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Asymmetric Phase-Transfer Catalysts Bearing Multiple Hydrogen-Bonding Donors: Highly Efficient Catalysts for Enantio- and Diastereoselective Nitro-Mannich Reaction of Amidosulfones

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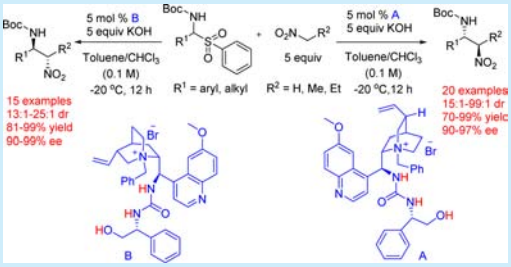
Supporting Information

ABSTRACT: Bifunctional asymmetric phase-transfer catalysts bearing multiple hydrogen-bonding donors have rarely been explored. The first quaternary ammonium type of these catalysts derived from cinchona alkaloids were readily prepared and found to be highly efficient catalysts for asymmetric nitro-Mannich reactions of amidosulfones. Compared with previous reports, very broad substrate generality was observed, and both enantiomers of the products were achieved in high enantio- and diastereoselectivity (90−99% ee, 13:1 to 99:1 dr).



In recent years, the multiple hydrogen-bonding strategy, frequently used in supramolecular chemistry,[1] has attracted increasing attention from organic chemists. Compared with catalysts containing single and double H-bonding donors, catalysts bearing multiple H-bonding donors have great potential to ehance their catalytic activity and give a better level of enantiocontrol. Based on this strategy, some kinds of chiral organocatalysts have been raised.[2] In contrast, bifunctional asymmetric phase-transfer (APT) catalysts[3,4] bearing multiple H-bonding donors are rare. In fact, only two examples can be found in the literature (Figure 1).[5]

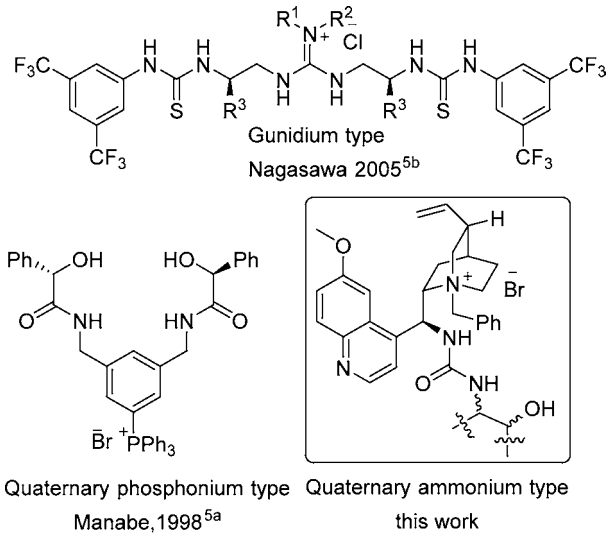


Figure 1. Bifunctional APT catalysts bearing multiple H-bonding donors reported in the literature.

The catalytic asymmetric nitro-Mannich (or aza-Henry) reaction is one of the most useful and attractive C−C bond forming reactions.[6,7,2f] In terms of stability, generality, and practicality of substrates, nitro-Mannich reactions of amidosulfones[8,4i−k,9] are more fascinating than *N*-acyl imines, but existing catalytic systems with a sufficiently broad substrate scope are rare,[9d] and are highly efficient either for aromatic series[4j] or the aliphatic series.[9a,b] Moreover, when cinchona alkaloids were employed as the chiral source, the corresponding pseudoenantiomeric catalysts often give enantiomeric products in significantly lower enantioselectivity.[4i,9d]

We envision that the disadvantages described above will be tackled when the multiple hydrogen-bonding strategy is used in bifuctional APT catalysis. Therefore, bifunctional chiral ammonium catalysts bearing multiple H-bonding donors were synthesized in our laboratory (Scheme 1). To the best of our knowledge, these are the first quaternary ammonium type bifunctional APT catalysts bearing multiple H-bonding donors. Herein, we wish to report the synthesis of these new catalysts and their catalytic performance in the nitro-Mannich reaction.

