ChemComm

Cite this: *Chem. Commun.*, 2011, **47**, 9621–9623

www.rsc.org/chemcomm

COMMUNICATION

Hydrogen bonding mediated enantioselective organocatalysis in brine: significant rate acceleration and enhanced stereoselectivity in enantioselective Michael addition reactions of 1,3-dicarbonyls to β-nitroolefins†

Han Yong Bae,‡[a] Surajit Some,‡[a] Joong Suk Oh,[a] Yong Seop Lee[a] and Choong Eui Song*[ab]

Received 19th June 2011, Accepted 14th July 2011
DOI: 10.1039/c1cc13637b

Brine provides remarkable rate acceleration and a higher level of stereoselectivity over organic solvents, due to the hydrophobic hydration effect, in the enantioselective Michael addition reactions of 1,3-dicarbonyls to β-nitroolefins using chiral H-donors as organocatalysts.

Nature uses water as a solvent for biosynthetic reactions to sustain life. The ''hydrophobic effect'' is a key element in such enzyme catalysis, in determining the structures of proteins and nucleic acids, and in the binding of antigens to antibodies.[1]

Due to the green chemistry perspective and an increased scientific effort to mimic nature, tremendous effort has been applied recently toward developing enantioselective organocatalytic reactions in an aqueous environment.[2] Chiral secondary amines have been shown to be viable catalysts in an aqueous environment for several C–C and C–heteroatom bond forming processes, which proceed *via* iminium or enamine intermediates.[3] However, introducing water as a solvent into the H-bonding mediated asymmetric catalysis[4] still remains a challenge because water can interfere with organocatalysis due to its capacity for disrupting hydrogen bonds and other polar interactions.

We report here the successful results of H-bonding mediated enantioselective organocatalysis in an aqueous environment. Enantioselective Michael addition using a bifunctional cinchona-based squaramide organocatalyst was dramatically accelerated in brine compared to the reaction in organic solvents due to the hydrophobic hydration effect (Fig. 1). Remarkably, in most cases, diastereo- and/or enantioselectivity also were enhanced in brine. Catalyst loading at 0.5 mol% was sufficient to complete most reactions within 10 min, affording the Michael adduct in up to >99% yield and >99% ee.

To assess the effect of water on the reaction rate and on the stereoselectivity for the H-bonding mediated asymmetric transformations, we initially examined the asymmetric Michael addition of 2,4-pentanedione (**2**) as a donor and β-nitrostyrene (**1a**) as an acceptor using 2.0 mol% of the three types of H-bond donor catalysts, **QN-TU**,[5] **QN-SA**,[6] and **QN-SQA**,[7] in brine or in CH_2Cl_2 at room temperature (Table 1). Gratifyingly, in all cases, brine provided remarkable rate acceleration and a higher level of enantioselection over CH_2Cl_2, due to the hydrophobic hydration effect (entries 2, 4, 6 *vs.* entries 1, 3, 5).[8] Squaramide catalysts **QN-SQA** showed superior catalytic

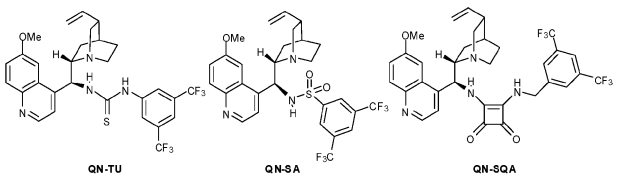
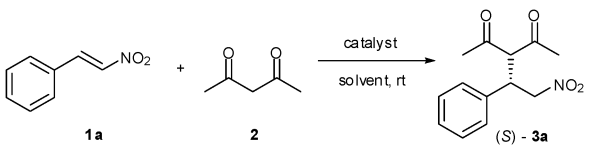


Fig. 1 Screened cinchona-based organocatalysts.

