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Highly Enantioselective Water-Compatible Organocatalyst for Michael Reaction of Ketones to Nitroolefins

Vishnumaya and Vinod K. Singh*

Department of Chemistry, Indian Institute of Technology Kanpur, India-208 016

vinodks@iitk.ac.in

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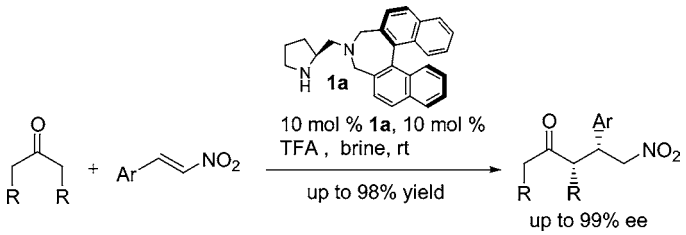
ABSTRACT



A chiral diamine was found to catalyze enantioselective addition of ketones to nitroolefins in aqueous/saline/organic media. The products were obtained with excellent diastereoselectivities (*syn*/*anti* = 99:1) and enantioselectivities up to 99%. The reaction could be facilitated using a mild acid.

Enantioselective reactions catalyzed by small organic molecules (asymmetric organocatalysis)[1] have attracted attention from a large number of organic chemists working in the area of asymmetric synthesis. This is mainly due to environmental concern where use of metals in organic reactions could be avoided. It would be a win−win situation from a green chemistry perspective if the above reaction could be carried out in aqueous media.[2] In our recent study, we reported a new organocatalyst for enantioselective direct aldol reaction.[3] While the work in the area with respect to environmentally clean and friendly conditions is still in progress, we got interested in the organocatalytic direct asymmetric Michael reaction of ketones with commonly used acceptors such as β-nitrostyrene for which some excellent papers have appeared using chiral amines as catalysts.[4] The reaction is supposed to proceed via an enamine intermediate.[1c] Although most of the reports deal with reactions in organic solvents, there are only two papers where aqueous medium has been used for the Michael reaction.[4b,c]

To the best of our knowledge, there is no universal catalyst which gives high enantioselectivity for this reaction, both in the presence of water and also in a wide range of organic solvents.[5] In this paper, we disclose such a catalyst which is compatible with water as well as with various conventional organic solvents providing high enantioselectivity and diastereoselectivity.

The diamine **1** (Scheme 1), having substituted nonpolar dibenzylic type groups in the tertiary amine part, was conceptualized based on an intuition that the binaphthyl group would enhance the hydrophobic hydration when the reaction is done in aqueous medium and should also work

(1) (a) For a special issue on asymmetric organocatalysis, see: *Acc. Chem. Res.* **2004**, *37*, 487. (b) Review: Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (c) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719. (d) Berkessel, A.; Groger, H. *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2005.

(2) For reviews on organic reactions in aqueous media, see: (a) Brogan, A. P.; Dickerson, T. J.; Janda, K. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 8100. (b) Hayashi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 8103. (c) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095. (d) Lindstrom, U. M. *Chem. Rev.* **2002**, *102*, 2751. (e) Li, C.-J.; Chan, T.-H. *Organic Reaction in Aqueous Media*; Wiley-VCH: Weinheim, Germany, 1997.

(3) Raj, M.; Vishnumaya; Ginotra, S. K.; Singh, V. K. *Org. Lett.* **2006**, *8*, 4097.

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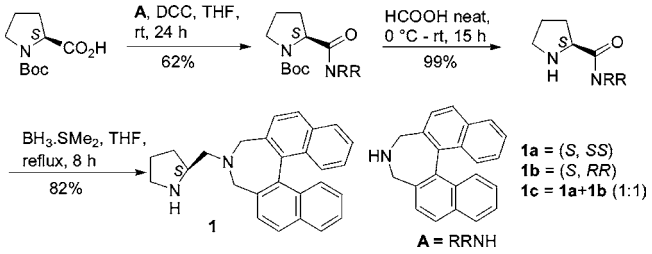
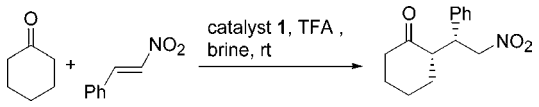
Scheme 1. Synthesis of Chiral Ligands



in organic medium due to the aromatic nature of the binaphthyl part. The coupling of L-proline with a chiral (*SS* or *RR*) amine **A**[6] under usual conditions gave an amide which was converted into the final diamine **1a** and **1b**, respectively, in two steps as described in Scheme 1. The preliminary experiments were conducted by taking cyclohexanone as a donor and β-nitrostyrene as an acceptor using 10 mol % of the diamine **1** and TFA in brine (Table 1). The diamine