Starting from known 9-amino-9-deoxyepiquinine,[10] the catalysts can be readily prepared through three steps in two pots as outlined in Scheme 1. 9-Amino-9-deoxyepiquinine was transformed with *N*,*N*′-carbonyldiimidazole to the corresponding carbamoylimidazole **1**,[11] without isolation; treatment of **1** with various *β*-aminoalcohols gave rise to ureas **2** bearing multiple H-bonding donors under basic conditions. Subsequent quaternization afforded catalysts **3a**−**g**. Apparently, the H-bond donor can be finely tuned and the pseudoenantiomeric catalysts can also be prepared easily.

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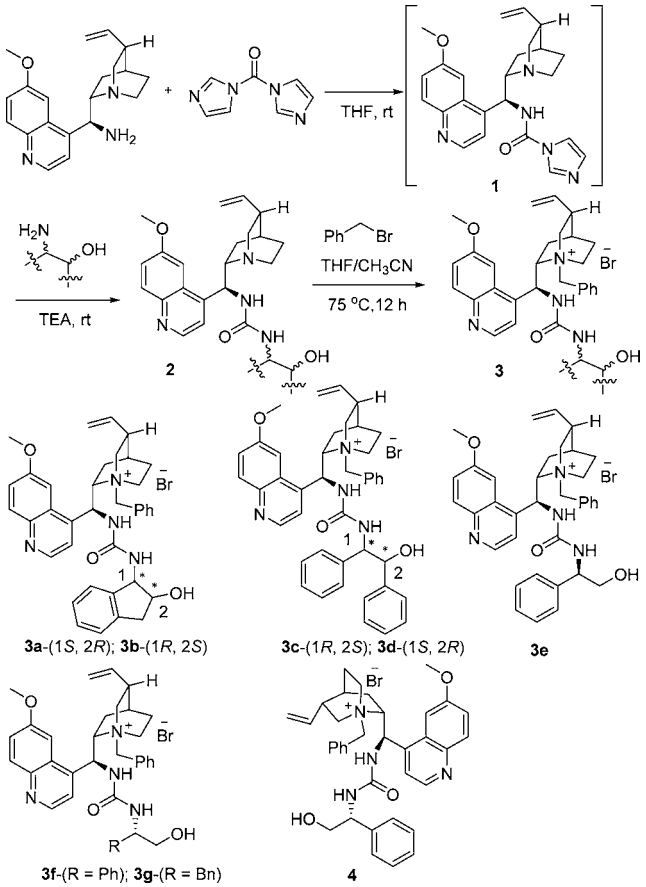
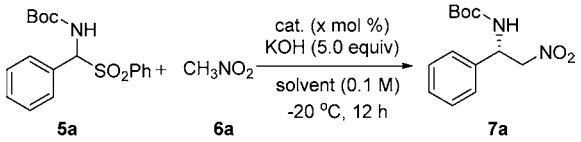
Scheme 1. Synthesis of the Catalysts



With catalysts **3a**–**g** in hand, we first investigated the reaction between amidosulfone **5a** and nitromethane **6a** in the presence of 5 equiv of KOH at −20 °C in toluene (Table 1). Initially, catalysts **3a**–**3f** were tested (entries 1–6); from Table 1, it can be seen that, in all cases, high yields were obtained. Catalyst **3f** including the L-phenylglycinol moiety gave the best result (entry 6, 95% yield, 94% ee). In terms of reactivity and enantioselectvity, **3f** showed significant improvement over the previous report which just used a urea unit as H-bonding donors (59% yield, 80% ee) under the same conditions.[4i] These results also indicate that matching the chirality is important and the absolute configurations of products are mainly determined by 9-amino-9-deoxyepicinchona alkaloid moieties (entry 1 vs 2, 3 vs 4, 5 vs 6). By replacing the moiety L-phenylglycinol with L-phenylalaninol, the enantioselectivity decreased slightly (entry 7, 91% ee). The ensuing investigation of solvent effect indicated that this reaction gave a slightly higher level of enantiocontrol in CH_2Cl_2 and $CHCl_3$, but the yields dropped significantly (entries 8 and 9). Finally mixed solvent optimization was performed, and a mixture of toluene and $CHCl_3$ (9:1) was chosen as the best solvent (entries 10 and 11). It is worth noting that high enantioselectivity was still achieved although the yield was dropped when the catalyst loading was reduced to 2.5 and 1 mol % (95% and 92% ee, entries 12 and 13).

