B-[(*E*)-3-(Diphenylamino)allyl]diisopinocampheylborane: an Excellent Reagent for the Stereoselective Synthesis of *anti*-β-Diphenylamino Alcohols

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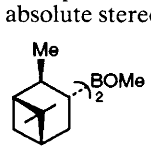
anti-β-Amino alcohols have been produced with high relative and absolute stereochemical control in a simple one-pot process *via* the reaction of aldehydes with *B*-[(*E*)-3-(diphenylamino)allyl]diisopinocampheylborane and alkaline hydrogen peroxide work-up.

The β-amino alcohol residue is a common structural unit in legions of biologically active natural products.[1] In consequence, a number of procedures have been developed for the stereoselective synthesis of these substances.[2–4] Generally, these methods depend upon the oxyamination of alkenes or ring opening of epoxides with nitrogen centered nucleophiles.[2] Methods which result in the generation of the amino alcohol unit with the simultaneous construction of the interconnecting carbon–carbon bond are less widely used in asymmetric synthesis.[3,4] For example, the Henry reaction of nitroalkenes with aldehydes is a most versatile and general method. However, both relative and absolute stereochemical control in this reaction still need very considerable improvement and optimization.[4] Recently, Brown and coworkers have introduced several allyl- and crotyl-boranes that are spectacularly useful for the conversion of aldehydes into homoallylic alcohols.[5] These methods are particularly useful for the preparation of 4-hydroxy- and 4-hydroxy-3-methyl-1-alkenes. In all cases, the products were formed with both excellent relative and absolute stereochemical control. In an adaptation



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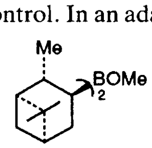

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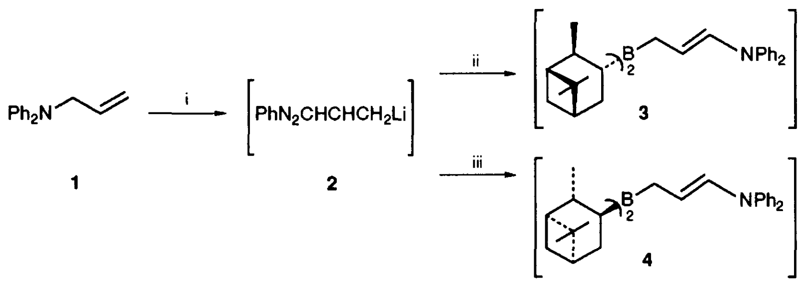


Scheme 1 *Reagents and conditions*: i, Bu^{n}Li, TMEDA, −10 °C; ii, **5**, THF, −78 °C; $BF_3·OEt_2$, −78 °C; iii **6**, THF, −78 °C; $BF_3·OEt_2$, −78 °C

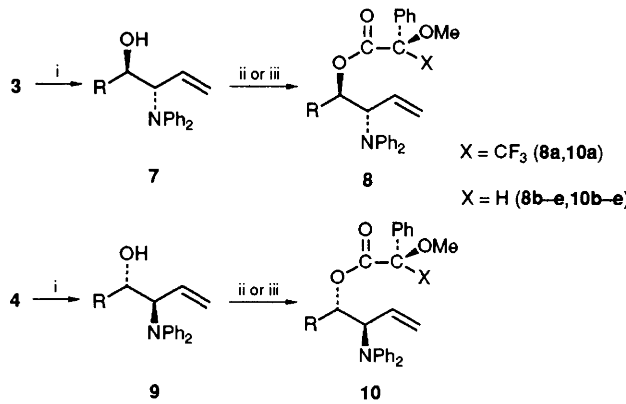
of this chemistry, we have introduced *B*-{(*E*)-3-[(diisopropylamino)dimethylsilyl]allyl}diisopinocampheylborane as a reagent for the synthesis of *anti*-vicinal diols.[6] Herein we report a convergent enantioselective method for the preparation of *anti*-β-diphenylamino alcohols using related organoboron chemistry.†

Following the Eisch precedent,[7] allyldiphenylamine **1** was metallated using n-butyllithium in tetramethylethylenediamine (TMEDA) at −10 °C. The resultant allyllithium species **2** was transmetallated by reaction with both (−)- and (+)-*B*-methoxydiisopinocampheylborane **5** and **6** and boron trifluoride–diethyl ether to provide the (*E*)-allylboranes **3** and **4** (Scheme 1). Without isolation and characterization, these reagents were reacted with aldehydes to give, on alkaline hydrogen peroxide work up, various 3-diphenylamino-4-hydroxy-1-alkenes (Scheme 2 and Table 1).‡ For example, reaction of acetaldehyde with allylboranes **3** and **4**, respectively, gave the amino alcohols **7** (R = Me) and **9** (R = Me).§ Several aspects of this reaction need further comment. Firstly, our original intention was to produce *syn*-amino alcohols since we expected that the utilization of **1** should be *Z*-specific on account of chelation control of lithiation. Thus, we expected that the allyl boranes **3** and **4** should have the *Z*-geometry. However, it is clear from the results that the reagents **3** and **4** are in fact *E*. Thus, the lithiation is either *E*-specific or geometric isomerization takes place on lithium–boron exchange perhaps owing to the enaminic character of the reagents. In all cases, the yields of amino alcohol products were only modest (28–48%). However, the reactions all proceeded with excellent *anti*-relative stereochemical control

† This work was presented in part, at the Boron USA III Conference, Pullman, Washington, July 8–11, 1992 by M.A.S.

