Generation of a highly enantioenriched α-phenylthio-substituted Grignard-reagent

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Letter

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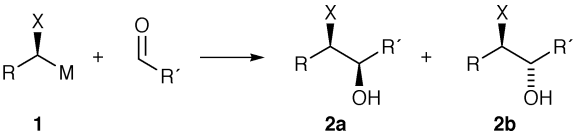
The α-phenylthio-substituted Grignard reagent 8 was generated in >95% ee by a sulfoxide/magnesium exchange reaction starting from the enantio- and diasteromerically pure α-phenylthio sulfoxide 6a. The α-thio-substituted Grignard reagent has been trapped with benzaldehyde to give the *syn*-β-phenylthio-substituted alcohol 9b in very high diastereoselectivity and enantiomeric purity.

α-Heterosubstituted alkylmetal reagents (**1**) are potentially useful chiral d[1]-synthons in organic synthesis.[1] On reaction with aldehydes two diastereomeric alcohols **2a** and **2b** are formed (Scheme 1). Simple diastereoselectivity is generally low using organolithium compounds.[2] There are indications that Grignard reagents of the type of **1** lead to higher diastereoselectivity,[3,4] possibly due to a change in the addition mechanism.[5]

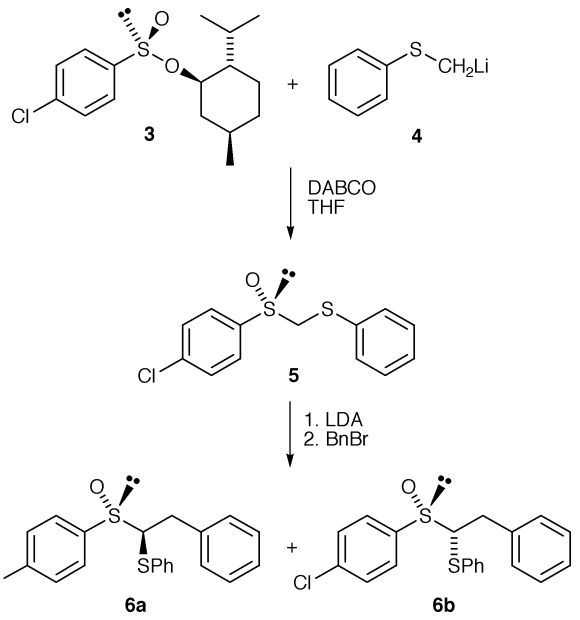
Configurational stability of the organometallic reagents **1** is another issue. For instance, in the case of the arylthio-substituted derivatives of **1** the organolithium compounds are configurationally labile, racemizing rapidly even at −110 °C.[6–9] Substantially higher configurational stability can be expected for the corresponding Grignard reagents.[3,10] Thus, for both reasons Grignard reagents such as **8** would be of interest, provided they can be generated in enantiomerically pure form. Grignard reagents can be generated by a sulfoxide/magnesium exchange, a reaction studied extensively by Satoh and Takano.[11] We used this reaction previously[12] to generate enantiomerically pure α-chloroalkyl Grignard reagents. This led us to investigate the sulfoxide/magnesium exchange reaction of the α-arylthio alkyl sulfoxides **6**.

The starting sulfoxide **6** was prepared (Scheme 2) by reacting α-phenylthio methyllithium (**4**) with a menthyl aryl sulfinate following precedent from the Gennari group.[13] We chose the *p*-chlorobenzene sulfinate **3**[14] instead of the more common *p*-toluene sulfinates in order to facilitate purification of the starting sulfoxides **6** by crystallization. Treatment of the menthyl sulfinate **3** with **4** at −78 °C thus generated the (+)-(*S*)-α-phenylthio sulfoxide **5** as white crystals (mp 71–72 °C) in 70% yield. The sulfoxide **5** was benzylated in 80% yield to furnish a 1 : 1 mixture of the diastereomeric sulfoxides **6a** and **6b**. The mixture was separated by column chromatography on silica gel to give **6a** {mp 103 °C, $[\alpha]_D^{20} = +17.9$ ($c = 1.09$, acetone)} and **6b** {mp 75 °C, $[\alpha]_D^{20} = -164.1$ ($c = 1.56$, acetone)}. The relative and absolute configuration of **6a** was assigned as (*S*,*S*) by X-ray structure analysis,† *cf.* Fig. 1.

