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Highly Enantioselective Nitro-Mannich Reaction Catalyzed by *Cinchona* Alkaloids and *N*-Benzotriazole Derived Ammonium Salts

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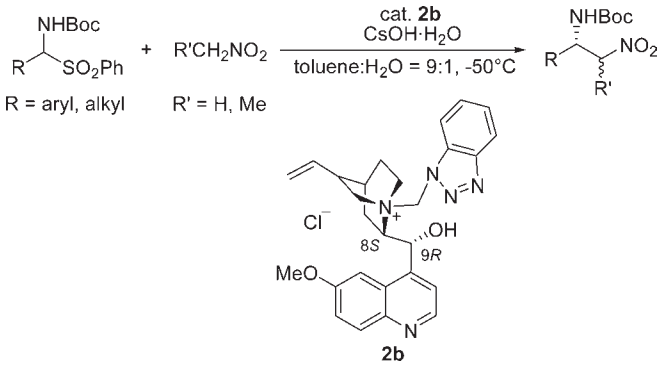
ABSTRACT



The catalytic enantio- and diastereoselective nitro-Mannich reaction of α-amido sulfones in the mixed solvent of toluene/H_2O has been realized using a phase-transfer catalyst (PTC) derived from *cinchona* alkaloids and *N*-benzotriazole. It performed well over a wide range of substrates to give the desired products in good yields (up to 94%) with excellent enantioselectivities (up to 99% ee) and diastereoselectivities (up to 99:1).

The enantioselective catalytic nitro-Mannich (or aza-Henry) reaction,[1] nucleophilic addition of nitroalkanes to imines, has emerged as a powerful tool for the preparation of some important building blocks since the resulting *β*-nitroamines adducts can either be reduced, producing vicinal diamines, or oxidized, affording α-amino carbonyl compounds.[2] The first asymmetric nitro-Mannich reaction was reported by Shibasaki using a heterobimetallic Yb-K-binaphthol complex as a catalyst in 1999.[3] Since then, several other groups have reported enantioselective nitro-Mannich protocols involving metallic[3,4] as well as purely organic catalysts.[5] In 2004, Takemoto reported the first organocatalytic nitro-Mannich reaction using chiral thiourea as a bifunctional catalyst.[5a] Afterward, other thiourea catalysts, bisamidine triflate salts, ammonium

(1) For a review about the asymmetric nitro-Mannich reactions, see: Marqués-López, E.; Merino, P.; Tejero, T.; Herrera, R. P. *Eur. J. Org. Chem.* **2009**, 2401.

(2) For a review about the application and preparation of vicinal diamines and α-amino acids, see: (a) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580. (b) Knudsen, K. R.; Risgaard, T.; Nishiwaki, N.; Gothelf, K. V.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 5843. (c) Handa, S.; Gnanadesikan, V.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 4900. (d) Chen, Z.-H.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 2170.

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betaines, and Brønsted acids have been succefully developed for this transformation in recent years.[5b−p] However, most of the substrates, N-protected imines, are unstable, and aliphatic enolizable aldehyde derived imines are even hard to isolate, thus resulting in a considerable limitation to the generality of their applications.[6]

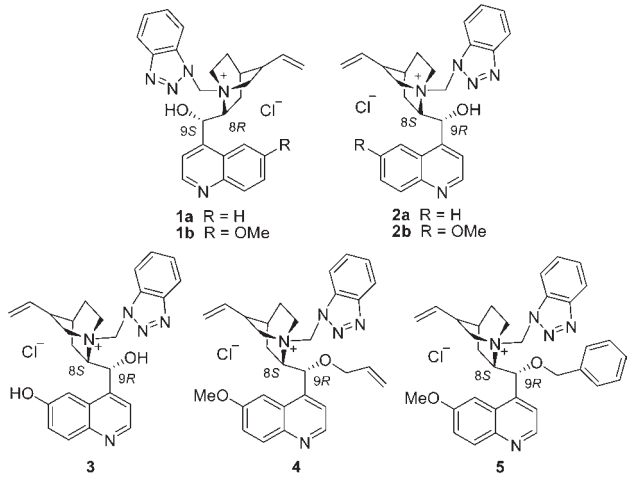
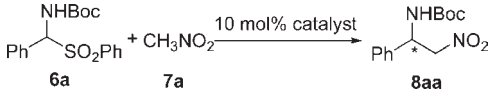


Figure 1. Phase-transfer catalysts evaluated.

