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Origin of the Diastereoselection in the Indium-Mediated Addition of Haloallylic Sulfones to Aldehydes

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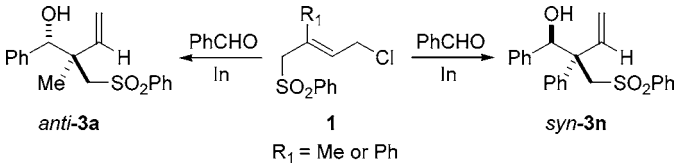
ABSTRACT



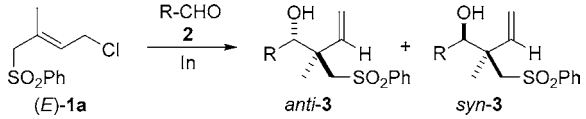
anti-**3a** **1** *syn*-**3n**

R_1 = Me or Ph

The R_1 substituents at C(2) of the haloallylic sulfones 1 play a pivotal role in controlling the diastereoselectivity of the indium-mediated addition reaction to benzaldehyde to produce the homoallylic alcohols 3. The R_1 Me group of 1 prefers the chair form in the In-coordinated six-membered cyclic transition state to give *anti*-3a, and the R_1 Ph group of 1 favors the twist boat form to give *syn*-3n, both in a high 13:1 selectivity.

The metal-mediated addition reaction of allylic halides to carbonyl compounds is an efficient method of producing homoallylic alcohols.[1] Sn, Zn, and Al as well as Mg have been utilized as a mediating metal. Recently, indium has been increasingly used in this Barbier-type reaction for the reason that diverse functional groups are compatible in environmentally benign aqueous solutions.[2] The selectivity and mildness of the In-mediated Barbier reaction led us to devise the reaction of the allylic halides (*E*)-**1a**[3] containing an allylic sulfone unit and aldehydes **2**, in which the expected homoallylic alcohols **3** containing a homoallylic sulfone moiety by the normal γ-addition[2a,4] might be useful building blocks in organic synthesis (Scheme 1). High diastereoselectivity and regioselectivity along with a high reaction yield for *anti*-**3a** (OH vs SO_2Ph) were obtained in the In-mediated reaction of (*E*)-**1a** and benzaldehyde (**2a**). The detailed studies on the In-mediated reaction of diverse allylic halides **1** and various aldehydes **2**, especially on the origin of the unusually high diastereoselection, are disclosed in this communication.

Scheme 1. Indium-Mediated Addition of Chloroallylic Sulfone (*E*)-**1a** to Aldehydes **2**



(*E*)-**1a** *anti*-**3** *syn*-**3**

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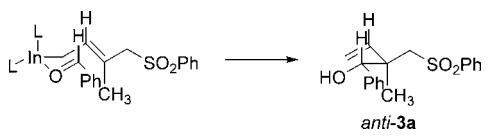
Optimization of the reaction condition for the In-mediated addition of the chloroallylic sulfone (*E*)-**1a** to benzaldehyde (**2a**, R = Ph in Scheme 1) has been studied first. Anhydrous THF and CH_2Cl_2 were not able to solvate indium, and the reaction did not proceed at all in these solvents even at reflux. Decomposition of the reagents was observed in refluxing DMF. The addition product **3a** (R = Ph in Scheme 1) was obtained in 55% and 62% yields under refluxing EtOH and H_2O, respectively. The yields were improved in a mixed solvent of H_2O and an organic solvent at reflux temperatures. The best result was obtained in a 4:1 volumetric mixture of H_2O and THF at reflux for 2.5 h, in which the homoallylic alcohol **3a** was obtained in 98% yield with a 13:1 (anti/syn) diastereomeric ratio. The reaction was sluggish at 25 °C, and a lower yield (68%) was obtained even after 24 h. When 6 equiv of H_2O (based on indium) was added to THF,[5] the reaction proceeded, but the yield (50%) and the selectivity (dr = 3:1) were much lower than those of the optimized condition.

The efficacy of indium in the Barbier reaction of (*E*)-**1a** and benzaldehyde (**2a**) was confirmed at this point by comparison with the reactions mediated by other metal species, such as Mg, Zn, and Sn. The Mg-mediated reaction of (*E*)-**1a** and **2a** did not produce **3a** at all, which manifested that the allylic sulfone unit served as a good leaving group in the allyl Grignard reagent. The Zn- or Sn-mediated Barbier reaction of (*E*)-**1a** and **2a** under the above optimized condition (the 4:1 mixed solvent of H_2O and THF at reflux for 2.5 h) produced **3a** in only 20% yield with 6:1 anti-diastereoselectivity.

