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Binary 1,4-asymmetric induction toward imines from a single allyltin reagent with a chiral oxygen functional group

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ABSTRACT

A single allyltin reagent possessing a chiral oxygen functional group afforded each diastereomeric product in the reaction with *N*-sulfonylimines promoted by appropriate Lewis acids in a binary stereoselective manner. $InCl_3$ selectively provided the *syn*-1,4-amino alcohol derivatives, while BF_3 and $TiCl_4$ gave the *anti*-products preferentially.

Asymmetric induction is well recognized as a useful and practical method to construct organic molecules with multi-chiral centers.[1] Most of such reactions involve intramolecular induction of chiral electrophiles such as carbonyl compounds and imines. For example, nucleophilic addition reactions toward aliphatic carbonyl compounds having chirality and imines with a chiral auxiliary on the imine nitrogen[2] have been investigated most frequently so far. In contrast, intermolecular asymmetric induction from a chiral nucleophile such as organometallic reagents is relatively scarce in spite of its potential importance. Accordingly, we have already reported asymmetric induction toward achiral aldehydes from allyl-silicon[3] and -tin[4] reagents bearing a chiral oxygen or nitrogen functionality and showed successful results as remote and binary control of the diastereoselectivity. Some other groups[5] have also realized similar interesting stereocontrol to obtain one diastereomer.

After these achievements, we have taken an interest in the asymmetric induction toward achiral imines from a chiral allylic nucleophile. Such reactions are still more limited[6] and thus challenging compared with those toward aldehydes. We herein report the results in asymmetric induction toward achiral imines from an allyltin reagent with a chiral oxygen functionality in a 1,4-remote and binary stereo-controlled manner (Scheme 1).[7]

As we mentioned in the earlier report,[4c] the carbamoyl protection of the hydroxy group as **1** was superior in the reaction with aldehydes especially from the viewpoint of the stereoselectivity. Thus, we have picked up reagent **1** again for the present reaction. At the first attempt, we employed benzylidene aniline (*N*-phenylimine) **2** as a simple imine substrate. Though typical Lewis acids were found to promote the allylation reaction with **1** to give the corresponding adduct **3** in various yields ($InCl_3$: 79%, $BF_3{\cdot}OEt_2$: 57%, $TiCl_4$:[8] trace), the diastereoselectivity was disappointing (1/1.5–1/2). Then, we turned our attention to *N*-sulfonylimines **4**, which are more electrophilic substrates owing to the electron-withdrawing sulfonyl group. In sharp contrast to benzylidene aniline **2**, *N*-benzenesulfonylimine **4** afforded good results with the aid of an appropriate Lewis acid as shown in Table 1. Though $SnCl_4$ which gave excellent selectivity in the reaction with aldehydes[4c] resulted in decomposition of the reagents (entry 1), $InCl_3$ exhibited excellent *syn*-diastereoselectivity (entry 2). On the other hand, BF_3 and $TiCl_4$ showed good *anti*-diastereoselectivity (entries 4 and 5), while $Yb(OTf)_3$ was nonselective (entry 3). Evaluated from these contrast selectivities, the reaction of sulfonylimine **4** could also exhibit binary diastereoselectivity as well as the reaction of aldehydes.

Having suitable Lewis acids in hand, we applied these to various sulfonylimines as shown in Tables 2 and 3. Aromatic ones were attempted to find that the $InCl_3$-promoted reactions also proceeded in almost quantitative yields and excellent *syn*-diastereoselectivity when the substituent was electron-donating (Table 2, entries 2–4). However, an electron-withdrawing substituent slightly decreased the *syn*-selectivity (entry 1). Heteroaromatic one was also successfully applied (entry 5). α,β-Unsaturated imine showed a good result in yield with somewhat decreased diastereoselectivity as depicted in entry 6. In cases of aliphatic imines, product yields

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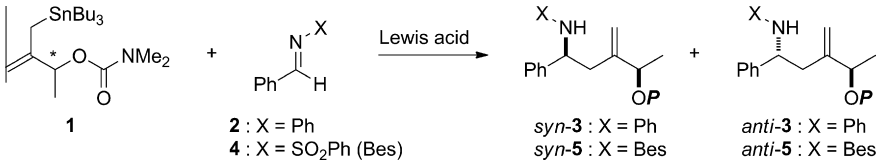


Scheme 1. 1,4-Asymmetric induction from **1** toward imines.