Recently, Palomo's and Herrera's groups independently reported the nitro-Mannich reaction between bench stable α-amido sulfones, which generate reactive *N*-carbamoyl imines in situ by inorganic base, and nitromethane using *N*-benzyl quininium chloride as a phase-transfer catalyst (PTC).[7] This method successfully expanded the substrate scope to both aromatic and aliphtic aldehyde derived azomethines. Although the phase-transfer catalysis appears highly attractive considering the mild conditions and the operational simplicity, the use of PTCs as a tool for the catalytic asymmetric nitro-Mannich reaction is still relatively undeveloped.

In 2009, we developed a series of quaternary ammonium salts **1**−**2** (Figure 1), prepared simply by a reaction of *cinchona* alkaloids with 1-chloromethyl benzotriazole, which exhibits excellent enantioselectivity in the asymmetric alkylation of glycine imines.[8] Herein we report the highly enantioselective nitro-Mannich reaction between nitroalkane and α-amido sulfones catalyzed by ammonium salts **1**−**5** (Figure 1). Under the optimized conditions, the new catalytic system is valid for both aromatic and aliphtic aldehyde derivatives, giving excellent enantioselectivities and high yields. More importantly, compared with the Palomo's work, we obtained a complete reversal of enantioselectivity of the products from the nitro-Mannich reaction by changing the *N*-benzyl group to a *N*-benzotriazole derivative even using the same chiral source quinine. As we know, it is very challenging in asymmetric catalysis to obtain both enantiomers of a given reaction in excellent enantioselectivity by using the same chiral source. Subtle modification of the catalyst structure, using the same chiral source, is an effective method for this purpose.[9] Our work added a nice contribution to this area.

Table 1. Screening of the Reaction Conditions in Asymmetric Nitro-Mannich Reaction



6a 7a 8aa

entry[a]	catalyst	solvent	base	yield (%)[b]	ee (%)[c]	config.[d]
1	**1a**	Toluene/H_2O[f]	$CsOH·H_2O$	42	20	*R*
2	**1b**	Toluene/H_2O	$CsOH·H_2O$	55	11	*R*
3	**2a**	Toluene/H_2O	$CsOH·H_2O$	51	54	*S*
4	**2b**	Toluene/H_2O	$CsOH·H_2O$	84	87	*S*
5	**3**	Toluene/H_2O	$CsOH·H_2O$	15	11	*S*
6	**4**	Toluene/H_2O	$CsOH·H_2O$	12	11	*S*
7	**5**	Toluene/H_2O	$CsOH·H_2O$	trace	ND[e]	—
8[f]	**2b**	Toluene	$CsOH·H_2O$	89	74	*S*
9	**2b**	CH_2Cl_2	$CsOH·H_2O$	72	77	*S*
10	**2b**	$CHCl_3$	$CsOH·H_2O$	56	80	*S*
11	**2b**	Toluene	$CsOH·H_2O$	71	70	*S*
12	**2b**	CH_2Cl_2/H_2O[g]	$CsOH·H_2O$	74	79	*S*
13	**2b**	$CHCl_3/H_2O$[g]	$CsOH·H_2O$	60	81	*S*
14	**2b**	Toluene/H_2O	DABCO[h]	8	14	*S*
15	**2b**	Toluene/H_2O	DBU[h]	67	64	*S*
16	**2b**	Toluene/H_2O	$CsCO_3$[h]	55	75	*S*
17	**2b**	Toluene/H_2O	NaOH[h]	37	42	*S*
18	**2b**	Toluene/H_2O	LiOH[h]	46	75	*S*
19	**2b**	Toluene/H_2O	KOH[h]	70	73	*S*

[a] All reactions were carried out with 0.1 mmol of α-amido sulfone and 0.5 mmol of nitromethane in solvent (1 mL) in the presence of 0.01 mmol of catalyst and 0.13 mmol of $CsOH·H_2O$ as the basic additive, at −50 °C for 24 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis using Chiralpak AD-H column. [d] The absolute configuration of the products was assigned by comparison optical rotation and HPLC result with the literature. [e] Not determined. [f] *N*-Boc benzaldimine was used instead of α-amido sulfones **6a** as substrate. [g] organic solvent/H_2O = 9:1. [h] 0.1 mmol of basic additive.

