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Organocatalytic Direct Michael Reaction of Ketones and Aldehydes with β-Nitrostyrene in Brine

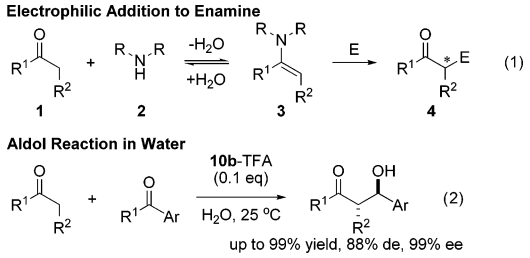
Nobuyuki Mase,† Kaori Watanabe,† Hidemi Yoda,† Kunihiko Takabe,*,† Fujie Tanaka,‡ and Carlos F. Barbas III‡

Department of Molecular Science, Faculty of Engineering, Shizuoka University, 3-5-1 Johoku, Hamamatsu 432-8561, Japan, and The Skaggs Institute for Chemical Biology and the Departments of Chemistry and Molecular Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037

Received January 17, 2006; E-mail: tcktaka@ipc.shizuoka.ac.jp

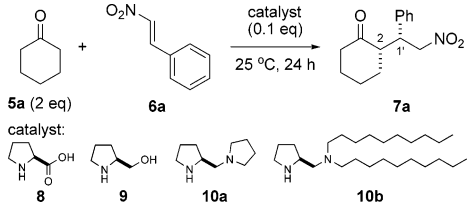
In 1954, Gilbert Stork showed that enamines could be used in the alkylation and acylation of aldehydes and ketones,[1] and in the years since then, enamines have been intensively studied in organic synthesis.[2] Recently, small chiral amines have become attractive and powerful catalysts for C−C bond forming reactions.[3] The reaction, in general, is carried out by stirring a carbonyl compound **1**, an amine **2**, and an electrophile in conventional organic solvents, such as DMSO, DMF, or $CHCl_3$, in a one-pot operation (eq 1). Removal of water is not required for the formation of enamine intermediates that proceed to directly react with an electrophile. While the one-pot procedure is convenient, toxic, flammable, and volatile, organic solvent is often required in these reactions.

In our recent studies, we reported that a designed, small organic molecule with appropriate hydrophobic groups catalyzes enantioselective, direct aldol reactions in water (eq 2).[4] Our artificial organocatalyst mimicked aldolase antibodies that act on hydrophobic organic reactants in water. Aggregation of the organocatalyst and the reactants reduces contact with bulk water as the reaction proceeds. Consequently, the outcome of the aldol reaction was similar to that performed in organic solvents. To further develop our catalyst system, we evaluated enamine-based, organocatalytic direct asymmetric Michael reactions[5] of ketones and aldehydes with β-nitrostyrenes in bulk water and/or brine without using any organic cosolvent. We found that yields in brine, including seawater, the most readily available aqueous media in the world, were superior to those in water.



Michael reactions of cyclohexanone (**5a**) with β-nitrostyrene (**6a**) were performed in water, as shown in Table 1. L-Proline (**8**) catalyzes the Michael reaction in DMSO in good yield;[5] however, our first attempt in water gave no product (Table 1, entries 1 and 2). Low conversions and yields were also observed using L-prolinol (**9**) (entry 3). Diamine catalyst **10a** improved the reactivity as well as the enantioselectivity, but resulted in low yield (entries 4 and 5). Diamine catalyst **10b**, bearing a hydrophobic alkyl group with TFA, was the best catalyst of those tested in the asymmetric aldol reaction in water;[4] here, it gave Michael product **7a** in moderate yield (entry 10). Despite high conversion in water, we could not obtain the Michael product in good yield because a powdery and insoluble solid side product was formed.

