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

Kayli M. Johnson,[†] Matt S. Rattley,[†] Filippo Sladojevich, David M. Barber, Marta G. Nuñez, Anna M. Goldys, and Darren J. Dixon*

Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford OX1 3TA, U.K.

darren.dixon@chem.ox.ac.uk

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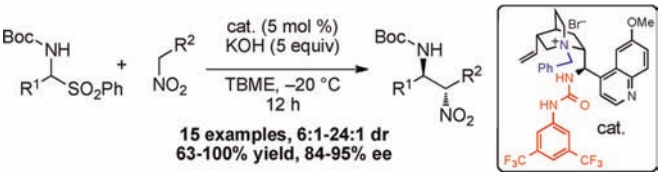
ABSTRACT



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 pronucleophiles to reactive electrophiles such as imines and Michael acceptors, two particularly successful classes of catalysts are bifunctional Brønsted base/H-bond donor organocatalysts[1] and asymmetric phase-transfer (APT)

[†] These authors contributed equally to this work.

(1) For selected recent reviews, see: (a) Marcelli, T.; Hiemstra, H. *Synthesis* **2010**, 1229–1279. (b) Takemoto, Y. *Chem. Pharm. Bull.* **2010**, *58*, 593–601. (c) Palomo, C.; Oiarbide, M.; López, R. *Chem. Soc. Rev.* **2009**, *38*, 632–653. (d) Connon, S. J. *Synlett* **2009**, 354–376. (e) Connon, S. J. *Chem. Commun.* **2008**, 2499–2510. (f) Yu, X.; Wang, W. *Chem. Asian J.* **2008**, *3*, 516–532. (g) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713–5743. (h) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520–1543. (i) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299–4306.

(2) For recent reviews, see: (a) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2007**, *107*, 5656–5682. (b) Ooi, T.; Maruoka, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 4222–4226.

(3) For a recent example with a bifunctional Brønsted base/H-bond donor organocatalyst, see: (a) Huang, X.; Broadbent, S.; Dvorak, C.; Zhao, S. H. *Org. Process Res. Dev.* **2010**, *14*, 612–616. For a recent example with a phase-transfer catalyst, see: (b) Mazzotta, S.; Gramigna, L.; Bernardi, L.; Ricci, A. *Org. Process Res. Dev.* **2010**, *14*, 687–691. For recent reviews of asymmetric phase-transfer catalysis in organic process research and development, see: (c) Howell, G. P. *Org. Process Res. Dev.* **2012**, DOI: 10.1021/op200381w. (d) Ikunaka, M. *Org. Process Res. Dev.* **2008**, *12*, 698–709. (e) Maruoka, K. *Org. Process Res. Dev.* **2008**, *12*, 679–697.

(4) (a) Greenaway, K.; Dambruoso, P.; Ferrali, A.; Hazelwood, A. J.; Sladojevich, F.; Dixon, D. J. *Synthesis* **2011**, 1880–1886. (b) Jakubec, P.; Cockfield, D. M.; Hynes, P. S.; Cleator, E.; Dixon, D. J. *Tetrahedron: Asymmetry* **2011**, *22*, 1147–1155. (c) Kyle, A. F.; Jakubec, P.; Cockfield, D. M.; Cleator, E.; Skidmore, J.; Dixon, D. J. *Chem. Commun.* **2011**, *47*, 10037–10039. (d) Sladojevich, F.; Trabocchi, A.; Guarna, A.; Dixon, D. J. *J. Am. Chem. Soc.* **2011**, *133*, 1710–1713. (e) Jakubec, P.; Kyle, A. F.; Calleja, J.; Dixon, D. J. *Tetrahedron Lett.* **2011**, *52*, 6094–6097. (f) Wang, Y.; Yu, D. F.; Liu, Y. Z.; Wei, H.; Luo, Y. C.; Dixon, D. J.; Xu, P. F. *Chem.—Eur. J.* **2010**, *16*, 3922–3925. (g) Moss, T. A.; Alonso, B.; Fenwick, D. R.; Dixon, D. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 568–571. (h) Wang, Y.; Han, R. G.; Zhao, Y. L.; Yang, S.; Xu, P. F.; Dixon, D. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 9834–9838. (i) Yang, T.; Ferrali, A.; Sladojevich, F.; Campbell, L.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 9140–9141. (j) Jakubec, P.; Cockfield, D. M.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 16632–16633. (k) Hynes, P. S.; Stupple, P. A.; Dixon, D. J. *Org. Lett.* **2008**, *10*, 1389–1391. (l) Moss, T. A.; Fenwick, D. R.; Dixon, D. J. *J. Am. Chem. Soc.* **2008**, *130*, 10076–10077. (m) Rigby, C. L.; Dixon, D. J. *Chem. Commun.* **2008**, 3798–3800. (n) Hynes, P. S.; Stranges, D.; Stupple, P. A.; Guarna, A.; Dixon, D. J. *Org. Lett.* **2007**, *9*, 2107–210. (o) Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481–4483.

