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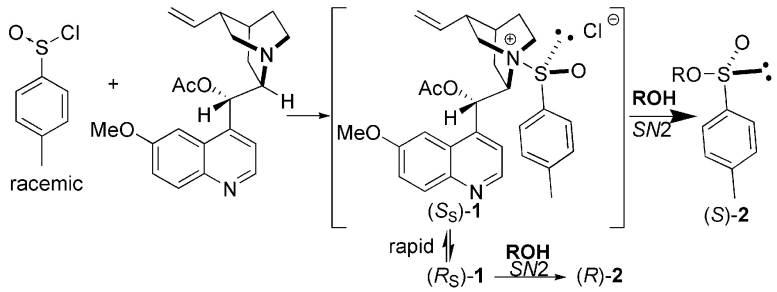
J. Am. Chem. Soc., **2005**, 127 (5), 1374-1375• DOI: 10.1021/ja0430189 • Publication Date (Web): 15 January 2005



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Published on Web 01/15/2005

Cinchona Alkaloid/Sulfinyl Chloride Combinations: Enantioselective Sulfinylating Agents of Alcohols

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Chiral sulfinates play an important role in organic chemistry as key precursors in many chiral sulfoxides that are useful building blocks for biologically active molecules and natural products.[1] Despite the development of many synthetic strategies to access chiral sulfinates in the last two decades,[2] the most industrially viable procedure is still the one based on the resolution of diastereomeric sulfinates prepared from sulfinyl halides and chiral alcohols such as menthol and diacetone-D-glucose.[2a−c] On the other hand, the enantioselective sulfinylation reaction of achiral alcohols with racemic sulfinyl chlorides is particularly attractive.[3] The initial report by Mikolajczyk and Drabowicz for the enantioselective sulfinylation reaction of alcohols with *p*-toluenesulfinyl chloride using chiral amines revealed limitations in enantioselectivities of the sulfinates.[3a−c] Very recently, Ellman and co-workers have reported the first catalytic enantioselective preparation of 1,1-dimethylethanesulfinate with up to 81% ee using chiral peptides,[3d] although its synthetic utility is somewhat limited by the lack of a route to chiral arenesulfinates which are the most useful precursors in the synthesis of chiral sulfoxides.[1] We now report a novel approach to the asymmetric sulfinylation reaction based on a cinchona alkaloid/sulfinyl chloride combination that acts as the first asymmetric sulfinylating agents of achiral alcohols (Figure 1). Both enantiomers of arenesulfinates are obtained with up to 99% ee.

We recently reported a new approach to enantioselective fluorination based on a cinchona alkaloid/Selectfluor combination. The enantioselective fluorination reaction is mediated by *N*-fluoroammonium salts generated in situ via transfer fluorination of cinchona alkaloids by Selectfluor.[4] We envisioned that chiral sulfinylating agents, *N*-sulfinylammonium salts, might be generated in situ via a cinchona alkaloid/sulfinyl chloride combination by transfer sulfinylation. Since *p*-toluenesulfinates are the most widely used precursors for building up chiral sulfoxides,[1] we chose *tert*-butyl *p*-toluenesulfinate (**2a**) as the initial synthetic target of this study. Treatment of *tert*-butyl alcohol (*t*-BuOH) with the combination prepared in situ from QDA and *p*-toluenesulfinyl chloride (**1a**) in MeCN/CH_2Cl_2 (3/4) for 1 h at −78 °C furnished product **2a** in 51% yield with 58% ee (Table 1, run 1). The preliminary result encouraged us to investigate other systems in an attempt to improve enantioselectivity.

After screening several cinchona alkaloids as a chiral source, we found that a QDA/**1a** combination in CH_2Cl_2 at −78 °C effected the enantioselective sulfinylation of *t*-BuOH to furnish (*S*)-**2a** with 87% ee (Table 1, run 7). Quinidine pivaloate (QDP) was also found to afford high enantioselectivity (80% ee, run 10). Excellent enantioselectivity could be achieved with a QDA/**1a** combination when the reaction was performed at −90 °C in CH_2Cl_2 (95% ee, run 8). Importantly, both enantiomers of the sulfinates **2a** can be accessed in excellent yield and enantioselectivity by using either of the pseudoenantiomeric quinine or quinidine derivatives. For example, when *t*-BuOH was treated with a hydroquinine acetate (HQA)/**1a** combination, the highly enantiopure product was obtained with reversal of facial selectivity (runs 14 and 15, (*R*)-**2a** with 81−96% ee). Asymmetric sulfinylation of other alcohols was