Table 1. Catalyst Screening in the Direct Asymmetric Michael Reaction of Cyclohexanone (**5a**) with β-Nitrostyrene (**6a**)[a]



entry	catalyst	solvent	conv. (%)	yield (%)[b]	*syn*:*anti*[c]	ee (%)[d]
1[e]	**8**	DMSO		94	>95:<5	23
2	**8**	H_2O	0	0 (88)[f]		
3	**9**	H_2O	58	2 (5)[f]	82:18	61
4	**10a**	H_2O	>99	16	92:8	82
5	**10a**/TFA	H_2O	83	13	94:6	84
6	**10a**/TFA	brine	>99	49	91:9	85
7	**10b**	H_2O	51	9 (19)[f]	95:5	91
8	**10b**	brine	31	19	92:8	89
9	**10b**/TFA	DMSO	79	76 (20)[f]	95:5	89
10	**10b**/TFA	H_2O	>99	54	95:5	89
11	**10b**/TFA	brine	>99	93	95:5	89
12	**10b**/TFA	seawater	>99	89	96:4	91
13[g]	**10b**/TFA	brine	>99	79	96:4	91

[a] Conditions: amine catalyst (0.05 mmol), additive (if used, 0.05 mmol), **5a** (1.0 mmol), and **6a** (0.5 mmol) in water and/or brine (0.5 mL) at 25 °C for 24 h with vigorous stirring. [b] Isolated yield. [c] Determined by ^{1}H NMR of the crude product. [d] Determined by chiral-phase HPLC analysis for *syn*-product. [e] See ref 5. [f] Recovered yield of **6a** is shown in parentheses. [g] Donor **5a** (0.5 mmol, 1.0 equiv) was used.

When **6a** and **10a** (0.1 equiv) were stirred in water and a small amount of toluene in the absence of **5a**, a quantitative amount of polymerization products of **6a** was obtained as a solid. Other studies have indicated that amine catalysts behave as initiators of polymerization.[6] We hypothesized that, if the anion intermediate derived from the addition of the amine catalyst to **6a** could be stabilized, polymerization should be inhibited and the chemical yield should be improved. We found that the best results were obtained when brine was used as a solvent. Brine provided excellent yield and a high level of diastereo- and enantioselection (entry 11). Yield and enantioselectivity were essentially the same in seawater taken directly from the Pacific Ocean (entry 12). In these electrolyte-rich aqueous solutions, the anion intermediate is readily complexed by metal cations, and this ionic complexation presumably reduces polymer propagation responsible for the side product.

Addition of TFA to the reaction in brine improved chemical yields by acceleration of enamine formation (entry 8 vs 11).[7] The diamine **10b**[5h] bearing dodecyl alkyl chains is a more suitable catalyst for the Michael reaction in brine than is the diamine **10a**

† Shizuoka University.
‡ The Scripps Research Institute.

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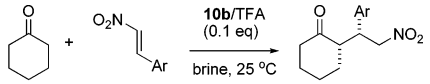
Table 2. Diamine **10b**/TFA-Catalyzed Michael Reactions of **5a** with Various β-Nitrostyrene **6** in Brine[a]

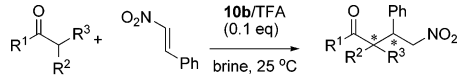


5a (2 eq) **6** **7**

entry	Ar	product	time (h)	yield (%)[b]	*syn*:*anti*[c]	ee (%)[d]
1	Ph	**7a**	12	93	95:5	89
2	4-$MeOC_6H_4$	**7b**	20	98	96:4	83
3	2-furyl	**7c**	24	94	96:4	86
4	2-naphthyl	**7d**	48	99	98:2	97
5	3-$NO_2C_6H_4$	**7e**	96	57	74:26	83

[a] Conditions: amine catalyst **10b** (0.05 mmol), TFA (0.05 mmol), **5a** (1.0 mmol), and **6a** (0.5 mmol) in brine (0.5 mL) at 25 °C with vigorous stirring. [b] Isolated yield. [c] Determined by ^{1}H NMR of the crude product. [d] Determined by chiral-phase HPLC analysis for *syn*-product.

Table 3. Diamine **10b**/TFA-Catalyzed Michael Reactions of Various Ketones and Aldehydes **5** with **6a** in Brine[a]



5 (2 eq) **6a** **7**

entry	R^1	R^2	R^3	product	time (h)	yield (%)[b]	*syn*:*anti*[c]	ee (%)[d,e]
1	$-(CH_2)_4-$		H	**7a**	12	93	95:5	89
2	$-(CH_2)_3-$		H	**7f**	96	75	77:23	80
3[f]	$-CH_2CH_2SCH_2-$		H	**7g**	96	67	97:3	87
4[g]	Me	H	H	**7h**	24	87		32
5	H	H	Et	**7i**	24	99	65:35	38
6	H	Me	Me	**7j**	30	76		76
7	H	Me	Et	**7k**	72	74	59:41	74
8	H	Me	Pr	**7l**	96	97	61:39	64

