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Recent developments in the chiral synthesis of homoallylic amines via organoboranes*

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Abstract: Among the plethora of protocols for the preparation of chiral homoallylic amines, the use of boron-based reagents remains relatively undeveloped. However, the recent advances in the use of α-pinene-based versatile reagents for the synthesis of such amines confirmed that very high enantioselectivity and outstanding diastereoselectivity can be readily achieved. Addition of the "allyl"boron reagents to various N-substituted imines provided the desired amine products in high yields and high to very high ee. The discovery that an addition of 1.0 equiv of methanol or water to the "allyl"boration reaction with *N*-masked imines is critical allowed for higher yields and noticeably improved ee. The use of *N*-aluminoimines, which are not only easy to prepare by a partial reduction of nitriles, but are also relatively stable for both enolizable and non-enolizable substrates, considerably expanded the scope of the reactions. In this review, the developments in the syntheses of chiral homoallylic amines using organoboranes, with the particular accent on the reagent-controlled reactions, are summarized. Additionally, the novel methodology for the crotyl- and alkoxyallylboration of imines using trialkylboron "ate" complexes is described.

Keywords: chiral homoallylic amines; N-substituted imines; allylboron reagents; organoboranes; homoallylic amines; *N*-aluminoimines.

INTRODUCTION

The homoallylic amine moiety is not widely present in natural products, however, compounds like eponemycin [1], which exhibits potent activity against B16 melanoma cells, or a depsipeptide cryptophycin 337 [2], which is an analog of a potent anti-tumor compound cryptophycin, contain this subunit (Fig. 1).

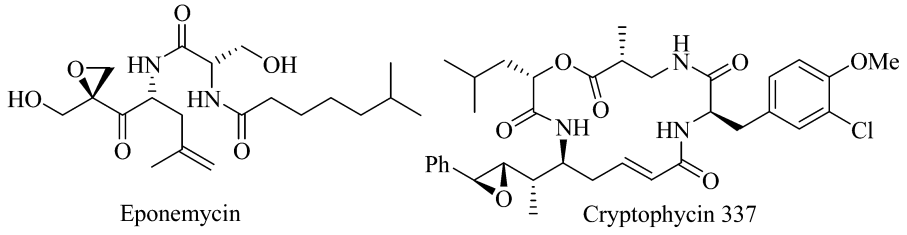

Fig. 1 Natural products containing homoallylic amine moiety.

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On the other hand, homoallylic amines are excellent building blocks for the synthesis of numerous nitrogen-containing natural products [3]. Chiral homoallylic amines were utilized as the key intermediates in the preparation of many natural products, such as an amino-sugar vancosamine isolated from vancomycin [4], a spirocycle alkaloid halichlorine isolated from a Japanese sponge *Halichondria okadai* Kadota [5], an alkaloid from *Prosopis africana*, desoxoprosopinine [6], and many others. Additionally, a variety of other nitrogen-containing compounds, including amino alcohols, β- and γ-amino acids, γ-amino alcohols, γ-lactams, and many other compounds can be easily accessed from homoallylic amines (Fig. 2). With the utilization of ring-closing metathesis methodology, numerous piperidine alkaloids can be easily prepared from the corresponding aminodienes [7]. Preparation of β-amino acids is of particular interest to medicinal and bioorganic chemists as various β-amino acid moieties can be found in taxoids, β-lactam antibiotics, HIV-protease inhibitors, and other compounds. Moreover, high proteolytic stability of β-amino acids makes them excellent substrates for the peptidomimetics [8].

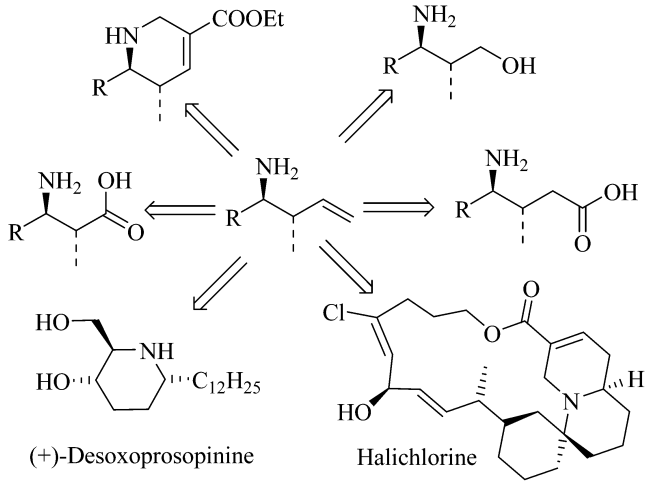


Fig. 2 Utility of homoallylic amines.

