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β-Hydroxysulfoxides as chiral cyclic ketone equivalents: enantioselective synthesis of polysubstituted cyclohexanones, cyclohexenones and cyclohexenediones†

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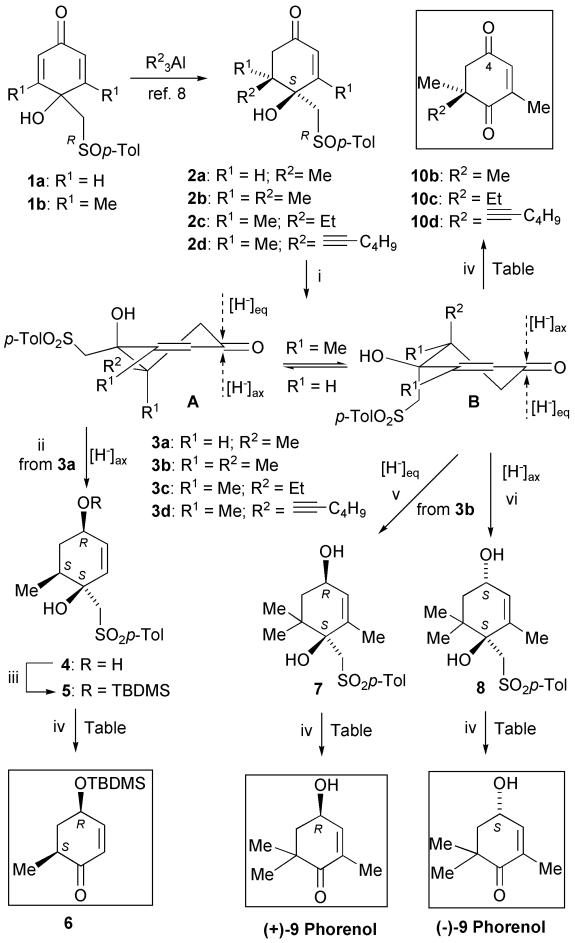
The β-hydroxysulfoxide moiety, after oxidation to sulfone, acts as a masked carbonyl group in a cyclic system, opening an easy access to differently substituted enantiomerically pure cyclic ketones by means of aluminium-mediated conjugate additions, stereoselective reductions and elimination by retrocondensation in basic medium.

The utilization of chiral cyclohexanones and 2-cyclohexenones in asymmetric synthesis continues to attract considerable interest as an important class of starting materials and synthetic intermediates *en route* to a wide range of natural products like cyclitols,[1] carbasugars[1b,2] or terpenes.[3] The stereocontrolled transformation of cyclic ketones is a general way of access to these important compounds. Currently, this is achieved through the conversion of ketones into their chiral acetals[4] or hydrazones.[5] Recently, enantiopure α-acetoxysulfones generated catalytically have been introduced into the synthetic arsenal as chiral aldehyde equivalents.[6] Although some of these methodologies allow an efficient control of the asymmetric transformations, new chiral carbonyl equivalents are welcome.

In connection with a program devoted to asymmetric synthesis mediated by sulfoxides,[7] we have recently reported a general synthetic approach to (*S*,*R*)-4-hydroxy-4-[(*p*-tolylsulfinyl)methyl]-2,5-cyclohexadienones **1** and studied the stereoselectivity of their conjugate additions.[8] This study revealed that the β-hydroxy sulfoxide exercises a differentiation between the diastereotopic faces of the double bonds directing conjugate additions of organoaluminium reagents from the face containing the OH group in a highly diastereoselective way and with efficient desymmetrization of the cyclohexadienone moiety. Synthetic applications of these results required the elimination of the chiral auxiliary once the *p*-quinol system had been adequately functionalized. We now report the liberation of ketone functionalities through the oxidation of the corresponding β-hydroxy sulfoxides and elimination of the resulting sulfone. This sequence shows that the readily accessible β-hydroxy sulfoxide moiety can be regarded as a chiral ketone equivalent. In spite of the extended use of β-hydroxy sulfoxides in asymmetric synthesis,[7a] this is the first example where such a fragment is used as a chiral ketone equivalent.‡

