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Enantioselective synthesis of optically active homoallylamines by allylboration of *N*-diisobutylaluminum imines

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Abstract

Diisobutylaluminum hydride (DIBAL-H) reduces nitriles to give *N*-diisobutylaluminum imines, which were asymmetrically allylated with chirally modified allylboron reagents. The corresponding chiral primary homoallylamines were obtained with up to 87% ee.

Keywords: Enantioselective synthesis; Optically active homoallylamine; *N*-Metalloimine; *N*-Diisobutylaluminum imine; Chirally modified allylboron reagents

1. Introduction

The enantioselective synthesis of optically active amines by nucleophilic addition of organometallic reagents toward imines is a topic of current interest [1]. Asymmetric addition of allylmetal species to imines is one of the useful approaches to synthesis of optically active homoallylamines which are indeed important compounds as starting or intermediate materials in the synthesis of biologically active substances [2]. They are also useful as resolving agents and chiral auxiliaries for asymmetric reactions [3]. However, enantioselective methods for homoallylamine synthesis are scarcely developed. Only an example of reaction of chiral allylzinc reagents with aldimines using chiral bis(oxazoline) promoter was described [4]. The major limitation of this methodology is that only cyclic aldimines can be allylated with high enantioselectivity.

On the other hand, the ability of *N*-masked imine derivatives of ammonia including *N*-metallo- [5], *N*-thio- [6], and *N*-phosphinylimines [7] to undergo various nucleophilic addition reactions is now well established and has been utilized in the synthesis of various kinds of primary amines and their derivatives [8]. In previous papers, we have reported that *N*-metalloimines such as *N*-boryl- [9] and *N*-aluminum imines [10] could react with organolithium or Grignard reagents to afford primary amines. In the presence of chiral ligand, optically active primary amines were obtained [9c, 10]. These *N*-metalloimines are easily prepared from partial reduction of nitrile with aluminum- or borohydride. Further study on the reaction of *N*-metalloimines revealed that treatment of *N*-diisobutylaluminum imines **2** and *N*-trimethylsilyl imines with triallylborane gave the desired homoallylamines in good yield. These results encouraged us to apply to the asymmetric version of allylboration reactions. We have already communicated the enantioselective allylboration of the *N*-trimethylsilyl imines by chirally modified allylboron reagents to afford primary homoallylamine [11]. In this paper we wish to describe the first application of *N*-aluminum imines to enantioselective allylboration. Since this appeared to be a potentially useful method for preparing certain chiral homoallylamines, we examined the scope and limitations of this procedure. Reactivity and stereoselectivity in asymmetric allylboration of *N*-aluminum imines are also discussed.

2. Results and discussion

We have first investigated the allylboration of *N*-borylimines prepared from nitrile reduction, since we have

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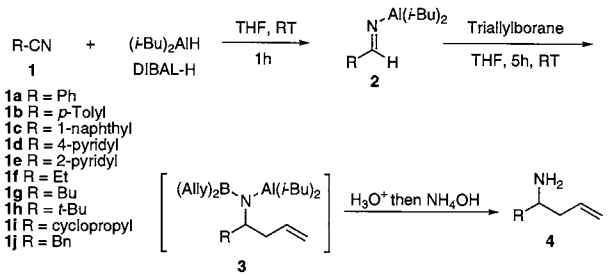


Scheme 1.

proposed that the reaction of *N*-borylimines with alkyllithiums at low temperature is one of the useful methods to obtain primary amines [9]. However, unfortunately, the *N*-borylimine derived from benzonitrile and borane or diethylborane as reducing agent reacted with triallylborane to yield only a complexed mixture of products.

