

A New Family of Cinchona-Derived Bifunctional Asymmetric Phase-Transfer Catalysts: Application to the Enantio- and Diastereoselective Nitro-Mannich Reaction of Amidosulfones

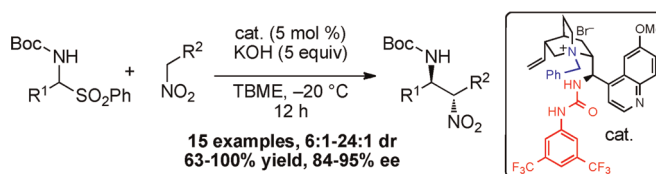
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ABSTRACT



A new family of bifunctional H-bond donor phase-transfer catalysts derived from cinchona alkaloids has been developed and evaluated in the enantio- and diastereoselective nitro-Mannich reaction of in situ generated *N*-Boc-protected imines of aliphatic, aromatic, and heteroaromatic aldehydes. Under optimal conditions, good reactivity and high diastereoselectivities (up to 24:1 dr) and enantioselectivities (up to 95% ee) were obtained using a 9-amino-9-deoxyepiquinidine-derived phase-transfer catalyst possessing a 3,5-bis(trifluoromethyl)phenylurea H-bond donor group at the 9-position.

For an efficient, enantioselective union of enolizable pro-nucleophiles to reactive electrophiles such as imines and

Michael acceptors, two particularly successful classes of catalysts are bifunctional Brønsted base/H-bond donor organocatalysts¹ and asymmetric phase-transfer (APT)

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catalysts² (Figure 1). Both continue to attract significant attention from the research community and show potential for industrial and scale-up applications.³ However, neither class is without their limitations, a number of which we have observed during the course of our own research investigations.⁴ For example, with cinchona-derived bifunctional Brønsted base/H-bond donor catalysis, although high levels of enantiocontrol can be observed with a range of pro-nucleophiles and electrophiles, poor reactivity can often be witnessed.^{1c,5} This is particularly apparent for high pK_a pro-nucleophiles where long reaction times, high reaction temperatures, and/or high catalyst loadings are commonly required. With APT catalysis, higher levels of reactivity can be achieved (for example, relatively nonacidic carbon-centered acids can be employed in conjunction with strong external bases). However, the levels of enantioinduction are highly dependent on the exact structure of the pro-nucleophile and/or electrophile, and small variations can result in substantial loss of enantiofacial selectivity.^{2b}

One design concept that could simultaneously address these issues is to link a (variable) H-bond donor group to an appropriate quaternary ammonium salt via a chiral scaffold (Figure 1).⁶ Potentially, this would combine pro-nucleophile activation (under strong base promotion) with substrate control, preorganization, and activation and thus lead to desirable levels of reactivity and stereoselectivity in a broad range of reactions. Tactically, we envisaged that a short and effective route to such catalysts would be to alkylate the nucleophilic bridgehead nitrogen atom of cinchona-derived bifunctional Brønsted base/H-bond donor catalysts. In turn, these would be readily prepared on scale in one step from 9-amino-9-deoxyepicinchona alkaloids. The late stage introduction of these two key catalyst features, namely the alkyl group of the quaternary ammonium salt and the H-bond donor group, would enable focused libraries of catalysts to be easily accessed, thus facilitating rapid optimization in any reaction of interest.

Herein we describe the synthesis of a new family of APT catalysts bearing ureas, amides, and sulfonamides as H-bond donor groups, and we also present an evaluation of their performance in the nitro-Mannich reaction of amidosulfones.

A library of cinchonium/H-bond donor bifunctional asymmetric phase-transfer catalysts **2–9** was readily formed