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catalysts[2] (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

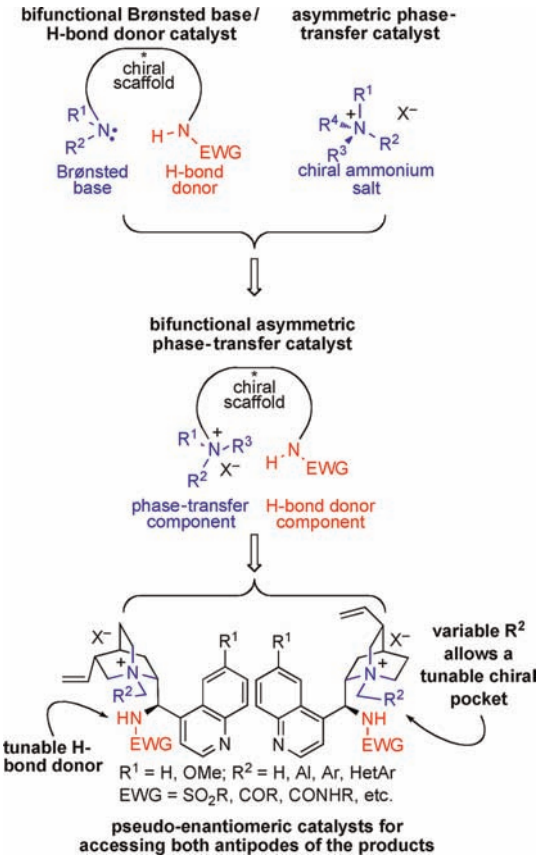


Figure 1. Concept and design of a new family of cinchona-derived bifunctional asymmetric phase-transfer catalysts.

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,[6e] and Palomo.[6d] This reaction is known to proceed well under asymmetric phase-transfer catalysis conditions.[7] However, we believed that

(5) Oh, S. H.; Rho, H. S.; Lee, J. W.; Lee, J. E.; Youk, S. H.; Chin, J.; Song, C. E. *Angew. Chem. Int. Ed.* **2008**, *47*, 7872–7875.

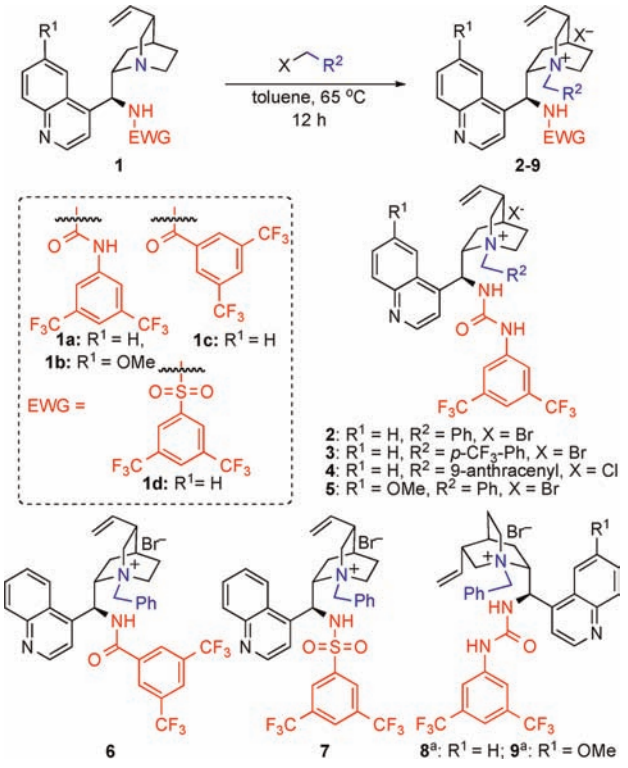
(6) For selected recent examples, see: (a) Wei, Y.; He, W.; Liu, Y.; Liu, P.; Zhang, S. *Org. Lett.* **2012**, *14*, 704–707. (b) Fiandra, C. D.; Piras, L.; Fini, F.; Disetti, P.; Moccia, M.; Adamo, M. F. A. *Chem. Commun.* **2012**, *48*, 3863–3865. (c) Maciver, E. E.; Knipe, P. C.; Cridland, A. P.; Thompson, A. L.; Smith, M. D. *Chem. Sci.* **2012**, *3*, 537–540. For representative examples, see: (d) Ohmatsu, K.; Kiyokawa, M.; Ooi, T. *J. Am. Chem. Soc.* **2011**, *133*, 1307–1309. (e) Gomez-Bengoa, E.; Linden, A.; López, R.; Múgica-Mendiola, I.; Oiarbide, M.; Palomo, C. *J. Am. Chem. Soc.* **2008**, *130*, 7955–7966. (f) Berkessel, A.; Guixá, M.; Schmidt, F.; Neudörfl, J. M.; Lex, J. *Chem.—Eur. J.* **2007**, *13*, 4483–4498. (g) Sohtome, Y.; Takemura, N.; Iguchi, T.; Hashimoto, Y.; Nagasawa, K. *Synlett* **2006**, 144–146. (h) Ooi, T.; Ohara, D.; Fukumoto, K.; Maruoka, K. *Org. Lett.* **2005**, *7*, 3195–3197. (i) Ooi, T.; Ohara, D.; Tamura, M.; Maruoka, K. *J. Am. Chem. Soc.* **2004**, *126*, 6844–6845. (j) Manabe, K. *Tetrahedron* **1998**, *54*, 14465–14476.