Table 1. Catalytic Screening of Ligands[a]



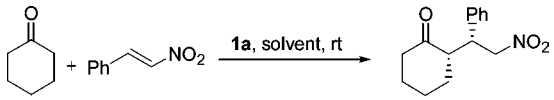
entry	catalyst	time (h)	yield (%)	*syn*/*anti*[b]	ee[c] (%) *syn*
1	**1a**	10	98	94:6	96
2	**1b**	10	96	97:3	94
3	**1c**	12	85	95:5	88

[a] 10 mol % of **1** and TFA used. [b] Diastereoselectivities were determined by ^{1}H NMR analysis of the products. [c] The ee's were determined by HPLC using a Chiralpak AS-H column.

(*S*,*SS*)-**1a** gave the best result: 98% yield and 96% ee (entry 1) for the *syn* diastereomer (dr = 94:6). Interestingly, it was observed that, by changing the chirality of the binaphthyl part as in **1b**, the results were equally good with enantioselectivity of 94% (entry 2). It appears that chirality of the binaphthyl group is not playing much of a role because 88% ee was obtained for the same reaction by using **1c**, a diastereomeric mixture of **1a** and **1b** (1:1) (entry 3).

The diamine **1a** was taken as the catalyst of choice and evaluated for the same reaction in different solvents with or without TFA (Table 2). Initially, the reaction was done by

Table 2. Screening of Solvents[a]



entry	solvent	time (h)	yield (%)	*syn*/*anti*[b]	ee[c] (%) *syn*
1	DMSO	16	77	94:6	62
2	DMF	18	65	94:6	85
3	CH_3CN	15	87	98:2	90
4	$CHCl_3$	18	48	97:3	91
5	DCM	18	80	98:2	92
6	EtOH	20	77	96:4	88
7	MeOH	20	77	95:5	89
8	IPA	15	90	98:2	92
9	THF	15	94	97:3	90
10	toluene	35	40	94:6	66
11	water	12	90	94:6	90[d]
12	brine	16	95	94:6	91[d]
13	water	10	95	97:3	90
14	brine	10	98	94:6	96
15	THF/water	16	91	95:5	92
16	THF/brine	10	92	98:2	86
17	DMSO/water	17	88	98:2	91
18	DMSO/brine	12	88	95:5	92

[a] 10 mol % of **1a** and TFA used unless stated otherwise. [b] Diastereoselectivities were determined by ^{1}H NMR analysis of the products. [c] The ee's were determined by HPLC using a Chiralpak AS-H column. [d] Reactions were carried out in the absence of TFA.

using 10 mol % of **1a** and TFA in a variety of organic solvents (entries 1−10). The most polar aprotic solvent, such as DMSO, and nonpolar aprotic solvent, such as toluene, gave poor enantioselectivity: 62 and 66% ee, respectively (entries 1 and 10). MeCN, $CHCl_3$, and CH_2Cl_2 gave excellent diastereoselectivity (*syn*/*anti* = 98:2) and high enantioselectivity (90−92% ee). Protic solvents such as MeOH, EtOH, and *i*-PrOH gave similar results (entries 6−8). When the medium was changed from organic to aqueous, the enantioselectivity remained in the same range. For example, when the Michael reaction was done in water, the enantioselectivity was 90% and TFA did not have any role to play on the results (entries 11 and 13). However, in brine, the enantioselectivity could be increased from 91 to 96% using TFA (entries 12 and 14). A combination of organic solvent and water also gave high enantioselectivities in the reaction (entries 15−18).

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(5) For a catalyst that works both in isopropanol and water, see ref 4c.

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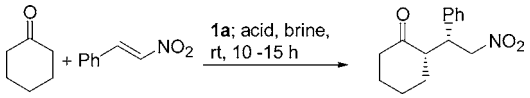
Table 3. Screening of Protonic Acids[a]



entry	acid	yield (%)	*syn/anti*[b]	ee[c] (%) *syn*
1	TFA	98	94:6	96
2	*p*-TSA	67	94:6	92
3	CSA	75	98:2	91
4	AcOH	85	97:3	92
5	DNBSA	90	98:2	93
6	C_6H_5COOH	85	95:5	92
7	p-$NO_2C_6H_4COOH$	87	94:6	92
8	p-$OMeC_6H_4COOH$	80	98:2	92
9	*n*-butyric acid	89	97:3	93

[a] 10 mol % of **1a** and an acid was used. [b] Diastereoselectivities were determined by ^{1}H NMR analysis of the products. [c] The ee's were determined by HPLC using a Chiralpak AS-H column.

