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Catalytic Enantioselective Sulfinyl Transfer Using Cinchona Alkaloid Catalysts

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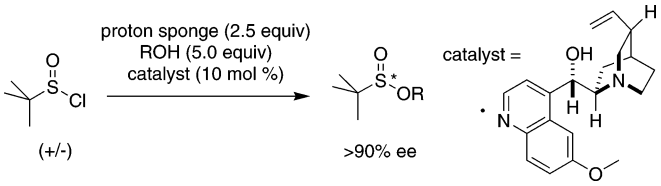
ABSTRACT



Practical reaction conditions for the catalytic enantioselective synthesis of sulfinate esters are reported. Commercially available cinchona alkaloids were found to be superior catalysts for the sulfinyl transfer reaction of *tert*-butanesulfinyl chloride and a variety of benzyl alcohols. Sulfinyl transfer with 2,4,6-trichlorobenzyl alcohol and 10 mol % of the commercially available, inexpensive catalyst quinidine provided the pure sulfinate ester product in 92% isolated yield and with 90% ee.

Chiral sulfinate esters are versatile intermediates from which diverse chiral sulfur compounds, including sulfoxides and sulfinamides, can rapidly be prepared.[1] While many diastereoselective methods exist for the formation of sulfinate esters,[2a−d] effective catalytic enantioselective methods are still lacking.[3a−d] Recently, our group reported the first example of a catalytic enantioselective synthesis of sulfinate esters through the dynamic resolution of racemic *tert*-butanesulfinyl chloride.[4] Chiral acyl transfer catalysts, in particular, an *N*-methylimidazole-containing octapeptide, successfully catalyzed sulfinyl transfer. However, this catalyst is prepared through a multistep sequence, thus decreasing the utility of this method. Very recently, dynamic resolution of arenesulfinyl chlorides was reported for the preparation of sulfinate esters with good enantioselectivities.[5] However, this method requires stoichiometric amounts of the chiral sulfinyl transfer reagent. We report here significant improvements to our previously reported catalytic sulfinyl transfer process, which features the use of the commercially available, inexpensive catalyst quinidine to afford *tert*-butanesulfinate esters with excellent enantioselectivities, providing an extremely facile method for the generation of chiral sulfur compounds.

Several commercially available chiral tertiary amines (Figure 1) were chosen for the initial catalyst screen due to the efficiency with which triethylamine and diisopropylethylamine catalyze sulfinyl transfer.[4] Benzyl alcohol was used as the sulfinyl acceptor, with Proton Sponge (1,8-bis(dimethylamino)naphthalene) serving as the amine base to consume the liberated HCl (eq 1). Importantly, proton sponge itself does not catalyze a background sulfinyl transfer reaction due to its nonnucleophilic nature.[6]

Utilizing 10 mol % of (−)-sparteine (**3**) as a catalyst provided both poor conversion and enantioselectivity after

(1) For leading references, see: Fernández, I.; Khiar, N. *Chem. Rev.* **2003**, *103*, 3651.

(2) (a) Solladié, G.; Hutt, J.; Girardin, A. *Synthesis* **1987**, 173. (b) Khiar, N.; Araújo, C. S.; Alcudia, F.; Fernández, I. *J. Org. Chem.* **2002**, *67*, 345. (c) Rebiere, F.; Samuel, O.; Ricard, L.; Kagan, H. B. *J. Org. Chem.* **1991**, *56*, 5991. (d) Han, Z.; Krishnamurthy, D.; Grover, P.; Fang, Q. K.; Pflum, D. A.; Senanayake, C. H. *Tetrahedron Lett.* **2003**, *44*, 4195.

(3) (a) Nemecek, C.; Dunach, E.; Kagan, H. B. *Nouv. J. Chim.* **1986**, *10*, 761. (b) Mikolajczyk, M.; Drabowicz, J. *Chem. Commun.* **1974**, 547. (c) Drabowicz, J.; Legedz, S.; Mikolajczyk, M. *Tetrahedron* **1988**, *44*, 5243. (d) Drabowicz, J.; Pacholczyk, M. *Phosphorus Sulfur* **1987**, *29*, 257.

