B-Methoxydiisopinocampheylborane (Ipc_2BOMe): A Pinene Based Auxiliary for Asymmetric C–C Bond-Forming Reactions

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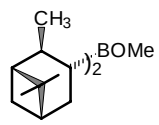
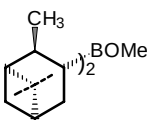
Contents

Homochiral organoboron compounds constitute an exceptionally useful class of reagents for the synthesis of optically active targets [1, 2]. In particular the pioneering work of H. C. Brown and coworkers resulted in a number of reagents like alpine-borane, DIPCl and oxazaborolidinones that are now routinely employed in synthesis to achieve asymmetric reductions, aldol reactions, and alkylations. Especially, the α-pinene-based reagents provide advantages for Organic Synthesis [3]. Both enantiomers of α-pinene are available from the chiral pool, the auxiliary may be easily recycled [4], and the configuration of the reagent-mediated products is predictable on the basis of reliable mechanistic models. Out of this group of reagents *B*-Methoxydiisopinocampheylborane, Ipc_2BOMe (**1**), has emerged as a versatile tool for creating new asymmetric C–C-bonds.

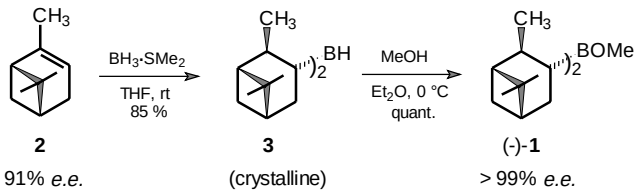


$^{d}Ipc_2BOMe$
(-)-**1**



$^{l}Ipc_2BOMe$
(+)-**1**

Both antipodes of Ipc_2BOMe are commercially available, but can also be cost-effectively prepared from excess α-pinene, $BH_3 \cdot SMe_2$ and MeOH [5]. Since the intermediate, diisocampheylborane **3**, readily precipitates as a crystalline solid, hydroboration of natural pinene (91% *e.e.*) is an efficient route towards enantiopure auxiliaries (> 99% *e.e.*, Scheme 1).

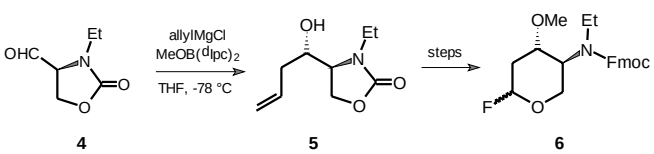


Scheme 1 Preparation of $^{d}Ipc_2BOMe$; optical upgrading of (1*R*)-(+)-pinene

1. Unsubstituted Allylation Agents

1.1 Allylboration of Aldehydes

The standard procedure for asymmetric allylboration of aldehydes [6] involves initial reaction of allyl Grignard reagents with **1** [7]. However, since Mg^{2+} ions slow down the allylation, it is recommended to precipitate the inorganic salts prior to alkylation. Under salt-free conditions, *B*-allyldiisopinocampheylborane reacts with aldehydes at low temperatures (–100 °C) yielding homoallylic alcohols of high optical purity (up to 100% *e.e.*) [5]. The stereochemistry of the products is highly predictable, based on the Zimmermann–Traxler model. Excellent diastereoselectivities are observed with achiral and α-chiral aldehydes and, in cases of double asymmetric induction, the *B*-reagent generally overrides the influence of the substrate. For example, reagent- controlled allylation of the oxazolidinone **4**, and subsequent oxidative cleavage of the alkoxyborane provides homoallyl alcohol **5** as a single diastereomer. Ozonolysis and cyclization of **5** provide **6**, a key intermediate for the calicheamycin γ_1 oligosaccharide fragment (Scheme 2) [8].

