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Highly Enantioselective Synthesis of Alkyl- and Aryl-Substituted α-Allenic Alcohols.

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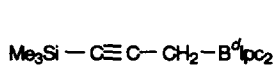
Abstract: Metalation of 2-alkynes with BuLi followed by treatment with diisopinocampheylchloroborane and warming to room temperature gives exclusively the propargylic diisopinocampbeylboron derivatives. These on treatment with aldehydes at -100 °C in ether, provide alkyl- and aryl-substituted α-allenic alcohols in high regiomeric and enantiomeric purities. Copyright © 1996 Elsevier Science Ltd

The synthesis of α-allenic alcohols continues to be an area of active interest because of their synthetic utility. For example, α-allenic alcohols can be stereoselectively converted into compounds such as *syn*-1,2-diols,[2a] *syn*-1,2-amino alcohols,[2b] 2,5-dihydrofurans,[2c] vinyl epoxides,[2d] vinyl cyclopropanes[2e] etc., which in turn can be used to prepare a variety of useful products. Moreover, functionally substituted allenes have been used as dienophiles in Diels-Alder reactions[3] and as substrates for 1,4-additions of organocuprates.[4]

Recently, we reported the development of an α-pinene based propargylborating reagent, *viz.* *B*-(γ-trimethylsilylpropargyl)diisopinocampheylborane (**1**), which gives trimethylsilyl-substituted α-allenic alcohols **2** in high optical purity.[5] This study indicated that α-pinene is a very good chiral auxiliary for asymmetric propargylboration reactions. Therefore, we decided to explore the possibility of extending this methodology to the preparation of other variously substituted α-allenic alcohols. As a result of this investigation, we have now developed a simple, highly enantioselective method for the preparation of alkyl- and aryl-substituted α-allenic alcohols **3**.



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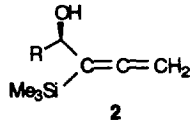

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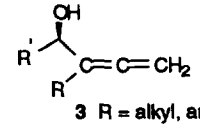
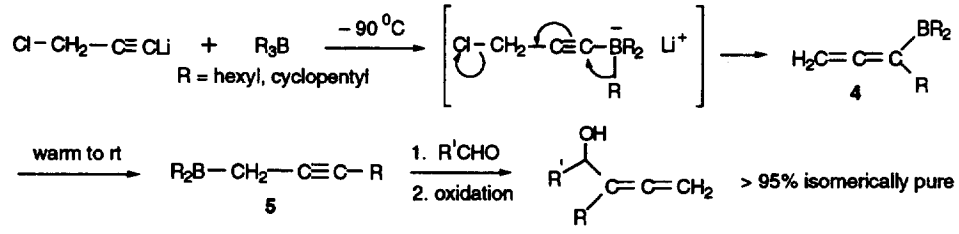


3 R = alkyl, aryl

A number of reports in the literature have described the preparation of racemic α-allenic alcohols of the type **3** mainly via the reaction of propargylmetal reagents with aldehydes.[6] However, except in rare instances, due to the ambident nature of these reagents, reactions with electrophiles leads to both allenic and acetylenic products in varying proportions. Moreover, except for a method (only one example shown) based on the use of a chiral auxiliary derived from 1,2-diphenyl-1,2-diaminoethane[7] (whose preparation involves mutiple steps including optical resolution), no other method is currently available for the preparation of alcohols **3** in high