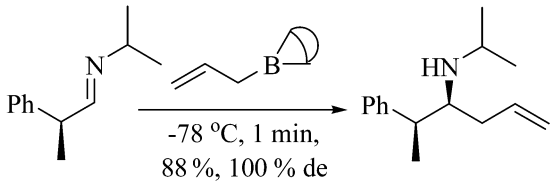
Hence, preparation of homoallylic amines in an optically pure form is a very important task in organic synthesis, leading to an abundance of protocols for their preparation that can be found in the literature [3,8]. Diastereoselective addition of allyl organometallic compounds to N-substituted aldimines is a widely recognized procedure for the preparation of homoallylic amines [9]. While the use of substrate-controlled asymmetric additions is quite commonly employed, the use of reagent control remains undeveloped [9]. However, in spite of aldimines being very attractive starting materials for the syntheses of homoallylic amines, the inherent instability of unsubstituted aldimines and the low reactivity of the more stable N-substituted ones significantly limit their use [9,10]. Furthermore, attempted 1,2-additions to aldimines quite often fail due to the tendency of enolizable compounds to undergo deprotonation instead of addition [9d]. Among the developments in allylations of aldimines, organoboron compounds have found significant synthetic utility due to the Lewis acidity of boron, which allows it for the coordination with nitrogen, thus improving the electrophilicity of the aldimines [9].

The α-pinene-based versatile reagents for asymmetric allyl-, crotyl-, and alkoxyallylboration that were developed by Brown and coworkers are being commonly used for the synthesis of homoallylic alcohols [11]. Due to their ease of preparation and use, ability to reliably deliver all isomers of the homoallylic products in very high ee and de, and low cost, they became very attractive reagents for the preparation of homoallylic amines as well.

The purpose of this review is to examine the developments in the utilization of the organoboranes for the asymmetric allylations of aldimines. Preparation of the homoallylic amines using a variety of other procedures has been recently summarized [12].

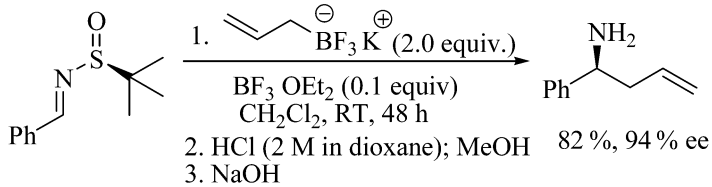
SUBSTRATE-CONTROLLED ADDITIONS

Allylboration and crotylboration of α-optically pure N-substituted aldimines using *B*-"allyl"-9-BBN was first described by Yamamoto and coworkers [13]. These reactions proceeded in high diastereoselectivity due to the sterically influenced chirality according to the Cram rules. With the use of properly matched N-protecting groups, up to 100 % de was obtained in the case of allylboration (eq. 1). However, application of the same concept to the crotylboration provided the products with only low diastereoselectivity [14].



(1)

The use of an *N*-borylimine containing a chiral auxiliary, followed by the addition of alkyllithium reagents, gave only poor enantioselectivity [15]. A method for the preparation of functionalized homoallylic amines from N-chirally modified imines was also developed [16]. As one of the isomers was obtained by the use of methallyl or prenallyl zinc reagents, the other required the use of an allylboronate. Among the recent developments in the substrate-controlled additions, the reaction of a chiral *N*-*tert*-butanesulphinamide with potassium allyltrifluoroborate in the presence of catalytic $BF_3{\cdot}OEt_2$, developed by Batey and coworkers, furnished, after hydrolysis, the desired homoallylic amine in high ee (eq. 2) [17].



