ORGANIC LETTERS

2009
Vol. 11, No. 15
3354−3356

Di(methylimidazole)prolinol Silyl Ether Catalyzed Highly Michael Addition of Aldehydes to Nitroolefins in Water

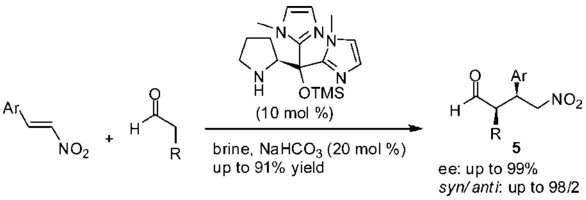
Jianbin Wu, Bukuo Ni,* and Allan D. Headley*

Department of Chemistry, Texas A&M University-Commerce,
Commerce, Texas 75429-3011

bukuo_ni@tamu-commerce.edu; allan_headley@tamu-commerce.edu

Received May 28, 2009

ABSTRACT



A new pyrrolidine-based organocatalyst for asymmetric reactions has been developed and shown to be a very effective catalyst for the Michael reaction involving various nitroolefins and aldehydes in water. This design is based on the introduction of a hydrophilic group into the pyrrolidine side chain. This catalyst, di(methylimidazole)prolinol silyl ether in combination with sodium bicarbonate as additive effectively catalyzed the Michael addition of aldehydes to nitroolefins in water as solvent in high yields and excellent enantioselectivities.

A homogeneous organocatalytic Michael addition reaction is without a doubt one of the most basic and useful reactions for the construction of C−C bonds in organic synthesis.[1] For these reactions, good yields and stereoselectivities are generally achieved and typically mild reaction conditions are required for these organocatalyzed transformations. Since the pioneering work by List and Barbas in 2001,[2] a great deal of effort has been devoted to the development of more selective and catalytic protocols for this cornerstone transformation, and significant progress has been made in recent years.[3] However, most of these reactions have typically been carried out in organic solvents despite the fact that organocatalysts have been recognized as the simplest mimicked "enzyme", which does act on organic reactions in water. This is mainly due to the fact that water can interfere with organocatalysts and disrupt hydrogen bonds and other polar interactions.[4] On the other hand, water, when compared to conventional organic solvents, is an ideal solvent for such reactions because it displays unparalleled and unique physical properties and it is nontoxic, cheap, hazardless in handing, and environmentally benign. To achieve highly catalytic activity and excellent enantioselectivitiy of organic reaction in water, much effort has gone into the development of organocatalytic asymmetric reactions for an aqueous environment.[5−7]

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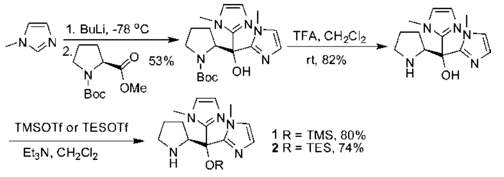
10.1021/ol901204b CCC: $40.75
Published on Web 07/02/2009

Compared to the widely reported aldol reaction, in which water is used as solvent,[5] only limited success has been obtained for the efficient Michael addition quite recently.[6] For these reported cases, the organocatalysts were specifically designed to be less water soluble or even water insoluble with a large hydrophobic group (Figure 1, modes **A**−**B**), which accurately served as a "concentrated organic phase", whereby the hydrophobicity of catalysts can aggregate organic reactants and drive the formation of enamine intermediate away from water. To the best of our knowledge, there is no water-soluble organocatalyst with large hydrophilic group (Figure 1, mode **C**), which gives high enantioselectivity for this reaction in water. However, it is still appealing to study the efficiency of water-soluble organocatalysts that influence the outcomes of the asymmetric Michael reactions. In this communication, we describe the study of water-soluble di(methylimidazole)prolinol silyl ether that catalyze highly enantioslective Michael addition reactions of aldehydes with nitroolefins using water as only solvent.

Figure 1. Various designs of organocatalysts for aqueous environments.

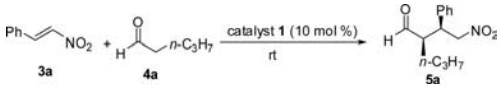
In this report, the catalysts **1**−**2** were readily prepared by a straightforward route from 1-methylimidazole and Boc-L-proline methyl ester in three steps with 32−35% overall yields (Scheme 1). These catalysts were conceived based on an intuition that the bimethylimidazole group would enhance the hydrophilic interaction when the reaction is done in water and should also act as an effective steric controller due to the bulky group near the catalytic site of the catalyst (Mode **C** in Figure 1).