Table 1. Optimization of Reaction Conditions[a]



entry	cat.	x (%)	solvent	yield[b] (%)	ee[c] (%)
1	**3a**	5	toluene	93	57
2	**3b**	5	toluene	92	65
3	**3c**	5	toluene	93	68
4	**3d**	5	toluene	95	88
5	**3e**	5	toluene	95	59
6	**3f**	5	toluene	95	94
7	**3g**	5	toluene	93	91
8	**3f**	5	CH_2Cl_2	70	95
9	**3f**	5	$CHCl_3$	80	96
10	**3f**	5	Tol/$CHCl_3$ (9:1)	93	95
11	**3f**	5	Tol/$CHCl_3$ (7:3)	90	95
12	**3f**	2.5	Tol/$CHCl_3$ (9:1)	75	95
13	**3f**	1	Tol/$CHCl_3$ (9:1)	70	92

[a]Reactions were conducted at 0.15 mmol scale in 1.5 mL of solvent. [b]Yield of isolated product. [c]Determined by HPLC using a chiral stationary phase.

The scope of this reaction was further explored under optimal conditions with a series of amidosulfones and nitroalkanes (Table 2). In all cases, high to excellent yields (70–99%) and excellent ee values (90–97% ee) were obtained. Aromatic aldehyde derived substrates having either electron-rich or -poor groups were well tolerated (entries 1–11), and the position of the substituents seemed to have limited influence (entry 4 vs 10, 3 vs 9 and 11). Poly- and heteroaromatic substrates also proved effective (entries 12–14). Moreover, the aliphatic amidosulfones also participated well (entries 15–17). Finally, we investigated the generality of the reaction with other nitroalkanes. Pleasingly, nitroethane **6b** and nitropropane **6c** showed the same reactivity as nitromethane **6a**, and high yields (95%, 99%) and excellent enantio-/diasteroselectivities (96% ee, 15:1 dr; 96% ee, 21:1 dr) were obtained respectively (entries 18 and 19). Larger nitroalkanes tend to give better stereocontrol (entry 18 vs 19). Notably, cyclohexyl aminosulfones **5o** and nitroethane **6b** yield the expected product **7t** with excellent stereocontrol (97% ee, 99:1 dr); after column chromatography, a pure *anti*-diastereomer was achieved.

Facile access to both enantiomers of products in high enantiopurity respectively is of great importance in asymmetric catalysis, especially regarding the direct or indirect application of this product in medical chemistry research. As cinchona alkaloids exist as pseudoenantiomers, one cinchona salt usually gives the enantiomeric product in slightly to drastically lower enantioselectivity than the corresponding pseudoenantiomeric one.[4f,i,9d] To the best of our knowledge, nitro-Mannich reactions using cinchona alkaloid-derived catalysts, giving both enantiomers of the products in high enantiopurity (≥90% ee), have never been reported so far. So we are eager to know whether this multiple H-bonding strategy can mitigate this negative effect; thus, catalyst **4** derived from quinidine and D-phenylglycinol was prepared and the catalytic efficiency of catalyst **4** was tested. A broad substrate scope was also observed, and high yields (81–99%) and excellent enantio-/ diastereoselectivities (90–99% ee, 13:1–25:1 dr) were obtained (Table 3). In most cases, a slightly higher enantiomeric purity was obtained than catalyst **3f** (entries 1–3, 5–7, 10–12). Notably, cyclohexyl aminosulfones **5o** reacted with nitomethane **6a** and nitroethane **6b** yielding the expected products **8j** and **8o** with excellent stereocontrol (95% ee; 96% ee, 25:1 dr; entries 10 and 15) compared with previous reports (84% ee; 95% ee, 9:1 dr).[4i]