Exclusive γ-addition of the chloroallylic sulfone (*E*)-**1a** to benzaldehyde (**2a**) was observed in the In-mediated Barbier reaction.[2a,4] Stereochemistry of the major product **3a** was confirmed by X-ray crystallographic analysis, in which the hydroxyl and the benzenesulfonyl groups were anti-disposed. The Zimmerman−Traxler pericyclic transition state model has been the central dogma in the prediction of the diastereoselectivity of the aldol reaction,[6] which similarly correlated the C=C bond configuration of allylic halides to the diastereochemistry of the adducts in the Barbier reactions (*E* to anti and *Z* to syn). The major product *anti*-**3a** was presumably formed through the chairlike transition state, where the bulky phenyl group of the aldehyde was preferentially disposed to the equatorial position (Scheme 2).

Scheme 2. Chairlike Transition State Model for the Indium-Mediated Addition of (*E*)-**1a** to **2a** Leading to *anti*-**3a**



anti-**3a**

Considering the little or no (2:1∼3:2) diastereoselection reported in the In-mediated addition of crotyl bromide to benzaldehyde,[2a,4] the above 13:1 ratio was very surprising. We wanted to know the generality and the origin of this unusually high diastereoselection. Steric and electronic effects of aldehydes on the diastereoselectivity have been evaluated first and were summarized in Table 1. The same

Table 1. In-Mediated Addition of the Chloroallylic Sulfone (*E*)-**1a** to Diverse Aldehydes **2**[a]

entry	R in compd **2**	*t* (h)	**3**	yield (%)	dr[b]	chemical shift[c]
1	**a**: Ph	2.5	**3a**	98	13:1	5.95 (6.29)
2	**b**: 2-$MeOC_6H_4$	5	**3b**	86	13:1	5.96 (6.09)
3	**c**: 4-$MeOC_6H_4$	3	**3c**	80	13:1	5.94 (6.25)
4	**d**: 4-HOC_6H_4	2.5	**3d**	93	13:1	5.94 (6.24)
5	**e**: 4-MeC_6H_4	4	**3e**	90	13:1	5.93 (6.24)
6	**f**: 4-ClC_6H_4	3	**3f**	98	13:1	5.92 (6.31)
7	**g**: 4-$(CN)C_6H_4$	4	**3g**	80	13:1	5.91 (6.39)
8	**h**: 4-$NO_2C_6H_4$	14	**3h**	0		
9	**i**: furan-3-yl	3.5	**3i**	72	6:1	6.02 (6.25)
10	**j**: furan-2-yl	4	**3j**	67	4:1	5.95 (6.12)
11	**k**: 1-pentenyl	2	**3k**	77	2:1	5.93 (6.05)
12	**l**: 2-HOC_6H_4	3	**3l**	82	1:3	5.95 (6.31)

[a] The stoichiometric ratio of (*E*)-**1a**/**2**/In was 1.0:1.2:1.1 in 0.3 M H_2O/THF (4:1) solution at reflux. [b] The diastereomeric ratio of *anti*-**3**/*syn*-**3**. [c] The chemical shift of the olefinic methine proton for the *anti*-**3** (*syn*-**3**) in ppm.

13:1 ratio was obtained for the benzaldehydes **2b**−**g** with substituents of a different electronic nature (entries 2−7). The stereochemistry of the major products was deduced to be anti for **3b**−**k** by comparison of the ^{1}H NMR spectra with that of **3a**.[7] The chemical shifts of the olefinic methine protons are upfield shifted for the anti products compared to those of the syn products (e.g., 5.95 ppm for *anti*-**3a** vs 6.29 ppm for *syn*-**3a**). *o*-Salicylaldehyde (**2l**), which would coordinate to indium as a bidentate ligand by placing the 2-hydroxyphenyl group into an axial position in the chair transition-state model contrary to the other benzaldehydes including *o*-anisaldehyde (**2b**), converted the anti-stereoselectivity to syn-selectivity (anti/syn = 1:3, entry 12).[8] The yields of the indium-mediated addition of (*E*)-**1a** to the substituted benzaldehydes were generally high (80∼98%). However, no **3h** was obtained for 4-nitrobenzaldehyde (**2h**) with a stoichiometric indium reagent (entry 8), in which indium presumably operated as a reducing agent for the nitro group.[9] There was a significant size effect of aldehydes on the stereoselectivity.[4b] The diastereomeric ratio was decreased

(5) No reaction has been observed for the chloroallylic sulfone (*E*)-**1a** and benzaldehyde (**2a**) when 6 equiv of H_2O was added to CH_2Cl_2 as a solvent. The α-addition of crotyl bromide to cyclohexanecarbaldehyde has been reported under this condition. For references, see: (a) Loh, T.-P.; Tan, K.-T.; Yang, J.-Y.; Xiang, C.-L. *Tetrahedron Lett.* **2001**, *42*, 8701−8703. (b) Loh, T.-P.; Tan, K.-T.; Hu, Q.-Y. *Tetrahedron Lett.* **2001**, *42*, 8705−8708. (c) Tan, K.-T.; Chng, S.-S.; Cheng, H.-S.; Loh, T.-P. *J. Am. Chem. Soc.* **2003**, *125*, 2958−2963.