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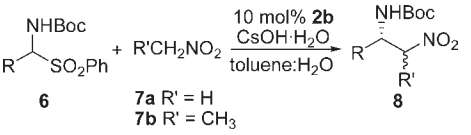
Initially, the reaction between α-amido sulfones **6a** and nitromethane **7a** was selected as the model reaction and the catalysts **1**–**5** were screened (Table 1, entries 1–7). Interestingly, the *pseudo*enantiomeric catalyst pairs (**1a** vs **2a**, **1b** vs **2b**) give opposite enantioselectivities in the nitro-Mannich reaction with different reactivity and stereocontrol. Among them, the catalyst **2b**, readily prepared from quinine and 1-chloromethylbenzotriazole, results in an 84% yield and 87% ee in the presence of 130 mol % of $CsOH \cdot H_2O$ as the basic additive and toluene/H_2O (9:1) - as the mixed solvent at −50 °C. Notably, the abolute configuration of the product catalyzed by **2b** is *S*, which is opposite to Palomo's results using the same chiral source quinine derived catalyst.[7] Moreover, N-Boc benzaldimine was directly treated with nitromethane in the presence of **2b** (entry 8), the *S*-product was also observed in high yield and moderate ee value. These results indicate the triazole moiety in the catalyst may play a crucial role in the chiral discrimination. Catalyst **3**, which has a hydroxyl on the quinoline ring of quinine results in poor reactivities and enantioselectivities (entry 5). The catalysts **4** and **5** with O-alkylated or O-arylated protected C-9 hydroxyl groups are significantly less reactive than the one containing a free hydroxyl group, which is consistent with the experimental work by Palomo and co-workers, suggesting the possibility of H-bonding as a mechanism of activation (entries 6–7).[7b]

As it can be seen from entries 4, 9–13, water has a positive impact on the reactivities and enantioselectivities. Especially, using toluene/H_2O as a cosolvent, both yield and ee value increased significantly (entry 4 vs 11). The presence of water in the reaction makes product isolation relatively easy and increases the yields and chemical purity with no extra expenditure.[10] Furthermore, in this reaction, a basic additive is needed to help the formation of imines by α-amido sulfones. Thus, several different bases have been examined (entries 14–19). It seems that a stronger base gives better results, e.g., DBU is better than DABCO (67% yield vs 8% yield, 64% ee vs 14% ee, entries 14, 15). All other tested inorganic bases, such as $CsCO_3$, NaOH, LiOH, and KOH, give good results but are still inferior to those when using $CsOH \cdot H_2O$ as a basic additive (entries 16–19 vs entry 4).

After further systematic optimization of the reaction parameters,[11] the scope of the nitro-Mannich reaction with nitroalkanes is explored (Table 2). The α-amido sulfones are derived from different kinds of aldehydes, including aromatic and aliphatic aldehydes. In general, excellent enantioselectivities and good yields are achieved for all the substrates. Compared to Herrera's and Palomo's research,[7] we not only expanded the substrate's scope to **6c**–**f**, **6n** but also improved the results of α-amido sulfone **6a**, **6h**–**i**, **6k**–**l** successfully. Overall, aromatic aldehyde derived substrates, regardless of possessing an electron-donating or -accepting group, react smoothly with nitromethane (entries 1–12, 72%–94% yield, 83%–99% ee). Essentially, enantiopure **8ba** (entry 3) and **8ja** (entry 6) can

Table 2. PTC Catalyzed Enantio- and Diastereoselective Nitro-Mannich Reactions



6 **7a** R' = H, **7b** R' = CH_3 **8**

entry[a]	R	R'	*t* (°C)	yield (%)[b]	dr (syn: anti)[c]	ee (%)[d]
1[e]	Ph (**6a**)	**7a**	-60	75	—	99
3	4-ClC_6H_4 (**6b**)	**7a**	-50	90	—	83 (98)[f]
2	2-ClC_6H_4 (**6c**)	**7a**	-50	76	—	96
5	4-FC_6H_4 (**6d**)	**7a**	-50	73	—	98
8	4-MeC_6H_4 (**6e**)	**7a**	-50	72	—	99
10	2-$MeOC_6H_4$ (**6f**)	**7a**	-50	78	—	93
9	4-$MeOC_6H_4$ (**6g**)	**7a**	-50	75	—	91
4	4-BrC_6H_4 (**6h**)	**7a**	-60	74	—	96
7	4-$NO_2C_6H_4$ (**6i**)	**7a**	-60	76	—	90
6	4-$CF_3C_6H_4$ (**6j**)	**7a**	-50	89	—	85 (97)[f]
11	1-naphthyl (**6k**)	**7a**	-50	80	—	96
12	2-furyl (**6l**)	**7a**	-50	94	—	91
13	$PhCH_2CH_2$ (**6m**)	**7a**	-50	71	—	97
14	PhCH=CH (**6n**)	**7a**	-50	65	—	97
15	cyclohexyl (**6o**)	**7a**	-50	85	—	>99
16	$(CH_3)_2CHCH_2$ (**6p**)	**7a**	-50	77	—	98
17	$(CH_3)_2CH$ (**6q**)	**7a**	-50	85	—	90
18	$CH_3CH_2CH_2$ (**6r**)	**7a**	-50	88	—	93
19	CH_3CH_2 (**6s**)	**7a**	-50	79	—	97
20	CH_3 (**6t**)	**7a**	-50	75	—	88
21[e]	Ph (**6a**)	**7b**	-40	67	99:1	98
22[e]	2-ClC_6H_4 (**6b**)	**7b**	-40	55	66:34	91
23[e]	4-$MeOC_6H_4$ (**6i**)	**7b**	-40	70	97:3	99
24[e]	2-$MeOC_6H_4$ (**6g**)	**7b**	-40	75	84:16	90
25[e]	2-furyl (**6l**)	**7b**	-40	78	93:7	88
26[e]	$PhCH_2CH_2$ (**6m**)	**7b**	-40	65	83:17	90

