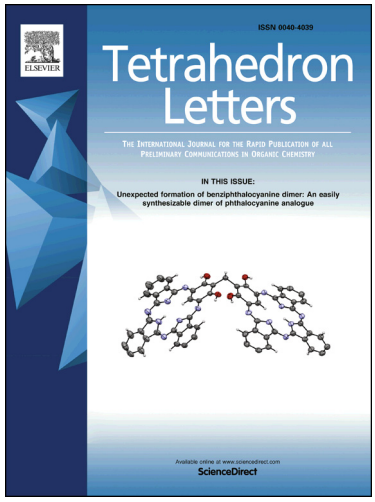

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Graphical Abstract

A series of bifunctional phase-transfer catalysts bearing multiple H-bonding donors derived from quine and amino alcohols, which has been successfully applied to the nitro-Mannich reactions of isatin-derived ketimines in excellent yields (yields 96-99%) and good enantioselectivities (82-95% ee).

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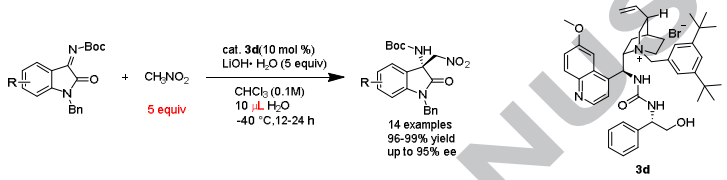

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ABSTRACT

A series of bifunctional asymmetric phase-transfer catalysts bearing multiple hydrogen-bonding donors derived from cinchona alkaloids are synthesized, and successfully applied to asymmetric nitro-Mannich of isatin-derived N-Boc ketimines. The products 3-substituted 3-amino-oxindoles were constructed in excellent yields (96–99%) and good enantioselectivities (up to 95% ee).

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Introduction

The multiple hydrogen-bonding strategy used in the synthesis of organic catalysts has attracted increasing attention in recent years, compared with single and double hydrogen-bonding donors catalysts, these catalysts with the multiple H-bonding donor generally displayed higher activity and better enantioselectivity in epoxidation reaction[1, 2], Henry reaction[3], Michael reaction[4-9], Mannich reaction[10], and others. Based on this strategy, a number of bifunctional asymmetric organocatalysts have been designed, such as ureas[11], thioureas[1-8] and squaramides[9, 10]. These bifuctional catalysts containing multiple-bonding donors were usually applicable for some weak acid- and base-catalyzed reactions[4, 12-14]. However, bifunctional phase-transfer catalysts bearing multiple H-bonding donors, which could be used in strong base-catalyzed reactions, are rarely synthesized and applied. [15, 16].

The asymmetric nitro-Mannich (or aza-Henry) reaction is one of the most efficient and attractive C–C bond forming reactions.[17-19] The addition products of this reaction can easily be transformed into vicinal diamines[20-25] and α-amino acids[26]. Although a lot of successful examples of nitro-Mannich reaction are based on aldimines[18, 27-37], the nitro-Mannich reaction with ketimines[38-41] is still rarely reported owing to their low reactivity and diffcult enantiocontrol. The nitro-Mannich reaction of isatin derived ketimines is the most efficient and rational approach to construct 3-substituted 3-amino-2-oxindoles[42-45], which bearing a stereogenic center and have been recognized as key structures in a variety of natural products and biologically active compounds[42]. Several successful asymmetric synthesis methodologies of these compounds have been developed. For metal catalyst system, Pedro and co-workers[46] reported Cu(II)–BOX complex, Arai and co-workers[47] reported (PyBidine)–NiCl2 complex to catalyze the nitro-Mannich reaction of isatin-derived N-Boc ketimines with good yields and enantioselectivities. Metal-free catalyst system with low toxicity, low cost, easy preparation and good stability could replace metal catalyst system. Several examples have been reported. Zhou's group reported a quinine-derived bifunctional organocatalyst and resulted in moderate to good enantioselectivities.[48] Chimn's group explored a quinine-derived organocatalyst and afforded nitro-Maanich reaction products with moderate to good yields and enantioselectivities.[49] Feng employed a chiral guanidine-amide and gave the corresponding products with good yields and enantioselectivities.[50] However, to the best of our knowledge, phase-transfer catalysts (PTC) system used in the nitro-Mannich reaction of isatin-derived ketimines has not been reported.