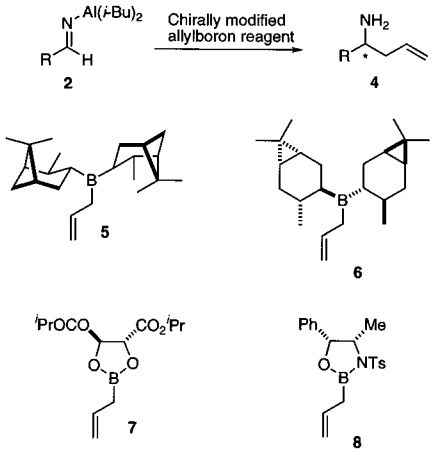
Next, we focused on the allylboration of *N*-aluminum imines **2**, which are readily available by partial reduction of nitriles with diisobutylaluminum hydride (DIBAL-H) (Scheme 1). The imines **2** have been successfully utilized for various organic transformations [12,13]. For example, Panunzio and co-workers reported the reaction of organometallic reagents including allyl Grignard reagents with **2** to give primary amines [14,15]. We thus examined the reaction sequence of DIBAL-H reduction of nitrile followed by allylation with triallylborane as shown in Scheme 1. We eventually found that **2a** reacted with triallylborane at room temperature to afford the desired primary homoallylic amine **4a** in 70% yield, although the imine possesses a bulky *N*-substituent. Other various *N*-aluminum imines derived from nitriles **1** were subjected to reactions with triallylborane in THF at room temperature. Table 1 shows that the *N*-aluminum imines could yield the corresponding homoallylamines except for pyridyl and benzyl derivatives (Runs 4, 5, and 10). In the case of **2d** and **2e**, under the conditions used for the allylboration, both imino functionality and pyridine ring seem to be allylated with triallylborane to give a complex mixture [16]. The DIBAL-H reduction of phenylacetonitrile **1j** involved undesired side reactions. For other nitriles this reaction sequence would be efficient for the synthesis of primary homoallylamines, since the N–Al bond could be cleaved readily during the aqueous work-up procedure. Another advantage in the use of such imines is that *N*-aluminum imines derived from DIBAL-H reduction of aliphatic nitriles could be also allylated with triallylborane to yield the homoallylic amines (Runs 6–9). In contrast to *N*-aluminum imines, the use of *N*-trimethylsilyl imines is generally restricted to nonenolizable imines since the enolizable ones give poor yields of the expected amines in the reactions with organometallic reagents such as Grignard reagents or alkyllithiums [17]. A lower isolated yield for **2f** derived from propionitrile may be caused by its high volatility. Bulkiness of naphthyl group in the imine **2c** and its side reaction resulted in low yield of the amine **4c**. However, the relatively higher reactivity of the other imines toward triallylborane prompted us to investigate the enantioselective synthesis of homoallylamines by nucleophilic addition of chirally modified allylboron reagents.

Table 1
Allylboration of various *N*-aluminum imines **2** with triallylborane[a]

Run number	*N*-Aluminum imines	Time (h)	Yield of homoallylamines (%)[b]
1	**2a**	5	70
2	**2b**	24	66
3	**2c**	20	11
4	**2d**	20	–[c]
5	**2e**	20	–[c]
6	**2f**	20	18
7	**2g**	5	54
8	**2h**	5	54
9	**2i**	5	54
10	**2j**	5	–[d]

[a] Reaction conditions: **2**, 5 mmol (prepared from nitrile, 5 mmol; DIBAL-H, 5 mmol; 0°C, 1 h); triallylborane, 6 mmol; THF 15 ml.
[b] Isolated yields based on the starting nitrile.
[c] Complexed mixture including ring allylated products were obtained.
[d] Complexed mixture.

