Chiral Synthesis via Organoboranes. 35. Simple Procedures for the Efficient Recycling of the Terpenyl Chiral Auxiliaries and Convenient Isolation of the Homoallylic Alcohols in Asymmetric Allyl- and Crotylboration of Aldehydes

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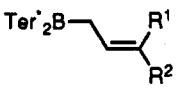
Asymmetric allyl- and crotylboration of aldehydes, RCHO, with terpenyl-based allyl- and crotylborane reagents Ter_2*BAll (1), Ter_2*BCrt^Z (2), and Ter_2*BCrt^E (3, Ter* = Ipc, 4-Icr and 2-Icr; All = allyl and Crt = crotyl), afford Ter_2*BOCH*(R)C*(^{1}R)(^{2}R)CH=CH_2 intermediates 4. In these reactions, the isolation of homoallylic alcohols, HOCH*(R)C*(^{1}R)(^{2}R)CH=CH_2 (5), can be accomplished via oxidation of 4 with alkaline hydrogen peroxide. Unfortunately, oxidative workup destroys the chiral auxiliary and produces a large amount of nonrecyclable byproduct, terpenol (Ter*OH). Further, isolation of the pure homoallylic alcohol by distillation can be difficult if it boils in the range of the abundant byproduct. Therefore, in order to recycle the chiral auxiliaries and isolate the product homoallylic alcohols in an efficient manner, we have developed the following procedures: (1) elimination workup, in which enantiomerically pure α-pinene and Δ^2- and Δ^3-carenes are liberated from terpenylborinates 4 by treatment with isobutyraldehyde and 1 mol % BF_3·OEt_2; (2) ethanolamine workup involving treatment of 4 with ethanolamine (EA) to achieve the precipitation of the ethanolamine adducts (EA–BTer_2*, Ter* = Ipc and 2-Icr, 11 and 12) from which the Ter_2*BOMe can be easily regenerated; and (3) 8-hydroxyquinoline workup, involving treatment of 4 with 8-hydroxyquinoline (8-HQ) to precipitate the 8-HQ adducts (8-HQ–BTer_2*, Ter* = Ipc, 4-Icr and 2-Icr, 13–15), from which the various Ter_2*BOMe intermediates can be conveniently liberated. It is hoped that these procedures will significantly enhance the scope of asymmetric allyl-/crotylboration of aldehydes with Ter_2*BAll (1), Ter_2*BCrt^Z (2), and Ter_2*BCrt^E (3) and serve as excellent alternatives for any catalytic versions yet to be discovered.

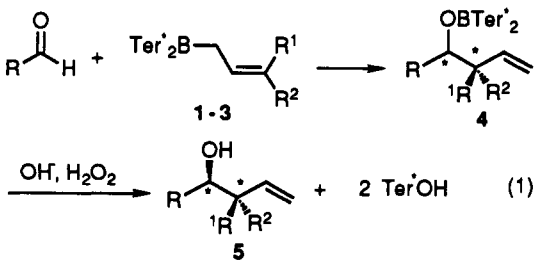
Introduction

Asymmetric allyl- and crotylboration of carbonyl compounds is valuable for highly enantio- and diastereoselective carbon-carbon bond formation.[1,2] In recent years, enantiomerically pure terpenyl based allyl- and crotylborane reagents, Ter_2*BAll (1), Ter_2*BCrt^Z (2), and Ter_2*BCrt^E (3, Ter = Ipc, 4-Icr, and 2-Icr; All = allyl and Crt = crotyl), have found numerous applications in stereoselective natural product synthesis.[3]



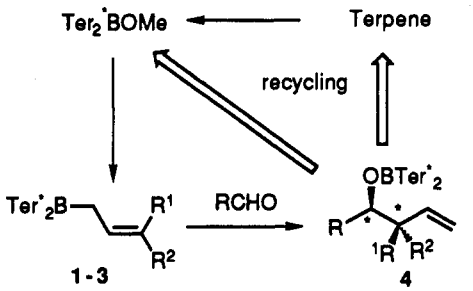
1 : Ter_2*BAll, ^{1}R = R^2 = H Ter* = ^{d}Ipc (a)
2 : Ter_2*BCrt^Z, ^{1}R = Me, R^2 = H = 4-^{d}Icr (b)
3 : Ter_2*BCrt^E, ^{1}R = H, R^2 = Me = 2-^{d}Icr (c)

In our initial studies on the asymmetric allyl- and crotylboration of carbonyl compounds with 1–3, we employed oxidation of the terpenyl borinate intermediates 4 with alkaline hydrogen peroxide for the isolation of product homoallylic alcohols 5 (eq 1):[4]



^{1}R = R^2 = H (a); ^{1}R = Me, R^2 = H (b);
^{1}R = H, R^2 = Me (c)

Scheme I



While this procedure works satisfactorily in many cases, it has two disadvantages: (1) the chiral auxiliary is de-

(1) For reviews of the reactions of allylorganometallics and aldehydes, see: (a) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 555. (b) Yamamoto, Y.; Maruyama, K. *Heterocycles* **1982**, *18*, 357. (c) Roush, W. R. In *Comprehensive Organic Synthesis*; Heathcock, C. H., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, pp 1–53.

