Asymmetric Synthesis of Secondary Alcohols and 1,2-Disubstituted Epoxides via Organocatalytic Sulfenylation

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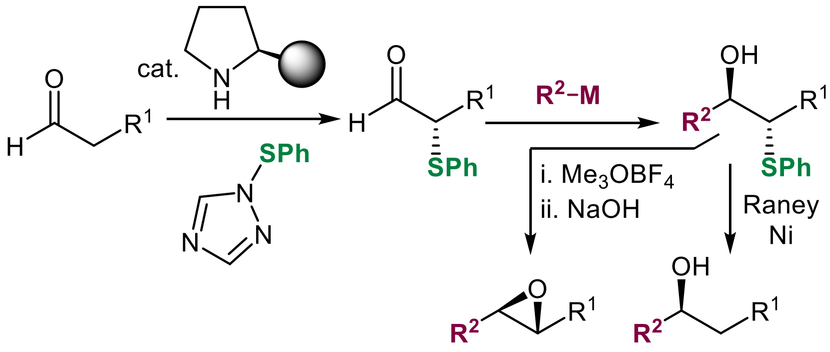
Dedicated to Professor Steven V. Ley CBE FRS; Happy 70th B'DA-y Steve!



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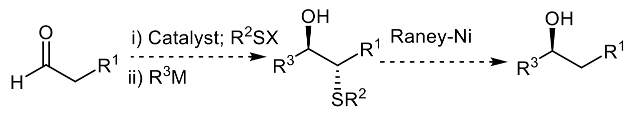
Abstract Enantioenriched secondary alcohols can be prepared via a short reaction sequence involving asymmetric organocatalytic sulfenylation of an aldehyde, organometallic addition and desulfurization. This process provides access to enantioenriched alcohols with sterically similar groups attached to the alcohol carbon atom. The intermediate β-hydroxysulfides can also serve as precursors to enantioenriched 1,2-disubstituted epoxides via alkylation of the sulfur and subsequent base-mediated ring closure.

Key words Asymmetric synthesis, Organocatalysis, Alcohols, Sulfur, Epoxides

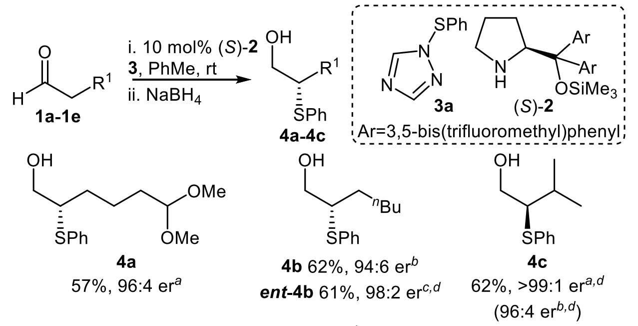
The asymmetric synthesis of secondary alcohols is a significant challenge in organic chemistry, with typical approaches including the asymmetric reduction of pro-chiral ketones[2] and the asymmetric addition of organometallic reagents to aldehydes.[3] Whilst both of these approaches have proved successful in many cases, it is often difficult to achieve high levels of enantioselectivity when the two groups attached to the alcohol carbon atom have similar steric demands. We envisaged that a general asymmetric synthesis of secondary alcohols could be achieved via organocatalytic sulfenylation of an aldehyde at the alpha position, diastereoselective addition of an organometallic reagent to the aldehyde, and subsequent sulfur removal using Raney-nickel (Scheme 1). Such an approach should be very versatile as the large sulfenyl group can be used as a 'traceless temporary chiral auxiliary' which controls the formation of the chiral alcohol centre even if the two groups R^1 and R^3 are sterically undemanding.



Scheme 1 Proposed new asymmetric synthesis of secondary alcohols.

The field of organocatalysis has grown enormously over the past 20 years, with many effective methods now available for carrying out asymmetric reactions using small molecule catalysts.[4] In particular, many different catalysts derived from amino acids have been developed for achieving asymmetric functionalisation of aldehydes via 'enamine' catalysis.[5] The Jørgensen-Hayashi catalyst **2**[6] has proved to be particularly versatile in this respect as it can be used to introduce a wide variety of groups at the alpha position of an aldehyde with high levels of asymmetric induction in most cases.[6-8] Organocatalytic sulfenylation reactions have been reported using *N*-sulfenylheterocycles as electrophiles, although to date only the synthesis of benzyl[8a] and hexyl[8b,8c] sulfides has been reported.