(2)

REAGENT-CONTROLLED ALLYLATIONS

Initial developments

The first report about the utilization of chiral organoboranes for the synthesis of homoallylic amines came from Itsuno's group. Having established high reactivity of *N*-trimethylsilylaldimines with triallylboron, successive study of allylations using various chiral "allyl"boron reagents derived from tartrate esters, diols, α-amino alcohols, and α-pinene on *N*-trimethylsilylbenzaldimine was done (Fig. 3). Hence, assorted homoallylic amines were obtained in moderate to good enantioselectivities [1]. Modification of the chiral ligands revealed that while *B*-allyldiisopinocampheylborane (**1**) provided high ee, norephedrine-derived allyloxazaborilidine (**2**) gave even better results in terms of yield and ee. Other evaluated reagents, based on Roush's tartrate (**3**), and camphor-derived sulfonylamino alcohol (**4**) were inferior as compared to the first two. In further studies, the evaluation was expanded to methallylboration, which proceeded satisfactorily as well [19].

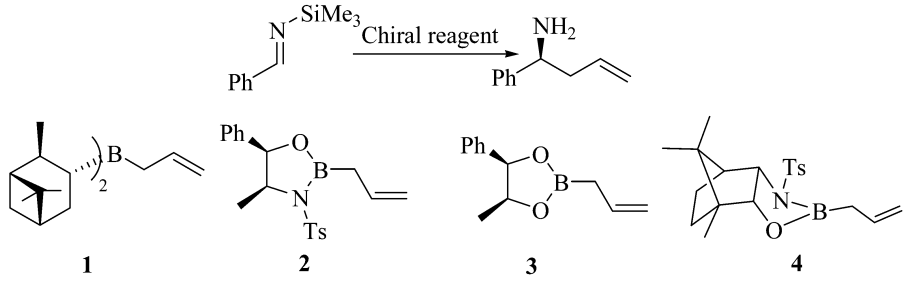
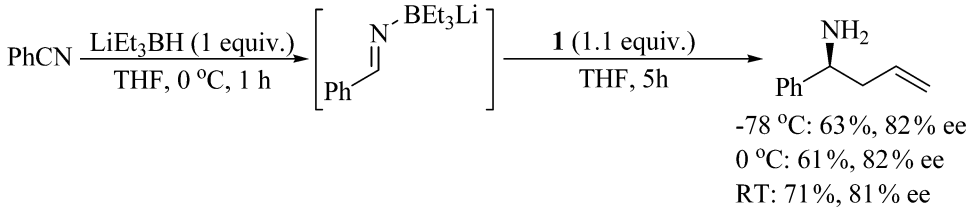


Fig. 3 Reagents for the asymmetric allylboration of *N*-silylimines.

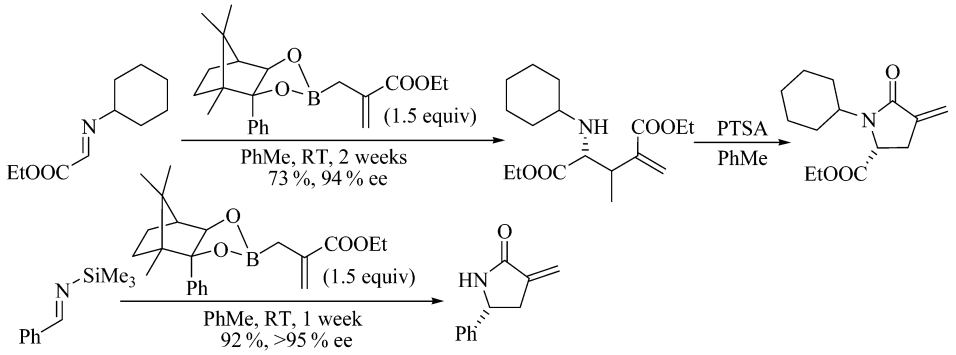
The use of non-enolizable *N*-borylimines, obtained by the partial reduction of nitriles with $LiEt_3BH$, followed by the addition of **1**, **2**, or **3** provided the desired amine products [20]. In this case, the reagent **1** afforded the best results. Interestingly, no influence of the reaction temperature on the enantioselectivity was observed (eq. 3) [20].