(2) (a) Hoffmann, R. W.; Herold, T. *Chem. Ber.* **1981**, *114*, 375. (b) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092; (c) *J. Org. Chem.* **1984**, *49*, 4089. (d) Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8786. (e) Brown, H. C.; Bhat, K. S. *Ibid.* **1986**, *108*, 293. (f) Roush, W. R.; Hatterman, R. L. *Ibid.* **1986**, *108*, 294. (g) Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1987**, *52*, 319; (h) *Ibid.* **1987**, *52*, 3701. (i) Garcia, J.; Kim, B. M.; Masamune, S. *Ibid.* **1987**, *52*, 4831. (j) Brown, H. C.; Jadhav, P. K.; Bhat, K. S. *J. Am. Chem. Soc.* **1988**, *110*, 1535. (k) Roush, W. R.; Banfi, L. *Ibid.* **1988**, *110*, 3979. (l) Roush, W. R.; Ando, K.; Powers, D. B.; Hatterman, R. L.; Palkowitz, A. D. *Tetrahedron Lett.* **1988**, 5579. (m) Reetz, M. T.; Zierke, T. *Chem. Ind.* **1988**, 663. (n) Hoffmann, R. W. *Pure Appl. Chem.* **1988**, *60*, 123 and references cited therein. (o) Short, R. P.; Masamune, S. *J. Am. Chem. Soc.* **1989**, *111*, 1892. (p) Brown, H. C.; Randad, R. K.; Bhat, K. S.; Zaidlewicz, M.; Racherla, U. S. *J. Am. Chem. Soc.* **1990**, *112*, 2389. (q) Brown, H. C.; Racherla, U. S.; Pellechia, P. J. *J. Org. Chem.* **1990**, *55*, 1868. (r) Roush, W. R.; Hoong, L. K.; Palmer, M. A. J.; Park, J. C. *Ibid.* **1990**, *55*, 4109. (s) Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348 and references cited therein. (t) Brown, H. C.; Bhat, K. S.; Jadhav, P. K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2633. (u) Brown, H. C.; Randad, R. S. *Tetrahedron Lett.* **1990**, *31*, 455. (v) Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401.

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Table I. Elimination Workup with Model Borinate Esters

Ter_2*BOR″ $\xrightarrow{RCHO}$ terpene + R″OH

entry	Ter_2*BOR″ model borinate	elimin proced[a]	products after workup (% yield)[b] terpene	alcohol
1	**6a**	A	α-pinene (92)[c]	1-phenylethanol (86)
2	**6b**	A[d]		
3	**6c**	A[d]		
4	**6a**	B	α-pinene (90)	1-phenylethanol (82)
5	**6b**	C	Δ^3-carene (85)	1-phenylethanol (85)
6	**6c**	C	Δ^2-carene (82)	1-phenylethanol (83)
7	**23**	B[e]	α-pinene (87)	
8	**24**	C	Δ^3-carene (83)[f]	

[a] Procedure A = acetaldehyde (2.4 equiv), neat, 1 mol % BF_3·OEt_2, 25 °C, 24 h; B = isobutyraldehyde (2.2 equiv), 1 mol % BF_3·OEt_2, 65 °C, 12 h; C = isobutyraldehyde (3 equiv), 1 mol % BF_3·OEt_2, 65 °C, 48 h. [b] Isolated yield of the distilled product. [c] **6a** is prepared from α-pinene of +91% optical purity, $[\alpha]^{23}_D$ = +47.1°, but the optical purity of the liberated α-pinene is ≥99%, $[\alpha]^{23}_D$ = +50.7°. [d] The elimination of Δ^3- and Δ^2-carenes is incomplete under these conditions even after 5 days. [e] The reaction is complete in 2 h. [f] The $[\alpha]^{23}_D$ of the starting material is +15° while that of the liberated product is +17.3°.