It is well known that cinchona alkaloids are one of superior chiral skeletons[51, 52], and amino acid derivatives are one of inexpensive and accessible chiral resources[53]. Theoretically, using cinchona alkaloids as privilege skeletons, and chiral amino alcohols as hydrogen bonding donors, we can construct a variety of structurally variable chiral quaternary ammonium salts containing multiple hydrogen-bonding donors. In terms of their applicability, these novel quaternary ammonium salts may be a kind of effective phase transfer catalysts for some conventional and challenging asymmetric reactions by structural screening and optimization. Based on this design strategy, we have synthesized a series of bifuctional chiral phase transfer catalysts with multiple hydrogen bonding donors (Figure 1, **3a–3c**), and successfully applied to asymmetric nitro-Mannich reactions of amidosulfones.[11] In order to extend their applicability in a wide range of asymmetric transformations including some challenging reactions, on basis of previous works, we further optimized the structure of this kind of catalysts and synthesized a variety of bifunctional phase transfer catalysts with multiple hydrogen bonding donors, derived from quinine and amino acohols. In the nitro-Mannich reaction of isatin-derived ketimines, these bifunctional chiral phase-transfer catalysts exhibited better asymmetric catalytic activity. Herein, we would like to report our results.

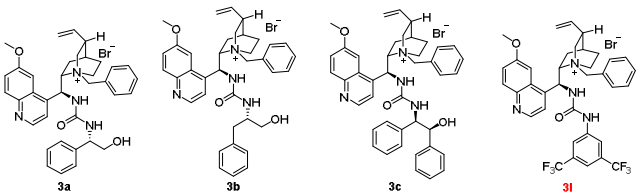
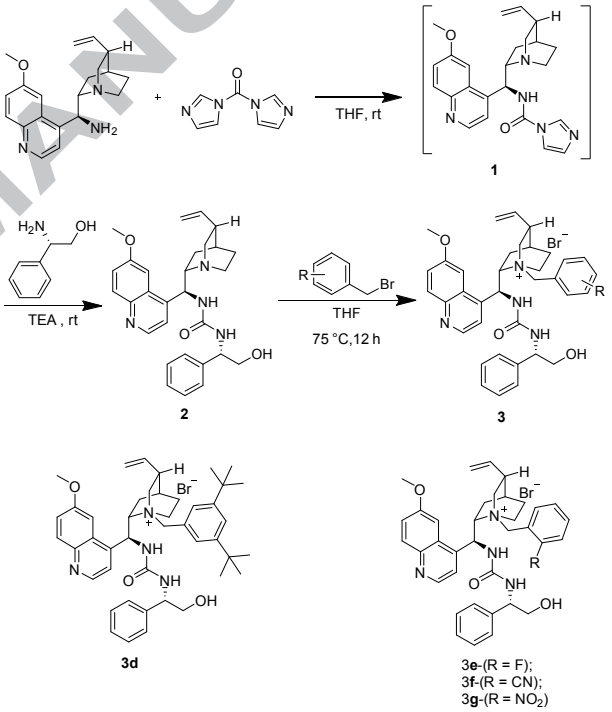


Figure 1. Bifunctional APT catalysts performed well in the nitro-Mannich reaction of aldimines.

Results and Discussion

Scheme 1. Synthesis of the Catalysts

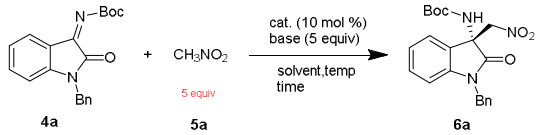


Starting from known 9-amino-9-deoxyepiquinine[54], we can get the catalysts through three steps in two pots in Scheme 1. 9-Amino-9-deoxyepiquinine was transformed with N,N′-carbonyldiimidazole to the corresponding carbamoylimidazole. Without isolation, treatment of **1** with L-phenylglycinol gave rise to urea **2**.[11] Subsequent quaternization with various benzyl bromides afforded catalysts **3d–3g**.