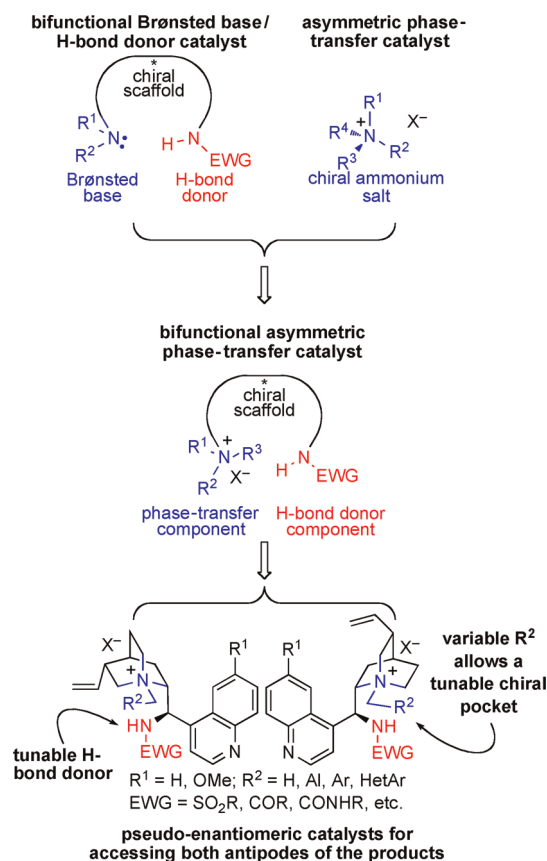


Figure 1. Concept and design of a new family of cinchona-derived bifunctional asymmetric phase-transfer catalysts.

by reaction of 9-amino-9-deoxyepicinchona-derived ureas, amides, and sulfonamides with benzyl bromide, *p*-(trifluoromethyl)benzyl bromide, and (9-anthracenyl)methyl chloride in toluene at 65 °C for 12 h (Scheme 1).

The new family of asymmetric phase-transfer catalysts was tested in the enantioselective nitro-Mannich reaction of in situ generated *N*-Boc-protected imines of aliphatic, aromatic, and heteroaromatic aldehydes, introduced by Herrera and Bernardi,^{6c} and Palomo.^{6d} This reaction is known to proceed well under asymmetric phase-transfer catalysis conditions.⁷ However, we believed that

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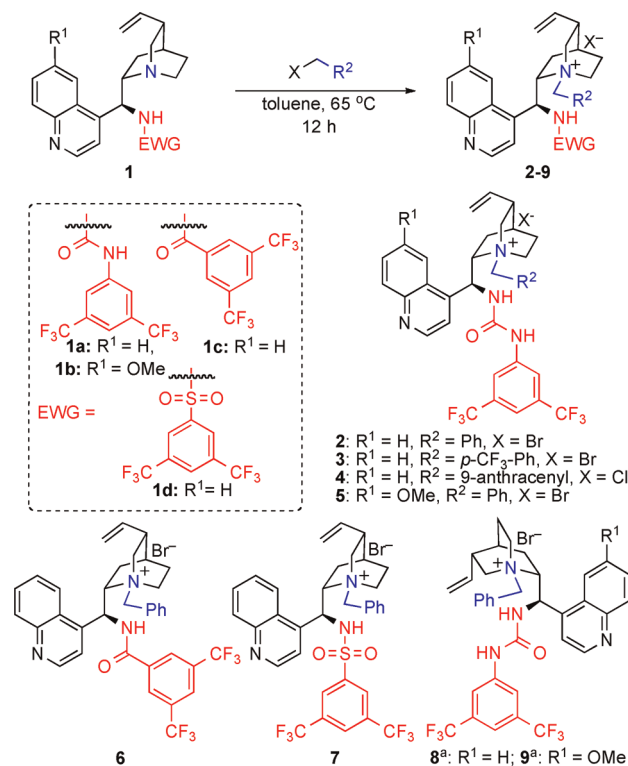
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good stereocontrol could arise from the linked H-bond donor groups, as has been seen previously in Mannich and nitro-Mannich reactions catalyzed by bifunctional cinchona-derived (thio)ureas.⁸

Scheme 1. Synthesis of Catalyst Library



^a Made from pseudo-enantiomeric starting materials.

Amidosulfone **10a** was chosen as a model substrate, and its base-mediated reaction with nitromethane under solid/liquid APT conditions with catalysts **2–9** was assessed for efficiency and stereocontrol (Table 1). Initially, a reactivity study was carried out using catalyst **2** in conjunction with finely ground KOH, K₂CO₃, Cs₂CO₃, and CsOH with toluene as solvent. Very pleasingly at –20 °C, KOH and catalyst **2** gave the desired nitro-Mannich product (*S*)-**12a** in 67% yield and 82% ee (entry 1). Interestingly, none of the other three bases effectively promoted the reaction.