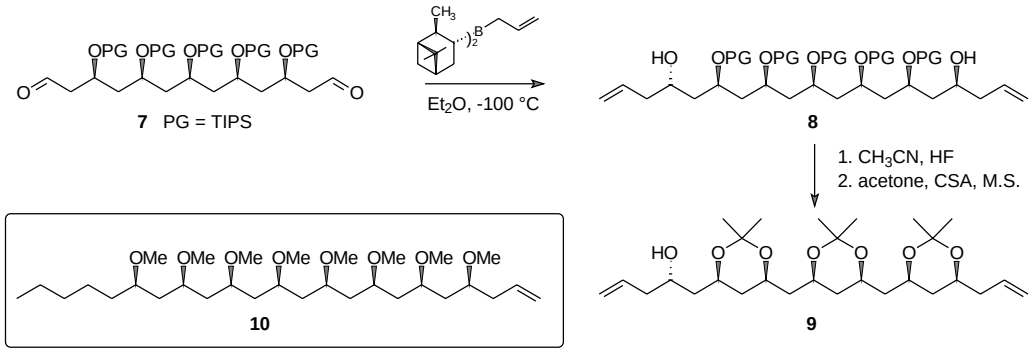


Scheme 2 Synthesis of a building block for the calicheamycin oligosaccharide fragment

  1436-9966/99/34101-83 $ 17.50 + .50/0

1.2 Dissymmetrization of meso-Compounds

The dissymmetrization of prochiral *meso* compounds is a valuable synthetic operation, most often performed using hydrolytic or oxidoreductive enzymes [9]. The first nonenzymatic, exclusively reagent controlled, dissymmetrization of a *meso* precursor involved allylation of *syn*-polyoldialdehyde **7** with Ipc_2BOMe and allylMgCl [10]. Diastereofacial selective allylation occurred simultaneously at both aldehyde termini and yielded the bis-homoallyl alcohol **8** with high diastereoselectivity (>15:1). **8** was further elaborated *via* the tris(acetonide) **9** into the isotactic polymethoxy-1-alkene **10**, previously isolated from tolytoxin-producing blue-green algae (Scheme 3) [11]. Due to greater thermodynamic stability of *syn*-1,3- rather than *anti*-1,3-acetonides, the protective groups facilitated terminal differentiation in the 1,3-diol system (Scheme 3).

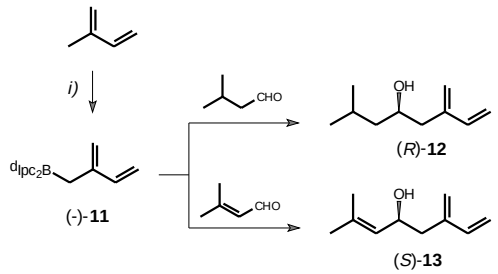


Scheme 3 Enantiodivergent synthesis of polyols

2. Branched Allylation Agents

2.1 Methallylboration and Isoprenylation

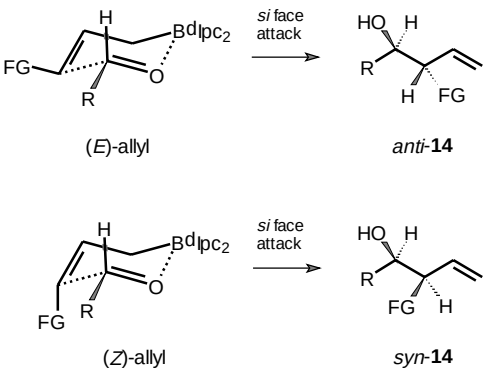
In addition to simple allyl-moieties, methallyl and isoprenyl allylation reagents can be employed for the stereocontrolled synthesis of branched homochiral alcohols. In a one-pot synthesis, *B*-2'-isoprenyldiisopinocampheylborane, prepared from isoprenylpotassium, **1** and borontrifluoride, reacts with aldehydes to give isoprenylated alcohols in good yield and high *e.e.* Using this protocol, both enantiomers of the bark beetle (*Ips confusus*) sex pheromones ipsenol, (*R*)-**12**, and ipsdienol, (*S*)-**13**, have been synthesized in one step (Scheme 4), a major improvement over precedent syntheses using 13 and 17 steps [12].



