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

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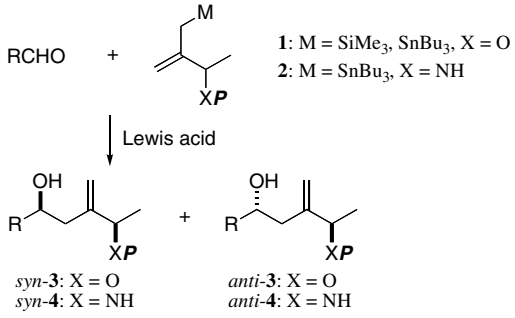
Abstract

Using a single allyltin reagent with a chiral nitrogen functionality, binary and remote asymmetric induction was realized toward various aldehydes. Either *syn*- or *anti*-1,4-amino-alcohols were selectively obtained with the use of $Yb(OTf)_3$ or $SnCl_4$, respectively. The structures of both diastereomers were identified by means of X-ray analysis.

To prepare one of the two diastereomers in an efficiently stereoselective manner from a chiral reagent is a fascinating way for the synthesis of complex molecules.[1] Most of such methods are based on the asymmetric induction from a chiral electrophile such as carbonyl compounds. One of the most well-known concepts for it is Cram's rule/chelation control. In contrast, asymmetric induction from an organometallic nucleophile is relatively unfamiliar. In the cases of allylsilicon and allyltin reagents, which are now versatile at organic synthesis[2] providing reliable selectivity, several reports are known concerning such stereoselective preparation of one diastereomer.[3,4] As an advanced version of such solitary asymmetric induction, we have already reported highly efficient *binary* 1,4-asymmetric induction from allylsilicon[5] and allyltin[6] reagents toward aldehydes. As shown in Scheme 1, the reagent **1** containing an oxygen functional group (X = O) such as ether, ester or carbamate produced both diastereomeric *syn*- and *anti*-1,4-diol derivatives **3** successfully and separately only by changing the combination of the protecting group (***P***) and the applied Lewis acid. Especially, in the reaction of the allyltin with a carbamate moiety, highly efficient binary diastereocontrol was realized from a single reagent (**1a**: M = $SnBu_3$, X***P*** = $OCONMe_2$).[6b] Consequently, we next focused our project on the examination of the applicability of this methodology to reagent **2**, a nitrogen analogue of **1**, and the stereoselective synthesis of 1,4-amino-alcohol derivatives **4** (Scheme 1, X = NH).



Scheme 1.

The first problem was the preparation of the allylic tin reagent **2** containing an amino group. In contrast to the oxygenated allyltin reagents, the corresponding nitrogenated ones were not prepared so far. After several attempts, we obtained it as a phthalimido-protected form **6** by the Mitsunobu reaction applied to the hydroxy-allyltin reagent **5**[7] in a moderate yield as summarized in Scheme 2. The reagent **6** was readily converted to primary amine **7**,

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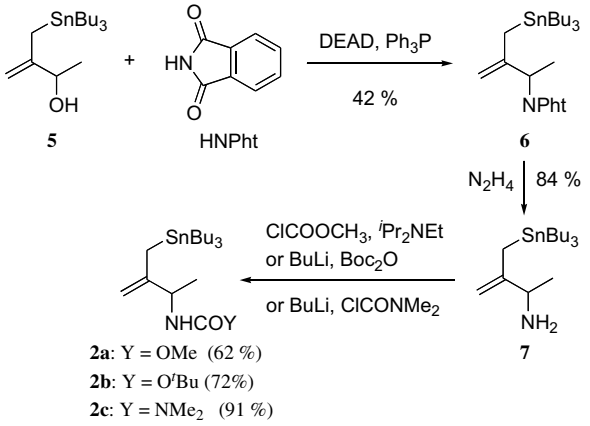
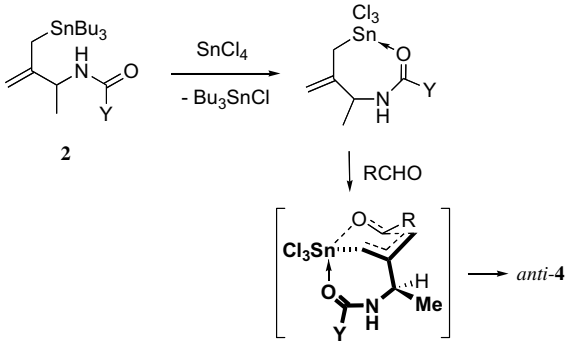


Scheme 2.



Scheme 3.

