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(CAMPHORYLSULFONYL)IMINE DIANION IN THE SYNTHESIS OF NEW OPTICALLY PURE (CAMPHORYLSULFONYL)OXAZIRIDINE DERIVATIVES

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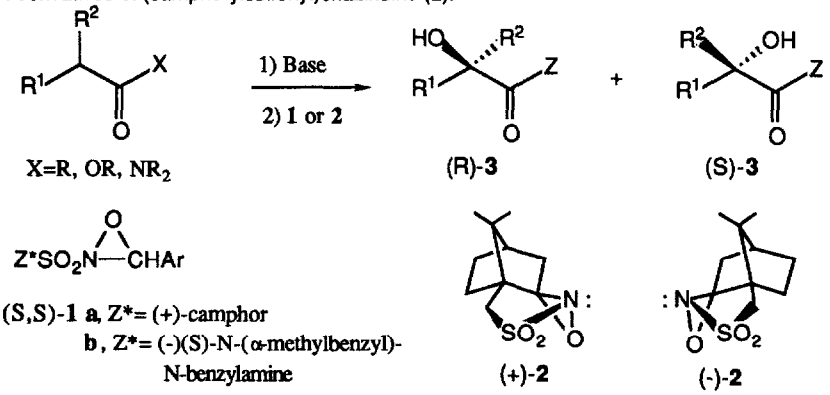
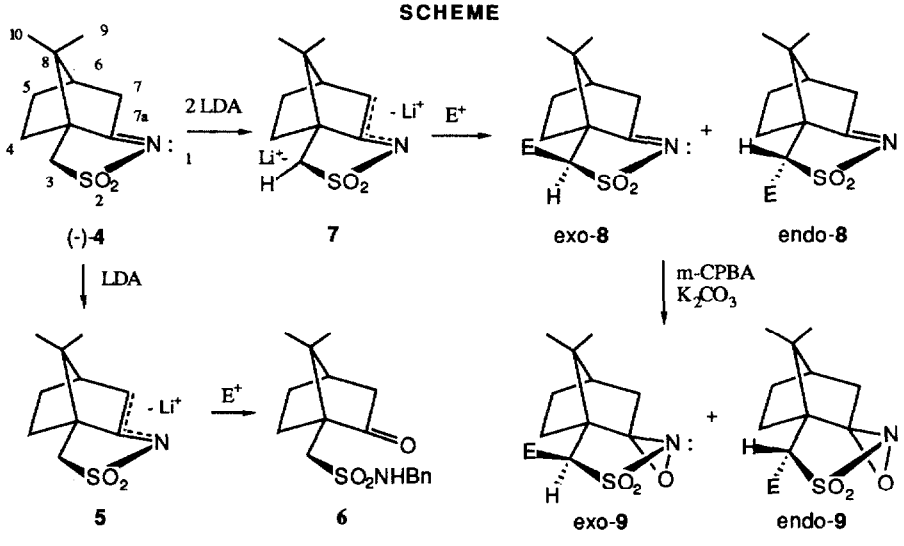
Summary: *New, more efficient enantiomerically pure (camphorylsulfonyl)oxaziridines are prepared by mono alkylation of the dianion of (camphorsulfonyl)imine at the carbon atom adjacent to the sulfonyl group.*

Optically active α-hydroxy carbonyl compounds **3** have been extensively exploited in asymmetric synthesis;[1] for example, as chiral synthons, chiral auxiliaries[2] and as chiral ligands.[3] This structural array is also featured in many biologically active natural products.[4] The most direct method for introducing a hydroxyl group adjacent to a carbonyl is the enolate oxidation protocol using an aprotic oxidizing reagent.[5] The only reagents currently available for the asymmetric oxidation of prochiral enolates to optically active α-hydroxy carbonyl compounds are the enantiomerically pure N-sulfonyloxaziridines **1** and **2**, recently introduced by us.[6] Both optical isomers of **3** are readily available because the configuration of the oxaziridine three-membered ring in **1** and **2** controls the product stereochemistry. Of these reagents the (+)- and (-)-(camphorylsulfonyl)oxaziridines (**2**) have proven to be the most useful, not only because of their efficiency (50-96% ee), but also because of their accessibility. These oxaziridine isomers are prepared in four steps from inexpensive (+) and (-)-camphorsulfonic acids in 77% overall yield.[6d] Furthermore, separation of the oxaziridine diastereoisomers, a problem with oxaziridines of type **1**, is not necessary for **2** because oxidation of the (camphorsulfonyl)imine (**4**) is sterically blocked from the exo-face of the C-N double bond. To maximize the efficiency of the these reagents we required simple methodology for introducing a variety of substituents into the ring-skeleton of **2** near the active site. In this context we describe the application of (camphorylsulfonyl)imine dianion **7** in the synthesis of new, more efficient derivatives of (camphorylsulfonyl)oxaziridine (**2**).