Scheme 4 Stereoselective one-pot synthesis of ipsenol (*R*)-**12** and ipsdienol (*S*)-**13**; *i)*: *n*-BuLi, TMPK, –78 °C, $^dIpc_2BOMe$, $BF_3 \cdot OEt_2$; (TMPK: potassium 2,2,5,5-tetramethylpiperidide)

2.2 Crotylboration

Condensation of aldehydes with allylboranes possessing unsymmetrical substitution at the allylic double bond, remote from the boron, represents a powerful method for carbon-carbon bond formation, with simultaneous generation of two new adjacent chiral centres. (*E*)- and (*Z*)-Crotylboranes (Table 1, entries 1 and 2), for example, readily accessible from Ipc_2BOMe and (*E*)- or (*Z*)-crotylpotassium (*Schlosser* procedure), undergo borotropic rearrangement in the presence of aldehydes to form the corresponding *erythro*- and *threo*-4-hydroxy-3-methylalk-1-enes with excellent relative and absolute stereochemical control, as outlined in Scheme 5 [13].



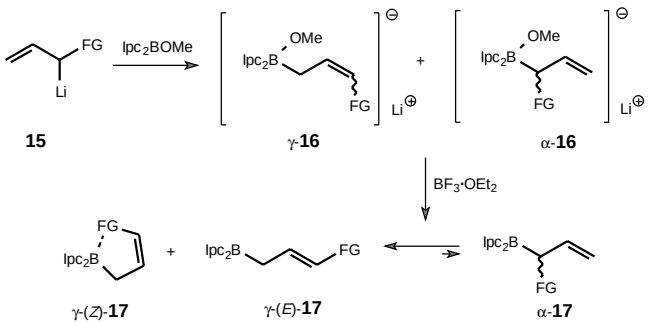
Scheme 5 Diastereoselective allylation of aldehydes with (*E*)- and (*Z*)-crotylborane reagents (FG = CH_3)

Typical examples of diastereo- and enantioselective crotylborations with Ipc_2BOMe represent key steps in the total syntheses of the antifungal agents nikkomycin B [14] and rapamycin [15].

3. Heterosubstituted Allylation Agents

Following treatment with Ipc_2BOMe, a variety of heterosubstituted allylmetal reagents react with aldehydes to give

polyfunctionalized vinylic compounds of high diastereomeric and enantiomeric excess (Table 1). For example, allyllithium compounds **15** first react with **1** to form boron ate-complexes of the type γ-**16** and α-**16**, which can be subsequently decomposed with Lewis acids such as $BF_3 \cdot OEt_2$. Owing to the electronic nature and steric hindrance of the functional group, the carbon–carbon double bond of the allylboron adopts (*E*)- or (*Z*)-configuration *via* allylic rearrangement of the ate-complexes γ- and α-**17** (Scheme 6). For steric and thermodynamic reasons α-**16** is disfavoured and, hence, the α:γ ratio of adducts is generally higher than 97:3.



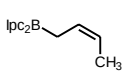
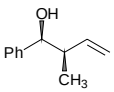
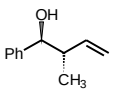
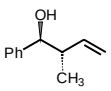
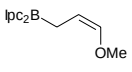
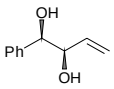
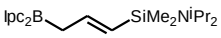
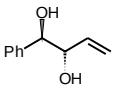
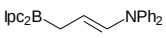
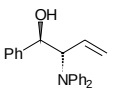
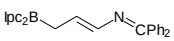
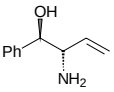
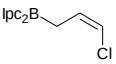
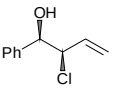
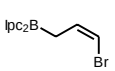
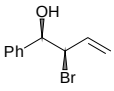
Scheme 6 Preparation of functionalized allylation reagents

With respect to functional groups present in the resulting organoboron reagents, *syn*- and *anti*-diols (entries 3 and 4) [16–18], *anti*-amino alcohols (entries 5 and 6) and *syn*-halohydrins, or vinyloxiranes respectively (entries 7 and 8), are accessible in high optical purity, thus providing alternatives to bishydroxylation, aminohydroxylation and Sharpless epoxidation. Results of benzaldehyde allylations are compiled in Table 1.