stroyed during hydrogen peroxide oxidation and a large quantity of nonrecyclable terpenol (Ter*OH) byproduct is produced (eq 1), and (2) separation of the product homoallylic alcohol **5** from Ter*OH by distillation is difficult if its boiling point is near that of the byproduct. Recently, in our examination of the asymmetric allylboration of heterocyclic aldehydes with Ter_2*BAll (**1**), Ter_2*$BCrt^Z$ (**2**), and Ter_2*$BCrt^E$ (**3**), we encountered unusual difficulties in the isolation of product alcohols for this particular reason.[5]

Therefore, it was clear to us that we needed workup procedures which would permit efficient recycling of the various chiral auxiliaries as well as convenient isolation of the product homoallylic alcohols. Since the starting materials for the synthesis of Ter_2*BAll (**1**), Ter_2*$BCrt^Z$, (**2**) and Ter_2*$BCrt^E$ (**3**) are optically active terpenes/Ter_2*BOMe intermediates, we envisioned that methods which can achieve the liberation of terpenes or Ter_2*BOMe from **4** at the conclusion of the allyl-/crotylboration stage would achieve this objective (Scheme I).

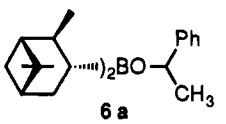
Accordingly, we decided to investigate the following procedures: (1) *elimination workup*, which enables the liberation of optically active terpenes (α-pinene and Δ^2- and Δ^3-carenes) from the terpenyl borinate intermediates **4**; (2) *ethanolamine workup*, involving a reaction of **4** with ethanolamine (EA) to achieve precipitation of the corresponding terpenyl borinate adducts of ethanolamine (EA–$BTer_2$*), followed by a convenient recovery of Ter_2*BOMe; and (3) *8-hydroxyquinoline workup*, involving treatment of **4** with 8-hydroxyquinoline (8-HQ) to effect the precipitation of 8-HQ–$BTer_2$*, followed by recovery of Ter_2*BOMe.

We hoped that these recycling procedures would also make possible a convenient and efficient isolation of the product homoallylic alcohols and thus enhance the scope of the asymmetric allyl- and crotylboration of aldehydes with the terpenyl-based reagents.

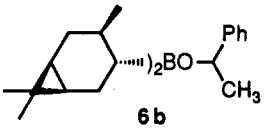
Results and Discussion

The products of allyl- and crotylboration of aldehydes with Ter_2*BAll (**1**), Ter_2*$BCrt^Z$ (**2**), and Ter_2*$BCrt^E$ (**3**) are terpenyl borinate esters, Ter_2*BOCH*(R)C*(^{1}R)(^{2}R)-CH=CH_2 **4**.

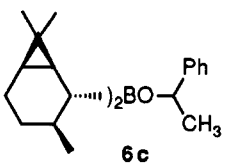
Since these are derivatives of secondary homoallylic alcohols, we decided to develop the standard workup procedures on the model borinate esters **6a–c** derived from 1-phenylethanol (also secondary) and later extend them to representative allyl- and crotylborations.



6a

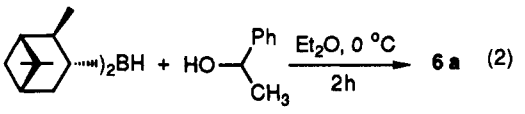


6b



6c

6a is conveniently prepared by the alcoholysis of diisopinocampheylborane (^{d}Ipc_2BH, **7a**) with 1-phenylethanol (eq 2):



7a (2)

The preparations of **6b** and **6c** are also performed in a similar manner from bis(4-isocaranyl)borane (4-^{d}Icr_2BH, **8**) and bis(2-isocaranyl)borane (2-^{d}Icr_2BH, **9**) under essentially the same conditions (0 °C, Et_2O/CH_2Cl_2, 1 h; 25 °C, 2 h).[6]

(a) Elimination Workup. The recovery of α-pinene (≥99% ee) by elimination from the chiral di- and trialkylboranes, resulting from the asymmetric hydroboration of alkenes with ^{d}Ipc_2BH (**7a**) and ^{d}$IpcBH_2$ (**10**), is well-known (eq 3,4):[7]