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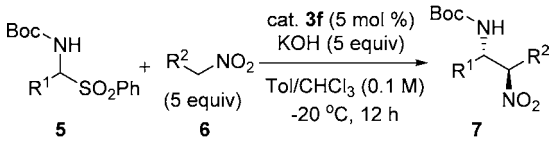
Table 2. Substrate Scope of Nitro-Mannich Reaction Using Catalyst 3f[a]

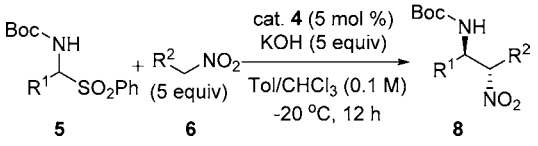


5 6 7

entry	5	R^1	6	R^2	7	yield[b] (%)	dr[d]	ee[c] (%)
1	**5a**	Ph	**6a**	H	**7a**	93		95
2	**5b**	*p*-MeC_6H_4	**6a**	H	**7b**	95		93
3	**5c**	*p*-$MeOC_6H_4$	**6a**	H	**7c**	87		90
4	**5d**	*p*-ClC_6H_4	**6a**	H	**7d**	89		96
5	**5e**	*p*-BrC_6H_4	**6a**	H	**7e**	85		95
6	**5f**	*p*-$NO_2C_6H_4$	**6a**	H	**7f**	70		90
7	**5g**	*p*-$CF_3C_6H_4$	**6a**	H	**7g**	98		97
8	**5h**	*o*-FC_6H_4	**6a**	H	**7h**	98		91
9	**5i**	*o*-$MeOC_6H_4$	**6a**	H	**7i**	90		92
10	**5j**	*m*-ClC_6H_4	**6a**	H	**7j**	93		95
11	**5k**	*m*-$MeOC_6H_4$	**6a**	H	**7k**	88		91
12	**5l**	*α*-naphthyl	**6a**	H	**7l**	99		93
13	**5m**	*β*-naphthyl	**6a**	H	**7m**	75		95
14[e]	**5n**	2-furyl	**6a**	H	**7n**	99		90
15	**5o**	cyclohexyl	**6a**	H	**7o**	90		93
16	**5p**	phenyl ethyl	**6a**	H	**7p**	99		91
17	**5q**	isobutyl	**6a**	H	**7q**	81		91
18[e]	**5a**	Ph	**6b**	Me	**7r**	95	15:1	96
19[e]	**5a**	Ph	**6c**	Et	**7s**	99	21:1	96
20[e,f]	**5o**	cyclohexyl	**6b**	Me	**7t**	95	99:1	97

[a]Unless otherwise noted, all reactions were conducted at 0.15 mmol scale in 1.5 mL of toluene/$CHCl_3$ (9:1). [b]Yield of isolated product. [c]Determined by HPLC using a chiral stationary phase. [d]Determined by chiral HPLC analysis or ^1H NMR. [e]$CHCl_3$ was used as solvent instead of toluene/$CHCl_3$. [f]Pure *anti* diastereomer was obtained after column chromatography.

Table 3. Substrate Scope of Nitro-Mannich Reaction Using Catalyst 4[a]