Derivatives **2a**–**d**, bearing the enantiopure β-hydroxy sulfoxide moiety, were prepared through the highly stereoselective organoaluminium conjugate addition[8] on the corresponding enantiopure *p*-quinols **1a**–**b**, as unique diastereomers in good yields (Scheme 1). Attempts to eliminate methyl *p*-tolyl sulfoxide from **2** through a retrocondensation in basic medium were unsuccessful, probably due to the poor quality of the methyl sulfinyl anion as nucleofuge. We then transformed sulfoxides **2** into sulfones **3**. Treatment of sulfone **3a** with different bases led to the expected elimination of methyl *p*-tolylsulfone but with simultaneous aromatization to the corresponding 2-methylhydroquinone. Reduction of **3a** with DIBALH afforded carbinol (4*R*)-**4** resulting from the exclusive axial hydride attack on the most stable conformation **A** of **3a** fixed by the equatorial (*p*-tolylsulfonyl)methyl substituent.

Attempts to recover the masked carbonyl group from **4** in the presence of different bases were again unsuccessful due to difficulties in the isolation of the final 4-hydroxyenone. Fortunately, the TBDMS protected derivative **5** could be transformed into cyclohexenone **6** in the presence of several bases under different conditions. The best results were obtained with 2 equivalents of the weak base Cs_2CO_3 in CH_3CN at rt (Table 1, entry 1) which gave a clean mixture of cyclohexenone **6** and methyl *p*-tolyl sulfone, from which **6** {$[\alpha]_D^{20}$ = +67.0 (*c* 0.4, acetone)} was isolated with 89% yield in enantiomerically pure form, as determined after desilylation into the corresponding carbinol.§



Scheme 1 *Reagents and conditions*: i, *m*-CPBA, CH_2Cl_2, rt, 1–2 h, 85–95%; ii, DIBALH, THF, −78 °C, 30 min, 95% from **3a**; iii, TBDMSOTf, 2,6-lutidine, CH_2Cl_2, rt, 2 h, 93%; iv, Cs_2CO_3, CH_3CN, rt; v, L-Selectride, THF, −78 °C, 3 h, 64%; vi, $NaBH_4$, $CeCl_3$, MeOH, −78 °C, 3–4 h, 64%.

† Electronic supplementary information (ESI) available: full experimental details and NMR spectra. See http://www.rsc.org/suppdata/cc/b2/b209121f/

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The stereoselective reductions of ketone **3b** on the now most stable conformation **B**, which avoids severe interactions between R[1] = Me and the equatorial (*p*-tolylsulfonyl)methyl substituent present in conformation **A** (Scheme 1), afforded carbinols **7** (L-Selectride, 95% equatorial attack) and **8** ($NaBH_4$, $CeCl_3$, 80% axial attack), whose treatment with Cs_2CO_3 (entries 2 and 3, respectively) allowed us to obtain in enantiomerically pure form§ both enantiomers of **9**, {$[\alpha]_D^{20}$ = +48 (*c* 2, EtOH) and −44 (*c* 0.2, EtOH)}, known as Phorenol, a synthetic intermediate used for the enantioselective syntheses of several natural products.[11] Till now, these chiral synthons were mainly accessible through enzymatic resolutions.[12]

We then focused our attention on the base-induced elimination of methyl *p*-tolylsulfone on cyclohexenones **3b**–**d** *en route* to chiral cyclohexenediones (Scheme 1). Stirring sulfone **3b** in CH_3CN solution with an excess of Cs_2CO_3 gave, after flash chromatography, achiral 4-oxoisophorone **10b** (entry 4). The synthesis of enantiomerically pure¶ oxoisophorone analogues **10c**[13] {$[\alpha]_D^{20}$ = +0.6 (*c* 0.6, $CHCl_3$)} and **10d** {$[\alpha]_D^{20}$ = −3.0 (*c* 0.8, $CHCl_3$)} could be achieved in a similar easy way from sulfones **3c** (entry 5) and **3d** (entry 6), respectively.