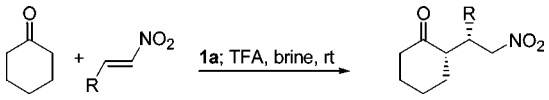
Since we had 96% enantioselectivity in doing the Michael reaction in brine by using 10 mol % of TFA, other acids were also evaluated with the hope to improve the enantioselectivity. Unfortunately, the results were unaffected (Table 3).

High yield and enantioselectivity in aqueous/brine medium can be explained by the hydrophobic environment created by the binaphthyl group in the reaction.[7] This helps solubilize the organic donor and acceptor molecule in a small volume. There are several unanswered questions about an appropriate transition state model for this reaction, but the absolute stereochemical outcome can be explained by a model based on the literature.[4b,p,8]

For the enantioselective Michael reaction with cyclohexanone, several substituted β-nitrostyrenes were evaluated under the best condition, and the results are summarized in Table 4. In most of the cases, we got high diastereoselectivity (>95%) and enantioselectivity (90−99% ee) for the *syn* adduct. The reaction was also facile as can be depicted by the reaction time and chemical yield in almost all of the substrates (Table 4).

The Michael reaction was evaluated with other ketones as well (Table 5). In most of the cases, we got high enantioselectivity and diastereoselectivity.

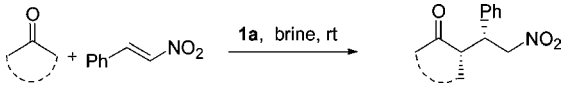
Table 4. Screening of Different Nitroolefins with Cyclohexanone[a]

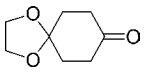
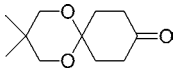


entry	R	time (h)	yield (%)	*syn/anti*[b]	ee[c] (%) *syn*
1	Ph	10	98	94:6	96
2	4-Cl−C_6H_4	19	75	94:6	94
3	2-Cl−C_6H_4	12	78	98:2	96
4	3-F−C_6H_4	22	75	94:6	95
5	4-F−C_6H_4	12	85	95:5	96
6	2-NO_2−C_6H_4	7	75	95:5	90
7	4-Br−C_6H_4	18	70	94:6	90
8	3,4-methylenedioxy−C_6H_3	7	92	99:1	99
9	4-*i*Pr−C_6H_4	30	80	97:3	86
10	2-Cl−6-F−C_6H_3	12	91	94:6	98
11	2,3-DiF−C_6H_3	18	90	94:6	93
12	2-MeO−C_6H_4	13	95	94:6	92[d]
13	4-MeO−C_6H_4	18	90	97:3	88[d]
14	2-furyl	18	80	99:1	97
15	2-thienyl	18	75	96:4	96
16	2-naphthyl	20	86	98:2	90
17	4-CN−C_6H_4	8	78	98:2	95
18	3-Me−C_6H_4	18	70	95:5	97
19	4-CF_3O−C_6H_4	24	71	95:5	82[d]
20	cyclohexyl	30	88	95:5	87

[a] 10 mol % of **1a** and TFA used. [b] Diastereoselectivities were determined by ^{1}H NMR analysis of the products. [c] The ee's were determined by HPLC using chiral columns. [d] 20 mol % of catalyst used.

Table 5. Screening of Different Ketones with β-Nitrostyrenes[a]



entry	ketone	time (h)	yield (%)	*syn/anti*[b]	ee[c] (%) *syn*
1	acetone	06	89	-	16
2	cyclopentanone	20	78	77:23	75
3	$-CH_2SCH_2-$	18	92	96:4	92[d]
4	$-CH_2OCH_2-$	16	95	93:7	93
5		20	90	96:4	89[d]
6		20	88	95:5	88[d]

[a] 10 mol % of **1a** and TFA used. [b] Diastereoselectivities were determined by ^{1}H NMR analysis of the products. [c] The ee's were determined by HPLC using chiral columns. [d] 100 μL of THF was added for solid carbonyls.

In summary, we have developed a highly efficient water-compatible diamine organocatalyst, which has been successfully applied to the asymmetric Michael reaction of ketones with both aryl and alkyl nitroolefins. The added advantage of the catalyst is that it gives high enantioselectivities in organic solvents as well. This broadens the scope of the reaction. Further investigation on the application of this organocatalyst in asymmetric catalysis is still in progress.

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Supporting Information Available: Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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