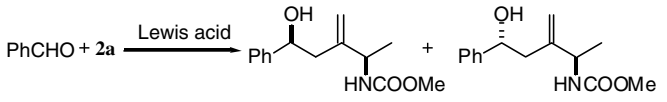
followed by successful protection as a carbamate **2a**, **2b** or a urea derivative **2c**.

As the reagents were in hand, various Lewis acids were employed to the reaction of **2a** toward benzaldehyde. Because the coordinating group at the chiral center in **2a** was also carbamate moiety as **1a**, we expected high diastereoselectivity from the previous study.[6b] The results are accumulated in Table 1. Actually, $SnCl_4$ gave a superior result for the *anti*-selective allylation (entry 1); exclusive formation of the *anti*-**4a** from benzaldehyde. This is rationally explained by the transmetallation[8] between **2a** and $SnCl_4$ and the six-membered cyclic transition state as shown in Scheme 3. Other Lewis acids that can promote the reaction via transmetallation such as $ZnCl_2$ and $InCl_3$[9] gave very poor stereoselectivity as shown in entries 2 and 3, respectively.

Attempts for *syn*-**4a** were conducted by using other types of Lewis acids, which simply activate the aldehyde without transmetallation. Mono-coordinating BF_3 resulted in only moderate *anti*-selection (entry 4). Bi-coordinating $TiCl_4$, which was deactivated toward transmetallation by the addition of THF and worked well with the oxygenated allyltin,[6b] gave a disappointing result (entry 5). Decomposition of the reagents proceeded and no allyl-adduct was obtained. The reason for this is not clear, but the protic NH hydrogen may be a concern.[10] Accordingly, after several Lewis acids were screened, lanthanide triflates[11] were found to be rather effective. $Sm(OTf)_3$ afforded *syn*-**4a** in about 3:1 ratio but the yield was too poor (entry 6). In contrast, $Yb(OTf)_3$ gave an acceptable yield with similar diastereoselectivity (entry 7). Lanthanide triflate is known as a multi-coordinating and water/proton-tolerating Lewis acid, so it can bind the reagents together as shown in Scheme 4 to promote the reaction via Yb-bridged acyclic transition state even in the presence of a protic amide.

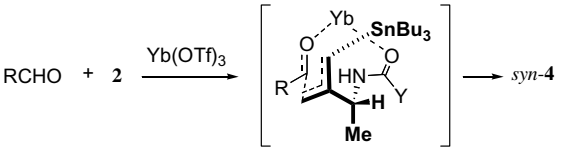
The stereochemistry of product **4** was concluded as follows: From the $SnCl_4$-mediated reaction between *p*-nitrobenzaldehyde and phthalimido-allyltin **6**, allyl-adduct **8b** (Scheme 5) was obtained in a moderate diastereoselectivity (72/28). The major isomer of **8b** fortunately crystallized and could be analyzed by the X-ray diffraction[12] to find its structure as a *syn*-form (Fig. 1).[13] Based on the comparison of ^1H NMR spectra with *syn*-**8b**, the major product from benzaldehyde was also established as *syn*-**8a**. It was then converted to the corresponding carbamate as in Scheme 5, which was confirmed to be identical with *syn*-**4a**.[14]

Table 1
Lewis acid effect toward diastereoselectivity[a]

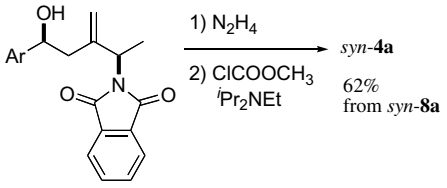


Entry	Lewis acid (equiv)	Conditions	*syn*/*anti* (yield/%)
1	$SnCl_4$ (1.5)	CH_2Cl_2, −78 °C, 1.5 h	0/100 (96)
2	$ZnCl_2$ (1.5)	Et_2O, rt, 12 h	42/58 (98)
3	$InCl_3$ (1.5)	CH_3CN, 0 °C, 1.5 h	57/43 (66)
4	$BF_3{\cdot}OEt_2$ (1.0)	CH_2Cl_2, −78 °C, 1.5 h	28/72 (70)
5	$TiCl_4$–THF (1.0)	CH_2Cl_2, −78 °C, 0.75 h	Decomposed
6	$Sm(OTf)_3$ (1.0)	Et_2O, rt, 12 h	73/27 (23)
7	$Yb(OTf)_3$ (1.0)	Et_2O, rt, 12 h	72/28 (80)

[a] Benzaldehyde (1.0 equiv) and **2a** (1.5 equiv) in the presence of the indicated amount of Lewis acid were allowed to react under the indicated conditions.