When the stereochemically homogeneous sulfoxide **6a** was treated with ethylmagnesium bromide at −78 °C in THF (Scheme 3), rapid sulfoxide/magnesium exchange ensued to give the α-phenylthio alkyl Grignard reagent **8**. The latter was trapped after 10 min by addition of benzaldehyde, providing 58% of the β-hydroxy thioether **9** along with 99% of the sulfoxide **7** of 99% ee. The β-hydroxy thioether was obtained as a single diastereomer (*syn* : *anti* >98 : <2).



Scheme 1



Scheme 2

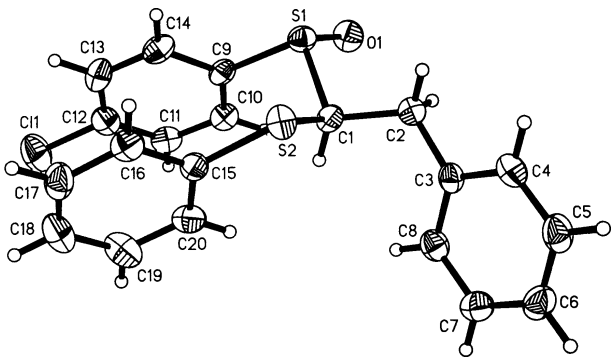
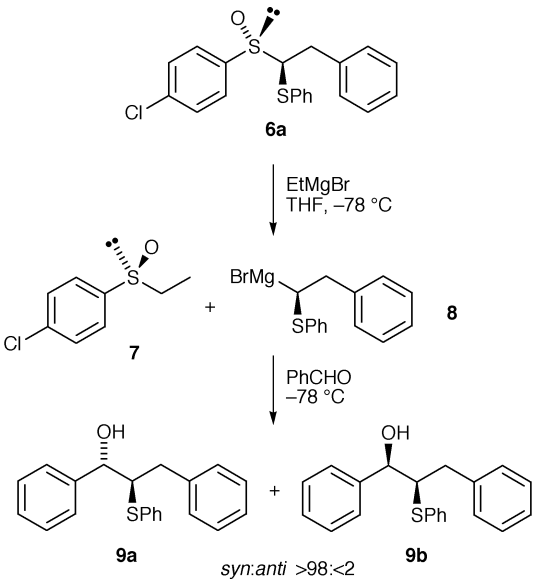


Fig. 1 Molecular structure of **6a**.



Scheme 3

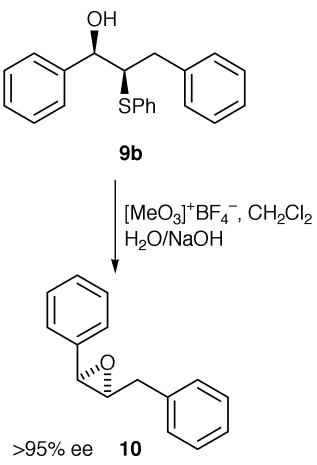
Its relative and absolute configuration could be assigned as **9b** by the following transformation. Methylation of the thioether with Meerwein's salt[15] generated a sulfonium ion, which on treatment with base (Scheme 4) furnished the epoxide **10** (67%, *cis* : *trans* >98 : <2). The enantiomeric purity of the epoxide was determined by ^{1}H NMR spectroscopy in the presence of Eu(hfc)$_3$ [hfc = 3-(heptafluoropropyl hydroxymethylene)-D-camphorate] to be >95%.

Since the absolute configuration of the epoxide **10**[16] and the sulfoxide **7**[17] is known, the stereochemical course of the sulfoxide/magnesium exchange can be shown to proceed with inversion at the sulfoxide sulfur atom and with retention of configuration in the formation of the carbon magnesium bond. This corresponds to our recent results found in the sulfoxide/magnesium exchange on α-chloroalkyl sulfoxides.[12]

The present study shows that α-arylthio alkyl Grignard reagents of type **8** can be generated in enantiomerically pure form by a sulfoxide/magnesium exchange reaction, that these reagents are configurationally stable at −78 °C for a sufficient period of time to be added to an aldehyde, and that this addition proceeds with very high (>98%) simple diastereoselectivity to provide the *syn*-diastereomer of **9**.