(7) (a) Kumaraswamy, G.; Pitchaiah, A. *Tetrahedron* **2011**, *67*, 2536–2541. (b) Błaszczyk, R.; Gajda, A.; Zawadzki, S.; Czubacka, E.; Gajda, T. *Tetrahedron* **2010**, *66*, 9840–9848. (c) Jiang, X.; Zhang, Y.; Wu, L.; Zhang, G.; Liu, X.; Zhang, H.; Fu, D.; Wang, R. *Adv. Synth. Catal.* **2009**, *351*, 2096–2100. (d) Palomo, C.; Oiarbide, M.; Laso, A.; López, R. *J. Am. Chem. Soc.* **2005**, *127*, 17622–17623. (e) Fini, F.; Sgarzani, V.; Pettersen, D.; Herrera, R. P.; Bernardi, L.; Ricci, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 7975–7978.

(8) (a) Bai, S.; Liang, X.; Song, B.; Bhadury, P. S.; Hu, D.; Yang, S. *Tetrahedron: Asymmetry* **2011**, *22*, 518–523. (b) Zhang, H.; Syed, S.; Barbas, C. F., III. *Org. Lett.* **2010**, *12*, 708–711. (c) Verkade, J. M. M.; van Hemert, L. J. C.; Quaedflieg, P. J. L. M.; Rutjes, F. P. J. T. *Chem. Soc. Rev.* **2008**, *37*, 29–41. (d) Song, J.; Shih, H. W.; Deng, L. *Org. Lett.* **2007**, *9*, 603–606. (e) Tillman, A. L.; Ye, J.; Dixon, D. J. *Chem. Commun.* **2006**, 1191–1193. (f) Song, J.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 6048–6049. (g) Bode, C. M.; Ting, A.; Schaus, S. E. *Tetrahedron* **2006**, *62*, 11499–11505. (h) Bernardi, L.; Fini, F.; Herrera, R. P.; Ricci, A.; Sgarzani, V. *Tetrahedron* **2006**, *62*, 375–380.

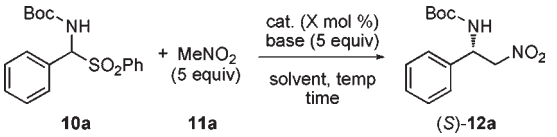
good stereocontrol could arise from the linked H-bond donor groups, as has been seen previously in Mannich and nitro-Mannich reactions catalyzed by bifunctional cinchona-derived (thio)ureas.[8]

Scheme 1. Synthesis of Catalyst Library



[a] Made from pseudo-enantiomeric starting materials.

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



	cat.	X (%)	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_2CO_3	toluene	0.1	−20	34	nd[c]	
3	**2**	10	Cs_2CO_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_2Cl_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

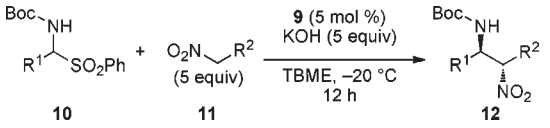
[a] Isolated yield. [b] Determined by chiral stationary phase HPLC. [c] Reaction did not proceed or proceeded very slowly to **12a**. [d] Enantiomeric (*R*)-**12a** was obtained. [e] The *R* configuration of (*R*)-**12a** was established through comparison of its specific rotation with literature data;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

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, K_2CO_3, Cs_2CO_3, 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 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 commerical *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 *anti*:*syn*[b]	ee_{anti}[c] (%)
1	**b**	*p*-Me-Ph	**a**	H	**b**	64		91
2	**c**	*p*-OMe-Ph	**a**	H	**c**	84		90
3	**d**	*p*-F-Ph	**a**	H	**d**	65		90
4	**e**	*p*-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**	$CH_2CH{=}CH_2$	**j**	64	6:1	95
10	**h**[d]	*tert*-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**	$CH_2CH{=}CH_2$	**n**	82	11:1	93
14	**j**	*iso*-butyl	**b**	Me	**o**	100	13:1[e]	90

[a] Isolated yield. [b] Determined by ^{1}H 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.