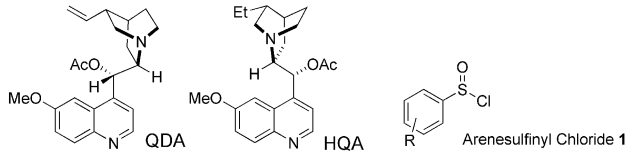
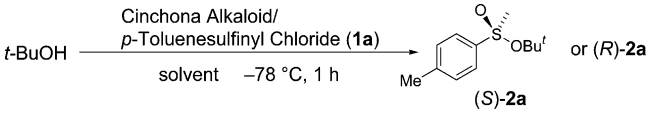


Figure 1. Structures of QDA, HQA, and arenesulfinyl chloride **1**.

Table 1. Asymmetric Sulfinylation of *t*-BuOH by a Cinchona Alkaloid/*p*-Toluenesulfinyl Chloride Combination[a]

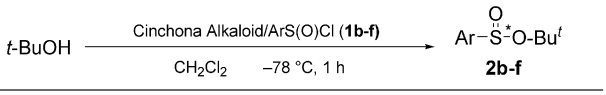


run	cinchona alkaloid[b]	solvent	yield (%)	ee (%)[c]	config[d]
1	QDA	MeCN/CH_2Cl_2	51	58	*S*
2	HQDA	MeCN/CH_2Cl_2	82	18	*R*
3	QDB	MeCN/CH_2Cl_2	89	54	*S*
4	QDA	toluene	74	24	*S*
5	HQDA	toluene	75	22	*S*
6	QDB	toluene	90	35	*S*
7	QDA	CH_2Cl_2	92	87	*S*
8[d]	QDA	CH_2Cl_2	70	95	*S*
9	HQDA	CH_2Cl_2	84	60	*S*
10	QDP	CH_2Cl_2	85	80	*S*
11	QDN	CH_2Cl_2	83	59	*S*
12	CDA	CH_2Cl_2	81	43	*R*
13	CNA	CH_2Cl_2	61	3	*R*
14	HQA	MeCN/CH_2Cl_2	93	81	*R*
15[e]	HQA	CH_2Cl_2	93	96	*R*
16[e,f]	HQA	CH_2Cl_2	93 (63)[k]	93 (99)[k]	*R*
17[g]	QDA	CH_2Cl_2	85	47	nd
18[h]	QDA	CH_2Cl_2	90	50	nd
19[i]	QDA	CH_2Cl_2	88	86	*S*
20[j]	QDA	CH_2Cl_2	89	86	*S*

[a] The combination was prepared from 1.3 equiv of **1a** and 1.4 equiv of cinchona alkaloid in the solvent at −78 °C for 30 min. [b] Legend: QDA, quinidine acetate; HQDA, hydroquinidine acetate; QDB, quinidine benzoate; QDP, quinidine pivaloate; QDN, quinidine naphthyl ether; CDA, cinchonidine acetate; CNA, cinchonine acetate. [c] Determined by HPLC analysis. [d] The absolute configuration of **2** was assigned by the stereospecific conversion to methyl *p*-tolyl sulfoxide or *p*-toluenesulfinamide. See the Supporting Information. [e] The reaction was performed at −90 °C for 4 h. [f] 1-Adamantanol was used instead of *t*-BuOH to furnish 1-adamantyl *p*-toluenesulfinate (**4a**). [g] Cyclohexanol was used instead of *t*-BuOH to furnish cyclohexyl *p*-toluenesulfinate (**4b**). [h] 9-Fluorenol was used instead of *t*-BuOH to furnish 9-fluorenyl *p*-toluenesulfinate (**4c**). [i] A large excess amount of the combination (11 equiv of **1a** and 12 equiv of QDA) was used. [j] The reaction was carried out using recovered QDA. [k] Results in parentheses were obtained after recrystallization from hexane.

10.1021/ja0430189 CCC: $30.25

Table 2. Asymmetric Sulfinylation of *t*-BuOH by a Combination of Various Arenesulfinyl Chlorides (1b−f) with HQA or QDA



entry	Ar	cinchona alkaloid	2	yield (%)	ee (%)[b]
1[a]	Ph	HQA	(*R*)-**2b**	88	83
2		QDA	(*S*)-**2b**	93	88
3[c]	4-chlorophenyl	HQA	(+)-**2c**	73	84
4[a]		QDA	(−)-**2c**	78	88
5[a]	4-methoxyphenyl	HQA	(+)-**2d**	74	96
6[a]		QDA	(−)-**2d**	70	99
7[a]	4-methoxy-3-methylphenyl	HQA	(+)-**2e**	74	94
8		QDA	(−)-**2e**	78	93
9[a]	2,4,6-trimethylphenyl	HQA	(+)-**2f**	72	92
10[a]		QDA	(−)-**2f**	68	92