A range of cinchonidine-derived catalysts presenting variations in both the H-bond donor group and *N*-alkyl group were then screened in the reaction with KOH in toluene at –20 °C (Table 1). With catalyst **6**, possessing a 3,5-bis(trifluoromethyl)benzoylamide, good reactivity was observed, but enantiocontrol was diminished (58% ee, entry 5) relative to urea **2**. On the other hand, sulfonamide **7** was incompetent as a phase-transfer catalyst in this reaction (entry 6). Comparing the performance of a series of ureas with variable ammonium salts, *p*-(trifluoromethyl)benzylammonium salt **3** gave similar results to benzyl catalyst **2** (70% yield, 81% ee, entry 7), whereas catalyst **4** possessing an anthracenyl group imparted slightly diminished enantioselectivity and the product

Table 1. Nitro-Mannich Optimization with Substrate **10a**

	X	cat. (%)	base	solvent	concn (M)	temp (°C)	time (h)	yield ^a (%)	ee ^b (%)
1	2	10	KOH	toluene	0.1	–20	12	67	82
2	2	10	K ₂ CO ₃	toluene	0.1	–20	34	nd ^c	
3	2	10	Cs ₂ CO ₃	toluene	0.1	–20	34	nd ^c	
4	2	10	CsOH	toluene	0.1	–20	13	nd ^c	
5	6	10	KOH	toluene	0.1	–20	12	78	58
6	7	10	KOH	toluene	0.1	–20	12	nd ^c	
7	3	10	KOH	toluene	0.1	–20	12	70	81
8	4	10	KOH	toluene	0.1	–20	12	53	71
9	8	10	KOH	toluene	0.1	–20	12	78	85 ^d
10	5	10	KOH	toluene	0.1	–20	12	59	80
11	9	10	KOH	toluene	0.1	–20	12	91	85 ^d
12	9	10	KOH	toluene	0.1	–40	40	71	84 ^d
13	9	10	KOH	toluene	0.05	–20	12	79	85 ^d
14	9	10	KOH	toluene	0.2	–20	12	77	85 ^d
15	9	5	KOH	toluene	0.1	–20	12	72	85 ^d
16	9	5	KOH	EtOAc	0.1	–20	12	78	80 ^d
17	9	5	KOH	CH ₂ Cl ₂	0.1	–20	12	73	84 ^d
18	9	5	KOH	tol/CHCl ₃	0.1	–20	12	35	86 ^d
19	9	5	KOH	TBME	0.1	–20	12	79	89 ^{d,e}
20	5	5	KOH	TBME	0.1	–20	24	66	84

^a Isolated yield. ^b Determined by chiral stationary phase HPLC. ^c Reaction did not proceed or proceeded very slowly to **12a**. ^d Enantiomeric (*R*)-**12a** was obtained. ^e The *R* configuration of (*R*)-**12a** was established through comparison of its specific rotation with literature data; see the Supporting Information.

was obtained in 53% yield (entry 8). From the above results, it was concluded, at this stage, that for maximum selectivity the combination of a urea at the 9-position of the 9-amino-9-deoxyepicinchonidine scaffold and an *N*-benzyl group on the bridgehead nitrogen were required. Importantly, a simple cross-check using commercial *N*-benzylcinchonidinium bromide as the catalyst, under identical reaction conditions, afforded the enantiomeric product in substantially reduced yield and with poor stereocontrol [(*R*)-**12a** was obtained in 34% ee and 29% yield]. This result confirmed that the urea functionality was playing a key role in controlling the stereochemical course of the reaction. The related cinchonine-, quinine- and quinidine-derived catalysts **8**, **5**, and **9**, respectively, were then subjected to the reaction conditions and, pleasingly, gave rise to good reactivity and similar levels of control across the series (entries 9–11). Quinidine derived catalyst **9** narrowly out-performed the others and was therefore selected as the catalyst of choice for the remainder of the optimization studies. Lowering the temperature of the reaction to –40 °C had no beneficial effect on enantiocontrol but did significantly decrease the reaction rate (entry 12). Neither concentrating nor diluting the reaction mixture, nor reducing the catalyst loading to 5 mol %, deleteriously affected

the enantioselectivity (entries 13–15). Finally, a solvent screen (entries 15–19) revealed TBME as the solvent of choice and the optimal conditions employed KOH (5 equiv) as base and 5 mol % catalyst **9** at –20 °C for 12 h; (*R*)-**12a** was obtained in 79% yield and 89% ee (entry 19). Under the fully optimized conditions but using pseudo-enantiomeric catalyst **5**, the enantiomeric product (*S*)-**12a** was obtained in 66% yield and 84% ee (entry 20).