Table 1 Michael addition of β-nitrostyrene and 2,4 -pentanedione[a]



Entry	Catalyst (mol%)	Solvent	Time	Conv. (%)[b]	ee (%)[c]
1	**QN-TU** (2)	CH_2Cl_2	13 h	>99	61
2	**QN-TU** (2)	Brine	<20 min	>99	81
3	**QN-SA** (2)	CH_2Cl_2	48 h	Trace	n.d.[d]
4	**QN-SA** (2)	Brine	1 h	>99	61
5	**QN-SQA** (2)	CH_2Cl_2	20 min	>99	>99
6	**QN-SQA** (2)	Brine	<3 min	>99	>99
7	**QN-SQA** (0.5)	CH_2Cl_2	2 h	>99	>99
8	**QN-SQA** (0.5)	Brine	<10 min	>99	>99
9	**QN-SQA** (0.5)	$LiClO_4$ in H_2O	30 min	<2	n.d.[d]
10	**QN-SQA** (0.5)	NaCl in D_2O	2 h	>99	>99
11	**CN-SQA** (0.5)[e]	Brine	<10 min	>99	98[f]

[a] Reactions were carried out with **1a** (0.5 mmol), **2** (2.0 equiv.), and catalyst (2.0 mol%) in 1.5 mL of solvent. [b] Determined by ^{1}H NMR. [c] Determined by HPLC analysis using a chiral AD-H column (see ESI†). [d] Not determined. [e] Using cinchonine squaramide catalyst. [f] Opposite enantiomer was obtained.

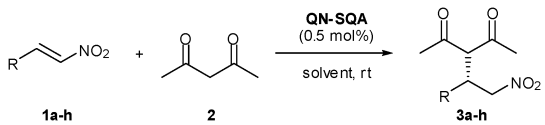
[a] *Department of Chemistry, Sungkyunkwan University, 300 Cheoncheon, Jangan, Suwon, Gyeonggi, 440-746, Korea. E-mail: s1673@skku.edu; Fax: +82 31-290-7075*
[b] *Department of Energy Science, Sungkyunkwan University, 300 Cheoncheon, Jangan, Suwon, Gyeonggi, 440-746, Korea*
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c1cc13637b
‡ These authors contributed equally to this work.

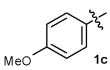
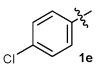
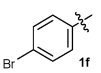
activity and enantioselectivity (entries 5 and 6) than other types of H-bond donors such as thiourea **QN-TU** and sulfonamide **QN-SA** (entries 1–4).[9] Catalyst loading at merely 0.5 mol% of **QN-SQA** was sufficient to complete the reaction within 10 minutes, affording the Michael adduct in up to >99% yield and >99% ee (entry 8). Of note, the cinchonine-derived catalyst **CN-SQA** gave the opposite enantiomer of **3a** with the same efficiency (entry 11). Evidence for the hydrophobic hydration effect on rate acceleration was obtained using a salting-out agent such as $LiClO_4$ (entry 9). The rate was dramatically slowed by the addition of $LiClO_4$, which is typically antihydrophobic.[10] Moreover, a significant solvent isotope effect also was observed, which provides additional support for the hydrophobic hydration mechanism: the reaction slowed noticeably when D_2O was used instead of water (entry 10).[11]

Next, the scope of the reaction with a range of β-nitroolefins **1a–h** as Michael acceptors was examined (Table 2). Excellent enantioselectivities (98%–>99% ee) were observed for a broad range of aryl, heteroaryl and alkyl substituted β-nitroolefins. Again, significant rate acceleration in brine was observed, which also can be attributed to the hydrophobic hydration effect.

Next, we probed the scope of the reaction with a variety of 1,3-dicarbonyl compounds **4a–h** as Michael-donors (Table 3). In all cases, rate acceleration and slightly increased diastereo- and/or enantioselectivity were observed in brine compared to

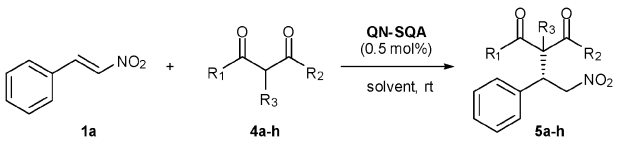
Table 2 Scope of Michael acceptors **1a–h**[a]

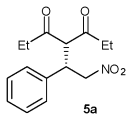
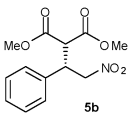
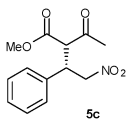
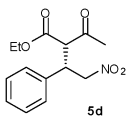
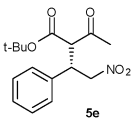
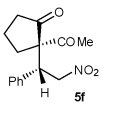
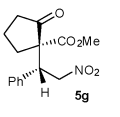
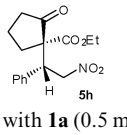