Table 1
Effect of Lewis acid on the asymmetric induction with sulfonylimine **4**

Entry	Lewis acid (equiv)	Conditions	Yield of **5**/% (diastereomeric ratio, *syn*/*anti*)
1	$SnCl_4$ (2.0)	−78 °C, CH_2Cl_2, 3 h	Decomp.
2	$InCl_3$ (2.0)	0 °C, CH_3CN, 3 h	Quant (96/4)
3	$Yb(OTf)_3$ (2.0)	rt, Et_2O, 12 h	66 (52/48)
4	$BF_3{\cdot}OEt_2$ (3.0)	rt, CH_2Cl_2, 4 h	59 (9/91)
5	$TiCl_4 + 3Et_2O$ (2.0)	−78 °C, CH_2Cl_2, 3 h	53 (17/83)

Table 2
$InCl_3$-promoted asymmetric induction toward various sulfonylimines[9]

Entry	Imine, R	Yield of products/% (diastereomeric ratio, *syn*/*anti*)
1	*p*-$O_2NC_6H_4$	96 (89/11)
2	*p*-MeC_6H_4	100 (100/0)
3	*p*-$MeOC_6H_4$	100 (98/2)
4	*o*-$MeOC_6H_4$	100 (100/0)
5	2-Furyl	99 (96/4)
6	(*E*)-PhCH=CH	80 (84/16)
7	*n*-Hexyl	27 (93/7)
8	Cyclohexyl	46 (90/10)

Table 3
BF_3- and $TiCl_4$-promoted asymmetric induction toward various sulfonylimines[10]

Imine, R	Yield of products/% (diastereomeric ratio, *syn*/*anti*)			
	Entry	$BF_3{\cdot}OEt_2$	Entry	$TiCl_4 + 3Et_2O$
p-$O_2NC_6H_4$	1	14 (31/69)	9	12 (12/88)
p-MeC_6H_4	2	59 (10/90)	10	47 (13/87)
p-$MeOC_6H_4$	3[a]	66 (7/93)	11	52 (14/86)
o-$MeOC_6H_4$	4	92 (11/89)	12	55 (36/64)
2-Furyl	5	70 (21/79)	13	39 (12/88)
(*E*)-PhCH=CH	6	62 (26/74)	14	61 (22/78)
n-Hexyl	7	Decomp.	15	63 (6/94)
Cyclohexyl	8	95 (25/75)	16	75 (1/99)

[a] Reaction was performed at 0 °C.

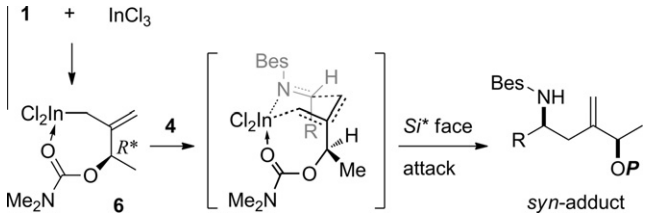
were significantly decreased, though the diastereoselectivities remained high (entries 7 and 8). This is likely due to the instability of the aliphatic imines.

As the benzaldehyde-derived imine exhibited fairly good stereoselectivity in BF_3- and $TiCl_4$-promoted reactions (vide supra), we next examined if they had wide scope as shown in Table 3. Though aromatic substrates with an electron-donating substituent in entries 2–4 showed similar or even better *anti*-selectivity by BF_3-promoted reaction, heteroaromatic and aliphatic ones resulted in poorer stereoselectivity (entries 5–8). In complementary way, $TiCl_4$ with ether provided higher *anti*-selectivity in the cases of heteroaromatic and aliphatic imines (entries 13–16), though the yields were moderate. It is noteworthy that an electron-deficient imine showed particularly low yield (entries 1 and 9). This would be explained in terms that the Lewis acid could not activate such an imine effectively due to poor coordination.