Scheme 4.



syn-**8a**: Ar = Ph
syn-**8b**: Ar = *p*-$O_2NC_6H_4$

Scheme 5.

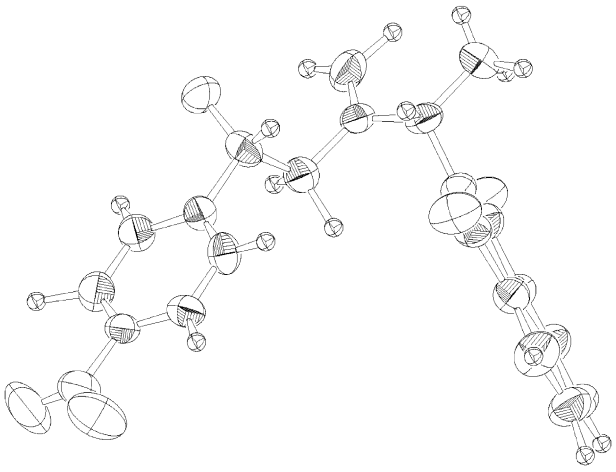


Fig. 1. X-ray structure of *syn*-**8b**.

As suitable Lewis acids were picked out, they were applied to the reactions of various aldehydes. The results are summarized in Table 2. In the $SnCl_4$-mediated reaction,[15a] the *anti*-selectivity was generally over 90% with sufficient yields for aromatic, aliphatic, and α,β-unsaturated aldehydes (entries 1–4). In contrast, the $Yb(OTf)_3$-mediated reactions[15b] never afforded more than 72% *syn*-selectivity with moderate to low product yields (entries 5–8).

Thus, to improve the *syn*-selectivity mediated by $Yb(OTf)_3$, steric influence of the carbamate moiety was first investigated employing the Boc-protected reagent **2b**. With all aldehydes attempted, the *syn*-selectivity increased slightly but remained in the range of 67–87%.[16]

Table 2
$SnCl_4$- and $Yb(OTf)_3$-mediated reactions of **2a**

Aldehyde/R	[Entry] *syn*/*anti* (yield/%)	
	$SnCl_4$	$Yb(OTf)_3$
p-$O_2NC_6H_4$	[1] 9/91 (97)	[5] 72/28 (96)
p-$MeOC_6H_4$	[2] 0/100 (96)	[6] 71/29 (16)
n-C_6H_{13}	[3] 8/92 (78)	[7] 68/32 (64)
n-$C_3H_7CH{=}CH$	[4] 6/94 (83)	[8] 60/40 (50)

Table 3
$SnCl_4$- and $Yb(OTf)_3$-mediated reactions of **2c**

Aldehyde/R	[Entry] *syn*/*anti* (yield/%)	
	$SnCl_4$	$Yb(OTf)_3$
p-$O_2NC_6H_4$	[1] 0/100 (95)	[6] 90/10 (81)
C_6H_5	[2] 0/100 (91)	[7] 93/7 (55)
p-$MeOC_6H_4$	[3] 0/100 (48)	[8] 96/4 (tr)
n-C_6H_{13}	[4] 5/95 (90)	[9] 85/15 (62)
n-$C_3H_7CH{=}CH$	[5] 13/87 (66)	[10] 87/13 (66)

Next, coordinating ability of the protecting group was examined by using a urea moiety as **2c**. As reported previously,[6b] electron-donation by the nitrogen to the carbonyl oxygen was expected to improve the diastereoselectivity. The results are shown in Table 3. The stereochemistry of the products was again deduced from the comparison of NMR spectra and undoubtedly confirmed by the X-ray analysis[12] of the product in entry 1, which showed its *anti*-configuration (Fig. 2). In the $Yb(OTf)_3$-promoted reaction, the *syn*-selectivity was dramatically improved up to 93% (entry 7). Saturated and α,β-unsaturated aldehydes exhibited more than 85% selectivity (entries 9 and 10). In addition, the *anti*-selectivity was also enhanced except for entry 5; almost complete selectivity was realized for the aromatic aldehydes. One drawback in the reaction of **2c** was the low reactivity of the aldehyde with an electron-donating substituent (entries 3 and 8).[17] This is probably due to the strong coordination of the urea moiety to the Lewis acid to reduce its activity. Nevertheless, efficient and binary diastereo-controlled allylation from a single reagent was achieved with the use of a good coordinating group.