With catalysts **3a–3g** in hand, we began the reaction between isatin-derived ketimine **4a** and nitromethane **5a** in the presence of 10% catalyst **3a** and 5 equiv base at −20 °C in $CHCl_3$ with 10 μL H_2O (Table 1). Initially, we tested finely ground 5 equiv K_2CO_3, KOH, NaOH, $LiOH·H_2O$ as the basic additive respectively, they all gave the desired nitro-Mannich product **6a** in 99% yield (entries 1–4), among them, $LiOH·H_2O$ gave the best enantioselectvity (entry 4, 75% ee). To the best of our knowledge,

compared with other inorganic bases, $LiOH·H_2O$ was rarely reported in some base-cataylzed reaction transformations. In the screening of catalysts **3b** and **3c** with 5 equiv $LiOH·H_2O$, catalyst **3b** and **3c** have no further enhancement in enantioinduction of this reaction compared with catalyst **3a** (entries 4–6). Next we modified N-benzyl groups of catalysts under the identical reaction conditions. As shown in Table 1, in all cases, product **6a** could be obtained in high yields. Gratifyingly, catalyst **3d** with 3,5-di-tert-butyl gave the best result in terms of the yield and ee of product **6a**. (81% ee, entries 4 vs 7–10). In addition, well-behaved catalyst **3h** (Figure 1), which was developed by Dixon group[34] and exhibited axcellent asymmetric activity in the nitro-Mannich reaction of aldimines, was also evaluated under the identical reaction conditions. However, compared with catalyst **3a**, **3d**, it did not have a positive impact on the enantioselectivity

Table 1. Optimization of Reaction Conditions[a]



	cat	base	solvent	temp (°C)	yield[b] (%)	time (h)	ee[c] (%)
1	**3a**	K_2CO_3	$CHCl_3$	–20	99	12	59
2	**3a**	KOH	$CHCl_3$	–20	99	5	50
3	**3a**	NaOH	$CHCl_3$	–20	99	6	73
4	**3a**	$LiOH·H_2O$	$CHCl_3$	–20	99	6	75
5	**3b**	$LiOH·H_2O$	$CHCl_3$	–20	99	6	73
6	**3c**	$LiOH·H_2O$	$CHCl_3$	–20	99	6	70
7	**3d**	$LiOH·H_2O$	$CHCl_3$	–20	99	6	81
8	**3e**	$LiOH·H_2O$	$CHCl_3$	–20	99	8	69
9	**3f**	$LiOH·H_2O$	$CHCl_3$	–20	99	8	63
10	**3g**	$LiOH·H_2O$	$CHCl_3$	–20	99	6	61
11	**3i**	$LiOH·H_2O$	$CHCl_3$	–20	99	12	63
12	**3d**	$LiOH·H_2O$	THF	–20	99	10	46
13	**3d**	$LiOH·H_2O$	toluene	–20	99	8	78
14	**3d**	$LiOH·H_2O$	CH_2Cl_2	–20	99	6	75
15	**3d**	$LiOH·H_2O$	CH_3CN	–20	97	12	5
16	**3d**	$LiOH·H_2O$	$CHCl_3$	–30	99	8	84
17	**3d**	$LiOH·H_2O$	$CHCl_3$	–40	99	10	87
18	**3d**	$LiOH·H_2O$	$CHCl_3$	–50	99	20	88
19[d]	**3d**	$LiOH·H_2O$	$CHCl_3$	–40	99	20	88

[a]Reactions were conducted at 0.1 mmol scale in 1 mL of solvent, when $CHCl_3$ was chosen as solvent 10 μL H_2O was added. The 10 μL H_2O is important, in the absence of 10 μL H_2O, the reaction time will increase.

[b]Yield of isolated product.

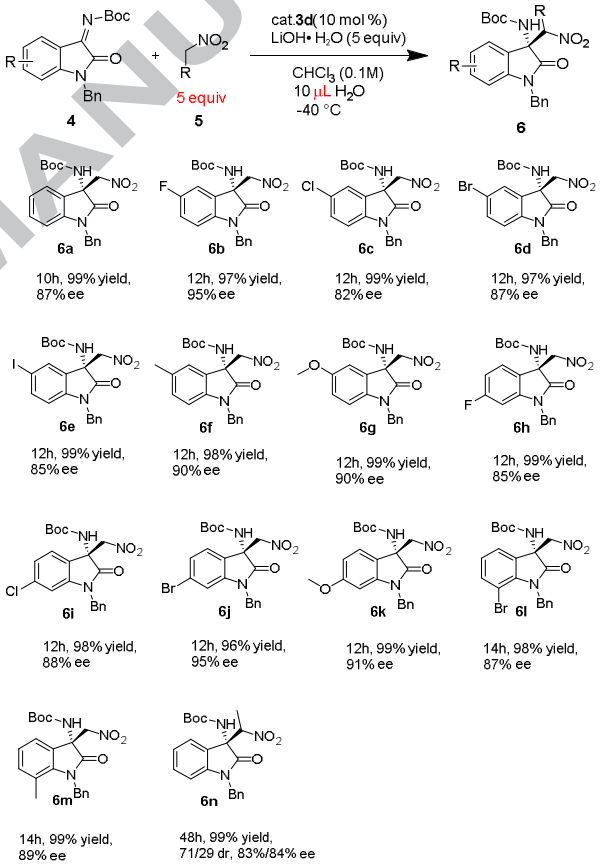
[c]Determined by HPLC using a chiral stationary phase.