(4) Evans, J. W.; Fierman, M. B.; Miller, S. J.; Ellman, J. A. *J. Am. Chem. Soc.* **2004**, *126*, 8134.

(5) Shibata, N.; Matsunaga, M.; Nakagawa, M.; Fukuzumi, T.; Nakamura, S.; Toru, T. *J. Am. Chem. Soc.* **2005**, *127*, 1374.

(6) Fujiwara, E.; Omoto, K.; Fujimoto, H. *J. Org. Chem.* **1997**, *62*, 7234.

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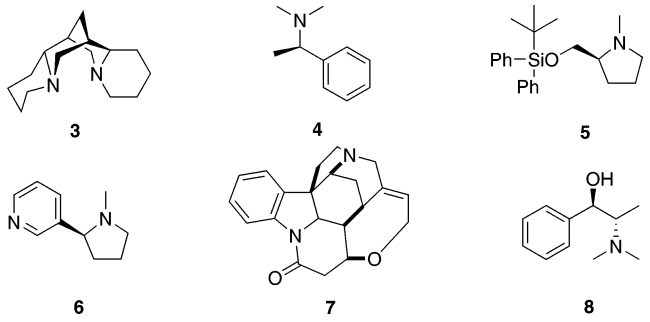
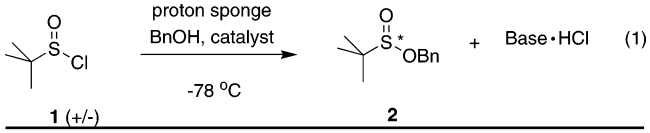


Figure 1. Tertiary amine catalysts.

40 h, and increasing the catalyst loading to 40 mol % afforded only slightly higher conversion (Table 1, entry 1). Use of 10 mol % of (*R*)-(+)-*N*,*N*-dimethyl-1-phenylethylamine (**4**) afforded encouraging results with moderate conversion and modest enantioselectivity being observed (entry 2). Increasing the catalyst loading in this case resulted in no significant change in reaction conversion. The TBDPS-protected derivative **5** resulted in moderate conversion, but with extremely poor selectivity (entry 3). Use of the aryl-substituted pyrrolidine, nicotine (**6**), afforded both poor conversion and selectivity (entry 4). Strychnine (**7**) proved to be an extremely active catalyst in both THF and toluene, providing 99% and 83% conversion, respectively; however, it provided poor selectivity (entry 5). The best results of the initial catalyst screen were obtained with the amino alcohol (1*R*,2*S*)-(−)-*N*-methylephedrine (**8**), which resulted in good conversion and a 38% ee in THF (entry 6).

Table 1. Initial Catalyst Screen (eq 1)



entry	catalyst (mol %)	solvent	time (h)	yield of **2**[a] (%)	ee of **2**[b] (%)
1	**3** (10)	THF	40	12	6
	(40)	THF	40	36	10
2	**4** (10)	THF	40	59	26
	(40)	THF	40	54	24
3	**5** (10)	THF	20	61	6
	(10)	toluene	20	58	2
4	**6** (10)	THF	20	6	6
	(10)	toluene	20	1	0
5	**7** (10)	THF	20	99	6
	(10)	toluene	20	83	15
6	**8** (10)	THF	20	42	38
	(10)	toluene	20	81	26

[a] Yields determined by ^{1}H NMR with comparison to 2,6-dimethoxytoluene as an internal standard. [b] Enantiomeric excess determined by chiral HPLC.

