcova, A.; Šebesta, R. *Org. Biomol. Chem.* **2013**, *11*, 7705−7711.

(11) Hynes, P. S.; Stupple, P. A.; Dixon, D. J. *Org. Lett.* **2008**, *10*, 1389−1391.

(12) Xu, F.; Corley, E.; Zacuto, M.; Conlon, D. A.; Pipik, B.; Humphrey, G.; Murry, J.; Tschaen, D. *J. Org. Chem.* **2010**, *75*, 1343−1353.

(13) For representative examples concerning Michael addition reactions of malonates with nitroolefins using hydrogen bonding organocatalysts, see: (a) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672−12673. (b) Ye, J. X.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481−4483. (c) McCooey, S. H.; Connon, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6367−6370. For comprehensive reviews regarding organocatalytic enantioselective Michael addition, see: (d) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, *2007*, 1701−1716. (e) Almaşi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299−365. (f) Vicario, J. L.; Badia, D.; Carrillo, L. *Synthesis* **2007**, *2007*, 2065−2092. (g) Zhang, Y.; Wang, W. *Catal. Sci. Technol.* **2012**, *2*, 42−53.

(14) Similar squaramide catalyzed Michael addition reactions of 1,3-dicarbonyl compounds to nitroolefins, see: (a) Dong, Z.; Jin, X. Q.; Wang, P. C.; Min, C.; Zhang, J.; Chen, Z.; Zhou, H. B.; Dong, C. N. *ARKIVOC* **2011**, *2011*, 367−380. (b) Dong, Z.; Qiu, G. F.; Zhou, H. B.; Dong, C. N. *Tetrahedron: Asymmetry* **2012**, *23*, 1550−1556. (c) Min, C.; Han, X.; Liao, Z. Q.; Wu, X. F.; Zhou, H. B.; Dong, C. N. *Adv. Synth. Catal.* **2011**, *353*, 2715−2720. (d) Kasaplar, P.; Riente, P.; Hartmann, C.; Pericas, M. A. *Adv. Synth. Catal.* **2012**, *354*, 2905−2910. (e) Kardos, G.; Soos, T. *Eur. J. Org. Chem.* **2013**, *2013*, 4490−4494. (f) Xu, X. M.; Cheng, T. Y.; Liu, X. C.; Xu, J. Y.; Jin, R. H.; Liu, G. H. *ACS Catal.* **2014**, *4*, 2137−2142.

(15) The pK_a values 2,4-pentanedione, ethyl acetoacetate (**4a**) and dimethyl malonate (**2a**) (in water) are 9, 11 and 13, respectively. See Evans' pK_a table.

(16) For selected reviews, see: (a) Lombardo, M.; Trombini, C. In *Eco-Friendly Synthesis of Fine Chemicals*; Ballini, R., Ed.; RSC Publishing: Cambridge, U.K., 2009; pp 1−15. (b) Mlynarski, J.; Paradowska, J. *Chem. Soc. Rev.* **2008**, *37*, 1502−1511. (c) Mlynarski, J.; Bas, S. *Chem. Soc. Rev.* **2014**, *43*, 577−587. For selected papers, see: (d) Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F. *J. Am. Chem. Soc.* **2006**, *128*, 734−735. (e) Hayashi, Y.; Sumiya, T.; Takahashi, J.; Gotoh, H.; Urushima, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 958−961. (f) Wu, Y. Y.; Zhang, Y. Z.; Yu, M. L.; Zhao, G.; Wang, S. W. *Org. Lett.* **2006**, *8*, 4417−4420. (g) Huang, J.; Zhang, X.; Armstrong, D. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 9073−9077. (h) Aratake, S.; Itoh, T.; Okano, T.; Nagae, N.; Sumiya,

DOI: 10.1021/acscatal.5b00685
ACS Catal. 2015, 5, 3613−3619

T.; Shoji, M.; Hayashi, Y. *Chem. - Eur. J.* **2007**, *13*, 10246−10256. (i) Giacalone, F.; Gruttadauria, M.; Lo Meo, P.; Riela, S.; Noto, R. *Adv. Synth. Catal.* **2008**, *350*, 2747−2760. (j) Kumar, A.; Singh, S.; Kumar, V.; Chimni, S. S. *Org. Biomol. Chem.* **2011**, *9*, 2731−2742. (k) For an experimental and quantum chemical study concerning hydrophobic substituent effects on a proline-derivative catalyzed aldol reaction under aqueous condition, see Zhao, Q. Q.; Lam, Y. H.; Kheirabadi, M.; Xu, C. S.; Houk, K. N.; Schafmeister, C. E. *J. Org. Chem.* **2012**, *77*, 4784−4792.

(17) The definition of "on water" conditions referred to insoluble reaction partners mixed in an aqueous suspension. For more details, see: Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 3275−3279.10.1002/anie.200462883

(18) For selected reviews concerning organic synthesis on water, see: (a) A Chanda, A.; Fokin, V. V. *Chem. Rev.* **2009**, *109*, 725−748. (b) Butler, R. N.; Coyne, A. G. *Chem. Rev.* **2010**, *110*, 6302−6337.

(19) Inorganic salts such as LiCl or NaCl decrease solubility of organic species in water by salting out, consequently resulting in increased hydrophobic effect. See Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159−164.