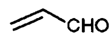
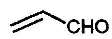
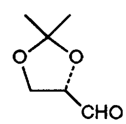
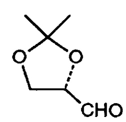
‡ All β-diphenylamino alcohols were fully characterized by spectral data and microanalyses or high resolution mass spectrometry (HRMS).

§ The preparation of aminol **7a** is representative: to a solution of allyldiphenylamine (1.05 g, 5.0 mmol) in dry tetrahydrofuran (THF) (10 ml) at −10 °C was added TMEDA (0.75 ml, 5.0 mmol) and Bu^{n}Li in hexane (2.5 mol dm^{-3}; 2 ml). The solution was kept at −10 °C for 3 h and subsequently cooled to −78 °C. The burgundy-red solution was treated with (−)-*B*-methoxydiisopinocampheylborane (1.58 g, 5 mmol) in dry THF (5 ml) and maintained at −78 °C for 2 h. To this solution was added $BF_3·OEt_2$ (0.82 ml, 6.65 mmol) and propenal (0.28 g, 5.0 mmol) in dry THF (1 ml). The reaction mixture was kept at −78 °C for 3 h and was allowed to warm up to 0 °C after which aqueous NaOH (2.5 mol dm^{-3}, 2 ml) and 30% H_2O_2 (2 ml) were added. The reaction mixture was stirred at room temp. for 12 h. The mixture was then diluted with diethyl ether (40 ml) and separated from the aqueous layer. The organic solution was dried ($MgSO_4$), concentrated *in vacuo*, and the residue was purified by flash chromatography (silica gel, 4 : 1 hexanes-EtOAc) to yield aminol **7a** (0.59 g 45%).



Scheme 2 *Reagents and conditions*: i, RCHO, THF, −78 °C; 30% H_2O_2, 2.5 mol dm^{-3} NaOH, 0 °C; ii, (*R*)-(+) Mosher acid, DCC, DMAP, CH_2Cl_2, 25 °C; iii (*R*)-*O*-methyl mandelic acid, DCC, DMAP, CH_2Cl_2, 25 °C; DCC = 1,3-dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine

Table 1

Entry	Aldehyde	Product (%)	D.e.[a]	% E.e.[b]
1		**7a** (45)	⩾95 : 5	⩾95
2		**9a** (47)	⩾95 : 5	⩾95
3	C_4H_9CHO	**7b** (43)	⩾95 : 5	⩾95
4	C_4H_9CHO	**9b** (40)	⩾95 : 5	⩾95
5	MeCHO	**7c** (40)	⩾95 : 5	⩾95
6	MeCHO	**9c** (41)	⩾95 : 5	⩾95
7	PhCHO	**7d** (48)	⩾95 : 5	⩾95
8	PhCHO	**9d** (47)	⩾95 : 5	⩾95
9		**7e** (23), **9e** (6)	3.8 : 1	—
10		**9e** (28)	⩾95 : 5	—

[a] D.e. = diastereoisomeric excess. [b] E.e. = enantiomeric excess.

(diastereoselectivity > 95:5) and this was readily apparent from the ^{1}H and ^{13}C NMR spectra. Additionally, the absolute stereochemistry of reaction was outstanding. In each case, the β-diphenylamino alcohols **7** and **9** were converted into the corresponding (*R*)-(+)-Mosher esters[8] **8a** and **10a** or the (*R*)-*O*-methyl mandelates[9] **8b–e** and **10b–e**. Comparisons of the ^{1}H and ^{13}C NMR spectra of each diastereoisomeric pair of esters clearly showed that enantiomeric excesses were at least 95%. Entries 9 and 10 in Table 1 illustrate reactions with matched and mismatched stereochemical biases. It is apparent from these two examples that *anti*-relative stereochemical control is consistently good. However, absolute stereochemical control is lower in the mismatched example (entry 9). Finally, we have rigorously established the stereochemistry of one *anti*-β-diphenylamino alcohol **7a** by carrying out an X-ray crystallographic study of the derived (*R*)-Mosher ester **8a**.¶ This study unequivocally established both the relative and absolute stereochemistry of alcohol **7a** and, by implication, all the other amino alcohols in Table 1.

This study further demonstrates the utility of pinene-derived compounds in asymmetric synthesis. The direct conversion of aldehydes into β-amino alcohols *via* an experimentally simple one-pot process should be of considerable use in synthesis. The method should be applicable to other allylamines and, with suitable protection or masking, to the synthesis of biologically active β-amino alcohols.

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¶ Details of the crystal structure of the Mosher ester **8a** will be published elsewhere.

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