Due to the catalytic activity and selectivity provided by **8**, the cinchona alkaloids, which also possess an α-amino alcohol scaffold, were chosen as the next class of tertiary amines to be screened (Figure 2). Moreover, these alkaloids

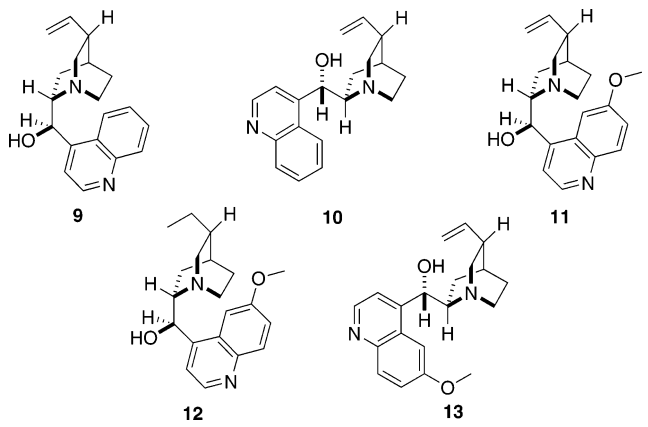


Figure 2. Cinchona alkaloid catalysts.

have served as effective enantioselective catalysts for a range of transformations.[7a−c]

Use of 10 mol % of cinchonidine (**9**) provided promising results (Table 2, entry 1), as sulfinate ester **2** was formed in

Table 2. Cinchona Alkaloid Catalyst Screen (eq 1)

entry	catalyst[a]	solvent	yield of **2**[b] (%)	ee of **2**[c] (%)
1	**9**	THF	98	59
		toluene	70	54
2	**10**	THF	93	70
		toluene	99	78
3	**11**	THF	15	56
		toluene	65	72
4	**12**	THF	12	50
		toluene	44	56
5	**13**	THF	28	78
		toluene	>99	87

[a] 10 mol % of catalyst was used, and all reactions were quenched after 20 h at −78 °C. [b] Yields determined by ^{1}H NMR with comparison to 2,6-dimethoxytoluene as an internal standard. [c] Enantiomeric excess determined by chiral HPLC.

good to excellent yields in both toluene and THF with moderate selectivities. Both the selectivity and yield increased with use of cinchonine (**10**) (70% ee, 93% yield in THF and 78% ee, 99% yield in toluene) (entry 2). Quinine (**11**) and hydroquinine (**12**) resulted in reduced yields and selectivities. Of the two, quinine performed better, giving product in 65% yield and 72% ee in toluene (entries 3 and 4). Excitingly, quinidine (**13**) afforded the best results providing the product in quantitative yield and in 87% ee in toluene (entry 5).

(7) (a) For leading references, see: Tian, S.-K.; Chen, Y.; Hang, J.; Tang, L.; McDaid, P.; Deng, L. *Acc. Chem. Res.* **2004**, *37*, 621. (b) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Ferraris, D.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 6626. (c) Zhu, C.; Shen, X.; Nelson, S. G. *J. Am. Chem. Soc.* **2004**, *126*, 5352.

The ether and ester derivatives of quinidine **14**−**17** along with the dimer of the cinchona alkaloid **18**, each of which has proven effective in enantioselective transformations,[7a−c] were also screened (Figure 3). Aryl ether **15** (Table 3, entry

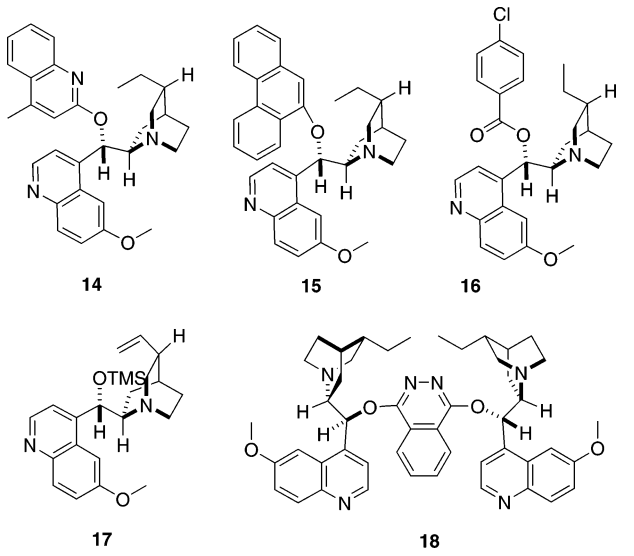


Figure 3. Cinchona alkaloid derivatives.