Various chirally modified allylboron reagents have been proposed for the asymmetric allylboration of aldehydes in the literature [18]. Some of them are highly effective for stereoselective allylboration of aldehydes. For the enantioselective allylboration of *N*-aluminum imines, we thus chose Brown's reagents **5** [19] and **6** [20] and Roush's reagent **7** [20,21], which are a family of readily accessible and synthetically convenient allylboron reagents that exhibit excellent selectivities in the allylboration of aldehydes. Another promising chiral allylboron reagent is **8** exploited by ourselves, which showed excellent enantioselectivity in the allylboration of *N*-silyl imines [11]. Structures of the chiral allylboron reagents used in this study are illustrated in Scheme 2. Table 2 shows the enantioselective allylboration of *N*-(diisobutylaluminum)benzaldehyde imine **2a** with chirally modified allylborating agents **5**–**8** at various temperature. Although these chiral allylboron reagents have quite bulky chiral substituents, the *N*-aluminum imine was allylated with this reagent even at low temperature to give homoallylic amine **4a**. All chiral allylboration reagents used successfully reacted with **2a** to afford the corresponding primary homoallylic amine **4a**. The isolated yield of the amine was sometimes moderate, since some of the amine product was lost during isolation process mainly owing to the difficulty of separation of the aluminum by-product.



Scheme 2.

In a number of asymmetric reactions, the level of enantioselectivity increased by decreasing the reaction temperature. Table 2 shows an unusual temperature dependence of the asymmetric allylboration of **2a** on the enantioselectivity. We have observed that the selectivity increased with increasing the temperature until an optimal range was reached (0–20°C) where the selectivity then began to decrease slowly. When **5** was used as the allylborating agent, no significant decrease of ee was observed even at the reflux temperature of THF. Whereas the THF solution of the reaction mixture is homogeneous above 0°C during allylboration reactions, a heterogeneous system was observed below −30°C. Somewhat different reactive species might participate in the reaction at lower temperatures, which would cause the decrease of the stereoselectivity. At a given temperature the use of different reagents (varying chiral ligand) resulted in different selectivity. Although Brown et al. reported that the allylboration of aldehydes by chiral reagent **6** exhibited quite high enantioselectivity (up to >99% ee) [19], the same reagent gave an enantioselectivity of 52% in the allylboration of the *N*-aluminum imine (Run 6). Roush's reagent **7** led to an *R* configuration of the product, while other reagents preferred *S* amine as a major enantiomer. In our previous communication, we found that chiral *B*-allyloxazaborolidine prepared from (−)-norephedrine exhibited excellent selectivity in the allylboration of *N*-trimethylsilyl imines [11a] and aldehydes [22]. However, the same reaction on the *N*-aluminum imine afforded only poor enantioselectivities (Runs 13–16, 15–33% ee).

Encouraged by the good enantioselectivities achieved with **5** at 25°C (Table 2), we extended the study to the allylborations of representative *N*-diisobutylaluminum imines derived from other nitriles. Table 3 shows the results of enantioselective allylboration of *N*-aluminum imines **2** with the chiral reagent **5**. In contrast with benzaldimine **2a**, higher enantioselectivities were obtained at lower temperatures in the allylboration of these imines. *N*-Aluminum imine **2b** derived from *p*-tolunitrile gave the highest enantioselectivities (up to 87% ee) in the imines used for the enantioselective allylboration. In all cases, reaction proceeded in a homogeneous system and significant change of enantioselectivity was not observed until the reaction temperature was raised to room temperature. It should be also emphasized that

Table 2
Enantioselective synthesis of homoallylamine by nucleophilic addition of chirally modified allylboron reagent to *N*-diisobutylaluminum imine **2a**

Run number	Chirally modified allylboron reagent	Temperature (°C)	1-Phenyl-3-butenamine (**4a**)		
			Yield%[a]	Ee%[b]	Configuration[c]
1	**5**	–78	59	33	*S*
2	**5**	–45	61	47	*S*
3	**5**	25	67	69	*S*
4	**5**	66	42	66	*S*
5	**6**	–78	78	20	*S*
6	**6**	0	61	52	*S*
7	**6**	25	65	47	*S*
8	**6**	66	71	28	*S*
9	**7**	–78	5	8	*R*
10	**7**	0	37	59	*R*
11	**7**	25	45	62	*R*
12	**7**	66	59	32	*R*
13	**8**	–78	19	15	*S*
14	**8**	0	35	33	*S*
15	**8**	25	30	23	*S*
16	**8**	66	64	24	*S*

[a] Isolated yield.
[b] Determined by HPLC analysis with a chiral stationary phase column. See Experimental.
[c] The absolute configuration of the product was determined by the comparison of the specific rotation with the reported value 26.

