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

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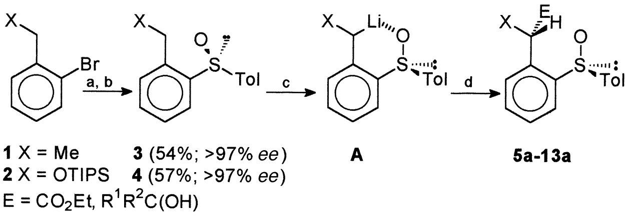
Enantioselective C–C bond formations via benzyllithium derivatives generated by deprotonation with organolithium bases has attracted the interest of several groups in the past two decades.[1] High asymmetric inductions were achieved by using the lithiation–substitution sequence when chiral auxiliaries 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 ^1H 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**.

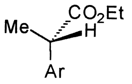
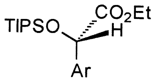
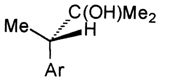
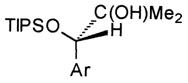
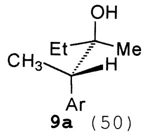
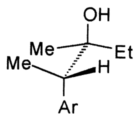
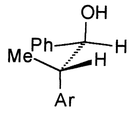
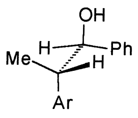
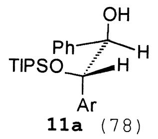
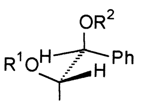
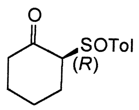
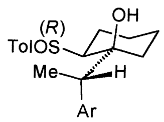
Regioselective deprotonation of **3** and **4** at the benzylic position with lithium diisopropylamide (LDA) at −78 °C[12] gave carbanions **A**. Quantitative formation of LDA was essential to avoid the partial racemization of the sulfoxide that occurred when traces of BuLi were present. Intermediates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



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*)- $TolSO_2Menthyl$, THF, −78 °C. c) LDA, THF, −78 °C. d) Electrophile, THF, −78 °C. OTIPS = $OSi\textit{i}Pr_3$.

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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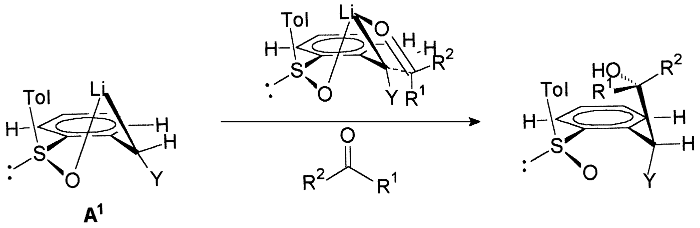
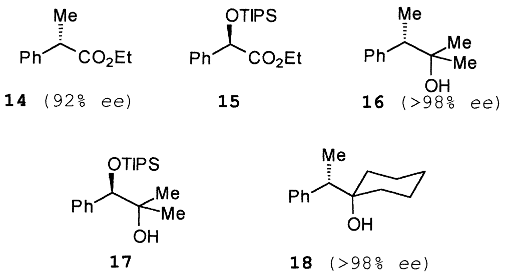
into a 1:1 mixture of carbinols **9a** and **9b**, which are epimers at the hydroxy-bearing carbon atom (entry 5). The stereogenic benzylic center showed the *S* absolute configuration. Reactions of **3** and **4** with benzaldehyde were more stereoselective. Starting from **3**, an 85:15 mixture of 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 $n\mathrm{Bu_4NF}$. 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 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).



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

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).

[15] See M. Lalonde, T. H. Chan, *Synthesis* **1985**, 817.

[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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