2) provided greater conversion and enantioselectivity than **14** (entry 1); however, both are less active and much less selective than quinidine (**13**). Ester **16** contains an electron-withdrawing group on the oxygen of the amino alcohol moiety, while silyl ether **17**[8] incorporates the bulky TMS group (entries 3 and 4). Both of these catalysts afford poor yield and selectivity, suggesting that both electronic and steric effects play an important role in sulfinyl transfer catalysis. Dimer **18** is also a poor catalyst for sulfinyl transfer, giving conversions that did not exceed 50% and selectivities under 57% ee (entry 5). As a group, the hydroxy-substituted cinchona alkaloids provided selectivity that was significantly worse than the cinchona alkaloids, demonstrating that the free alcohol plays a critical role in enantioselection.[9]

Table 3. Screen of Cinchona Derivatives as Catalysts (eq 1)

entry	catalyst[a]	solvent	yield of **2**[b] (%)	ee of **2**[c] (%)
1	**14**	THF	43	22
		toluene	32	8
2	**15**	THF	82	27
		toluene	72	17
3	**16**	THF	34	32
		toluene	24	8
4	**17**	THF	<5	28
		toluene	<5	8
5	**18**	THF	40	57
		toluene	50	53

[a] 10 mol % of catalyst was used, and all reactions were quenched after 20 h at −78 °C. [b] Yields determined by ^{1}H NMR with comparison to 2,6-dimethoxytoluene as an internal standard. [c] Enantiomeric excess determined by chiral HPLC.

Using the optimized catalyst **13**, a number of alcohol nucleophiles were evaluated in THF and toluene (Table 4). Generally, reactions performed in THF resulted in higher yields, while reactions in toluene gave higher enantioselectivities. Electron-rich and electron-poor benzyl alcohols provided poor conversion (entries 1−4), but the electron-deficient *p*-chlorobenzyl alcohol in toluene resulted in increased % ee. In contrast, lower selectivities were observed for 2-naphthalene methanol (entries 5 and 6) (73% ee in THF and 64% ee in toluene), which we had previously employed with Miller's peptide catalyst.[4] Interestingly, 1-naphthalene methanol in toluene provided comparatively higher selectivity (84% ee) (entry 8), suggesting that substitution at the ortho position of the aromatic ring may be important for providing selectivity. To test this hypothesis, 2,6-dichlorobenzyl alcohol and 2,6-dimethylbenzyl[10] alcohol were evaluated. At −78 °C, both bis-ortho-substituted benzyl alcohol derivatives provided excellent selectivities, albiet in poor yields (entries 9−10 and 16−17). Increasing the temperature to −50 °C increased the yield of the sulfinyl transfer reaction of these alcohols; however, the selectivity suffered (entries 11−12 and 18−19). A short solvent screen was carried out with 2,6-dichlorobenzyl alcohol. Although yields and enantioselectivites did not exceed that of the reaction performed in THF, butyl acetate did give a promising 51% yield and 83% ee (entry 15). 2,4,6-Trichlorobenzyl alcohol was also examined in both THF and toluene, and the enantiopurity of the resultant sulfinate ester **19g** was improved to 95% ee in toluene (entry 21). Increasing the temperature to −40 °C resulted in complete conversion to sulfinate ester **19g** without dramatically affecting the selectivity. Indeed, pure product could be isolated in 92% yield and 90% ee upon performing the reaction under these conditions followed by straightforward filtration through alumina (entry 25). Notably, use of 10 mol % of quinine under these optimized reaction conditions afforded **19g** in 82% yield and 82% ee with the opposite sense of induction (entry 26).