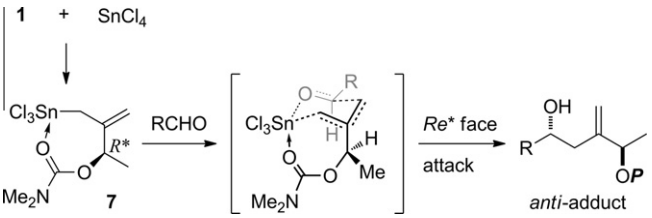
In our previous report,[4c] aldehydes with the reagent **1** gave the *anti*-adduct predominantly in the presence of $SnCl_4$, which facilely undergoes transmetallation[11] with an allyltin reagent. Though $InCl_3$ is also known to undergo transmetallation to give corresponding allylindium species,[12] the high *syn*-diastereoselectivity was achieved in the present reaction with imines contrary to that with aldehydes. This difference can be reasonably explained as follows (Schemes 2 and 3). The transmetallated species (i.e., allylindium **6** and allyltin **7**) would be subject to the coordination both by the intramolecular carbamoyl oxygen and by the imine nitrogen (Scheme 2) or the aldehyde oxygen (Scheme 3) intermolecularly at the transition state. While an aldehyde as a substrate coordinates **7** at the position *anti* to R,[13] an imine does **6** at the position *syn* to R inevitably due to the pre-existing N-substituent. Thus, in the cyclic six-membered transition states, the R group occupies the axial position with the imine, while the equatorial position with the aldehyde. Accordingly, these two reactions lead to the opposite stereoselectivity; the imine was attacked from its *Si** face to give the *syn*-adduct (Scheme 2) and the aldehyde was done oppositely from its *Re** face to give the *anti*-adduct (Scheme 3).

In a similar fashion, the $TiCl_4$-promoted reaction of imines **4** showed the opposite stereoselectivity to that of aldehydes. Coordination of Ti *syn* to R of **4** (*syn*-coordination) would lead to the selective attack of **1** from *Re** face of **4** (Scheme 4A) via Ti-bridged transition state. Thus, the *anti*-isomer was favored. When an aldehyde was employed as a substrate, allyltin **1** would attack the *Si** face of the aldehyde due to *anti*-coordination to give the *syn*-isomer. In the case of BF_3 as a Lewis acid, allyltin reagent **1** would also attack from *Re** face of **4**, though boron cannot accept chelation like titanium. Thus, the transition model **B** in Scheme 4 may be adopted with the shown conformation of the chiral substituent to avoid the steric repulsion with R.

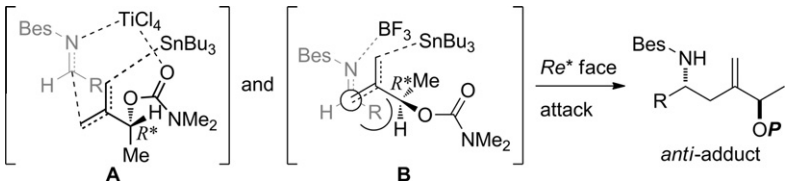
Stereochemistry of the product was confirmed by the X-ray crystal analysis. Fortunately, the major product of the BF_3-mediated reaction in entry 4 of Table 1 afforded a single crystal, of



Scheme 2. Cyclic transition state model with an imine for the *syn*-adduct.



Scheme 3. Cyclic transition state model with an aldehyde for the *anti*-adduct.



Scheme 4. Ti-bridged (A) and acyclic (B) transition state models with an imine for the *anti*-adduct.

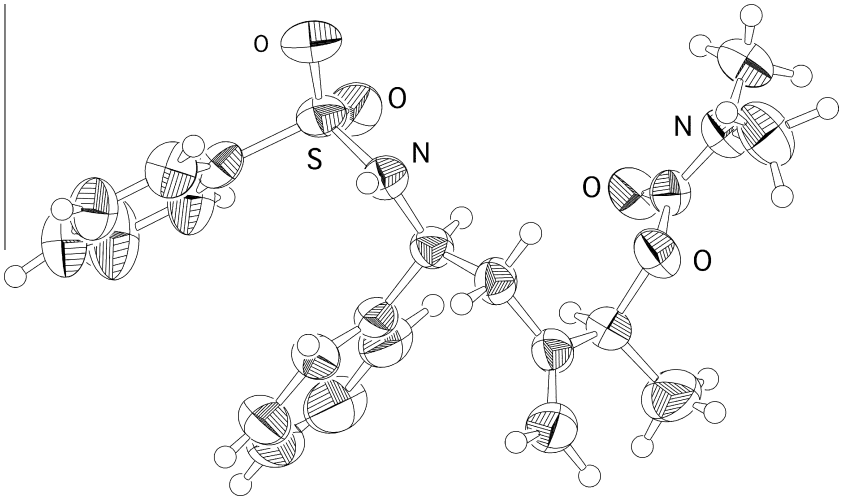


Figure 1. ORTEP drawing of the *anti*-product.