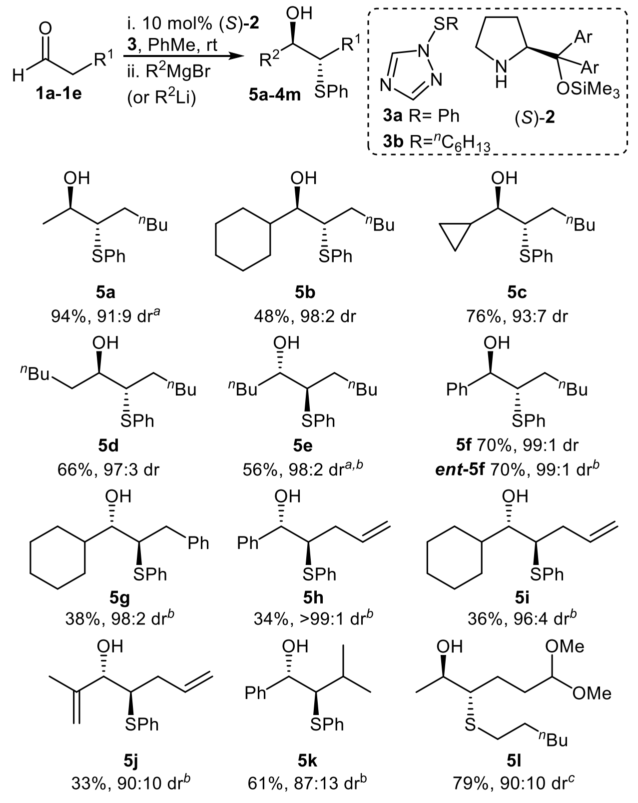
The choice of sulfur group for our proposed asymmetric synthesis of secondary alcohols is crucial as a high diastereoselectivity in the organometallic addition reaction is a pre-requisite for an efficient synthesis. From a study of the literature[9] and preliminary experiments we noted that higher diastereoselectivities were obtained from addition of organometallic reagents to aldehydes bearing bulkier groups such as *tert*-butyl or phenyl sulfides. The latter group was selected for further exploration, due to the extremely potent odor of *tert*-butyl thiol and its derivatives. As to the best of our knowledge the asymmetric introduction of a phenylsulfenyl group[9d] has never been previously reported using organocatalysis, we began our investigation by preparing the requisite *N*-phenylsulfenyl triazole **3a**.[10] With this compound in hand, we were then able to identify a procedure for organocatalytic sulfenylation[8] to provide the desired α-phenylsulfenyl aldehydes in high enantiopurity (Scheme 2). As noted previously,[8] the α-sulfenylaldehydes were prone to partial racemization during chromatographic purification. As can be seen from the measured enantiopurities, even brief exposure of the aldehydes to silica gel can cause some racemization.[11]



[a]No purification of intermediate aldehyde; [b]The intermediate aldehyde was purified by filtration through a plug of silica gel; [c]The intermediate aldehyde was purified by rapid vacuum filtration through a plug of silica gel [d](*R*)-2 used as catalyst;

Scheme 2 Asymmetric organocatalytic α-phenylsulfenylation of aldehydes using the Jorgensen-Hayashi catalyst.

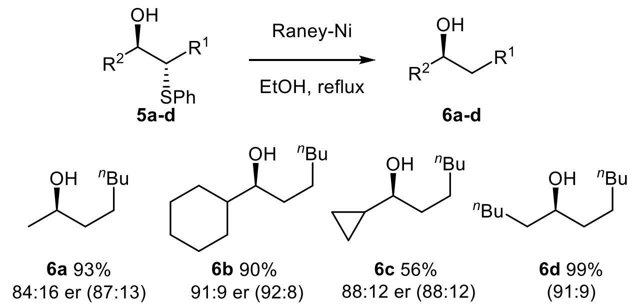
Direct addition of an organometallic reagent to the crude reaction mixture obtained from the asymmetric sulfenylation reaction typically resulted in low yields of the resulting β-hydroxysulfide and low diastereoselectivity, so a two-step procedure was developed in which the intermediate α-sulfenylaldehyde was purified by vacuum filtration through a plug of silica gel, eluting with toluene.[12] The crude toluene solution of aldehyde was then directly reacted with the required organometallic reagent. This typically resulted in moderate to high yields of the desired β-hydroxysulfides **5** and excellent diastereoselectivity in most cases.