[a] The reaction was performed at −90 °C. [b] Determined by HPLC analysis. [c] $MeCN/CH_2Cl_2$ (3/4) was used as a solvent.

also examined using the QDA/**1a** combination. While 1-adamantanol was sulfinylated by the combination to give 1-adamantyl *p*-toluenesulfinate (**4a**) with very high ee, asymmetric sulfinylation of cyclohexanol and 9-fluorenol slightly lowered the enantioselectivity (runs 16−18, 47−93% ee). Importantly, the optically pure adamantyl sulfinate **4a** was obtainable in a 63% overall yield from 1-adamantanol after single recrystallization from hexane (run 16 in parentheses). To examine the possibility of reusing the alkaloids, we repeated the sulfinylation of *t*-BuOH using QDA recovered from the first reaction mixture by acid−base extraction/short-column chromatography (QDA was recovered in 80−90% yield). Formation of (*S*)-**2a** having 86% ee demonstrates that recycling of QDA causes no erosion in enantioselectivity of the combination (runs 7 and 20).

Having identified an asymmetric process, its scope was investigated with the aim of producing a general enantioselective sulfinylation reaction. Table 2 shows the range of arenesulfinates **2b**−**f** that can be formed by this method. *t*-BuOH reacts with a combination of a variety of racemic arenesulfinyl chlorides[5] **1b**−**f** with HQA to form *tert*-butyl arenesulfinates **2b**−**f** in good yield and with high ee (up to 96% ee). The opposite enantiomer is also accessible by using the QDA-derived combinations (up to 99% ee). It should be noted that the cinchona alkaloid derivative and sulfinyl chloride must be mixed prior to the addition of substrates to achieve enantioselective sulfinylation. For example, after a mixture of *t*-BuOH and QDA was stirred in CH_2Cl_2 at −78 °C for 30 min, addition of **1a** gave racemic **2a**. This result gives useful information on the reaction mechanism of this new sulfinylation procedure, since the involvement of an alkaloid−alcohol complex in stereochemical control seems to be ruled out. This has certain implications regarding the *N*-arenesulfinylammonium salt, which must be taken into account. Although the *N*-sulfinylammonium salt has not been isolated yet, ^{1}H NMR tentatively ascertained the structure. The 600 MHz ^{1}H NMR spectrum of QDA in $CDCl_3$ at room temperature showed characteristic peaks at 2.72−2.95 ppm (4H, m) and 3.25 ppm (1H, dd, J = 7.2, 8.8 Hz), whereas the spectrum of the QDA/**1** combination (QDA:**1** = 1:1) displayed corresponding signals at 3.50−3.70 ppm (4H, m) and 3.30 ppm (1H, br q, J = 8.5 Hz). These signals could be assigned to α-protons of tertiary or quaternary nitrogen, and the low-field shifts observed are attributable to the cationic character of the ammonium salt. The enantioselectivity increased at lower reaction temperature (runs 7 and 8, Table 1) and the reaction with much fewer equivalents of *t*-BuOH

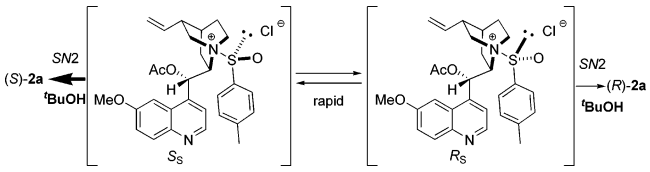


Figure 2. Proposed structures for the QDA/**1a** combination and the dynamic kinetic resolution pathway to (*S*)-**2a**.

with **1a** to stop the sulfinylation before completion gave **2a** with an enantioselectivity similar to that under the usual conditions (runs 7 and 19). The significantly high enantioselectivity observed in our case could be explained by dynamic kinetic resolution,[6] in which the enantioselectivity depends on the rate of the alcohol with the diastereomeric sulfinylammonium salts through rapid epimerization on the sulfinyl stereocenter of the *N*-arenesulfinylammonium salt. The proposed mechanism is shown in Figure 2, assuming that an alcohol approaches from the direction opposite the sulfur−nitrogen bond.