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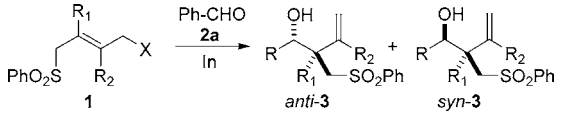
as the size of R in aldehydes **2** was reduced from phenyl to furyl (entries 9 and 10). A marginal selectivity of 2:1 was obtained for the acyclic aldehyde **2k** (entry 11).

The high anti-stereoselection for **3a** should originate from either the benzenesulfonyl group or the methyl group of (*E*)-**1a**. The diverse haloallylic sulfones **1** with different R_1 and R_2 substituents have been prepared, and the stereoselectivity of the In-mediated addition to **2a** was investigated (Table 2). It was the methyl group of (*E*)-**1a** that induced

Table 2. Stereoselectivity of the In-Mediated Addition of the Substituted Haloallylic Sulfones **1** to Benzaldehyde (**2a**)[a]



ent	compd **1**					**3**	yield (%)	dr[b]
		R_1	R_2	X	*E*/*Z*			
1	**a**	Me	H	Cl	*E*	**3a**	98	13:1[c]
2	**b**	H	H	Br	*E*	**3m**	86	2:1
3	**c**	Ph	H	Cl	*E*	**3n**	36	1:13[c]
4	**c**	Ph	H	Cl	*Z*	**3n**	45	1:13
5	**c**	Ph	H	Cl	1.3:1	**3n**	38	1:13
6	**d**	4-$MeOC_6H_4$	H	Cl	1:1	**3o**	40	1:13
7	**e**	4-ClC_6H_4	H	Cl	3:2	**3p**	33	0:100
8	**f**	H	Me	Cl	*E*	**3q**	90	2:1
9	**g**	H	Me	Br	*E*	**3q**	71	3:2
10	**h**	H	Ph	Cl	*E*	**3r**	72	1:4[c]
11	**h**	H	Ph	Cl	2:1	**3r**	77	1:4

[a] The 1.0:1.2:1.1 mixture (stoichiometric ratio) of **1**/**2a**/In in 0.3 M H_2O/THF (*v* 4:1) solution was heated at reflux for 1.5∼3 h. [b] The diastereomeric ratio of *anti*-**3**/*syn*-**3**. [c] The stereochemistry of the products *anti*-**3a**, *syn*-**3n**, and *anti*-**3r** was determined by X-ray crystallographic analysis; see the Supporting Information.

the high stereoselection for *anti*-**3a** because only a 2:1 anti-selectivity of **3m** was obtained for the bromoallylic sulfone **1b** with no R_1 substituent (R_1, R_2 = H, entry 2). Even more surprising was that the chloroallylic sulfone **1c** with the R_1 phenyl substituent (R_1 = Ph, R_2 = H) provided the opposite syn-stereoselection with a high 13:1 ratio regardless of the geometry of the C=C bond (entries 3−5). The stereochemistry of the major product **3n** was confirmed by X-ray crystallographic analysis. The 13:1 syn-selectivity was maintained for the chloroallylic sulfone **1d** with a 4-methoxyphenyl substituent at R_1 (R_1 = 4-$MeOC_6H_4$, R_2 = H, entry 6). When the chloroallylic sulfone **1e** with a 4-chlorophenyl substituent at R_1 (R_1 = 4-ClC_6H_4, R_2 = H) was used, *syn*-**3p** was exclusively formed (entry 7). The yields of **3n**−**p** were somewhat low, which reflected the steric congestion at the reaction center. No α-addition product of the haloallylic sulfones **1** was obtained in any cases. The Barbier reaction of the haloallylic sulfones **1f**−**h** containing an R_2 substituent and benzaldehyde (**2a**) did not provide high diastereoselection, but slight preferences to *anti*-**3q** for **1f** and **1g** with the R_2 methyl group and to *syn*-**3r** for **1h** with the R_2 phenyl group were observed (entries 8−11). It was noticed that the reaction was faster for allylic bromides (entries 2 and 9) and that the geometry of the C=C bond of **1** was not correlated to the stereochemistry of the addition product **3** (entries 3−5).[4b]

