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New Chiral Auxiliary: Optically Active Thiol Derived from Camphor

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Abstract: A new camphor based mercapto chiral auxiliary has been prepared, and demonstrated to induce very high chiral inductions in the diastereoselective reductions of α-sulfinylketones, in the presence of bivalent Lewis acids.

The search for new chiral auxiliaries which can induce high stereoselectivities has been the major target for most researchers in the field of asymmetric synthesis.[1] Among many successful cases, camphor derived chiral auxiliaries have certainly attracted great attention of organic chemists.[2] Herein, we report a new chiral thiol 1 which could be used in the preparations of many useful sulfur containing chiral compounds.[3] (eg. chiral sulfoxide[4,5,6] and sulfones).[6,7] An illustrative reaction is given here to demonstrate the usefulness of thiol 1 as an excellent chiral auxiliary.

Thiol 1 could be readily prepared from camphor through a few simple steps. The synthesis began with the *exo*-sulfurization of camphor with LDA and phenylthiotosylate as reported by Australian chemists.[8] The resulted *exo*-sulfenyl ketone 2 was submitted to DIBAH reduction to give *exo*-alcohol 3 in 92% yield, followed by debenzylation of sulfide 3 to give thiol 1 in 91% yield.[9,10] In order to test the asymmetric induction capability of thiol 1, the Solladie type chiral reduction was chosen as the model reaction.[11] Thus thiol 1 was condensed with 2-chloroacetophenone, followed by oxidation of the sulfide 4 to give sulfoxide 5 as a single diastereomer with the oxygen atom toward the hydroxy side due to the chelating effect with MCPBA.[8]

Scheme I:

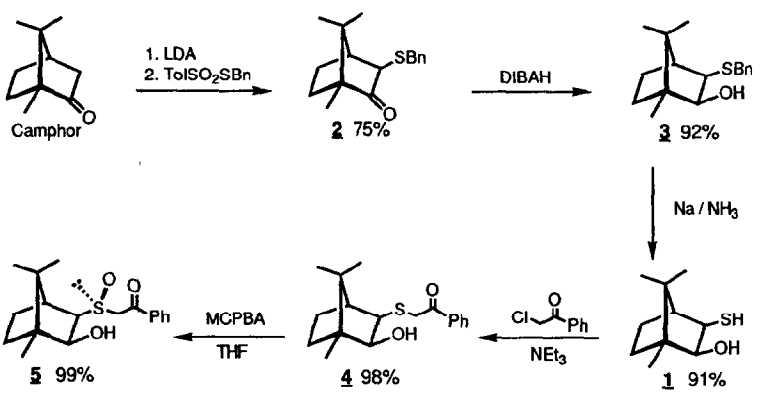


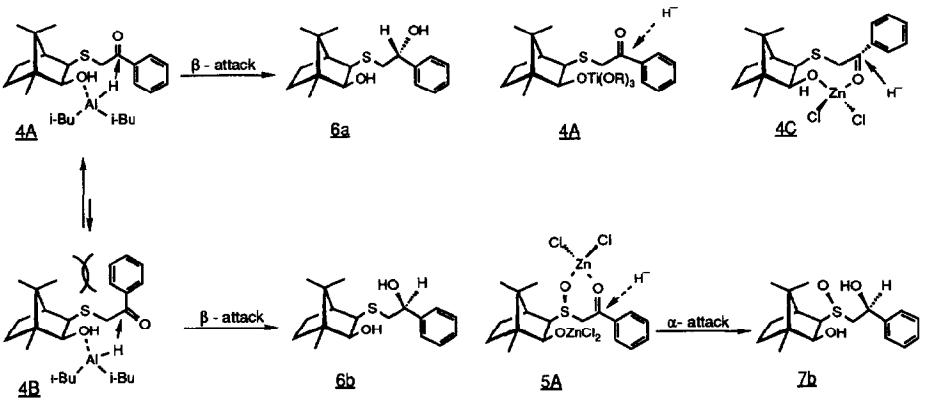
Table I: Reductions of chiral ketones with hydrides

Entry[a]	Substrates	Reductants	Solvents	Catalysts	Products	Yields[b]	ratio a : b[c]
1	4	DIBAH	THF		6	90	75:25
2	4	DIBAH	THF	$TiCl(OiPr)_3$	6	100	30:70
3	4	DIBAH	THF	$ZnCl_2$	6	83	85:15
4	4	DIBAH	CH_2Cl_2		6	82	70:30
5	4	LAH	THF	Li^+	6	82	85:15
6	5	DIBAH	THF		7	91	75:25
7	5	DIBAH	THF	$TiCl(OiPr)_3$	7	92	30:70
8	5	DIBAH	THF	$ZnCl_2$	7	99	0:100

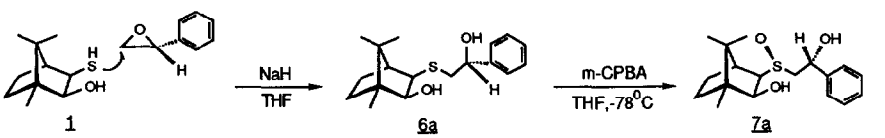
a) All reactions were carried out at –78°C.
b) All yields were based on products purified by chromatography, except entry 2 was crude yield.
c) Products ratios were determined by 200MHz or 300MHz NMR as well as chromatography.

