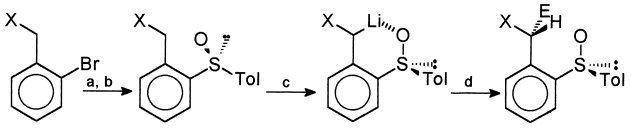
Enantioselective Generation of Benzylic Stereocenters Mediated by a Remote Sulfoxide**

José L. García Ruano,* M. Carmen Carreño,*
Miguel A. Toledo, José M. Aguirre, M. Teresa Aranda, and Jean Fischer

Enantioselective C–C bond formations via benzyllithium derivatives generated by deprotonation with organolithium bases has attracted the interest of several groups in the past two decades.[1] High asymmetric inductions were achieved by using the lithiation–substitution sequence when chiral auxiliaries are located in a remote position of the aliphatic chain[2] or by starting from tricarbonyl chromium arene complexes.[3] (−)-Sparteine[4] has been effectively used as chiral ligand to promote enantioselective synthesis of benzylic carbanions from alkylbenzenes bearing *ortho* substituents such as R_2NCO[5] and *t*BuCONH.[6] Enantiopure bis(oxazolines)[7] have also been applied with variable success.

In our continuing search for new applications of sulfoxides in asymmetric synthesis,[8] we found that association of the sulfinyl oxygen atom with lithium was essential to achieve highly diastereoselective 1,2-induction processes such as aldol-type reactions.[9] These results prompted us to investigate whether enantiopure *ortho*-sulfinyl groups[10] can stabilize benzyllithium carbanions and promote diastereoselective reactions with electrophiles by a 1,4-induction process.

This possibility was evaluated for (*S*)-2-ethylphenyl *p*-tolylsulfoxide (**3**) and (*S*)-2-(triisopropylsiloxymethyl)phenyl *p*-tolylsulfoxide (**4**; Scheme 1), which are easily accessible in high *ee* (98% by ^{1}H NMR) by Andersen synthesis[11] from *ortho*-bromo derivatives of ethylbenzene (**1**) and triisopropylsilyloxymethylbenzene (**2**). Organomagnesium reagents were used for the reaction with menthyl *p*-toluene sulfinate despite the better yields obtained with lithium analogues, since these afforded partially racemized **3** and **4**.



Scheme 1. Synthesis of **3** and **4** and reaction of their benzyllithium derivatives with electrophiles. a) Mg/diethyl ether, RT, for **1**; 1) *n*BuLi/THF, −78 °C; 2) $MgBr_2$, RT, for **2**. b) (*S*,*S*)- $TolSO_2$Menthyl, THF, −78 °C. c) LDA, THF, −78 °C. d) Electrophile, THF, −78 °C. OTIPS = OSi*i*Pr$_3$.

[*] Prof. J. L. García Ruano, Prof. M. C. Carreño, Dr. M. A. Toledo, M. T. Aranda
Departamento de Química Orgánica (C-I)
Universidad Autónoma
Cantoblanco, 28049-Madrid (Spain)
Fax: (+349) 1-397-3966
E-mail: joseluis.garcia.ruano@uam.es
carmen.carrenno@uam.es
Prof. J. M. Aguirre
Universidad de Lujan, Lujan (Argentina)
Prof. J. Fischer
Lab. de Cristallochimie, Université Louis Pasteur
67070-Strasbourg (France)

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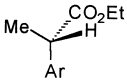
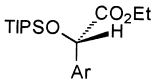
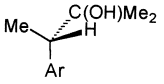
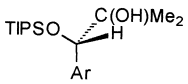
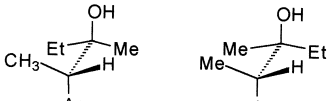
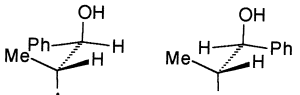
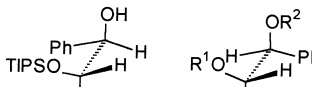
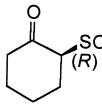
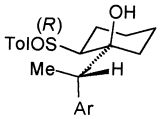
Regioselective deprotonation of **3** and **4** at the benzylic position with lithium diisopropylamide (LDA) at −78 °C[12] gave carbanions **A**. Quantitative formation of LDA was essential to avoid the partial racemization of the sulfoxide that occurred when traces of BuLi were present. Intermediates **A** reacted with electrophiles to give **a** as the major diastereomers (Scheme 1, Table 1).

As shown in Table 1, reaction of carbanions derived from **3** and **4** with ethyl chloroformate afforded diastereomerically pure esters **5a**[13] and **6a** (entries 1 and 2). In a similar way, acetone yielded pure diastereomers **7a** and **8a** from **3** and **4**, respectively (entries 3 and 4).[14] With asymmetrically substituted electrophiles, such as 2-butanone, compound **3** evolved

Table 1. Reactions of carbanions derived from **3** and **4** with electrophiles (Scheme 1).