In conclusion, binary asymmetric induction from a single allyltin reagent toward aldehydes was found to be applied successfully to the reagent with a nitrogen functionality to prepare both diastereomers of 1,4-amino-alcohol **4**. Strong coordination of the carbonyl group of **2** toward a Lewis acid was a key for the effective stereocontrol like **1**. Though present stereoselection for both diastereomers can be understood in a similar way to the reaction of **1**, it is interesting that the suitable Lewis acid

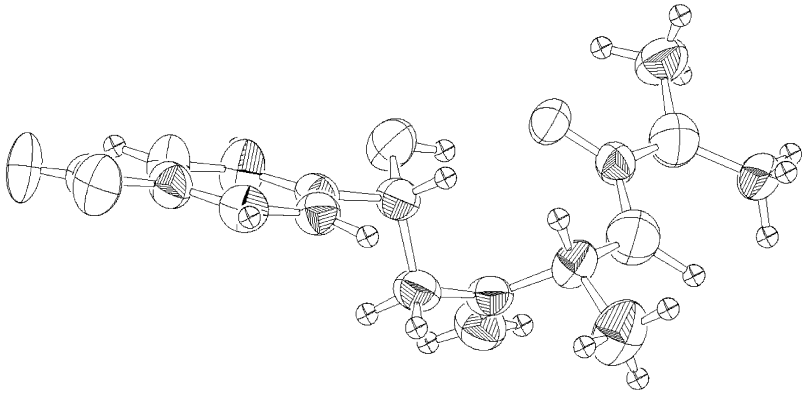


Fig. 2. X-ray structure of *anti*-**4** (R = *p*-$O_2NC_6H_4$, ***P*** = $CONMe_2$).

was dependent on the functional group in the allyltin reagent. Because such structure as 1,4-amino-alcohol can be found in natural products, this methodology will be applied to the synthesis of the compounds containing amino and hydroxy functionalities. At this stage, deprotection of the dimethylurea group is not successful, thus interconversion of the urea moiety is now being explored including the use of other more easily deprotective derivatives.

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12. CCDC 671467 and 671468 contain the supplementary crystallographic data for this Letter (*syn*-**8b** and *anti*-**4**, respectively). 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.
13. Stereochemical discrepancy between the $SnCl_4$-mediated reactions of **2a** and of **6** may be attributed to the cyclic structure of the imido moiety, of which coordination would cause steric strain. Thus, a different transition state should be adopted.
14. ^{1}H NMR spectra: *syn*-**4a**, 1.27 (3H, d, $J = 6.8$ Hz), 2.30 (1H, dd, $J = 13.9$, 9.5 Hz), 2.54 (1H, dd, $J = 14.0$, 3.3 Hz), 3.46 (1H, br, OH), 3.68 (3H, s), 4.22–4.33 (1H, m), 4.85–4.89 (1H, m), 4.94 (1H, br, NH), 5.02 (1H, s), 5.14 (1H, s), 7.22–7.39 (5H, m). *anti*-**4a**, 1.25 (3H, d, $J = 6.8$ Hz), 2.44 (2H, d, $J = 6.8$ Hz), 3.55 (1H, br, OH), 3.64 (3H, s), 4.21–4.30 (1H, m), 4.92 (1H, br, NH), 4.95 (1H, s), 5.11 (1H, s), 5.28–5.32 (1H, m), 7.22–7.39 (5H, m).
15. (a) *$SnCl_4$-mediated reaction*: To a stirred CH_2Cl_2 solution (2 mL) of **2** (0.3 mmol) was added $SnCl_4$ (0.3 mmol) in CH_2Cl_2 under nitrogen at −78 °C. After a few minutes, an aldehyde (0.2 mmol) in CH_2Cl_2 (2 mL) was added to the mixture and stirring was continued for 1.5 h at the same temperature. The reaction was quenched with 2 N-HCl and the product was extracted with ether. The extract was washed continuously with water, a $NaHCO_3$ solution and a KF solution, dried over Na_2SO_4, condensed, and chromatographed to isolate the product; (b) *$Yb(OTf)_3$-mediated reaction*: To a flask containing $Yb(OTf)_3$ (0.2 mmol) were added an aldehyde (0.2 mmol) in ether (2 mL) and **2** (0.3 mmol) in ether (2 mL) at room temperature under nitrogen with stirring. After 12 h, the reaction mixture was worked up as above.
16. The $SnCl_4$-mediated reaction of **2 b** resulted in poor diastereoselectivity; nearly equal amounts of *syn*- and *anti*-adducts were obtained.
17. Considerable decomposition of **2c** proceeded with most of the aldehyde intact.