We tentatively explain the high and opposite stereoselections for *anti*-**3a** and for *syn*-**3n** according to the R_1 substituent of **1** using the model proposed by Hoffmann.[10] Hoffmann connected the conformation of the complex between metal enolate and aldehyde to the stereochemistry of the aldol product through the pericyclic transition state. With the same notion, we speculated that the extended conformation **A** of the In complex between **1** and **2** led to the chair transition state with very little nuclear motion thereby producing *anti*-**3**, whereas the U-shaped conformation **B** led to the twist boat transition state producing *syn*-**3**, where the phenyl group of benzaldehyde was placed in the equatorial position in both cases (Scheme 3). We assumed that the *Z*-configuration of the haloallylic sulfones **1** equilibrated to the more stable *E*-configuration while indium was being inserted. This was presumably the reason that the geometry of the C=C bond of **1** was not important in controlling the stereoselectivity of the In-mediated addition reaction. The energy difference between the conformations **A** and **B** would thus decide the ratio of *anti*-**3**/*syn*-**3**.

There might be a very little energy difference between the conformations **A** and **B** for **1b** (R_1, R_2 = H),[11] and a slight 2:1 selectivity for *anti*-**3m** was obtained. The high stereoselection of **1a** (R_1 = CH_3, R_2 = H) for *anti*-**3a** might be explained by the destabilizing steric effect of the R_1 methyl group in the conformation **B**,[12] which significantly favored the conformation **A** to lead to the chair transition state. The opposite high stereoselections of **1c**, **1d**, and **1e** (R_1 = Ph derivatives, R_2 = H), respectively, for *syn*-**3n**, *syn*-**3o**, and *syn*-**3p**, on the other hand, ascribed to the stabilizing electronic effect of the R_1 phenyl derivatives in conformation **B** by having $\pi-\pi$ interactions[13] with the formyl group to lead to the twist boat transition state.[14] There might be only a slight steric effect of the R_2 substituents on the diastereoselectivity of the addition reaction. A slight preference for conformation **A** in **1f** and **1g** with the R_2 methyl substituent (anti/syn = 2:1 and 3:2, respectively) was reversed to the

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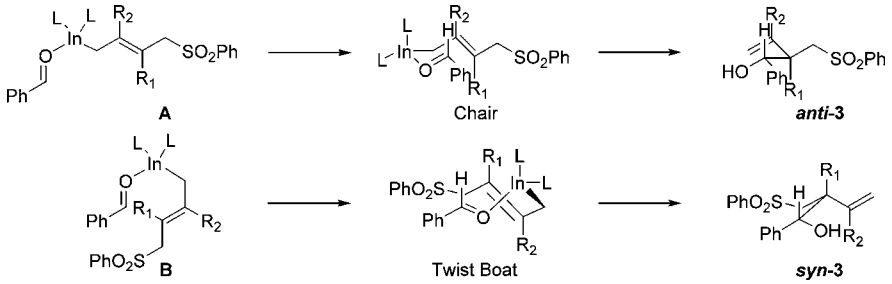
Scheme 3. Conformations **A** (Extended) and **B** (U-Shaped) Leading to Each of the *anti*-**3** and *syn*-**3** Diastereomers, Respectively, through the Chair and the Twist Boat Transition States Based on the Nature of R_1 and R_2 Substituents



preference for conformation **B** in **1h** with the bigger R_2 phenyl group (anti/syn = 1:4), which presumably destabilized the conformation **A** by the steric interactions with the ligands on indium.

In summary, the In-mediated addition reaction of the haloallylic sulfones **1** to aldehydes **2** efficiently produces the homoallylic alcohols **3** containing a homoallylic sulfone moiety, which are useful building blocks in organic synthesis. This reaction is highly anti-stereoselective (13:1) when the R_1 substituent at C(2) of the haloallylic sulfone **1** is Me. High syn-stereoselectivity (13:1) in the opposite sense can be obtained for the R_1 Ph-substituted haloallylic sulfone **1**. These substituent-controlled diastereoselectivities can be explained on the basis of the different transition state models (chair or twist boat) according to the conformational analysis of the reagent complexes.

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Supporting Information Available: The crystallographic information files (CIF) for *anti*-**3a**, *syn*-**3n**, and *anti*-**3r**. Experimental procedures, analytical data, and $^1H/^{13}C$ NMR spectra for **3a**−**g** and **3i**−**r**. This material is available free of charge via the Internet at http://pubs.acs.org.

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