Entry	Carbanion Precursor	Electrophile	Products (diastereomer ratio)[a]	Yield [%]
1	**3**	$ClCO_2Et$	 **5a**	75
2	**4**	$ClCO_2Et$	 **6a**	75
3	**3**	MeCOMe	 **7a**	81
4	**4**	MeCOMe	 **8a**	78
5	**3**	MeCOEt	 **9a** (50) **9b** (50)	81
6	**3**	PhCHO	 **10a** (85) **10b** (15)	65[b]
7	**4**	PhCHO	 **11a** (78) **11b** (22)[c]	57[d]
8	**3**	 **12**	 **13a**	75

[a] Ar = (*S*)-2-*p*-tolylsulfinylphenyl. [b] Yield of pure **10a**. [c] Characterized as 50:50 mixture of R^1 = OTIPS; R^2 = H and R^1 = H; R^2 = OTIPS. [d] Yield of pure **11a**.

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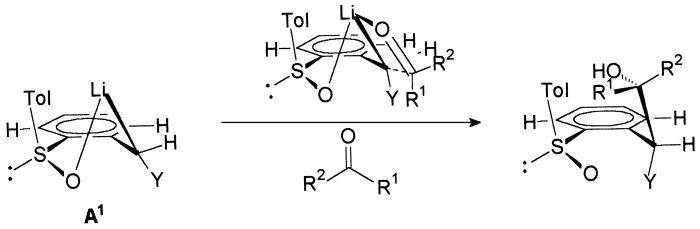
into a 1:1 mixture of carbinols **9a** and **9b**, which are epimers at the hydroxy-bearing carbon atom (entry 5). The stereogenic benzylic center showed the *S* absolute configuration. Reactions of **3** and **4** with benzaldehyde were more stereoselective. Starting from **3**, an 85:15 mixture of epimeric carbinols **10a** and **10b** was formed (entry 6); pure **10a** was isolated by chromatography. Under similar conditions, **4** yielded a 78:22 mixture of diol derivatives **11a** and **11b** (entry 7). The latter was characterized as a 50:50 regioisomeric mixture of 1- and 2-TIPS derivatives, which evolved into the diol after treatment with nBu$_4$NF. The rearrangement of silyl groups in similar 1,2-diols has already been reported.[15] To control the absolute configuration of both new stereogenic centers, a double asymmetric induction was performed in the reaction between **3** and [2*S*,(S)*R*]-2-(*p*-tolylsulfinyl)cyclohexanone (**12**).[9] The exclusive formation of diastereoisomer **13a** (entry 8) was consistent with the known stereochemical behavior of **12** in nucleophilic additions.

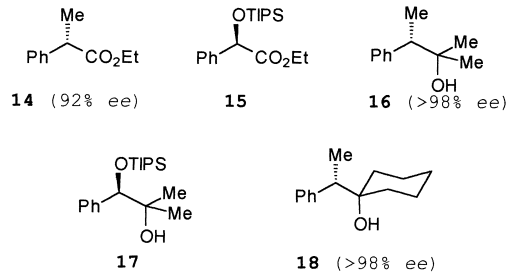
According to these results, the new benzylic stereogenic centers were always generated in a highly diastereoselective manner and with the same asymmetric induction, independent of the electrophile. When additional stereogenic centers were created, the stereoselectivity of the process was electrophile-dependent. A plausible mechanism that accounts for our current observations is shown in Scheme 2. Benzyllithium



Scheme 2. Favored transition state for reaction of intermediates **A** with electrophiles.

derivative $\mathbf{A^1}$ must be the most stable among all diastereomers and conformers since it lacks allylic strain.[16] The metal-assisted pseudoequatorial approach of the electrophile would yield the observed *S* configuration at the benzylic center if the configuration of the carbanion were retained. When the electrophile is prochiral, the stabilities of the transition states depend on the relative size of R^1 and R^2. When they are similar, equimolar mixtures of two epimers are formed (entry 5), while higher diastereoselectivies are observed when R^1 and R^2 are very different (entries 6 and 7).

Important for preparative applications of this methodology is the removal of the auxiliary. This was quantitatively achieved in compounds **5a**–**8a** and **13a** by reaction with Raney nickel, which gave **14**–**18** (Scheme 3). Formation of known **14**[17] and **16**[18] confirmed the absolute configuration of **5a** and **7a**. The enantiomeric purity of desulfurized products **14**, **16**, and **18** was identical to that of the starting materials. For OTIPS derivatives **6a** and **8a** the enantiomeric excess of the resulting compounds **15** and **17** could be determined neither by ^{1}H NMR spectroscopy nor by HPLC.



Scheme 3. Products of desulfurization of **5a**, **7a**, and **13a**. For **14** and **16**, the *ee* was determined by comparison with reported $[\alpha]_D^{20}$ values.[17, 18]

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[13] Characterization of **5a** was carried out immediately after crystallization since it readily epimerizes at C-2.
[14] The structures of **8a** and **10a** were established by X-ray diffraction. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications nos. CCDC-139404 and -139405. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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[16] The chelate structure proposed for $\mathbf{A^1}$ is consistent with the result observed when reaction of **3** with acetone (entry 3) was conducted in the presence of hexamethylphosphoric triamide (6 equiv). Under these conditions, an 87:13 mixture of **7a** and its epimer at the benzylic carbon atom was isolated.
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