Initially we planned to introduce substituents into **4** at C-7 by reaction of azaenolate **5** with various carbon electrophiles. However, no reaction occurred on treatment of lithium azaenolate **5**, prepared by reaction of (-)-**4** (8 mmoles) at 0 °C in THF with 1.1 eq of LDA , with excess benzyl bromide or methyl iodide. That **5** was formed under these conditions was confirmed by quenching experiments with D_2O. Addition of HMPA to **5**, followed by reaction with 4 eq of benzyl bromide, however, gave after 30 min and standard work-up a quantitative yield of camphorsulfonamide **6**.[7] As a result of the anion stabilizing sulfonyl group, alkylation apparently occurs at nitrogen to afford an unstable enamine derivative which hydrolyzes to **6** on work-up (Scheme).[8]

SCHEME

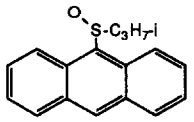
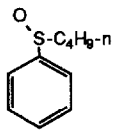
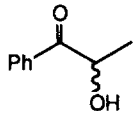
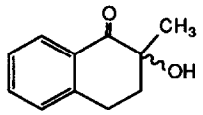
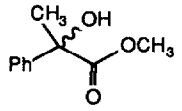


E = a) $PhCH_2$, b) CH_2CH_2OH, c) $CH_2CH_2OCH_2Ph$

In contrast to **5**, lithio dianion **7**, prepared by treating (-)-**4** with 2.2 eq of LDA at 0 °C, reacts smoothly with carbon electrophiles exclusively at C-3. Thus addition of 1.1 eq of benzyl bromide or excess ethylene oxide to **7** at -78 °C and warming to 0 °C gave after 1 h 50:50 and 30:70 mixtures of exo-**8a-b** and endo-**8a-b**, respectively, in 90-95% isolated yield. Although exo:endo-**8a** were readily separated by flash chromatography, all attempts to separate exo:endo-**8b** were unsuccessful.[8,9] For this reason **8b** was benzylated by treating with NaH (THF for 4 h) followed by addition of 2.0 eq of benzyl bromide to give **8c** in 61% yield following purification by flash chromatography.[8] Unfortunately all attempts to separate exo:endo-**8c** were also unsuccessful. Oxidation of exo-**8a** and endo-**8a** in CH_2Cl_2 with 1.5 eq of *m*-CPBA and sat. K_2CO_3 solution gave exo-**9a** and endo-**9a**, respectively in 90-95% isolated yield.[8,10] Oxidation of the exo:endo-**8c** in a similar fashion gave **9c** in 90-95% yield.[8] Crystallization from ethyl ether gave endo-**9c** in greater than 55% yield.[11] To date all attempts to isolate exo-**9c** have been unsuccessful. The assignments of stereochemistry are supported by the result of difference NOE experiments conducted on exo- and endo-**9a**. The fact that exo-**8a** is oxidized to exo-**9a** about 50 times faster than is endo-**8a** to endo-**9a** is also in accord with these assignments. The structure of endo-**9c** is based on the kinetically more favorable approach of the electrophile to **7** from the sterically least hindered direction.

To evaluate the efficiency of these new oxaziridines **9** the asymmetric oxidation of selected sulfides to sulfoxides (entries 1-2) and the asymmetric oxidation of enolates to α-hydroxy carbonyl compounds (entries 3-6) was performed employing methodology described earlier (Table).

Table : Asymmetric Oxidations Using (Camphorylsulfonyl)oxaziridine Derivatives (+)-2 and 9.

entry	PRODUCT	CONDITIONS	OXAZIRIDINE (+)-2[a]	exo-9a % ee (Config.)[b] [% Isolated Yield]	endo-9a	endo-9c
1		$CHCl_3$ (25 °C)	66 (S)[d][c]	75 (S)[d]	80 (S)[d]	71 (S)[d]
2		$CHCl_3$ (25 °C)	3 (S)[d][c]	18 (S)[d]	37 (S)[d]	6 (S)[d]
3		LDA	43 (S)[51][e]	40 (S)[58][f]	6 (R)[48][f]	6 (R)[68][f]
4		NHMDS	55 (S)[77][e]	83 (S)[50][f]	61 (S)[54][f]	42 (S)[82][h]
5		LDA	30 (R)[82][e]	54 (R)[80][i]	26 (S)[45][i]	21 (S)[63][i]
		NHMDS	16 (R)[90][e]	67 (R)[61][f]	31 (R)[64][f]	19 (R)[76][f]
6		LDA	41 (R)[61][j,k]	64 (R)[51][f]	48 (R)[65][f]	54 (R)[72][f]