Experimental

All NMR experiments were performed on a Bruker AC300 spectrometer operating at 300 MHz (^{1}H) or 75.5 MHz (^{13}C).



Scheme 4

All manipulations were carried out under an argon atmosphere. All solvents were dried and deoxygenated prior to use. The (−)-(1*R*,3*R*,4*S*)-menthyl (*S*)-*p*-chlorobenzenesulfinate **3** was prepared according to the procedure of Klunder and Sharpless.[14]

Syntheses

(+)-(*S*)-*p*-Chlorophenyl 1-phenylthiomethyl sulfoxide, 5. An *n*-BuLi solution (18.3 mL, 26.6 mmol) in hexane was added to a solution of methyl phenyl sulfide (3.00 g, 24.2 mmol) and DABCO (2.71 g, 24.2 mmol) in 35 mL of dry THF at 0 °C. After stirring for 15 min and subsequently cooling to −78 °C a solution of (−)-(1*R*,3*R*,4*S*)-menthyl (*S*)-*p*-chlorobenzene sulfinate **3** (3.81 g, 12.1 mmol) in 40 ml of dry THF was added dropwise. Stirring overnight and the usual workup afforded **5** in 70% yield (2.40 g), which was purified by crystallization from acetone {$[\alpha]_D^{20}$ = +103.0 (*c* = 2.17, acetone), mp 71–72 °C}. ^{1}H NMR ($CDCl_3$): δ 7.64–7.21 (m, 9H, C*H* of Ar), 4.22 (d, ^2J = 13.6 Hz, 1H, CH*H*), 4.07 (d, ^2J = 13.5 Hz, 1H, C*H*H); ^{13}C NMR ($CDCl_3$): δ 141.07, 137.91, 133.25, 130.92 (2*C*), 129.29 (2*C*), 129.27 (2*C*), 127.77, 126.31 (2*C*), 60.77 (CH_2). Calc. for $C_{13}H_{11}ClOS_2$: C, 55.21; H, 3.92. Found: C, 55.13; H, 3.85%.

***p*-Chlorophenyl (2-phenyl-1-phenylthio-ethyl) sulfoxide, 6.** A lithium diisopropylamide solution (1.5 M, 3.07 mL, 4.60 mmol) in THF was added to a solution of **5** (1.15 g, 4.06 mmol) in 5 mL of dry THF at −78 °C. After 20 min, addition of benzyl bromide (0.90 g, 5.29 mmol), further stirring overnight, and the usual workup yielded **6** as a mixture of diastereomers (1 : 1) in 80% yield (1.22 g). Separation by column chromatography on silica gel (pentane : *tert*-butyl methyl ether 15 : 1) yielded 0.60 g of diastereomer (*S*,*S*)-**6** {$[\alpha]_D^{20}$ = +17.9 (*c* = 1.09, acetone), mp 103 °C}. ^{1}H NMR ($CDCl_3$): δ 7.62–7.33 (m, 4H, C*H* of Ar), 7.32–6.89 (m, 10H, C*H* of Ar), 4.01 (dd, ^3J = 3.3 Hz, ^3J = 10.8 Hz, 1H, C*H*S), 3.53 (dd, ^2J = 14.3 Hz, ^3J = 3.2 Hz, 1H, CH*H*), 2.94 (dd, ^2J = 14.3 Hz, ^3J = 10.9 Hz, 1H, C*H*H); ^{13}C NMR ($CDCl_3$): δ 140.27, 137.88, 136.41, 132.73, 132.46 (2*C*), 129.68 (2*C*), 129.07 (2*C*), 128.95 (2*C*), 128.56 (2*C*), 127.96 (2*C*), 127.39, 127.10, 75.95, 34.20. Diastereomer (*S*,*R*)-**6** (0.59 g) {$[\alpha]_D^{20}$ = −164.1 (*c* = 1.56, acetone), mp 75 °C}. ^{1}H NMR ($CDCl_3$): δ 7.77–7.48 (m, 4H, C*H* of Ar), 7.30–7.10 (m, 10H, C*H* of Ar), 4.20 (dd, ^3J = 3.5 Hz, ^3J = 11.2 Hz, 1H, C*H*S), 3.58 (dd, ^2J = 14.0 Hz, ^3J = 3.4 Hz, 1H, CH*H*), 2.18 (dd, ^2J = 14.0 Hz, ^3J = 11.3 Hz, 1H, C*H*H); ^{13}C NMR ($CDCl_3$): δ 137.92, 136.73, 132.14 (2*C*), 129.62 (2*C*), 129.21 (2*C*), 128.80 (2*C*), 128.63 (2*C*), 128.14 (2*C*), 127.70 (2*C*), 127.08, 73.57, 32.63, 1*C* not detected. Calc. for $C_{20}H_{17}ClOS_2$: C, 64.41; H, 4.59. Found: C, 64.41; H, 4.64%.