[a] Conditions: amine catalyst **10b** (0.05 mmol), TFA (0.05 mmol), **5** (1.0 mmol), and **6a** (0.5 mmol) in brine (0.5 mL) at 25 °C with vigorous stirring. [b] Isolated yield. [c] Determined by ^{1}H NMR of the crude product. [d] Determined by chiral-phase HPLC analysis for *syn*-product. [e] (2*S*)-*syn*-Isomers were obtained as a major product in entries 1−4, and (2*R*)-*syn*-isomers were obtained in entries 5−8. [f] Toluene (100 μL) was added. [g] Donor (10 equiv) was used.

in terms of chemical yield (entries 6 and 11). The reaction rate in brine is also faster than that in DMSO (entry 9 vs 11). Generally, an excess amount of a ketone donor (10−20 equiv) is employed in conventional organic solvents;[5] however, here, an equal amount of **5a** was sufficient to complete the Michael reaction in brine in 79% yield with 91% ee (entry 13).

We propose that brine improves the chemical yield and stereoselectivity compared to reaction in organic solvent or water through the following mechanism:[8,9] A liquid organic donor **5** assembles in brine due to hydrophobic interactions. Diamine **10b**/TFA catalyst with its hydrophobic tails and the acceptor **6** dissolve in the liquid organic phase. Aggregation of the organic molecules excludes water from the organic phase and drives the equilibrium toward enamine formation. This is further facilitated by a salting-out effect. Michael reactions occur quickly in this highly concentrated organic phase through a transition state similar to that observed in organic solvents.

Catalyst **10b**/TFA was chosen for the further study of asymmetric Michael reactions with various nitroalkene acceptors (Table 2). The reaction appears quite general with respect to the nature of the aromatic Michael acceptors. Generally, excellent yields and high stereoselectivities, ranging from 83 to 97% ee, were observed.

Next we probed the scope of the reaction with a variety of ketones and aldehydes (Table 3). Cyclic ketones were suitable as Michael donors, providing high diastereoselectivity as well as enantioselectivity (entries 1−3). Addition of a small amount of toluene (100 μL) was sufficient to facilitate the Michael reaction of the thiopyran **5g** with **6a**, although both substrates are solid and insoluble in water (entry 3). Michael products **7j**−**l** bearing an all-carbon quaternary stereocenter[5f] were obtained with enantioselectivities similar to or slightly lower than those obtained in reactions with DMSO solvent (entries 6−8). These experiments indicate that our catalyst system in brine should be broadly applicable to the synthesis of γ-nitro carbonyl compounds.

To study a multigram-scale synthesis, TFA (0.1 equiv) and **10b** (0.1 equiv) were stirred with **6a** (10 mmol, 1.51 g) and **5a** (1.2 equiv) in brine (10 mL) at 25 °C. Solid Michael product **7a** gradually formed. The mixture was stirred for 24 h, and the brine was removed to give the crude product (99% conversion, *syn*:*anti* = 97:3, 89% ee) that was then purified by recrystallization from ethyl acetate to afford **7a** (1.80 g, 73%, *syn*-isomer, >99% ee). No extraction, washing, nor chromatography were needed to obtain the product with excellent purity; therefore, this procedure may afford great advantage to pharmaceutical and industrial processes.

The major product **7a** generated from the **10b**/TFA-catalyzed reaction had (1′*R*,2*S*) absolute stereochemistry.[5] The absolute stereochemical results can be explained by related transition state models previously discussed for diamine **10a**/acid-catalyzed Michael reactions in organic solvent.[5f,g]

In summary, we have developed a catalytic direct asymmetric Michael reaction that can be performed in brine without addition of organic solvents. The diamine **10b**/TFA bifunctional catalyst system demonstrated excellent reactivity, diastereoselectivity, and enantioselectivity in brine. Further studies focusing on the full scope of this catalyst in aqueous media and related systems are currently under investigation and will be reported in due course.

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Supporting Information Available: Experimental procedures and HPLC data. This material is available free of charge via the Internet at http://pubs.acs.org.

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