a) See Ref. 6d. b) The optical purities and absolute configurations of the sulfoxides were determined using a Regis Pirkle covalent phenylglycine HPLC column as described in ref. 12. The optical purities of the α-hydroxy ketones were determined using the chiral shift reagent $Eu(hfc)_3$ and absolute configurations determined by the sign of rotation as described in Ref. 6b. For the absolute configuration for 2-hydroxy-2-methyl-1- tetralone see Ref. 13. c) See Ref 6d. d) Yields >90%. e) Oxidation at 0 °C as described in Ref. 6b. f) Oxidation at -78 °C. g) Oxidation at -78 °C as described in Ref. 6b. h) Oxidation at -42 °C. i) Oxidation at 0 °C. j) Oxidation at -78 °C as describe in Ref. 6a. k) Enolate ratio 75:25 E:Z.

Only when the group size difference for substituents attached to the sulfide (R'SR) is large does (+)-**2** afford useful stereoselectivities for the asymmetric oxidation of sulfides to sulfoxides; i.e. for the 9-anthryl sulfides (compare entries 1 and 2).[6d] Both exo- and endo-**9a** gave modest increases in stereoselectivities for the oxidation of sulfides to sulfoxides. As anticipated the efficiency of endo-**9a** was better than exo-**9a** (18 vs 37% ee for n-butyl p-tolyl sulfide), undoubtedly due to the close proximity of the benzyl group to the active site oxygen. Unexpectedly the stereoselectivities for the oxidation of sulfides to sulfoxides using endo-**9c** is nearly identical to (+)-**2**.

The transition state control elements for the asymmetric oxidation of enolates to optically active α-hydroxy carbonyl compounds **3** using (camphorylsulfonyl)oxaziridine (**2**) are poorly understood, but thought to involve an "open" transition state.[6] The stereoselectivites are influenced by the geometry of the enolate, the enolate substitution pattern, the counter

ion and the solution structure of the enolate.[6f] The sodium enolates of ketones are generally oxidized at -78 °C by (+)-**2**, whereas the less reactive lithium enolates require warming to 0 °C.[6b] The sodium and lithium enolates of 2-methyl-1-tetralone, a tetrasubstituted enolate, required warming to 0 °C for complete oxidation.[6b] All of the new oxaziridines **9** proved to be more reactive than (+)-**2** as suggested by the fact that it was possible to oxidize the lithium enolate of propiophenone at -78 °C (entry 3). Unexpectedly exo-**9a**, where the benzyl group seemingly cannot interact with the active site, gave *higher* stereoselectivities than did endo-**9a** or endo-**9c** and was more efficient than (+)-**2**. For example, the enantioselectivities for oxidation of the sodium enolates of propiophenone and 2-methyl-1-tetralone with endo-**9a** were 83 and 67% ee compared to 55 and 16% ee using (+)-**2**, respectively (entries 4 and 5). Improved stereoselectivities for oxaziridine **9** compared to (+)-**2**, were also noted for the asymmetric oxidation of lithium enolate of methyl atrolactic acid, with exo-**9a** again proving to be the more efficient oxaziridine (entry 6).

Enolates are generally assumed to exist and react as aggregates or "super" molecules in solution.[14] Our results suggest that there can be significant, stereospecific interactions between metal enolates and sites in substrates that are seemingly remote from the reactive active site; i.e., exo-**9a** gave higher stereoselectivites for enolate oxidations than did endo-**9a**. The origin of this interaction is currently under study.

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8. Details of this aspect of (camphorsulfonyl)imine chemistry will be described elsewhere.
9. For exo-**8a**: mp 133-4 °C, $[\alpha]_D$ -25.0 (c 1.0 $CHCl_3$); endo-**8a**: mp 132-3 °C, $[\alpha]_D$ -30.0 (c 2.0 $CHCl_3$). All new compound gave satisfactory elemental analysis and had spectra consistent with their structures.
10. For exo-**9a**: mp 166-7 °C, $[\alpha]_D$ -66.0 (c 2.4 $CHCl_3$); endo-**9a**: mp 157-9 °C, $[\alpha]_D$ +62.0 (c 3.7 $CHCl_3$).
11. For endo-**9c**: mp 108-110 °C, $[\alpha]_D$ -13.3 (c 0.20 $CHCl_3$).
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