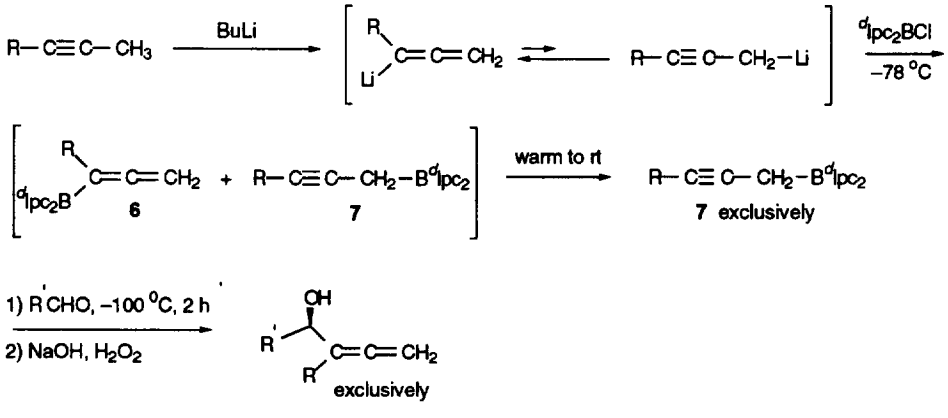
enantiomeric purity. The present report thus provides the first simple procedure for the preparation of these alcohols in high enantiomeric purity.

Our approach is based on the observation in 1978 by Zweifel *et al.* that allenylboron reagents of the type **4** rearrange almost completely on warming to room temperature[8] to the propargylic derivatives **5** (Scheme 1).



Scheme 1

We thought that if the mixture of allenyl and propargyllithium derivatives obtained by metalation of 2-alkynes[9] is treated with optically pure diisopinocampheylboron chloride (Ipc_2BCl), then any allenylboron derivative **6** formed would rearrange completely on warming to room temperature to give exclusively the thermodynamically more stable propargylboron derivative **7** (Scheme 2). Moreover, based on the success of the reactions of the trimethylsilylpropargylboron reagent **1** with aldehydes,[5] we expected that reactions of **7** with aldehydes at low temperature would provide the alkyl-substituted α-allenic alcohols in high enantiomeric excess. This proved to be true, as revealed by the results summarized in Table 1.



Scheme 2

It can be seen from Table 1 that good enantioselectivity is realized with various 2-alkynes and aldehydes. Since both $^{d}Ipc_2BCl$ and $^{l}Ipc_2BCl$ are commercially available,[10] either enantiomer of the α-allenic alcohols **3** can be prepared in high ee. No acetylenic isomers of **3** were detected by ^{1}H and ^{13}C NMR which demonstrates the high regioselectivity of this methodology.

Table 1. Synthesis of α-allenic alcohols **3** from 2-alkynes.[a]

entry	RC≡CMe R	R'CHO R'	yield[b] %	ee[c] %	$[\alpha]_D$ (c, solv)	configuration[d]
1	Pr	*i*-Pr	80	96[e]	−19.1° (*c* 0.78, $CHCl_3$)	R
2	Pr	Me	74	87[f]	+13.4° (*c* 2.02, $CHCl_3$)	R
3	Pr	Ph	77	87[g]	−114.6° (*c* 1.07, $CHCl_3$)	R
4	Me	*i*-Pr	72	96[f]	−19.3° (*c* 1.07, $CHCl_3$)	R
5	Me	Me	68	89[f]	+6.2° (*c* 0.54, $CHCl_3$)	R
6	Ph	*i*-Pr	70[h]	96[i]	+4.7° (*c* 1.97, $CHCl_3$)	R

[a] All new compounds exhibited satisfactory ^1H, ^{13}C NMR and elemental analysis. [b] Isolated yield. [c] Racemic alcohols **3** for comparison were prepared using dicyclohexylboron chloride instead of [d]Ipc_2BCl. [d] Predicted by analogy with those obtained in the reactions of **1**.[5] [e] By ^{19}F NMR analysis of the corresponding Mosher esters. [f] By chiral capillary GC analysis of the corresponding acetate. [g] By ^1H NMR analysis of the corresponding Mosher ester. [h] The metalation was carried out at −78 °C for 1.5 h. [i] By capillary GC analysis of the corresponding menthyl carbonate.