which structure was determined to be *anti* as shown in Figure 1.[14] Other products were assigned by ^{1}H NMR spectra compared with this reference compound.[15]

In conclusion, it is interesting that remote and binary stereocontrolled reaction with chiral allylic tin reagent can also be applied to sulfonylimines. Both diastereomers of 1,4-aminoalcohol derivatives were successfully obtained. These protocols would be able to provide the stereoselective synthesis of useful organic molecules. It is also striking that the stereoselectivity here was entirely opposite to that in the reaction of aldehydes for both promoting methods. These results reveal both sulfonylimine and aldehyde follow similar reaction paths except for the coordination site. In other words, the coordination site of the Lewis acid determines the stereoselectivity, which shows a similarity to our previous report on the reaction of alkoxyaldehydes.[16] Further investigations to develop the more efficient reaction systems (e.g., chiral functionality other than oxygen, optically active reagents,[4a] and catalytic Lewis acids) are now in progress.

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7. Hereafter, the configuration of the chiral center derived from the racemic tin reagent **1** is shown as *R* for simplicity and it is described as R^*.
8. We used $TiCl_4$ with 3 equiv of diethyl ether to suppress transmetallation.
9. *Typical experimental procedure for the syn-selective reaction*: To a mixture of a sulfonylimine (0.2 mmol) and $InCl_3$ (0.4 mmol) in 1 mL of CH_3CN at 0 °C under a N_2 atmosphere, the allyltin reagent **1** (0.3 mmol) dissolved in 1 mL of CH_3CN was added, and the mixture was stirred for 3 h at the same temperature. Then, $NaHCO_3$ solution was added and the products were extracted with ether. The organic layer was washed with 10% KF solution, dried over Na_2SO_4, and condensed under reduced pressure. The residue was chromatographed on a silica gel TLC to isolate the product.
10. *Typical experimental procedures for the anti-selective reaction*: BF_3 promoted reaction: to a solution of a sulfonylimine (0.2 mmol) in 1 mL of CH_2Cl_2 at −78 °C under a N_2 atmosphere, **1** (0.3 mmol) in 1 mL of CH_2Cl_2 and $BF_3{\cdot}OEt_2$ (0.6 mmol) were added successively. After 4 h, the reaction was quenched and the products were isolated as Ref.[9] $TiCl_4$ promoted reaction: to a mixture of a sulfonylimine (0.2 mmol) and Et_2O (1.2 mmol) in 1 mL of CH_2Cl_2 at −78 °C under a N_2 atmosphere, 0.4 mmol of $TiCl_4$ as a 1 M CH_2Cl_2 solution was added followed by the addition of **1** (0.3 mmol) in 1 mL of CH_2Cl_2. After 3 h, the reaction was quenched and the products were isolated as Ref.[9]
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14. CCDC 791980 contains the supplementary crystallographic data for this Letter. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.
15. ^{1}H NMR (400 MHz, $CDCl_3$) δ (multiplicity, *J*/Hz, integration): (S^*,R^*)-*syn*-adduct (R = Ph) 7.64 (dd, 8.4, 1.2, 2H), 7.44 (t, 7.6, 1H), 7.32 (t, 8.1, 2H), 7.13–7.18 (m, 5H), 5.52 (d, 4.6, 1H), 5.07 (s, 1H), 4.92 (q, 6.6, 1H), 4.77 (s, 1H), 4.52 (ddd, 9.0, 5.4, 4.6, 1H), 2.95 (br s, 3H), 2.93 (br s, 3H), 2.51 (dd, 15.0, 5.4, 1H), 2.37 (dd, 15.0, 9.0, 1H), 1.22 (d, 6.6, 3H). (R^*,R^*)-*anti*-adduct (R = Ph) 7.64 (d, 8.5, 2H), 7.39 (t, 7.3, 1H), 7.28 (t, 8.3, 2H), 7.11–7.10 (m, 3H), 7.01–7.04 (m, 2H), 6.60 (d, 7.3, 1H), 5.08 (q, 6.1, 1H), 4.97 (s, 1H), 4.67 (q, 6.3, 1H), 4.39 (s, 1H), 2.98 (br s, 3H), 2.96 (br s, 3H), 2.46–2.48 (m, 2H), 1.26 (d, 6.3, 3H).
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