Entry	R	Solvent	Time	Yield (%)[b]	ee (%)[c]
1	 1a	CH_2Cl_2	2 h	97	>99
2		Brine	<10 min	98	>99
3	 1b	CH_2Cl_2	4 h	97	98
4		Brine	<10 min	92	98
5	 1c	CH_2Cl_2	3 h	91	99
6		Brine	<20 min	91	98
7	 1d	CH_2Cl_2	48 h	89	>99
8		Brine	<40 min	89	>99
9	 1e	CH_2Cl_2	1 h	98	>99
10		Brine	<20 min	99	>99
11	 1f	CH_2Cl_2	1 h	93	>99
12		Brine	<20 min	96	>99
13	 1g	CH_2Cl_2	2 h	94	>99
14		Brine	<10 min	91	>99
15[d]	 1h	CH_2Cl_2	8 h	88	>99
16[d]		Brine	<10 min	90	>99

[a] Reactions were carried out with **1a–h** (0.5 mmol), **2** (2.0 equiv.), and **QN-SQA** (0.5 mol%) in 1.5 mL of solvent. [b] Isolated yields. [c] Determined by chiral HPLC (see ESI†). [d] Reaction carried out with 2 mol% of **QN-SQA**.

Table 3 Scope of Michael donors **4a–h**[a]



Entry	Solvent	Time	Product **5**[b]	Yield (%)[c]	dr[d]	ee (%)[e]
1	CH_2Cl_2	12 h	 5a	97	—	>99
2	Brine	<20 min		96	—	>99
3[f]	CH_2Cl_2	168 h	 5b	65	—	93
4[f]	Brine	22 h		92	—	90
5	CH_2Cl_2	1.5 h	 5c	94	1 : 1	>99, >99
6	Brine	<10 min		95	1 : 1	>99, >99
7	CH_2Cl_2	40 min	 5d	95	1.4 : 1	>99, >99
8	Brine	<10 min		94	1.5 : 1	>99, >99
9	CH_2Cl_2	9 h	 5e	92	2.1 : 1	97, 94
10	Brine	<10 min		90	4.9 : 1	98, 98
11[g]	CH_2Cl_2	120 h	 5f	78	3.2 : 1	94, 72
12[g]	Brine	20 h		85	7.3 : 1	97, 75
13	CH_2Cl_2	1 h	 5g	90	99 : 1	>99, 68
14	Brine	<20 min		87	99 : 1	>99, 84
15	CH_2Cl_2	2 h	 5h	94	>99 : 1	98, 72
16	Brine	<10 min		98	>99 : 1	99, 78

[a] Reactions were carried out with **1a** (0.5 mmol), **4a–h** (2.0 equiv.), and **QN-SQA** (0.5 mol%) in 1.5 mL of solvent. [b] The configuration of the main diastereomer was determined by comparison of the HPLC retention time with the literature data (see ESI†). [c] Isolated yields. [d] Determined by ^1H NMR. [e] Determined by chiral HPLC (see ESI†). [f] Reaction carried out with 5 mol% of **QN-SQA**. [g] Reaction carried out with 2 mol% of **QN-SQA**.

those obtained in CH_2Cl_2.[12] Of note, more hydrophobic substrates seemed to display greater activities and stereoselectivities relative to less hydrophobic substrates, perhaps as a result of enhanced aggregation between the organocatalysts and the substrates in the aqueous environment (compare entries 4, 6, 8, and 10).

Finally, to study a multigram-scale synthesis, β-nitrostyrene (**1a**) (7.5 g) and 2,4-pentanedione (2 equiv.) were vigorously stirred in the presence of **QN-SQA** (0.5 mol%) in brine (150 mL) at 25 °C. A solid white Michael product gradually

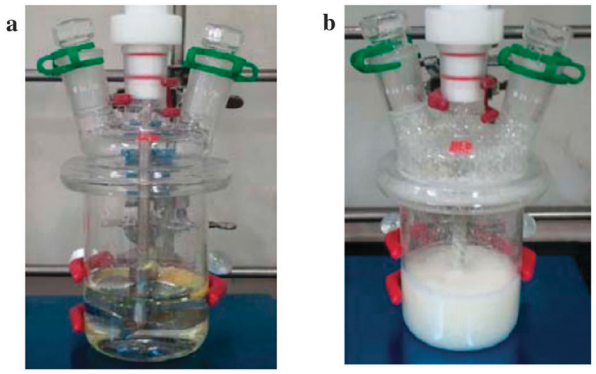


Fig. 2 The scale-up reaction setup of 2,4-pentanedione with β-nitrostyrene (**1a**) in the presence of **QN-SQA** in brine. (a) Reaction mixture before mixing. (b) Reaction mixture after completion of the reaction.

formed (Fig. 2). After 15 minutes, aqueous HCl solution (1 N, 10 mL) was added to quench the reaction. Filtration, washing with water, and drying yielded the white solid product. Neither extraction nor chromatography was needed to obtain the product with excellent purity.