[a]R^2Li was used; [b](*R*)-2 used as catalyst; [c]3b was used

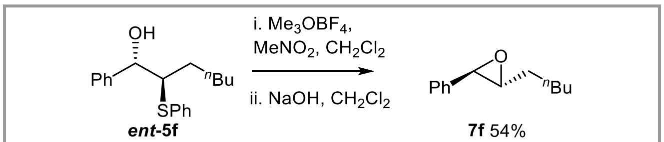
Scheme 3 Synthesis of β-hydroxysulfides via organocatalyitc sulfenylation of aldehydes followed by organometallic addition.

The major diastereoisomer was found to be the *anti*-diastereoisomer in accordance with previous reports.[9,13] A selection of β-hydroxysulfides **5a**-**5l** was prepared (Scheme 3), including examples containing linear and branched alkyl groups (**5a**-**5e**, **5k**), benzene rings (**5f**-**5h**, **5k**), alkenes (**5h**-**5j**) and an acetal (**5l**). With a selection of β-hydroxysulfides in hand, the key desulfurization step was explored. We had some concerns about the desulfurization as similar transformations of sugar-derived sulfides containing free alcohols have been reported to be low yielding.[14] Pleasingly, however, treatment of a small selection of β-hydroxysulfides **5a**-**5d** with Raney-nickel in ethanol, resulted in clean desulfurization to give the desired alcohols **6a**-**6d** in generally excellent yield in most cases (Scheme 4).[15] This provided access to enantioenriched secondary alcohols, including examples which would be extremely difficult to prepare using existing methods (e.g. **6d**), due to the very similar steric demands of the groups attached to the alcohol carbon atom. The enantiopurity of the secondary alcohols, as measured using Mosher's acid,[11] was in close agreement with the calculated enantiopurity[16] suggesting that only low levels of racemization took place during the reaction sequence. However, in the case of alcohol **6d**, it was not possible to determine the enantiomeric ratio directly as the two Mosher's ester derivatives had identical NMR spectra.[17]



Scheme 4 Desulfurisation of β-hydroxysulfides to give enantioenriched secondary alcohols. Enantiomeric ratios were determined via formation of the Mosher's esters;[11] calculated enantiomeric ratios are shown in parentheses.[15]

We envisaged that the β-hydroxysulfides could also be used to synthesise 1,2-disubstituted epoxides via conversion of the sulfide group into a suitable leaving group.[18] For β-hydroxysulfide ***ent*-5f** this was achieved via alkylation with Meerwein's salt, followed by treatment with base to give the epoxide **7f** in moderate yield. There are relatively few methods available for accessing this type of unfunctionalised 1,2-disubstituted epoxide[19] in high enantiopurity, so this approach may prove extremely useful.



Scheme 5 Conversion of a β-hydroxysulfide into an enantioenriched 1,2-disubstituted epoxide

In conclusion, we have demonstrated that asymmetric organocatalytic sulfenylation of aldehydes can be employed in the synthesis of enantioenriched secondary alcohols and 1,2-disubstituted epoxides via short synthetic routes. This approach can provide access to enantiomerically enriched chiral building blocks which are difficult to access via existing approaches.

Acknowledgment

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO (this text will be deleted prior to publication)