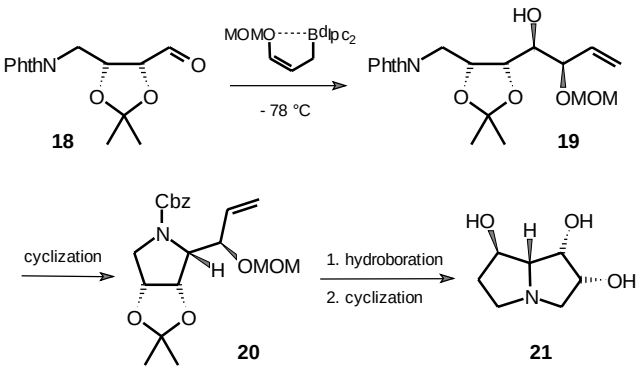
3.1 Synthesis of syn- and anti-Diols

The homologation of aldehydes to vicinal diols is of special interest for the synthesis of carbohydrates and antibiotics. Simple treatment of alkoxyallyl lithium with Ipc_2BOMe and $BF_3 \cdot Et_2O$ provides [(Z)-γ-alkoxyallyl]diisopinocampheylborane (Table 1, entry 3) that gives rise to *syn*-diols (Scheme 5, FG = MeO, MEMO). In natural product synthesis, this transformation has found numerous applications, and the antibiotics calicheamycin γ'_1 [19] and herbimycin A, a herbicidal, antiviral and antitumor active metabolite of a Streptomyces strain, were first synthesized using [(Z)-γ-alkoxyallyl]diisopinocampheylborane in key steps [20]. The stereoselective alkoxyallylboration of amino compounds like **18** opens a versatile route to polyhydroxylated alkaloids, for example castanospermine and swainsonine [16, 21], both known as potent glucosidase inhibitors, and analogues such

Table 1 Allylation of benzaldehyde with functionalized $^dIpc_2B$-based reagents. *(DIPCl was used)

entry	allylation agent	product	*syn*/*anti*	*e.e.* (%)	yield (%)	ref.
1			>99:1	>90	72	[13]
2			<1:99	>90	79	[13]
3			>99:1	90	72	[16, 17]
4			5:95	>90	50	[18]
5			5:95	>95	48	[23], [24]
6*			5:95	90–93	53	[25]
7			99:1	99	78	[27]
8			94:6	86	76	[28]

as **21**, that are considered as promising leads in medicinal chemistry.

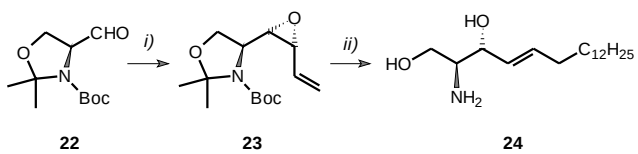


Scheme 7 Synthesis of a ring contracted swainsonine analogue

Since the direct lithiation of allyl ethers is highly (*Z*)-selective, because of chelatization, access to an (*E*)-selective Ipc_2B-based reagent leading to vicinal *anti*-diols is only viable employing a non Lewis-basic surrogate. Such a reagent is formed upon treatment of lithiated allyl(diisopropylamino) dimethylsilane with Ipc_2BOMe and $BF_3 \cdot Et_2O$ (Table 1, entry 4) [22]. The allylation products, *anti*-β-hydroxysilane boronate esters, are treated *in situ* with basic H_2O_2 to cleavage the boron–oxygen and the carbon–silicon-bond. The resulting *anti*-diols are obtained with remarkably high selectivity. As a first application of this strategy, the synthesis of the antitumor compound calyculin A, a protein phosphatase inhibitor isolated from a Japanese marine sponge (*Discodermia calyx*), has been accomplished [18].