Table 2. Scope of the Nitro-Mannich Reaction

	10	R ¹	11	R ²	12	yield ^a (%)	dr <i>anti</i> : <i>syn</i> ^b	ee _{anti} ^c (%)
1	b	<i>p</i> -Me-Ph	a	H	b	64		91
2	c	<i>p</i> -OMe-Ph	a	H	c	84		90
3	d	<i>p</i> -F-Ph	a	H	d	65		90
4	e	<i>p</i> -CF ₃ -Ph	a	H	e	65		91
5	f	2-naphthyl	a	H	f	87		92
6	g	3-pyridyl	a	H	g	73		92
7	a	Ph	b	Me	h	83	24:1	94
8	a	Ph	c	Et	i	94	17:1	92
9	a	Ph	d	CH ₂ CH=CH ₂	j	64	6:1	95
10	h^d	<i>tert</i> -butyl	a	H	k	63		90
11	i	cyclohexyl	a	H	l	100		84
12	i	cyclohexyl	b	Me	m	75	9:1	95
13	i	cyclohexyl	d	CH ₂ CH=CH ₂	n	82	11:1	93
14	j	<i>iso</i> -butyl	b	Me	o	100	13:1 ^e	90

^a Isolated yield. ^b Determined by ¹H NMR or chiral stationary phase HPLC analysis. ^c Determined by chiral stationary phase HPLC. ^d Toluenesulfinic acid-derived amidosulfone was used. ^e See the Supporting Information for proof of absolute and relative stereochemistry.

With optimal conditions in hand, the scope of the reaction with respect to the amidosulfone was surveyed (Table 2). A variety of amidosulfones derived from aromatic aldehydes proved effective, with substitution in the para position being well-tolerated with excellent enantioselectivities observed with both electron-rich (90–91% ee, entries 1 and 2) and electron-poor (90–91% ee, entries 3 and 4) aromatics. Polycyclic aromatic and heteroaromatic amidosulfones also proved effective, with 2-naphthyl and 3-pyridinyl amidosulfones both giving their respective products in 92% ee (entries 5 and 6). Next, we set out to assess the generality of the reaction with other nitroalkane pro-nucleophiles. Pleasingly, the reaction of phenyl amidosulfone **10a** with nitroethane proceeded smoothly to

give product **12h** in 83% yield with excellent diastereoselectivity (24:1 *anti:syn*) and enhanced enantioselectivity (94% ee, entry 7) relative to the analogous experiment with nitromethane. This same enhancement was observed with other substituted nitroalkanes such as nitropropane (92% ee, 17:1 dr, entry 8) and 4-nitrobut-1-ene (95% ee, 6:1 dr, entry 9).

Finally, we investigated the performance of amidosulfones derived from aliphatic aldehydes. Good results were obtained with sterically hindered amidosulfones; *tert*-butyl amidosulfone **10h** yielded the expected product with excellent enantiocontrol (90% ee, entry 10). Less hindered aliphatic amidosulfones such as cyclohexyl amidosulfone **10i** led to a slight decrease in enantioinduction (84% ee), but as with aromatic amidosulfones, an enhancement in enantiocontrol was also observed when larger nitroalkanes were used. The reactions of **10i** with nitroethane (95% ee, entry 12) and 4-nitrobut-1-ene (93% ee, entry 13) proceeded with excellent enantioselectivity and good diastereoselectivity.

In summary, we have developed a new family of cinchonium/H-bond donor bifunctional asymmetric phase-transfer catalysts. Their straightforward two-stage synthesis from 9-amino-9-deoxyepicinchona alkaloids readily allows variation of both the alkyl group of the quaternary ammonium salt and the H-bond donor group and thus rapid access to focused libraries of novel catalysts. These catalysts combine the good reactivity profile of previously reported asymmetric phase-transfer catalysts with the tunable stereocontrol of bifunctional Brønsted base/H-bond donor catalysts. We have also successfully demonstrated the application of this new family of catalysts to the enantio- and diastereoselective nitro-Mannich reaction of in situ generated *N*-Boc-protected imines of aliphatic, aromatic, and heteroaromatic aldehydes. Other applications of catalysts **2–9**, and their analogues, are under active investigation in our laboratories and will be reported in due course.

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Supporting Information Available. Experimental procedures and spectral data for compounds **1c**, **2–9**, **10h**, and **12a–o**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.