Typical procedure for sulfoxide/magnesium exchange. The lower compartment of a two-compartment reaction vessel[18] was charged with 109 μL of a solution of ethylmagnesium bromide (2.05 M, 0.22 mmol, diethyl ether) in 2 mL of dry THF. The upper compartment was charged with (*S*,*S*)-**6** (64 mg, 0.17 mmol) and 2 mL of dry THF. After cooling of both compartments to −78 °C the content of the upper chamber was added to the lower one and the reaction mixture was stirred for 10 min. Addition of precooled (−78 °C) benzaldehyde (54 mg, 0.51 mmol), stirring for 30 min, and the usual workup afforded the β-phenylthio-substituted alcohol **9b** in 58% yield (31 mg) as a colorless oil (*syn* : *anti* >98 : <2). ^{1}H NMR ($CDCl_3$): δ 7.31–7.04 (m, 15H, C*H* of Ar), 4.58 (dd, ^3J = 3.4 Hz, ^3J = 6.8 Hz, 1H, C*H*OH), 3.39 (ddd, ^3J = 5.3 Hz, ^3J = 6.7 Hz, ^3J = 9.5 Hz, 1H, C*H*S), 3.12 (d, ^3J = 3.4 Hz, 1H, O*H*), 2.86 (dd, ^2J = 14.3 Hz, ^3J = 5.3 Hz, 1H, CH*H*), 2.61 (dd, ^2J = 14.3 Hz, ^3J = 9.5 Hz, 1H, C*H*H); ^{13}C NMR ($CDCl_3$): δ 142.05, 139.00, 133.10 (2*C*), 129.25 (2*C*), 128.82 (2*C*), 128.36

(2*C*), 128.31 (2*C*), 127.64 (2*C*), 127.49 (2*C*), 126.83, 126.41, 74.95, 61.33, 29.69. HRMS Calc. for $C_{21}H_{20}OS$: 320.1235. Found: 320.1232 ± 0.3 amu.

Acknowledgements

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Notes and references

† Crystal structure analysis: (*S*,*S*)-**6**: $C_{20}H_{17}ClOS_2$: $M = 372.91$, monoclinic, space group $P2_1$, $a = 925.1$ (1), $b = 904.0$ (1), $c = 1140.1$ (1) pm, $\alpha = 90$, $\beta = 111.656$ (5), $\gamma = 90°$, $U = 886.1(1) \times 10^{-30}$ m^3, $Z = 2$, μ(Cu-Kα) = 4.129 mm^{-1}, $T = 213(2)$ K, 2767 reflections measured, $R_{int} = 0.0719$, reflections with $I > 2\sigma(I) = 2598$, final $R(F) = 0.0486$, $wR(F^2) = 0.1336$. Refinement of an inversion twin parameter[19] [$x = 0.00(2)$, where $x = 0$ for the correct absolute structure and + 1 for the inverted structure] confirmed the absolute structure of **6a**.

CCDC reference number 440/138. See http://www.rsc.org/suppdata/nj/1999/973/ for crystallographic files in .cif format.

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