Sulfinate ester **19g** (90% ee), obtained from use of 10 mol % quinidine as a catalyst, was recrystallized two times from heptane to provide enantiomerically pure material in 72% yield. The absolute sense of induction was determined by addition of phenyllithium to enantiomerically pure **19g** with inversion of configuration[11a,b] to provide (*R*)-*tert*-butyl phenyl sulfoxide in 99% yield.[12] This addition reaction also clearly demonstrates the utility of sulfinate ester **19g** as a versatile

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(9) Under the reaction conditions, minimal sulfinylation of the secondary alcohol occurs.

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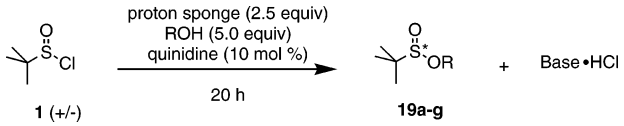
(12) Cogan, D. A.; Liu, G.; Kim, K.; Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 8011.

Table 4. Alcohol Screen Using 10 mol % of Quinidine



entry	alcohol	solvent	T (°C)	sulfinate ester	yield[a] (%)	ee[b] (%)
1	*p*-methoxybenzyl	THF	−78	**19a**	23	86
2		toluene	−78	**19a**	0	0
3	*p*-chlorobenzyl	THF	−78	**19b**	41	76
4		toluene	−78	**19b**	15	90
5	2-naphthalene methanol	THF	−78	**19c**	17	73
6		toluene	−78	**19c**	<5	64
7	1-naphthalene methanol	THF	−78	**19d**	25	70
8		toluene	−78	**19d**	36	84
9	2,6-dichlorobenzyl	THF	−78	**19e**	40[c]	91
10		toluene	−78	**19e**	17	94
11		THF	−50	**19e**	>99 (86)[c,d]	85
12		toluene	−50	**19e**	24	83
13		CH_3CN	−50	**19e**	16	23
14		$CHCl_3$	−50	**19e**	20	23
15		butyl acetate	−50	**19e**	51	83
16	2,6-dimethylbenzyl	THF	−78	**19f**	18	88
17		toluene	−78	**19f**	12	97
18		THF	−50	**19f**	50	80
19		toluene	−50	**19f**	56	82
20	2,4,6-trichlorobenzyl	THF	−78	**19g**	26	92
21		toluene	−78	**19g**	22	95
22		THF	−50	**19g**	60	90
23		toluene	−50	**19g**	41	91
24		THF	0	**19g**	94	70
25		THF	−40	**19g**	>99 (92)[d]	90
26		THF[e]	−40	**19g**[e]	82	82[f]

[a] Yields determined by ^{1}H NMR with comparison to 2,6-dimethoxytoluene as an internal standard. [b] Enantiomeric excess determined by chiral HPLC. [c] Reaction run at 0.4 M. [d] Isolated yield of pure material. [e] Quinine (10 mol %) used as catalyst. [f] Product obtained with opposite sense of induction.

intermediate in the production of synthetically useful chiral sulfur-containing building blocks.

In conclusion, we have developed a catalytic enantioselective sulfinyl transfer reaction that utilizes a commercially available, inexpensive catalyst. Quinidine (**13**) at 10 mol % catalyst loading affords sulfinate esters with excellent selectivities. A number of benzyl alcohol derivatives are tolerated, with higher selectivities obtained for alcohols that have ortho substitution. Indeed, the 2,4,6-trichlorobenzyl sulfinate ester **19g** can be produced in a 92% isolated yield with 90% ee. This procedure greatly improves the utility and practicality of the sulfinyl transfer process and makes possible the facile production of *tert*-butyl sulfoxides.

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Supporting Information Available: Full experimental details and characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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