Remote Asymmetric Induction in Michael Additions of Allylic Sulfones

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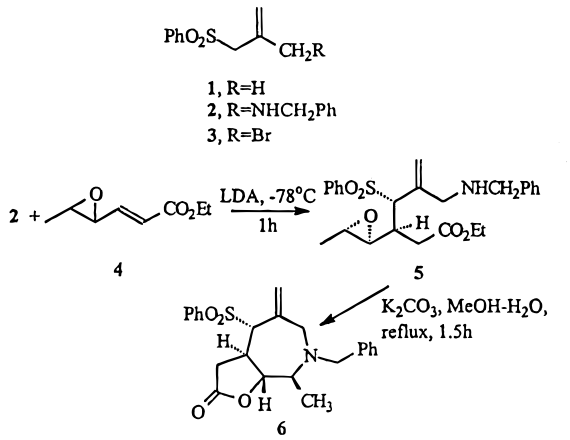
Chiral auxiliary-controlled asymmetric Michael reactions are a topic of current interest in asymmetric synthesis.[2] In this context, Michael additions of allylic-type anions, part of chiral donor moieties, were mostly related to organophosphorus[3] and α-sulfinyl[4] anions. The reported conjugate additions were γ-regioselective, and the achievement of diastereofacial selectivity was assisted by cyclic platforms on the anionic substrate or by cyclic Michael acceptors, to reduce the conformational flexibility of the chelated intermediates. Extension of this methodology to acyclic substrates is more challenging. We report herein on the possibility to convey remote asymmetric information in conjugate additions involving acyclic substrates, with allylic α-sulfonyl anions as part of the transferred chiral moiety.

Taking advantage of our[5] and Najera's group's[6] findings concerning the high anti diastereoselectivity[7] and α-regioselectivity obtained in Michael reactions of allylic α-sulfonyl carbanions with open-chain α,β-unsaturated esters, we envisaged the possibility of transmitting asymmetry in these reactions by placing a remote chiral auxiliary in the allylic sulfone donor. The aminated sulfone **2**[6] was chosen as the model compound because intramolecular Li bridging in the lithiated intermediate[8] was assumed to enhance a facially selective approach: we indeed found that the high anti diastereoselectivity (>97%) obtained in the conjugate addition of **2** with ethyl crotonate (LDA, THF) was less affected by adding to the reaction mixture chelation-disrupting cosolvents[9] than in identical reactions of **1**. Moreover, the reaction of **2** with the epoxy ester **4** afforded a major stereomer **5** (>72% yield) with four contiguous stereocenters, which was further cyclized under basic conditions to the lactone-fused hexahydroazepine **6**[10] (21%, Scheme 1). Hence, the (*S*)-*N*-(1′-phenylethyl) aminated sulfone **7** was prepared and treated with LDA (1.2 equiv) in THF at −78 °C, followed by an unsaturated ester (1.4 equiv). As determined by ^{1}H NMR analysis of the crude product mixture and subsequent chromatographic purification, only two out of four possible diastereomers were formed, both with an anti arrangement at the newly formed stereogenic centers (**8**−**11a,b**, Scheme 2 and Table 1).[10] The diastereomeric ratio (dr) (82:18) was further improved to a remarkable remote asymmetric induction of ∼9:1 (entries 3−5) by changing the Li base and lowering the temperature, under otherwise similar conditions. The introduction of a bulky *tert*-butyl ester group resulted in a less selective diastereomeric ratio (entry 6). Conjugate addition of **7** to 4-bromocrotonate and tandem ring closure (eq 1)[11] gave the cyclopropane carboxylate **12a,b** (9:1 dr). Separation of the major diastereomer of **12** (mp 114−115 °C, 60%, $[\alpha]_D = -133°$) enabled the determination of its absolute configuration by X-ray crystallography as the (3*S*,1′*S*) amine derivative; by analogy, the same absolute configuration can be assigned for all major diastereomers designated as **a** in Table 1.

Scheme 1



Scheme 2

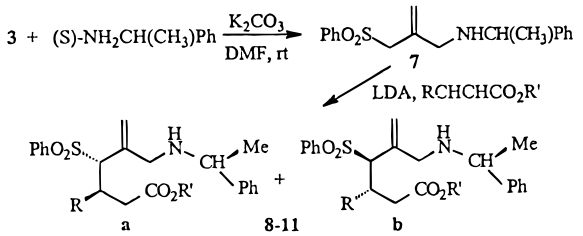


Table 1. Diastereomeric Ratio (dr) of Adducts Shown in Scheme 2

entry	R	R′	reaction conditions	yield (%)	dr **a**:**b**
1	Me	Et	LDA, −78 °C, 1 h	72	**8**, 82:18
2	Me	Et	LHMDS, −95 °C, 1.5 h	89	**8**, 87:13
3	Me	Et	LHMDS, −108 °C, 2 h	77	**8**, 89:11
4	Ph	Et	LHMDS, −108 °C, 3.5 h	80	**9**, 89:11
5	*n*-propyl	Me	LHMDS, −108 °C, 3 h	75	**10**, 90:10
6	Me	^{t}Bu	LDA, −60 °C, 5 h[a]	57	**11**, 62:38

[a] No reaction at lower temperature.