[d]the reactions was performed with **3d** (5 mol %).

(entry 11). In the subsequent optimization, several different solvents were examined. All tested solvents, such as THF, toluene, CH_2Cl_2 and CH_3CN are inferior to $CHCl_3$ (entries 12–15).Finally the optimization of reaction temperature was performed, –40°C was chosen as the optimal temperature (entries 16–18). Suprisingly, high enantioselectivity of the product was still achieved although the catalyst loading was reduced to 5% (88% ee, entry 19). Taking into account both reaction rate and ee value, the optimal reaction conditions were as follows: 10% of **3d** used as catalyst and 5 equiv $LiOH·H_2O$ used as base in $CHCl_3$ (10 μL H_2O) at –40°C.

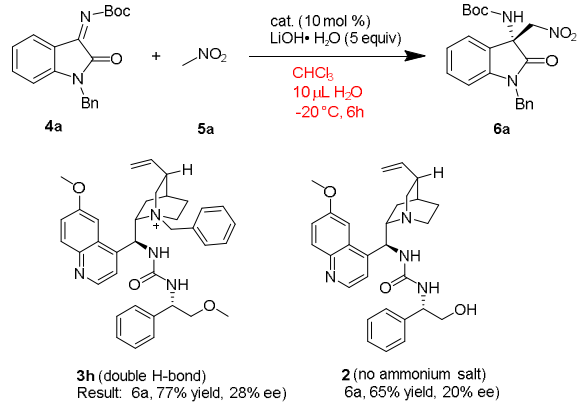
With optimal conditions in hand, the substrate scope of the nitro-Mannich reactions was investigated using nitroalkane and various substituted isatin-derived ketimines as substrates, and corresponding results were shown in Scheme 2. As shown in Scheme 2, all corresponding products were obtained in excellent yields (96–99%) and high enantioselectivities (82–95% ee) (see **6a–6i**). The ketimines containing a halogen atom (F, Cl, Br, I) at the C5-position reacted smoothly with nitromethane and provided the corresponding adducts **6b–6e** in 97–99% yield and 82–95% ee. The ketimines containing electron-donating groups (Me, OMe) at the C5-position showed 98–99% yields and 90% ee (see **6f–6g**). Different groups at the C6- or C7-position also provided the corresponding adducts **6h–6m** in 96–99% yields and 85–95% ee. It is worth noting that nitroethane could also react efficiently with ketimine **4a**, and provided **6n** in 99% yield, 71:29 dr and 83%/84%ee.

Scheme 2. Substrate Scope of the Catalytic Asymmetric nitro-Mannich reaction



Ultimately, two control experiments were carried out to assess the role of the multiple H-bonding donors playing in the reaction and gain insight into the cooperative catalysis of the catalyst as shown in Scheme 3. Using methylated **3h** as the catalyst under the same conditions compared to **3a** (Table 1, entry 4) the

Scheme 3. Control Experiment for Mechanistic Study



enantioselectivity of the product was significantly decreased (77% yield, 28% ee). When we employed catalyst **2** the reaction became sluggish (65% yield), and a nearly racemic product was obtained (20% 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.

Conclusions

In summary, we have developed a novel kind of bifunctional phase-transfer catalysts bearing multiple H-bonding donors, which were derived from quine and amino alcohols, and has been successfully applied to the nitro-Mannich reactions of isatin-derived ketimines with a wide range of substrate scope. All products can be obtained in excellent yields (96-99%) with good enantioselectivities (82-95% ee). Further efforts to apply these catalysts to other useful and challenging asymmetric transformations and explore their catalytic mechanism are underway in our laboratory.

Acknowledgments

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