In order to know if the driving force for the easy elimination of methyl *p*-tolylsulfone was the formation of the conjugated cyclohexenone or cyclohexenedione fragment, we decided to explore the synthetic sequence *en route* to trisubstituted cyclohexanones **11** and **12** (Scheme 2). The precursors were obtained as follows. The stereoselective addition of Et_3Al on **2a** afforded cyclohexanone **13** as the unique diastereoisomer with the *R* absolute configuration at the new chiral center.[8] *m*-CPBA oxidation of sulfoxide **13** gave sulfone **14** which was stereoselectively reduced to carbinol **15** (L-Selectride, 90% equatorial attack) or to the epimer **16** ($NaBH_4$, $CeCl_3$, 95% axial attack). The elimination of methyl *p*-tolyl sulfone was once again unsuccessful on free carbinols **15** and **16** and had to be carried out on the TBDMS protected derivatives **17** and **18**. Simply stirring a CH_3CN solution of **17** or **18** with Cs_2CO_3 (entries 7 and 8) afforded, respectively, the desired trisubstituted cyclohexanones **11** {$[\alpha]_D^{20}$ = −1.7 (*c* 1.1, $CHCl_3$)} and **12** {$[\alpha]_D^{20}$ = −4.5 (*c* 1.1, $CHCl_3$)} in enantiomerically pure form, as determined after desilylation into the corresponding carbinols.§

In summary, the enantiopure β-hydroxysulfoxide moiety can be considered as a chiral cyclic ketone equivalent which can be recovered after oxidation to a sulfone and mild basic treatment. An additional advantage of the β-hydroxysulfone as carbonyl protecting group in cyclic systems is that further transformations on such rigid systems occur in a stereocontrolled manner. Moreover, both the α-hydroxysulfoxides and the corresponding sulfones are very stable and can be easily handled and purified either by chromatography or crystallization. We are now applying this new efficient methodology to the total enantioselective synthesis of several natural products.

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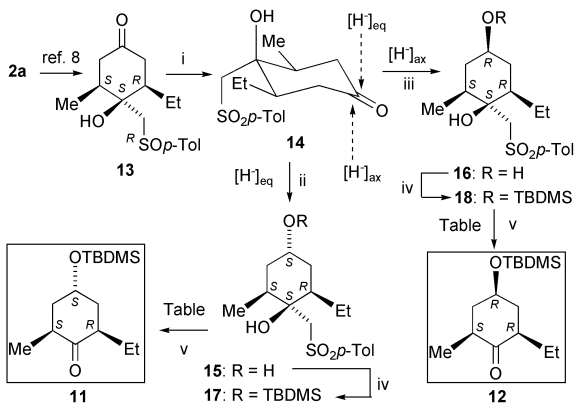
Table 1 Treatment of cyclic β-hydroxysulfones with Cs_2CO_3 in CH_3CN at rt

Entry	β-Hydroxy sulfone	Cs_2CO_3 equiv.	*t*/h	Cyclic ketone	Yield (%)	Ee (%)
1	**5**	2	17	(4*R*,6*S*)-**6**	89	> 95
2	**7**	3	1	(4*R*)-**9**	90	> 95
3	**8**	3	0.25	(4*S*)-**9**	93	> 95
4	**3b**	2	0.3	**10b**	54	—
5	**3c**	2	0.5	(6*S*)-**10c**	70	> 95
6	**3d**	2	0.25	(6*R*)-**10d**	68	> 95
7	**17**	2	20	(2*R*,4*S*,6*S*)-**11**	89	> 95
8	**18**	2	6	(2*R*,4*R*,6*S*)-**12**	82	> 95



Scheme 2 *Reagents and conditions*: i, *m*-CPBA, CH_2Cl_2, rt, 1–2 h, 98%; ii, L-Selectride, THF, −78 °C, 2 h, 73%; iii, $NaBH_4$, $CeCl_3$, MeOH, −78 °C, 3–4 h, 75%; iv, TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 2 h, 81–87%; v, Cs_2CO_3, CH_3CN, rt.

Notes and references

‡ β-Hydroxy sulfoximines have been used to resolve chiral racemic cyclic ketones.[9]

§ The optical purity was determined from the Mosher's esters.[10]

¶ The optical purity for **10c**,**d** was determined after reduction at C-4 using $NaBH_4$–$CeCl_3$ and formation of the Mosher's esters.[10]

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