(3)

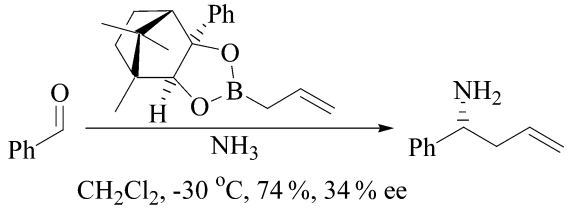
Allylboration of the *N*-trimethylsilylaldimines was limited to the non-enolizable substrates. However, this inefficiency was avoided by expansion of the protocol to *N*-aluminoimines. Thus, partial reduction of nitriles with DIBAL-H provided *N*-aluminoimines, which reacted with **1** to yield the desired amine products. Due to the higher stability of enolizable *N*-aluminoimines, the allylations were quite successful even in the case of aliphatic substrates [21]. Additionally, the reactions run on polymeric support provided the desired amines as well [22].

The addition of camphor-derived functionalized chiral allylboronate to *N*-trimethylsilyl and *N*-alkylaldimines provided the desired homoallylic amines in moderate to good yields and high ee, however, prolonged reaction times were required (Scheme 1) [23]. In situ formation of α-methylene-γ-lactams was observed in the cases of the more reactive substrates and with the labile N-protecting groups.



Scheme 1 Synthesis of α-methylene-γ-lactams.

Kobayashi's group recently reported a three-component coupling between benzaldehyde, ammonia and Hoffmann's chiral allylboronate providing the corresponding chiral homoallylic amine, *albeit*, with low enantioselectivity (eq. 4) [24].



(4)

Investigation of the rate of allylations of *N*-trimethylsilylimines with the reagent **1** with ^{11}B NMR spectroscopy revealed that the reactions would not proceed unless a molar equivalent of water was added to the reaction [25]. Indeed, the yields of several homoallylic amines prepared with the inclusion of water exhibited improved yields, higher enantioselectivities, and shortened reaction times (Fig. 4, Table 1). Further study showed that methanol could replace water [26]. Later, the reaction was expanded to *N*-aluminoimines, which in the reactions with **1** required 1.0 equiv of methanol as well, to provide homoallylic amines (Fig. 4) [27]. In the case of the less reactive aliphatic substrates, increased reaction temperature allowed for improved yields, however, the observed ee was somewhat lower.

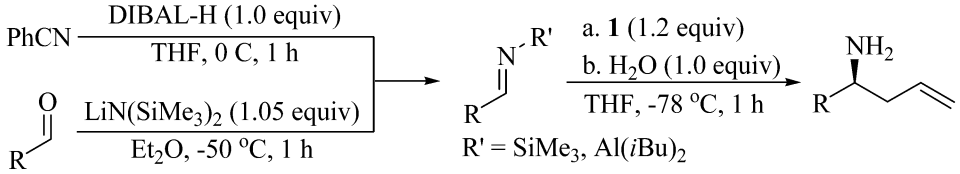


Fig. 4 Asymmetric allylboration of aldimines with (–)-*B*-allyldiisopinocampheylborane in the presence of 1.0 equiv of water.

Table 1 Allylboration of *N*-trimethylsilylimines with **1** in the presence and absence of water at –78 °C.

R	Yield (%)		ee (%)	
	Without water[a]	With water[b]	Without water[a]	With water[b]
Ph	73 (59)[c]	90 (90)[c]	73 (33)[c]	92 (88)[c]
2-Cl-(C_6H_4)	62	69	46	82
4-MeO-(C_6H_4)	65	74	52	92

[a]The values obtained from refs. [18b,21].
[b]The values obtained from ref. [25].
[c]The values in parentheses are for *N*-aluminoimines.

In the postulated reaction mechanism, the addition of methanol allowed for the liberation of a "naked" C=NH aldimine, which rapidly reacted with the organoboron reagent (Fig. 5). Coordination between boron and the aldimine's nitrogen was found to be critical, as evidenced by the relative stability of the aldimines to methanolysis [26,27].