[a] All the reactions were carried out with 0.1 mmol of α-amido sulfone and 0.5 mmol of nitroalkanes in toluene/H_2O = 9:1 (1 mL) in the presence of 10 mol % catalyst **2b**, 130 mol % $CsOH \cdot H_2O$, reacted at intended temperature for 24 h. [b] Isolated yield. [c] Assigned by HPLC data combination with ^1H NMR data and comparison with literature report. [d] Determined by HPLC analysis. [e] Reaction time was 50 h. [f] After a single crystallization.

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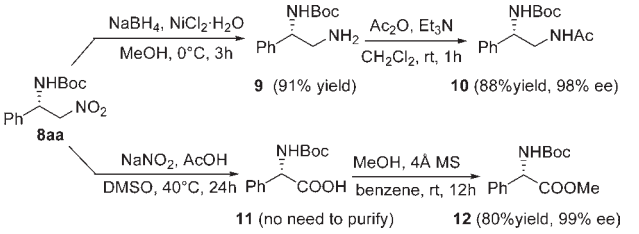
(11) See Supporting Information for details of condition screening.

be obtained by direct crystallization of the crude products. In particular, enolizable aliphatic aldehyde drived substrates, such as 3-phenylpropionaldehyde derived **6m**, 3-phenyl-2-propenal derived **6n**, cyclohexanecarbaldehyde derived **6o**, branched or unbranched aldehyde derived **6p**–**6t**, also are suited to this reaction to afford the corresponding adducts in good yields and excellent enantioselectivities (entries 13–20). Moreover, nitroethane **7b** has been proven to be a good substrate in this new catalytic system. All the aromatic compounds with either an electron-donating or -withdrawing group, heterocyclic compounds, and aliphatic compounds reacted well with nitroethane **7b**, forming two stereocenters simultaneously, affording the products with high diastereomeric ratios and enantiomeric excess (entries 21–26).

The β-nitroamines obtained in the nitro-Mannich reaction are valuable intermediates for the synthesis of a variety of enantioenriched compounds. To indicate this, here we demonstrate two transformations (Scheme 1). First, the NO_2 moiety in product **8aa** is readily reduced with $NaBH_4$/$NiCl_2$ at 0 °C, followed by acetylation of **9** to give the known compound α,β-diamino ester **10**, allowing the absolute configuration of the adducts to be confirmed. Second, the products are used for the Nef oxidation,[12] followed by methylation, directly to afford the *N*-Boc-protected-(α)-phenylglycine methyl ester **12** without loss of optical integrity. In particular, our new catalytic system which catalyzes the reaction of enolizable aldehyde-derived α-amido sulfone with nitroalkanes provides a new access to a wide range of important building blocks in organic synthesis.

In conclusion, the highly enantio- and diastereoselective nitro-Mannich reaction of α-amido sulfones and nitroalkanes in the mixed solvent of toluene/H_2O has been realized using a PTC derived from *cinchona* alkaloids and *N*-benzotriazole. It performed well over both aromatic and aliphatic aldehyde derivatives to give the desired products in good yields (up to 94%) with excellent enantioselectivities (up to 99% ee) and diastereoselectivities (up to 99:1). By changing the *N*-benzyl group to a *N*-benzotriazole derivative of quinine, opposite enantiomers of β-nitroamines were obtained, which is a valuable supplement to the reported method. Moreover, the optically active products can be easily converted into chiral vicinal diamines or α-amino acids, which demonstrates the practicability of this methodology. Further investigation into the mechanism and applications of this methodology is ongoing in our laboratory.

Scheme 1. Conversion of the Product to 1,2-Diamine and α-Amino Acid



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

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