Scheme 1. Synthesis of Di(methylimidazole)prolinol Silyl Ether



A model reaction was carried out in aqueous solution of valeraldehyde and *trans*-β-nitrostyrene in the presence of 10 mol % of catalysts **1** and **2** separately; the screening results are shown in Table 1. As can be seen, our first attempt in water gave very poor yield using **1** as catalyst (Table 1, entry 1). It has been reported that the addition of an acid to the Michael reaction can improve chemical yields by acceleration of enamine formation.[8] However, no product was observed using TsOH or TFA as additive (Table 1, entries 2−3). To our surprise, the addition of 20 mol % $NaHCO_3$ gave the desired Michael adduct **5a** in 65% yield with excellent enantioselectivity (97% ee) and high diastereoselectivity (*syn*/*anti* 94/6) (Table 1, entry 4). When a little stronger base

Table 1. Optimization of the Michael Reaction Conditions[a]



entry	solvent	additive	time (h)	yield[b] (%)	ee[c] (%)	syn/anti[d]
1	H_2O	none	96	<10	[e]	[e]
2	H_2O	TsOH	96	0	[e]	[e]
3	H_2O	CF_3CO_2H	96	0	[e]	[e]
4	H_2O	$NaHCO_3$	96	65	97	94/6
5	H_2O	Na_2CO_3	96	85	94	95/5
6	H_2O	Li_2CO_3	96	40	96	93/7
7	H_2O	K_2CO_3	96	77	95	91/9
8	H_2O	$KHCO_3$	96	45	95	96/4
9	brine	none	96	93	98	98/2
10	brine	$NaHCO_3$	48	90	99	91/9
11[f]	brine	$NaHCO_3$	48	90	96	91/9

[a] Aldehyde (5 equiv) and additive (0.2 equiv) were used. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Determined by ^1H NMR. [e] Not determined. [f] Catalyst **2** was used.

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[6] Michael reactions in aqueous media, see: (a) Mase, N.; Watanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 4966. (b) Luo, S.; Mi, X.; Liu, S.; Xu, H.; Cheng, J.-P. *Chem. Commun.* **2006**, 3687. (c) Zu, L.; Wang, J.; Li, H.; Wang, W. *Org. Lett.* **2006**, *8*, 3077. (d) Yan, Z.-Y.; Niu, Y.-N.; Wei, H.-L.; Wu, L.-Y.; Zhao, Y.-B.; Liang, Y.-M. *Tetrahedron: Asymmetry* **2006**, *17*, 3288. (e) Cao, Y.-J.; Lai, Y.-Y.; Wang, X.; Li, Y.-J.; Xiao, W.-J. *Tetrahedron Lett.* **2007**, *48*, 21. (f) Singh, V.; Singh, V. K. *Org. Lett.* **2007**, *9*, 1117. (g) Palomo, C.; Landa, A.; Mielgo, A.; Oiarbide, M.; Puente, A.; Vera, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 8431. (h) Zhu, S.-L.; Yu, S.-Y.; Ma, D.-W. *Angew. Chem., Int. Ed.* **2008**, *47*, 545. (i) Alza, E.; Cambeiro, X. C.; Jimeno, C.; Pericàs, M. A. *Org. Lett.* **2007**, *9*, 3717.

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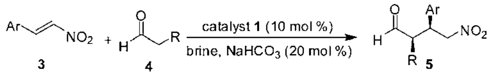
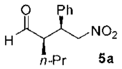
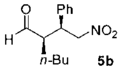
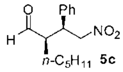
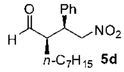
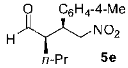
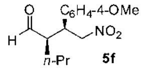
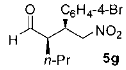
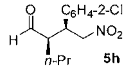
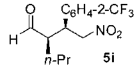
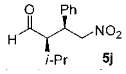
[8] Mase, N.; Tanaka, F.; Barbas, C. F., III. *Org. Lett.* **2003**, *5*, 4369.