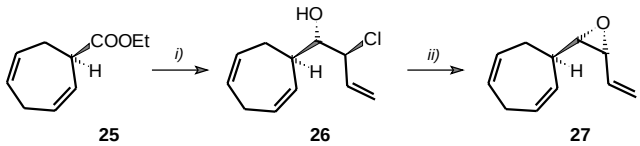
3.2 Synthesis of syn-Halohydrins and cis-Vinyloxiranes

During the last decade, homochiral *cis*-vinyloxiranes have been recognized as highly valuable intermediates in organic synthesis, especially for copper- or palladium mediated cross coupling reactions [26]. For the stereoselective preparation of vinyloxiranes, aldehydes may be allylated with chloroallyl lithium, Ipc_2BOMe and $BF_3 \cdot OEt_2$ (FG = Br, Cl, Scheme 5), yielding *syn*-α-halohydrins, which are smoothly cyclized to the corresponding epoxides in a basic medium [27, 28] (Table 1, entry 7). Chloroallylation of protected serinal **22** (Garner aldehyde), for example, with *in situ* formed γ-(*Z*)-chloroallylborane and subsequent cyclization of the resulting chlorohydrin with DBU, as a non-aqueous and non-nucleophilic base, provides vinyloxirane **23**, a versatile precursor of optically pure amino alcohols such as *D*-erythro-sphingosine **24** and its analogues (Scheme 8) [29].



Scheme 8 Serinal-derived vinyloxirane **23** as a precursor for the synthesis of sphingoid bases. i) γ-(*Z*)-chloroallyl $B(^lIpc)_2$, 8-hydroxyquinoline, DBU, ii) $C_{12}H_{25}CuCN$, hydrolysis.

Configurationally labile aldehydes may be allylated *in situ*, following low temperature reduction of esters, such as **25**, and lactones with DIBAL-H and subsequent trapping of the ensuing aldehyde with the allylation reagent [30]. It is observed that, under these conditions, the highly stereoselective feature of the boron reagent is not altered and, hence, sensitive substrates can be transformed in the usual manner, without razemization. Reductive chloroallylation has been successfully applied to the double diastereoselective synthesis of all four stereoisomers of lamoxirene (**27**, >97% *d.e.*, >95% *e.e.*), the gamete-releasing and attracting pheromone of the large kelps (Laminariales) [31].



Scheme 9 Double stereoselective synthesis of lamoxirene; i) DIBAL-H, γ-(*Z*)-chloroallyl$B(^lIpc)_2$, 8-hydroxyquinoline; ii) DBU.

In conclusion, *B*-methoxydiisopinocampheylborane (**1**) is a highly versatile chiral auxiliary that is compatible with great variety of functional groups, either in the reagent or the substrate. Thus, this reagent allows direct access to complex molecules without extensive use of protecting groups. Of particular advantage is the ability of heteroatom substituents, on the boron reagents, to affect the stereochemical course of the reaction. This can then be used to yield products of predictable and well defined relative and absolute stereochemistry.

References

[1] A. Hassner (Ed.), Advances in Asymmetric Synthesis, Vol. 1, JAI Press, Greenwich, CT, **1995**
[2] G. J. McGarvey (Ed.), Advances in Asymmetric Induction, JAI Press, Greenwich, CT, **1995**
[3] H. C. Brown, P. V. Ramachandran, J. Organomet. Chem. **1995**, *500*, 1
[4] H. C. Brown, U. S. Racherla, Y. Liao, V. V. Khanna, J. Org. Chem. **1992**, *57*, 6608
[5] U.S. Racherla, H.C. Brown, J. Org. Chem. **1991**, *56*, 401. (and references cited herein)
[6] R. W. Hoffmann, Angew. Chem. Int. Ed. Engl. **1982**, *21*, 555; W. R. Roush, Allyl Organometallics, in: Comprehensive Organic Synthesis, Vol. 2, (B. M. Trost, I. Fleming and C. H. Heathcock, Eds.), Pergamon Press, Oxford 1991, 1
[7] H. C. Brown, P. K. Jadhav, J. Am. Chem. Soc. **1983**, *105*, 2092; H. C. Brown, K. S. Bhat, R. S. Randad, J. Org. Chem. **1987**, *52*, 320
[8] R. D. Groneberg, T. Miyazaki, N. A. Stylianides, T. J. Schulze, W. Stahl, E. P. Schreiner, T. Suzuki, Y. Iwabucchi, A. L. Smith, K. C. Nicolaou, J. Am. Chem. Soc. **1993**, *115*, 7593
[9] K. Faber, in: Biotransformations in Organic Chemistry, Springer Verlag, Heidelberg 1997, and ref. cited therein; C. Hertweck, W. Boland, J. Prakt. Chem. **1997**, *339*, 200; C. Hertweck, W. Boland, J. Prakt. Chem. **1997**, *339*, 754
[10] Z. Wang, D. Deschenes, J. Am. Chem. Soc. **1992**, *114*, 1090
[11] Y. Mori, Y. Kohchi, M. Suzuki, J. Org. Chem. **1991**, *56*, 631, and ref. cited therein