Table 3
Enantioselective synthesis of homoallylamine **4** by nucleophilic addition of **5** to *N*-diisobutylaluminum imine **2**

Run number	Nitrile	Temperature (°C)	Yield of **4**%[a]	Ee%[b]
1	**1g**	–78	60	73
2	**1g**	–30	54	71
3	**1g**	0	63	67
4	**1g**	25	47	63
5	**1g**	Reflux	39	45
6	**1h**	–78	32	79
7	**1h**	–30	22	85
8	**1h**	0	21	66
9	**1h**	25	41	60
10	**1h**	Reflux	37	36
11	**1i**	–78	32	80
12	**1i**	–30	49	67
13	**1i**	0	53	78
14	**1i**	25	53	70
15	**1i**	Reflux	51	43
16	**1b**	–78	46	87
17	**1b**	–30	73	83
18	**1b**	0	70	82
19	**1b**	25	66	78
20	**1b**	Reflux	27	53

[a] Isolated yields based on the starting nitrile.
[b] Determined by GC analysis with a trifluoroacetylated γ-cyclodextrin column (30 m × 0.25 mm) (Astec, Chiraldex G-TA) for the products **4g**, **4h**, and **4i** and HPLC analysis using Daicel, Chiralcel OD-H (250 × 4.6 mm) with hexane:2-propanol:diethylamine (90:10:0.1) for the product **4b**.

aliphatic imines derived from **1g**, **1h**, and **1i** were asymmetrically allylated to the corresponding homoallylamines in good to high enantioselectivities.

In conclusion, we have shown that optically active homoallylamines, which are interesting intermediates in the synthesis of biologically active natural products, are readily prepared from enantioselective allylboration of *N*-aluminum imines with chirally modified allylboron reagents. This is a convenient and direct procedure for the synthesis of such amines. A further advantage of the use of *N*-aluminum imines is that primary homoallylamines were easily obtained after usual aqueous work-up.

3. Experimental

3.1. General

All experiments were carried out under an atmosphere of dry nitrogen. Tetrahydrofuran (THF) was dried over sodium-benzophenone ketyl, and was freshly distilled just before use. All nitriles were distilled from calcium hydride before use. DIBAL-H (diisobutylaluminum hydride, 1.01 M solution in hexanes) and (−)-*B*-chlorodiisopinocampheylborane [(−)-DIP-Cl™] were purchased from Aldrich, Inc. Reactions were monitored by thin layer chromatography (TLC) using Merck precoated silica gel plates (Merck 5554, $60F_{254}$). Flash column chromatography was performed over Wako silica gel (Wakogel C-200, 100–200 mesh). ^{1}H-NMR spectra were measured on a JEOL JNM-GX270 spectrometer using Me_4Si as an internal standard. Infrared spectra (IR) were recorded with a JEOL JIR-7000 FT-IR spectrometer and are reported in reciprocal centimeters (cm^{-1}). Optical purity was determined by a Shimadzu Capillary Gas Chromatograph 14A with a chiral capillary column (Astec Chiraldex G-TA, 30 m × 0.25 mm). HPLC analyses were performed with a TOSOH HLC-8020 equipped with a chiral column (Chiralcel OD-H, Daicel) using hexane:2-propanol:diethylamine (90:10:0.1). A UV detector (TOSOH UV-8011) was used for the peak detection. Optical rotations were taken on a JASCO DIP-140 digital polarimeter using 10 cm thermostated microcell.