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(8) See, e.g.: Eisch, J. J.; Galle, J. E. *J. Org. Chem.* **1980**, *45*, 4534−4536.

(9) For **1**, addition of 10% DMPU resulted in a change of the anti/syn ratio of adducts from 88:12 (84%) to 67:33 (83%); with 10% HPMA the ratio was 40:60. For the donor **2**, the anti/syn ratio changed from >97% anti to 89:11 (with 10% DMPU, 92%) and to 60:40 (with 10% HMPA, 76%).

(10) The stereochemistry was established by ^{1}H and ^{13}C NMR analysis and NOESY data.

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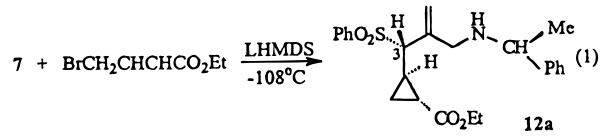
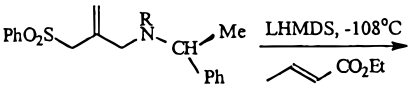
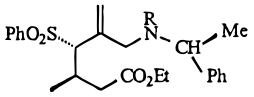


(1)

Donors with additionally substituted amines (**13** and **14**) gave diastereomeric pairs (**15**, **16**, eq 2) with lower diastereoselectivity; hence, hindering groups obstruct the transmission of asymmetry, as found above also for *tert*-butyl esters.



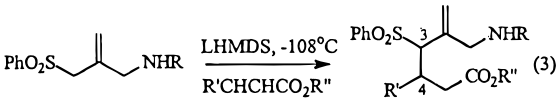
13: R=Me
14: R=CH_2Ph



(2)

15: R=Me, 88% yield, 78:22 dr
16: R=CH_2Ph, 76% yield, 67:33 dr

Variation of the chiral auxiliary can influence asymmetric induction.[12] In an effort to rationalize the remote transmission of asymmetry, several allylic sulfones with different amine-bound chiral substituents were reacted with unsaturated esters under identical reaction conditions (eq 3 and Table 2). The most striking effect was observed by changing



(3)

17: R=(S)-CH(CH_2OMe)Ph
18: R=(S)-CH(CH_2OCH_2Ph)Ph
19: R=(S)-CH(CH_3)-cyclohexyl
20: R= (S)-CH(CH_3)-1-naphthyl

a: 3S, 4R
b: 3R, 4S

the phenyl group at the chiral center to a cyclohexyl: the asymmetric induction was reduced to nil, an equal amount of diastereomers being formed (entries 3 and 4). Hence, the intramolecular Li bridging in the transition state and stereofacial approach is not sufficient for conveying asymmetry in the product unless there is an additional interaction, presumably of Li with the π electrons of an aromatic ring bound to the chiral center.[13] Starting from this premise, we performed conjugate additions with donors bearing a naphthyl instead of a phenyl group at the chiral center with the hope that the bulkier aromatic group would improve the proximity effect. Indeed, enhancement of dr (93:7) was determined in the obtained high-yield products (entries 5−7).

Table 2. Influence of the Chiral Auxiliary on dr (Eq 3)

entry	donor	ester R′	ester R″	reaction time (h)	yield (%)	dr **a**:**b**
1	17	Me	Et	2	83	**21**, 74:26
2	18	Me	Et	1	84	**22**, 73:27
3	19	Me	Et	1.5	73	**23**, 1:1
4	19	Ph	Et	3	76	**24**, 1:1
5	20	Me	Et	1	94	**25**, 93:7
6	20	Ph	Et	5.5	95	**26**, 94:6
7	20	*n*-propyl	Me	4	89	**27**, 93:7
8	20	CH_2Br	Et	4	73	**28**,[a] 93:7

[a] Cyclopropanecarboxylate, analogue of **12** was obtained.

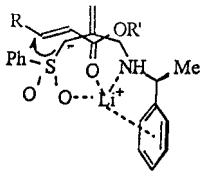


Figure 1. Preferential transitional structure for Michael addition.

Complex-induced proximity effects have been shown to control the course of some chemical reactions.[14] Recently, dilithiated enolates of amide-bound chiral auxiliaries have been found to lead to diastereoselective substitutions[15] and to exert long-distance diastereocontrol over substitutions at sulfone-activated carbanions.[16]

In summary, a new pathway of remote asymmetric induction in Michael reactions involving allylic α-phenylsulfonyl carbanions in chiral donors has been disclosed. The transmission of asymmetry was found to depend on the presence of an aromatic nucleus bound to the chiral center.

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Supporting Information Available: Experimental procedures, NMR spectral data for new compounds, and X-ray data for compound **12** (79 pages).

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