A typical procedure for the preparation of alcohols **3** is as follows (entry 1): To a stirred solution of BuLi (4.0 mL, 10.0 mmol, 2.5 M solution in hexane) and THF (4.0 mL) at −10 °C was added 2-hexyne (1.18 mL, 10.5 mmol). After stirring for 10 min, the cold bath was removed and the reaction mixture was allowed to come to room temperature and held at that temperature for 30 min. It was then cooled to −78 °C and a solution of [d]Ipc_2BCl (3.53 g, 11.0 mmol) in ether (20.0 mL) cooled to 0 °C was added to it dropwise via a double ended needle. After stirring for 10 min, the cold bath was removed and the reaction mixture was allowed to come to room temperature and held for 30 min at that temperature. Solvents were evaporated under vacuum (12 mm) and the residue was diluted with ether (20.0 mL). The reaction mixture was then cooled to −100 °C (ethanol-liquid N_2 bath) and a solution of isobutyraldehyde (0.91 mL, 10.0 mmol) in ether (5.0 mL) cooled to −78 °C was added to it slowly via a double ended needle. After 2 h, it was allowed to come to room temperature and subjected to oxidation by addition of 30% aqueous H_2O_2 (5.0 mL, 44.1 mmol) and 3M NaOH (5.0 mL,15.0 mmol) with vigorous stirring for 4 h. The aqueous layer was discarded and the ether layer was washed with water (2 X 25 mL), dried over $MgSO_4$ and concentrated. Flash column chromatography over silica gel with hexane : ethyl acetate (98 : 2) as eluant gave pure **3** (R=Pr, R^1=*i*-Pr) (1.23 g,80% yield). ^1H NMR ($CDCl_3$) δ 4.8- 4.91(m, 2H), 3.7- 3.78 (m, 1H), 1.76- 2.06 (m, 3H), 1.55 (bs, 1H), 1.48 (sextet, J = 7.2 Hz, 2H), 0.87- 0.97 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 204.71, 106.85, 78.56, 77.06, 31.74, 30.13, 20.88, 19.66, 16.73, 13.95; Anal. Calcd for $C_{10}H_{18}O$: C, 77.86; H, 11.76. Found: C, 77.63; H, 11.97.

There are a few points worth mentioning about the procedure. 1. It is important to cool the reaction mixture to −78 °C before the addition of Ipc_2BCl. This is because at that low temperature the ate complex formed by the attack of the lithium salt of 2-alkynes on Ipc_2BCl is stable and does not split out LiCl until the reaction mixture is warmed after the addition of Ipc_2BCl is complete. However, if the addition of Ipc_2BCl is carried out at higher temperatures, the ate complex breaks up immediately forming LiCl, which catalyses the ring opening of THF by the Ipc_2BCl that is being added, leading to the formation of significant amounts of the undesired borinate (δ 53, ^{11}B NMR). 2. It was found that the propargylboration of aldehydes with **7** proceeds

with somewhat higher enantioselectivity in ether alone as a solvent as compared to that carried out in ether-THF-hexane solvent mixture. Therefore, prior to cooling the reaction mixture to –100 °C for propargylboration, it is subjected to vacuum to remove ether, THF and hexane and then the residue is diluted with ether and 3. In the case of 1-phenyl-1-propene (entry 6), the metalation is carried out at –78 °C for 1.5 h, instead of from –10 °C to rt, as is performed in the case of simple 2-alkynes (entries 1-5). This is because, at higher tempeartures, the lithium salt of 1-phenyl-1-propyne undergoes rearrangement to give the undesired alkynyl lithium derivative.[11]

In conclusion, we have developed a simple and highly efficient methodology for the preparation of various alkyl- and aryl-substituted α-allenic alcohols in high optical purity from readily available 2-alkynes. All the steps in this synthesis can be carried out in the same pot which makes it operationally very simple and helps keep the losses to a minimum. We are currently trying to further extend this methodology to the synthesis of other types of α-allenic alcohols.

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