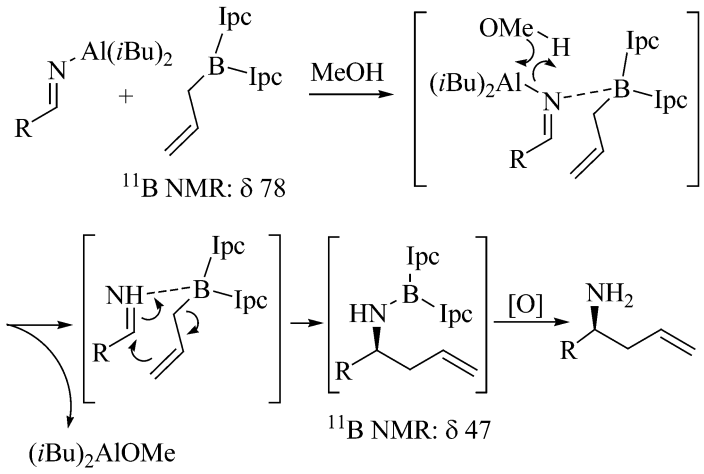


Fig. 5 Proposed reaction mechanism for allylboration of *N*-aluminoimines in the presence of methanol.

The spectroscopic data and the observed stereochemistry of the amine products support the postulated mechanism and imply that the reaction proceeds through a six-member transition state (Fig. 6), similar to the allylboration of aldehydes [11,27,28].

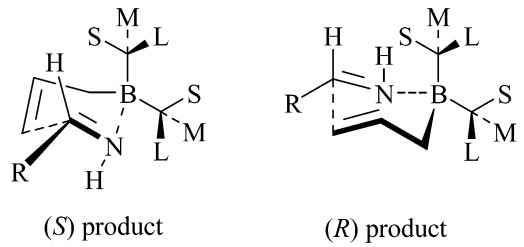


Fig. 6 Transition states in the allylboration of aldimines.

CROTYL- AND ALKOXYALLYLBORATION OF IMINES

Successful reagent-controlled crotylboration and alkoxyallylboration of N-masked aldimines has been recently reported for the first time [27]. Studies by ^{11}B NMR spectroscopy revealed that these reactions, similarly to allylboration, would not proceed unless a molar equivalent of water or methanol was added. Moreover, these reactions would not provide the desired products unless boron "ate" complexes (**5–8**) were used (Fig. 7), rather than the trialkylboranes used for the corresponding additions to aldehydes.

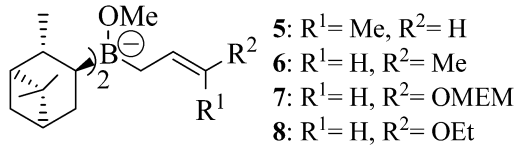


Fig. 7. Boron "ate" complexes for the crotyl- and alkoxyallylboration of aldimines.

Excellent diastereoselectivity and very high ee were obtained not only in the case of non-hydrolyzable *N*-silyl or *N*-aluminoimines, but also with the aliphatic *N*-aluminoimines (Fig. 8, Table 2). The last ones did, however, require slightly modified conditions in the use of pentane as solvent [27].