Na_2CO_3 was used as an additive, the reaction yield was increased affording the product with slightly decreased enantioselectivity and comparable diastereoselectivity (Table 1, entry 5). Other bases, such as Li_2CO_3, K_2CO_3, and $KHCO_3$, were used as additives; the reaction did not give the increased enantioselectivity (Table 1, entries 6−8). Quite interesting, the reaction yield increased to 93% with 98% ee by using brine as solvent (Table 1, entry 9). Furthermore, the reaction rate was further increased by using 20 mol % of $NaHCO_3$ and catalyst **1** in brine affording comparable enantioselectivity although the diastereoselectivity was slightly decreased (Table 1, entry 10). However, for the more bulky catalyst **2** only slightly decreased enantioselectivity was observed (Table 1. entry 11).

On the basis of the results summarized in Table 1, the reaction conditions of entry 10 (Table 1) were chosen to study the scope of the Michael reactions using a series of aldehydes and nitroolefins, and the results are summarized in Table 2. From these results, it is obvious that all aldehydes tested can efficiently undergo Michael reactions with different aryl-substituted nitroolefins in the presence of 10 mol % of catalyst **1** with 20 mol % of additive $NaHCO_3$ in brine at room temperature to give the Michael adducts **5a−j** in moderate to high yields with excellent enantio- (86−99% ee) and diastereoselectivities (*syn/anti* ratio up to 98/2). As demonstrated in Table 2, the length of the linear chain aldehydes can influence the yields and enantioselectivities. It was observed that the long chain of the linear aldehydes gave the Michael adducts with relative lower yields and enantioselectivities, but not diastereoselectivities, comparing to the short chain (Table 2, entries 1−4). Next, the reactions of various substituted nitroolefins and linear aldehyde *n*-pentanal were studied. Generally, the nature of the substituents on aryl groups slightly influences the yields and enantioselectivities. For nitroolefins with electron-rich groups (methyl and methoxy), the reaction proceeded smoothly to afford Michael adduct **5e−f** in excellent enantio- (97% ee) and diastereoselectivities (*syn/anti* up to 97/3) (Table 2, entries 5−6). For nitroolefins with electron-deficient groups, the Michael adducts **5g−i** were also obtained in moderate to high yields (55−91%) with excellent enantio- (up to 99% ee), but relative low diastereoselectivities (*syn/anti* ratio up to 92/8) (Table 2, entries 7−9). The branched aldehyde isovaleraldehyde was also a suitable substrate as Michael donor affording the product **5j** in excellent stereoselectivity and moderate yield (Table 2, entry 10).

Table 2. Organocatalytic Asymmetric Michael Reaction Using Aldehydes and Nitroolefins[a]



entry	product	time (h)	yield (%)[b]	ee (%)[c]	syn/anti[d]
1	 5a	48	90	99	91/9
2	 5b	16	77	98	96/4
3	 5c	48	78	96	96/4
4	 5d	48	59	93	96/4
5	 5e	72	69	97	93/7
6	 5f	96	72	97	97/3
7	 5g	34	89	99	92/8
8	 5h	34	91	86	90/10
9	 5i	40	55	98	91/9
10	 5j	72	32	99	98/2

[a] Aldehyde (5 equiv) and additive (0.2 equiv) were used. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Determined by ^1H NMR.

The absolute stereochemistry of major product **5a** was determined to be 2*R*, 3*S* by comparing its optical rotation.[3k] The absolute stereochemical results can be explained by related transition state models previous discussed for (*S*)-diphenylprolinol silyl ether catalyzed Michael reactions.[3k]

In conclusion, we have developed a new and water-soluble organocatalyst di(methylimidazole)prolinol silyl ether **1**, which can be used to promote highly efficient asymmetric Michael addition reactions of aldehydes to nitroolefins. The main advantages of this catalyst are the ease of synthesis, low catalyst loading (10 mol %), and the use of brine as solvent for high stereoselectivities (ee up to 99%; *syn/anti* up to 98/2) at room temperature. Further studies focusing on the scope of this catalyst to catalyze asymmetric transformations and the modification on the imidazole part by synthesis of imidazolium ionic liquid-supported catalysts are currently under investigation and will be reported in due course.

Acknowledgment. We are grateful to the Robert A. Welch Foundation (T-1460) for financial support of this research.

Supporting Information Available: Experimental procedures, spectral data, HPLC data, ^1H NMR and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL901204B