(20) Readily available quinine-based sulfonamide **QN-SA**, thiourea **QN-TU** and squaramide **QN-N-SQA** were also tested in this study. However, all these catalysts led to unsatisfactory turnover numbers and low to moderate enantioselectivities (r.t., 60 min, 8−68% conv., 34−81% ee). See the Supporting Information for details.

(21) The **QN-SQA** was prepared according to the literature procedure. Malerich, J. P.; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2008**, *130*, 14416−14417.

(22) Cinchonidine-derived squaramide **CD-SQA** and cinchonine-derived squaramide **CN-SQA** were also investigated under the same reaction conditions to investigate the effect of the C6′ substituent. The ee and reactivity (**CD-SQA**: 4% conversion, 85% ee; **CN-SQA**: 5% conversion, 87% ee) were conspicuously lower than those obtained with **QN-SQA** or **QD-SQA**, indicating that the methoxy group in the C6′-position of the quinoline ring is an important moiety for efficient catalysis. See the Supporting Information for details.

(23) (a) The *P* (*n*-octanol/ water partition coefficient) is defined as the ratio of the equilibrium concentration of a substance dissolved in a two-phase system, formed by two immiscible solvents (ranges of *P* is from 10^{-4} to 10^{8}, Log $P > 0$: hydrophobic; Log $P < 0$: hydrophilic). $P = (\mathbf{c}(n - octanol))/(\mathbf{c}(n - water))$. (b) Merck Molecular Force Field (MMFF) was employed. For detailed calculation data, see the Supporting Information. *SPARTAN '14*; Wavefunction, Inc: Irvine, CA, 2014.

(24) We performed the same reaction under different aqueous conditions (r.t., 60 min). $LiClO_4$ in H_2O (sat.) = 14% conv.; NaCl in D_2O (sat.) = 22% conv.; H_2O = 96% conv.; NaCl in H_2O (sat.) (brine) = >99% conv. See the Supporting Information for details.

(25) We also performed the same reaction in organic solvents (r.t., 60 min). 1,4-Dioxane = 7% conv.; MeOH = 34% conv.; Acetonitrile = ∼1% conv.; THF = 21% conv.; Toluene = 17% conv.; DCM = 52% conv. See the Supporting Information for details.

(26) The viscosity of D_2O is ca. 20% higher than that of water, which makes the efficient mixing difficult and thus reduces the hydrophobic effect. See ref 17.

(27) Study was conducted to determine the optimal structure of malonates for the Michael addition to **1a** on water. Among the screened substrates, superior reactivities and enantioselectivities were observed when dimethyl malonate (**2a**) or dibenzyl malonate were used as the Michael donors (5 mol% of **HQN-SQA**, r.t.). Dimethyl malonate (**2a**) = 30 min, >99% conv., 92% ee; Dibenzyl malonate = 20 min, >99% conv., 91% ee; Diethyl malonate = 40 min, >99% conv., 66% ee; Diisopropyl malonate = 420 min, >99% conv., 68% ee; Di-*tert*-butyl malonate = 1440 min, no reaction.

(28) The reaction of **1j** with **2a** smoothly converted to (*R*)-**3j** using **HQN-SQA** (at r.t., 180 min, >99% conv.), whereas the same reaction proceeded sluggishly when the less hydrophobic catalyst **QN-SQA** was used (at r.t., 180 min, 32% conv.; 720 min, 58% conv.) (for detailed kinetic data, see Supporting Information).

(29) Examples of dimethyl methylmalonate (**2c**) as a Michael donor, see: (a) Evans, D. A.; Seidel, D. *J. Am. Chem. Soc.* **2005**, *127*, 9958−9959. (b) Nichols, P. J.; DeMattei, J. A.; Barnett, B. R.; LeFur, N. A.; Chuang, T.-H.; Piscopio, A. D.; Koch, K. *Org. Lett.* **2006**, *8*, 1495−1498. (c) Terada, M.; Ube, H.; Yaguchi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 1454−1455. (d) Evans, D. A.; Mito, S.; Seidel, D. *J. Am. Chem. Soc.* **2007**, *129*, 11583−11592. (e) Andrés, J. M.; Manzano, R.; Pedrosa, R. *Chem. - Eur. J.* **2008**, *14*, 5116−5119.

(30) (a) List, B.; Yang, J. W. *Science* **2006**, *313*, 1584−1586. (b) MacMillan, D. W. C. *Nature* **2008**, *455*, 304−308.

(31) Giacalone, F.; Gruttadauria, M.; Agrigento, P.; Noto, R. *Chem. Soc. Rev.* **2012**, *41*, 2406−2447.

(32) Ratjen, L.; van Gemmeren, M.; Pesciaioli, F.; List, B. *Angew. Chem., Int. Ed.* **2014**, *53*, 8765−8769.

(33) Palomo, C.; Landa, A.; Mielgo, A.; Oiarbide, M.; Puente, A.; Vera, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 8431−8435.

(34) CCDC 1011363 contains the supplementary crystallographic data for compound **8**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre (CCDC) via www.ccdc.cam.ac.uk/data_request/cif or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44)-1223−336−033.

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