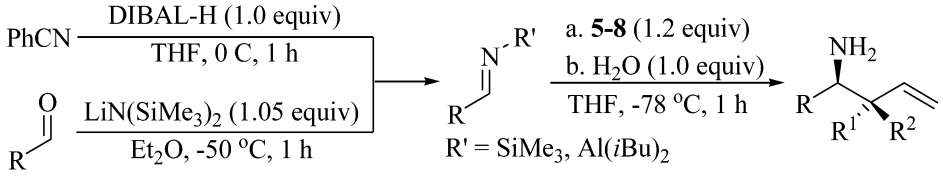


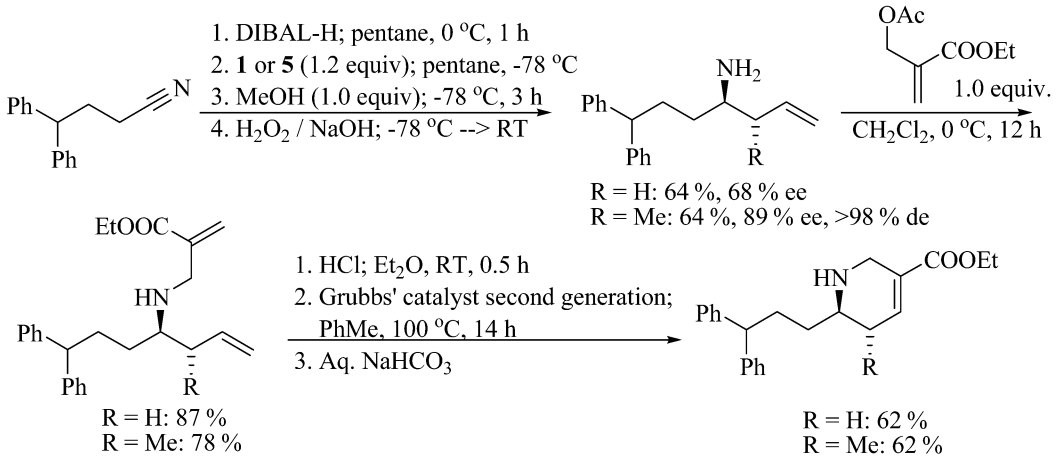
Fig. 8 Asymmetric crotyl- and alkoxyallylboration of aldimines.

Table 2 Crotyl- and alkoxyallylboration of *N*-aluminoimines[a].

Reagent	R	R^1	R^2	Yield (%)	de (%)	ee (%)
5	Ph	Me	H	80 (78)[b]	98 (96)[b]	89 (92)[b]
5	$Ph_2CHCH_2CH_2$	Me	H	64	>98	89
5	2-Thp	Me	H	71	98	89
5	*n*-Bu	Me	H	64	>98	79
5	Chx	Me	H	74	>98	89
6	Ph	H	Me	78 (76)[b]	>98 (98)[b]	90 (90)[b]
6	2-Thp	H	Me	76	>98	88
6	*n*-Bu	H	Me	61	>98	81
6	Chx	H	Me	78	>98	87
7	Ph	H	OMEM	65 (65)[b]	>98 (98)[b]	95 (95)[b]
8	Ph	H	OEt	72	>98	89
7	2-Thp	H	OMEM	71	>98	87
7	*n*-Bu	H	OMEM	60	>98	92
7	Chx	H	OMEM	62	>98	89

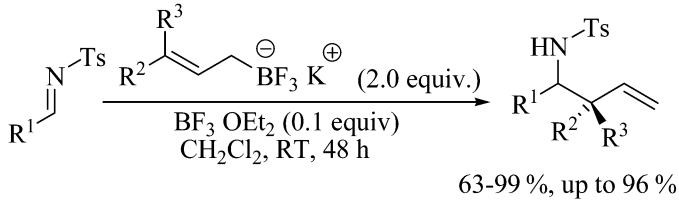
[a]Data obtained from refs. [27,29].
[b]Data in parentheses were obtained with *N*-trimethylsilylimines.

This methodology has been used by us for the synthesis of densely functionalized tetrahydropyridine 3-carboxylates that are analogs of known GABA-uptake inhibitors [29]. This expedient preparation (Scheme 2) included the synthesis of homoallylic amines from nitriles via allylboration of *N*-aluminoimines, followed by a conjugate addition-elimination reaction of the obtained amines on the acetate derived from vinylalumination of formaldehyde [30], and the ring-closing metathesis on the resulting aminodiene [7].



Scheme 2 Application of the allyl- and crotylboration of *N*-aluminoimines for the synthesis of functionalized tetrahydropyridine 3-carboxylates.

Among other recent developments, highly diastereoselective *syn*- or *anti*-crotylation of *N*-toluenesulfonylimines using potassium crotyltrifluoroborates were reported [17]. Like in the case of the similar allylation, the presence of a Lewis acid was required (eq. 5).



(5)

CONCLUSIONS

In spite of the few reports regarding chiral allylboration of N-masked imines, reactions of these and other boron-based chiral reagents with imines to form homoallylic amines remain significantly underdeveloped. Consistent results in terms of yields and enantioselectivity were obtained only after the discovery that allylboration of aldimines require the addition of 1.0 equiv of water or methanol to proceed. Among the numerous aldimines that have been reported in the literature, only a few were successfully used as the substrates for allylboration. Additionally, the research on the preparation of the highly useful crotyl- and alkoxyallylboration products has only just begun. Clearly, the investigation of additions of chiral organoboron compounds to imines will require considerable efforts.

ACKNOWLEDGMENTS

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