Both chiral ketones 4 and 5 were submitted to the reductions of DIBAH or $LiAlH_4$, and the results are listed in table I. We found that all yields of these reactions are excellent, and most importantly the facial-selectivities of these reductions could be manipulated through the control of 2-hydroxy group. In entries 1, 4, 5 and 6, the 2-hydroxy group associated with DIBAH or $LiAlH_4$, so that the hydride approached the carbonyl group from the β-face as indicated in scheme II. However, the α-sulfenylketone 4 has two reactive conformers 4A and 4B which produced alcohols 6a and 6b respectively. Possibly due to the steric interaction between 8-methyl and the phenyl groups, the equilibrium would lie in favor of 4A, and the alcohol 6a was formed predominantly as a consequence.[12] In the presence of a bidentated Lewis acid catalyst ($ZnCl_2$), the conformational rigidities of the ketones were greatly enhanced. Therefore, the diastereoselectivities became better as revealed in 4C and 5A. (Entry 3 and 8). In particular, in entry 8 where the conformation of α-sulfinylketone 5 was locked into conformation 5A and a complete diastereoselectivity was observed.[13] On the other hand, addition of the mono-chelating $Ti(OR)_3Cl$ would block the β-face of the ketone and prevent the chelation of reducing metal hydride with the 2-hydroxy group. Thus, in this case the S-form alcohol was formed preferentially. We also found that a change of solvent (THF vs CH_2Cl_2) did not improve the facial-selectivities of this reaction. (Entry 4) However, the use of $LiAlH_4$ as the reducing agent does give a better diastereoselectivity. (Entry 5) According to these observations, we learned that thiol 1 has provided a great chiral template for compounds capable of attachment by a sulfur atom. The 2-hydroxy group can play either a directing role to bring in the incoming hydride, or it can serve as a shielding zone when chelated with a Lewis acid. Thus selective approach to both sides of the substrate can be achieved simply by changing the reaction conditions rather than inverting the chirality of the chiral auxiliary. Nevertheless, the absolute stereochemistry of the diastereomers 6a and 7a were proved through chemical correlation from the basic opening of (R)-styrene oxide by thiol 1 (yield 80%).[13,14] The resulting alcohol 6a wa oxidized by MCPBA to give a single compound 7a,[15] which gave spectroscopic and optical rotation data, identical with the chiral alcohols 6a and 7a obtained from the reductions.[16] (Scheme III).

Scheme II:



Scheme III:



In summary thiol 1 has been shown to be capable of producing extremely high asymmetric induction in Solladie type chiral reductions. Moreover, we are currently using thiol 1 in making other sulfur containing chiral compounds.

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10. Compound 1: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.775 (s, 3H, CH_3), 0.947 (s, 3H, CH_3), 1.076 (s, 3H, CH_3), 1.000 - 1.150 (m, 1H), 1.400 - 1.550 (m, 1H), 1.698 (d, J = 9.6 Hz, 1H, SH), 1.700 - 1.840 (m, 2H), 2.550 (br s, 1H, OH), 3.255 (dd, J = 9.6, 7.2 Hz, 1H, CHS), 3.560 (d, J = 7.2 Hz, 1H, CHO). ^{13}C NMR (75.4 MHz, $CDCl_3$) d, 11.717, 21.367, 21.600, 28.999, 33.267, 47.214, 48.422, 49.668, 54.249, 79.396.
IR($CHCl_3$) 3465(br), 3032, 1198, 1070. mp = 131 - 132°C,
$[\alpha]_D^{20}$ = 5.09 (*c* 1.18, $CHCl_3$).
Anal. calcd for $C_{10}H_{18}OS$: C, 64.47; H, 9.47, S, 17.21. Found: C, 64.42; H, 9.47, S, 17.23.
11. G. Solladie, G. Demailly and C. Greck, *Tetrahedron Letters*, **1985**, *26*, 435; For more recent application see: Carreno and et al. *J. Org. Chem.* **1990**, *55*, 2120 and references cited therein.
12. Typically, 3.0 equivalents of Lewis acid ($ZnCl_2$) was first flame dried under vacuum, then added 1.0 equivalent of ketone in solvent an a 0.1M solution, followed by addition of 1.0 M hydride solution at -78°C. The reaction was monitored by TLC analysis of the aliquote until the starting ketone disappeared, the resulting mixture was quenched with methanol and 1N aqueous hydrochloric acid and washed with brine. After evaporation of solvent, the crude NMR spectrum was clear enough to determine the diastereomeric ratio of products. The reaction yield was recorded after chromatographed through silica gel (eluted with ethyl acetate) and the products ratio was reconfirmed.
13. (R) Styrene oxide was purchased directly from Merck cat. No. 818436.
14. 6a $[\alpha]_D^{18}$ -11.60 (*c* 2.570, $CHCl_3$), 7a $[\alpha]_D^{18}$ -23.45 (*c* 1.305, $CHCl_3$).
15. The optical rotation data of alcohols prepared from (R)-styrene oxide were 6a $[\alpha]_D^{18}$ -11.65 (*c* 2.500, $CHCl_3$), 7a $[\alpha]_D^{18}$ -23.48 (*c* 1.300, $CHCl_3$).
16. The similar process was carried out on thiol 1 and (S)-Styrene oxide (Aldrich) to prove the stereochemistry of alcohol 6b, and 7b.