3.2. Preparation of *N*-(diisobutylaluminum)benzaldehyde imine (**2a**)

The preparation of **2a** was based on that of Andreoli et al. [13]. To a solution of benzonitrile (0.5 ml, 5 mmol) in THF (5 ml) was added dropwise a solution of DIBAL-H (1.01 M, 5 mmol) at 0°C. The reaction mixture was stirred at room temperature (r.t.) for 1 h. Evaporation of the solvent in vacuo gave **2a** as viscous oil in quantitative yield. ^{1}H-NMR (270 MHz, $CDCl_3$) δ 8.95 (s, 1H), 7.74–7.46 (m, 5H), 1.84 (m, 2H), 0.96–0.74 (m, 12H); IR 1635 (C=N). For the following allylboration reaction, a THF solution of **2a** was used without purification.

3.3. Preparation of chirally modified allylboron reagents

3.3.1. Chirally modified allylborane (**5**)

Chirally modified allylboranes were prepared from the corresponding *B*-chlorodialkylboranes, such as (−)-DIP-Cl or (−)-*B*-chlorodiisocaranylborane, with allylmagnesium chloride in THF, according to Brown's procedure [23,24]. To a solution of (−)-DIP-Cl (1.92 g, 6 mmol) in THF (10 ml) was added dropwise allylmagnesium chloride in THF (1.1M, 6 mmol) at 0°C under a nitrogen atmosphere. After the reaction mixture was stirred for 1 h at r.t., the resulting solution of **5** was used for the enantioselective allylboration reaction.

3.3.2. Chirally modified allylboronate (**7**)

The preparation of chirally modified allylboronates was based on Roush's method [25]. To a solution of (+)-diisopropyl tartrate (1.41 g, 6 mmol) in THF (10 ml) was added dropwise a THF solution of triallylborane (6 mmol) at r.t. The reaction mixture was stirred

for 2 h and then heated under reflux for another 1 h. The solution was cooled, and all volatile components were removed in vacuo. The resulting allylboronate **7** was dissolved in THF (10 ml) and then used for the enantioselective allylboration reaction.

*3.3.3. Chirally modified B-allyloxazaborolidine (**8**)*

According to the procedure described before [11b], **8** was prepared from the *N*-sulfonylamino alcohol, derived from (−)-norephedorine with triallylborane in THF.

*3.4. Enantioselective allylboration of N-diisobutylaluminum imine **2a** with chirally modified allylboron reagent **5***

To a solution of **5** (6 mmol) prepared from (−)-DIP-Cl (1.92g, 6 mmol) and allylmagnesium chloride (6 mmol), a THF solution of **2a** prepared from benzonitrile (0.5 ml, 5 mmol) and DIBAL-H (4.95 ml, 5 mmol) in THF (5 ml) was added. The reaction mixture was then stirred for 5 h at r.t., and quenched with 2M HCl. The aqueous layer was separated, washed with ether, neutralized with NH_4OH and extracted with ether. The combined extracts were dried over $MgSO_4$ and concentrated by rotary evaporator to yield a colorless oil which is essentially pure 1-phenyl-3-butenamine (0.49 g, 67%). ^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.34–7.22 (m, 5H), 5.81–5.70 (m, 1H), 5.15–5.06 (m, 2H), 3.98 (dd, $J = 7.81$ and 5.37 Hz, 1H), 2.46–2.32 (m, 2H), 1.53 (br, 2H); IR 3300 (NH_2), 1630 (C=C), 1300 (C–N). The product was purified by flash-column chromatography on silica gel (ether). The enantioselectivity 69% ee was determined by HPLC analysis using a chiral stationary phase column (Daicel, Chiralcel OD-H; hexane:2-propanol:diethylamine = 90:10:0.1, flow rate; 0.5 ml min^{-1}): tR 16.3 min (*R*), tR 20.7 min (*S*). The absolute configuration of the product was correlated to that described in the literature [26].

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