5 6 8

entry	5	R^1	6	R^2	8	yield[b] (%)	dr[d]	ee[c] (%)
1	**5a**	Ph	**6a**	H	**8a**	93		96
2	**5b**	*p*-MeC_6H_4	**6a**	H	**8b**	99		99
3	**5c**	*p*-$MeOC_6H_4$	**6a**	H	**8c**	81		91
4	**5d**	*p*-ClC_6H_4	**6a**	H	**8d**	87		96
5	**5f**	*p*-$NO_2C_6H_4$	**6a**	H	**8e**	94		95
6	**5h**	*o*-FC_6H_4	**6a**	H	**8f**	99		93
7	**5k**	*m*-$MeOC_6H_4$	**6a**	H	**8g**	95		97
8	**5l**	*α*-naphthyl	**6a**	H	**8h**	98		92
9[e]	**5n**	2-furyl	**6a**	H	**8i**	99		90
10	**5o**	cyclohexyl	**6a**	H	**8j**	93		95
11	**5p**	phenyl ethyl	**6a**	H	**8k**	99		95
12	**5q**	isobutyl	**6a**	H	**8l**	95		95
13[e]	**5a**	Ph	**6b**	Me	**8m**	95	13:1	95
14[e]	**5a**	Ph	**6c**	Et	**8n**	99	16:1	95
15[e,f]	**5o**	cyclohexyl	**6b**	Me	**8o**	85	25:1	96

[a]Unless otherwise noted, all reactions were conducted at 0.1 mmol scale in 1.0 mL of toluene/$CHCl_3$ (9:1). [b]Yield of isolated product. [c]Determined by HPLC using a chiral stationary phase. [d]Determined by chiral HPLC analysis or ^1H NMR. [e]$CHCl_3$ was used as solvent instead of toluene/$CHCl_3$. [f]Pure *anti* diastereomer was obtained after column chromatography.

In order to assess the role of the multiple H-bonding donors played in the reaction and gain insight into the cooperative catalysis of the catalyst.[12] Two control experiments were carried out as shown in Scheme 2. Using methylated **3f** (**3h**) as the catalyst under the optimized conditions, the reaction became a little sluggish and the enantioselectivity of the product was significantly decreased (83% yield, 62% ee). When we employed catalyst **2f** which lacks the quaternary ammonium center

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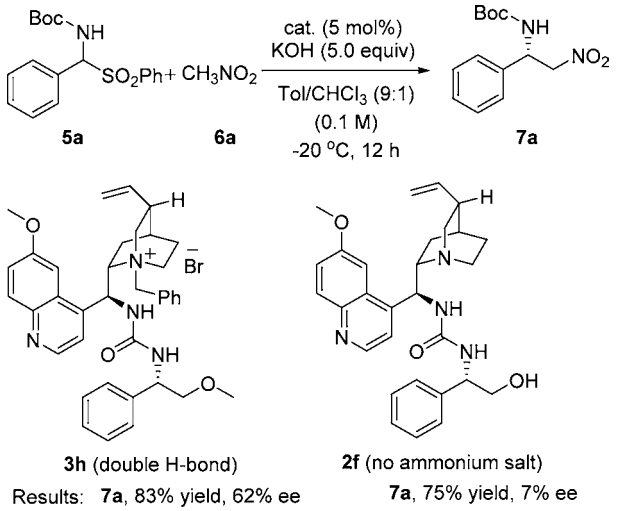
Scheme 2. Control Experiment for Mechanistic Study



compared with **3f**, the reaction became sluggish (75% yield), and a nearly racemic product was obtained (only 7% ee). These results support cooperative catalysis of the bifunctional catalysts and indicate that the hydroxy on the phenylalaninol moiety plays a significant role in this nitro-Mannich reaction.

In summary, we have developed a new class of bifunctional phase-transfer catalysts bearing multiple H-bonding donors derived from cinchona alkaloids and various β-aminoalcohols, which has been successfully applied to the nitro-Mannich reactions of amidosulfones, with a very broad substrate scope; both enantiomers of the products can be obtained in excellent enantio-/diastereoselectivity (90–99% ee, 13:1–99:1 dr). Since reports about the synthesis and application of phase-transfer catalysts bearing multiple H-bonding donors are rare, we believe that this work will encourage development in this area. Further efforts to investigate the mechanism and apply these catalysts to other useful asymmetric transformations are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures including complete characterizations (^{1}H NMR and ^{13}C NMR spectra, spectral data, and HRMS).This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(12) Similar control experiments were conducted by Wang and Zhao; see refs 2e–g and 4j.