In summary, we have developed a highly enantioselective preparation of chiral sulfinates based on the cinchona alkaloid/sulfinyl chloride combination. Importantly, our process can have access to both enantiomers of sulfinates depending on the cinchona alkaloids via a dynamic kinetic resolution pathway in the sulfinylation reaction. This new sulfinylation system will complement or even substitute the most commonly used preparative method for chiral sulfoxides through diastereomeric sulfinates.

Supporting Information Available: Text giving experimental procedures, determination of the absolute stereochemistry of **2**, and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Mikolajczk, M.; Drabowicz, J.; Kielbasinski, P. *Chiral Sulfur Reagents*; CRC Press: Boca Raton, FL, 1997. (b) Carreño, M. C. *Chem. Rev.* **1995**, *95*, 1717. (c) Toru, T.; Nakamura, S. *J. Synth. Org. Chem. Jpn*. **2002**, *60*, 115. (d) Nakamura, S.; Watanabe, Y.; Toru, T. *J. Org. Chem.* **2000**, *65*, 1758. (e) Khiar, N.; Fernández, I.; Alcudia, A.; Alcudia, F. In *Advances in Sulfur Chemistry 2*; Rayner, C. M., Ed.; JAI Press: Stamford, CT, 2000; Chapter 3. (f) Matsugi, M.; Shibata, N.; Kita, Y. In *Advances in Sulfur Chemistry 2*; Rayner, C. M., Ed.; JAI Press: Stamford, CT, 2000; Chapter 6.

(2) (a) Phillips, H. *J. Chem. Soc.* **1925**, *127*, 2552. (b) Fernández, I.; Khiar, N.; Llera, J. M.; Alcudia, F. *J. Org. Chem.* **1992**, *57*, 6789. (c) Fernández, I.; Khiar, N.; Roca, A.; Benabra, A.; Alcudia, A.; Espartero, J. L.; Alcudia, F. *Tetrahedron Lett.* **1999**, *40*, 2029. (d) Khiar, N.; Araújo, C. S.; Alcudia, F.; Fernández, I. *J. Org. Chem.* **2002**, *67*, 345. (e) Alayrac, C.; Nowaczyk, S.; Lemarié, M.; Metzner, P. *Synthesis* **1999**, 669. (f) Whitesell, J. K.; Wong, M. S. *J. Org. Chem.* **1991**, *56*, 4552. (g) Whitesell, J. K.; Wong, M. S. *J. Org. Chem.* **1994**, *59*, 597. (h) Mase, N.; Watanabe, Y.; Ueno, Y.; Toru, T. *J. Org. Chem.* **1997**, *62*, 7794. (i) Watanabe, Y.; Mase, N.; Tateyama, M.; Toru, T. *Tetrahedron: Asymmetry* **1999**, *10*, 737.

(3) (a) Drabowicz, J.; Lagedz, S.; Mikolajczyk, M. *Tetrahedron* **1988**, *44*, 5243. (b) Drabowicz, J.; Legedz, S.; Mikolajczyk, M. *J. Chem. Soc., Chem. Commun.* **1985**, 1670. (c) Mikolajczyk, M.; Drabowicz, J. *J. Chem. Soc., Chem. Commun.* **1974**, 547. (d) Evans, J. W.; Fierman, M. B.; Miller, S. J.; Ellman, J. A. *J. Am. Chem. Soc.* **2004**, *126*, 8134.

(4) (a) Shibata, N.; Suzuki, E.; Takeuchi, Y. *J. Am. Chem. Soc.* **2000**, *122*, 10728. (b) Shibata, N.; Suzuki, E.; Asahi, T.; Shiro, M. *J. Am. Chem. Soc.* **2001**, *123*, 7001. (c) Shibata, N.; Ishimaru, T.; Suzuki, E.; Kirk, K. L. *J. Org. Chem.* **2003**, *68*, 2494. (d) Shibata, N.; Ishimaru, T.; Nakamura, M.; Toru, T. *Synlett* **2004**, 2509.

(5) (a) Youn, J. H.; Herrmann, R. *Tetrahedron Lett.* **1985**, *27*, 1493. (b) Peyronneau, M.; Roques, N.; Mazieres, S.; Roux, C. L. *Synlett* **2003**, 631.

(6) (a) Busu, A.; Gallagher, D. J.; Beak, P. *J. Org. Chem.* **1996**, *61*, 5718. (b) Khiar, N.; Araújo, S. S.; Alcudia, F.; Fernández, I. *J. Org. Chem.* **2002**, *67*, 345. (c) Balcells, D.; Maseras, F.; Khiar, N. *Org. Lett.* **2004**, *6*, 2197. (d) Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn*, **1995**, *68*, 36.

JA0430189