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Asymmetric phase-transfer catalysts bearing multiple hydrogen-bonding donors: Synthesis and application in nitro-Mannich reaction of isatin-derived N-Boc ketimines

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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).

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 difficult 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

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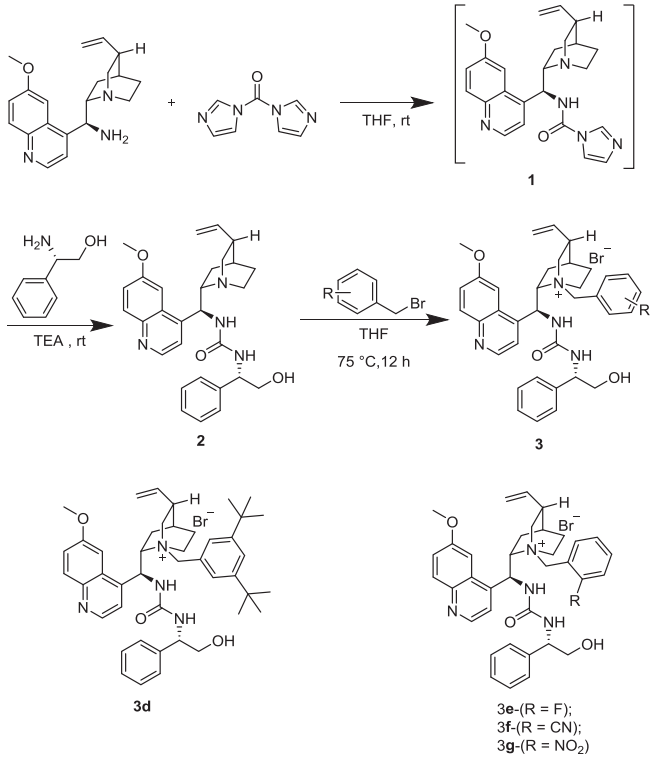
cinchona alkaloids as privilege skeletons, and chiral amino alcohols as hydrogen bonding donors, we can construct a variety of structurally variable chiral quaternary ammonium salts containing multiple hydrogen-bonding donors. In terms of their applicability, these novel quaternary ammonium salts may 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 (Fig. 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.



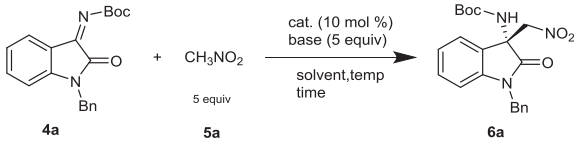
Scheme 1. Synthesis of the Catalysts.

Results and discussion

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, $LiOH{\cdot}H_2O$ as the basic additive respectively, they all gave the desired nitro-Mannich product **6a** in 99% yield

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**	$LiOH{\cdot}H_2O$	$CHCl_3$	−20	99	6	75
5	**3b**	$LiOH{\cdot}H_2O$	$CHCl_3$	−20	99	6	73
6	**3c**	$LiOH{\cdot}H_2O$	$CHCl_3$	−20	99	6	70
7	**3d**	$LiOH{\cdot}H_2O$	$CHCl_3$	−20	99	6	81
8	**3e**	$LiOH{\cdot}H_2O$	$CHCl_3$	−20	99	8	69
9	**3f**	$LiOH{\cdot}H_2O$	$CHCl_3$	−20	99	8	63
10	**3g**	$LiOH{\cdot}H_2O$	$CHCl_3$	−20	99	6	61
11	**3i**	$LiOH{\cdot}H_2O$	$CHCl_3$	−20	99	12	63
12	**3d**	$LiOH{\cdot}H_2O$	THF	−20	99	10	46
13	**3d**	$LiOH{\cdot}H_2O$	Toluene	−20	99	8	78
14	**3d**	$LiOH{\cdot}H_2O$	CH_2Cl_2	−20	99	6	75
15	**3d**	$LiOH{\cdot}H_2O$	CH_3CN	−20	97	12	5
16	**3d**	$LiOH{\cdot}H_2O$	$CHCl_3$	−30	99	8	84
17	**3d**	$LiOH{\cdot}H_2O$	$CHCl_3$	−40	99	10	87
18	**3d**	$LiOH{\cdot}H_2O$	$CHCl_3$	−50	99	20	88
19[d]	**3d**	$LiOH{\cdot}H_2O$	$CHCl_3$	−40	99	20	88

[a] Reactions were conducted at 0.1 mmol scale in 1 mL of solvent, when $CHCl_3$ w as 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%).