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(12) **General procedure for preparation of β-hydroxysulfides 5:** A solution of aldehyde (1 eq) and catalyst **2** (0.1 eq) was stirred in toluene (1.3 M) for 15 min. A solution of sulfenyltriazole **3** (1.3 eq) in toluene (1.6 M) was added dropwise and the resulting mixture was stirred under argon at RT for 24 hr. The reaction mixture was then quickly sucked under vacuum through a pre-wet (toluene) pad of silica (~1.5g per 100 mg of aldehyde) and washed with toluene (10 ml per 100 mg of aldehyde). The filtrate was added dropwise to a solution of the organometallic reagent (3-4 eq) cooled to −78 °C (for Li reagents) or −10 °C (for Grignard reagents). The reaction was monitored by TLC and stirred until all the intermediate α-sulfenylaldehyde was consumed. The reaction was then quenched with sat NH_4Cl, and partitioned between water and Et_2O. The aqueous layer was extracted with Et_2O and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The crude β-hydroxysulfide was purified by column chromatography (Pet/Et_2O). **(*2R*,*3S*)-3-(Phenylthio)octan-2-ol (5a):** $[\alpha]_D^{25}$ −4.2 (c. 1.0, $CHCl_3$); ν_{max} (film/cm^{-1}) 3414, 3060, 2959, 2929, 2858, 1584, 1466, 1439, 1279, 1139. Isolated as a 91:9 mixture of diastereoisomers; ***major isomer*** δ_H (600 MHz, $CDCl_3$) 0.88 (3H, t, *J* = 6.8, CH_2CH_3), 1.19 (3H, d, *J* = 6.4, $CHCH_3$), 1.27-1.71 (8H, m, 4 × CH_2), 2.33 (1H, br s, O*H*), 3.16 (1H, ddd, *J* = 9.4, 5.8, 3.2, SC*H*), 3.89 (1H, qd, *J* = 6.4, 3.2, C*H*OH), 7.22-7.30 (3H, m, 3 × Ar*H*), 7.44 (2H, d, *J* = 7.7, 2 × Ar*H*); δ_C (150 MHz, $CDCl_3$) 14.2, 19.1, 22.6, 27.5, 30.1, 31.8, 58.7, 68.3, 127.1, 129.2, 132.0, 135.5; ***minor isomer*** δ_H (600 MHz, $CDCl_3$) 0.88 (3H, t, *J* = 6.8, CH_2CH_3), 1.25 (3H, d, *J* = 6.1, $CHCH_3$), 1.27-1.71 (8H, m, 4 × CH_2), 2.91 (1H, ddd, *J* = 9.6, 6.5, 3.2, SC*H*), 3.72 (1H, dq, *J* = 6.5, 6.1, C*H*OH), 7.22-7.30 (3H, m, 3 × Ar*H*), 7.44 (2H, d, *J* = 7.7, 2 × Ar*H*); δ_C (150 MHz, $CDCl_3$) 14.2, 20.2, 22.7, 27.0, 30.1, 31.1, 59.3, 68.3, 127.3, 129.1, 132.5, 135.5, Found (EI): $[M]^+$ 238.13884, $C_{14}H_{22}OS$ requires 238.13859.

(13) The absolute stereochemistry of the alcohol **5l** was determined by NMR analysis of the Mosher's ester derivatives (see Ref 11). Full experimental details are provided in the supporting information.

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(15) **General procedure for preparation of alcohols 6:** A solution of β-hydroxysulfide (1 mmol) and Raney-Ni (2 g) in EtOH (0.05 M) was stirred at reflux for 2-4 hours. The mixture was cooled to RT and filtered through a pad of Celite®. The filtrate was evaporated to dryness to afford the alcohol. **(*R*)-Octan-2-ol (6a):** $[\alpha]_D^{25}$ −5.4 (c. 1.0, $CHCl_3$); ν_{max} (film/cm^{-1}) 3339, 2960, 2927, 2857, 1462, 1373, 1279, 1177, 1141, 1115; δ_H (400 MHz, $CDCl_3$) 0.91 (3H, t, *J* = 6.9, CH_2CH_3), 1.21 (3H, d, *J* = 6.1, $CHCH_3$), 1.27-1.51 (10 H, m, 5 × CH_2), 3.81 (1H, m, C*H*OH); δ_C (100 MHz, $CDCl_3$) 14.1, 22.6, 23.5, 25.7, 29.3, 31.8, 39.4, 68.2. These spectroscopic data are in agreement with those reported previously: M. Maywald, A. Pfaltz, *Synthesis*, **2009**, 3654-3660.

(16) The diastereomeric β-hydroxysulfides were not readily separable. Thus, the enantiomeric ratio of the alcohol **6** was calculated from the enantiopurity of the intermediate α-sulfidoaldehyde (determined by reducing a sample to the primary alcohol **4**) and the diastereomeric ratio of the purified β-hydroxysulfide **5** used in the desulfurization reaction. Please see supporting information for further details.

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