[12] H. C. Brown, R. S. Randad, Tetrahedron **1990**, *46*, 4463; H. C. Brown, R. S. Randad, Tetrahedron Lett. **1990**, *31*, 455
[13] H. C. Brown, K. S. Bhat, J. Am. Chem. Soc. **1986**, *108*, 293; H. C. Brown, K. S. Bhat, J. Am. Chem. Soc. **1986**, *108*, 5919
[14] A. G. M. Barrett, S. Lebold, J. Org. Chem. **1991**, *56*, 4875
[15] K. C. Nicolaou, P. Bertinato, A. D. Piscopio, T. K. Chakraborty, N. Minowa, J. Chem. Soc., Chem. Commun. **1993**, 619
[16] K. Burgess, I. Henderson, Tetrahedron Lett. **1990**, *31*, 6949
[17] H. C. Brown, P. K. Jadhav, K. S. Bhat, J. Am. Chem. Soc. **1988**, *110*, 1535
[18] A. G. M. Barrett, J. W. Malecha, J. Chem. Soc., Perkin Trans. 1 **1994**, *14*, 1901
[19] A. L. Smith, E. N. Pitsinos, C.-K. Hwang, Y. Mizuno, H. Saimoto, G. R. Scarlato, T. Suzuki, K. C. Nicolaou, J. Am. Chem. Soc. **1993**, *115*, 7612
[20] M. Nakata, T. Osumi, A. Ueno, T. Kimura, T. Tamai, K. Tatsuka, Tetrahedron Lett. **1991**, *32*, 6015; M. Nakata, T. Osumi, A. Ueno, T. Kimura, T. Tamai, K. Tatsuka, Bull. Chem. Soc. Jpn. **1992**, *65*, 2974
[21] K. Burgess, D. A. Chaplin, I. Henderson, Y. T. Pan, A. D. Elbein, J. Org. Chem. **1992**, *57*, 1103
[22] A. G. M. Barrett, J. W. Malecha, J. Org. Chem. **1991**, *56*, 5243
[23] A. G. M. Barrett, M. A. Seefeld, Tetrahedron **1993**, *49*, 7857
[24] A. G. M. Barrett, M. A. Seefeld, J. Chem. Soc., Chem. Commun. **1993**, 339
[25] A. G. M. Barrett, M. A. Seefeld, D. J. William, J. Chem. Soc., Chem. Commun. **1994**, 1053; A. G. M. Barrett, M. A. Seefeld, A. J. P. White, D. J. Williams, J. Org. Chem. **1996**, *61*, 2677
[26] C. Hertweck, W. Boland, in: "Recent Developments in Synthetic Organic Chemistry. (S. G. Pandalai, Ed.) Transworld Research Network 1999 in press.
[27] S. Jayaraman, S. Hu, A. C. Oehlschlager, Tetrahedron Lett. **1995**, *36*, 4765
[28] S. Hu, S. Jayaraman, A. C. Oehlschlager, J. Org. Chem. **1996**, *61*, 7513
[29] C. Hertweck, H. Goerls, W. Boland, J. Chem. Soc., Chem. Commun. **1988**, *18*, 1955
[30] C. Hertweck, W. Boland, Eur. J. Org. Chem. **1998**, 2143
[31] C. Hertweck, W. Boland, Tetrahedron **1997**, *53*, 14651

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