In summary, we describe here the successful results of H-bonding mediated enantioselective organocatalysis in an aqueous environment. Enantioselective Michael addition of 1,3-dicarbonyl to nitroolefins using a bifunctional cinchona-based squaramide organocatalyst in brine was dramatically accelerated compared to that in organic solvents due to the hydrophobic hydration effect; moreover, in most cases, diastereo- and enantioselectivity also were enhanced in brine. Merely 0.5 mol% catalyst loading was enough to complete most reactions within a very short reaction time, affording the Michael adduct in up to >99% yield and >99% ee.

Further studies focusing on the full scope of this catalytic system in aqueous medium and related systems are currently under investigation and will be reported in due course. Calculation studies for better understanding the role of water also are currently under investigation in our laboratory.

This work was supported by grants NRF-20090085824 (Basic Science Research Program, MEST), NRF-2010-0029698 (Priority Research Centers Program, MEST), 2011-0001334 (SRC program, MEST), R31-2008-10029 (WCU program, MEST), B551179-10-03-00 (Cooperative R&D Program, Korea Research Council Industrial Science and Technology), and the Postdoctoral Research Program of Sungkyunkwan University (2010).

Notes and references

1 C. Palomo, A. Landa, A. Mielgo, M. Oiarbide, A. Puente and S. Vera, *Angew. Chem., Int. Ed.*, 2007, **46**, 8431–8435.
2 (*a*) M. Raj and V. K. Singh, *Chem. Commun.*, 2009, 6687–6703; (*b*) M. Gruttadauria, F. Giacalone and R. Noto, *Adv. Synth. Catal.*, 2009, **351**, 33–57; (*c*) N. Mase and C. F. Barbas, III, *Org. Biomol. Chem.*, 2010, **8**, 4043–4050.
3 X. Yu and W. Wang, *Org. Biomol. Chem.*, 2008, **6**, 2037–2046.
4 M. Rueping and T. Theissmann, *Chem. Sci.*, 2010, **1**, 473–476.
5 S. H. McCooey and S. J. Connon, *Angew. Chem., Int. Ed.*, 2005, **44**, 6367–6370.
6 S. H. Oh, H. S. Rho, J. W. Lee, J. E. Lee, S. H. Youk, J. Chin and C. E. Song, *Angew. Chem., Int. Ed.*, 2008, **47**, 7872–7875.
7 (*a*) J. P. Malerich, K. Hagihara and V. H. Rawal, *J. Am. Chem. Soc.*, 2008, **130**, 14416–14417; (*b*) H. Jiang, M. W. Paixão, D. Monge and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2010, **132**, 2775–2783.
8 Heterogeneity was crucial for observing large rate acceleration. Thus, the reaction time can be strongly dependent on the efficiency of mixing of the reaction mixture. Thus, we used several magnetic stir bars for efficient mixing and grinding of the solid formed during the reaction. More efficient mixing of the reaction mixture would further shorten the reaction time.
9 Other solvents were also screened for the reaction using the catalyst **QN-SQA**, but the conversion and enantioselectivity were found to be significantly inferior in comparison to those obtained in brine; *e.g.*, DMSO (1 h for 99% conversion, racemic), MeOH (96 h for 99% conversion, 99% ee), see ESI†.
10 R. Breslow, *Acc. Chem. Res.*, 2004, **37**, 471–478.
11 D_2O has a *ca.* 20% higher viscosity which may make mixing more difficult, and is a better solvent for nonpolar solutes; this must reduce the hydrophobic hydration effect; S. Narayan, J. Muldoon, M. G. Finn, V. V. Fokin, H. C. Kolb and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2005, **44**, 3275–3279.
12 The enhanced stereoselectivity might be explained by the difference of hydrophobic character in the transition states for the each stereomers.