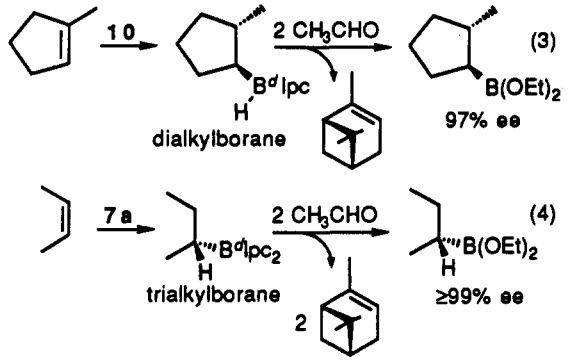
(3) (a) Khandekar, G.; Robinson, G. C.; Stacey, A. N.; Steel, P. G.; Thomas, E. J.; Vather, S. *J. Chem. Soc., Chem. Commun.* **1987**, 877. (b) Merifield, E.; Steel, P. G.; Thomas, E. J. *Ibid* 1826. (c) Boeckman, R. K., Jr.; Charette, A. B.; Asberom, T.; Johnson, B. H. *J. Am. Chem. Soc.* **1987**, *109*, 7553. (d) Ireland, R. E.; Wipf, P.; Roper, T. D. *J. Org. Chem.* **1990**, *55*, 2284. (e) Merifield, E.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1990**, 464. (f) Stork, G.; Zhao, K. *J. Am. Chem. Soc.* **1990**, *112*, 5875. (g) Barrett, A. G. M.; Lebold, S. A. *J. Org. Chem.* **1990**, *55*, 5818. (h) Nicolaou, K. C.; Gronberg, R. D.; Stylianides, N. A.; Miyazaki, T. *J. Chem. Soc., Chem. Commun.* **1990**, 1275. (i) Brown, H. C.; Randad, R. *Tetrahedron*, **1990**, *46*, 4463. (j) Barrett, A. G. M.; Lebold, S. A. *J. Org. Chem.* **1991**, *56*, 4875. (k) Wang, Z.; Desche'nes, D. *J. Am. Chem. Soc.* **1992**, *114*, 1090. (l) Smith, A. L.; Hwang, C.-K.; Pitsinos, E.; Scarlato, G. R.; Nicolaou, K. C. *Ibid.* **1992**, *114*, 3134. (m) Ley, S. V.; Armstrong, A. In *Strategies and Tactics in Organic Synthesis*; Academic Press: New York, 1991; Vol. 3, Chapter 7, pp 237–293.

(4) (a) Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432. See also ref 2v and references cited therein.

(5) See the following paper in this issue on the allylboration of heterocyclic aldehydes for discussion.

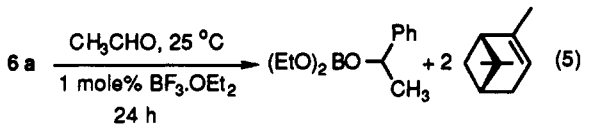
(6) Bis(2-isocaranyl)borane (2-^{d}Icr_2BH, **9**) is a highly crystalline solid and is essentially insoluble in Et_2O. The dialkylborane is, however, highly soluble in dichloromethane and undergoes rapid alcoholysis with 1-phenylethanol.

(7) (a) Brown, H. C.; Jadhav, P. K.; Desai, M. *J. Am. Chem. Soc.* **1982**, *104*, 4303. (b) Brown, H. C.; Vara Prasad, J. V. N.; Gupta, A.; Bakshi, R. K. *J. Org. Chem.* **1987**, *52*, 310. See also: (c) Meerwein, H.; Hintz, G.; Majert, H.; Sonke, H. *J. Prakt Chem.* **1936**, *147*, 226. (d) Mikhailov, B. M.; Kiselev, V. G.; Bubnov, Y. N. *Izv. Acad. Nauk SSSR, Ser. Khim.* **1965**, 898. (e) Mikhailov, B. M.; Bubnov, Y. N.; Kiselev, V. G. *Zh. Obshch. Khim.* **1966**, *35*, 62.



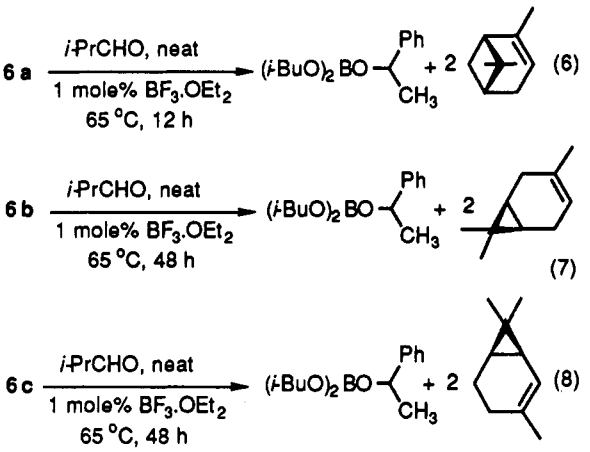
In these cases, α-pinene is eliminated from the R*B^{d}Ipc$_2$ and R*B(H)^{d}Ipc derivatives to the R*B(OEt)$_2$ stage.[8] In the past, elimination of α-pinene from the RO-B^{d}Ipc$_2$ derivatives (such as **6a**) to the RO–B(OEt)$_2$ stage, using acetaldehyde, has never been systematically explored. The same is also true for the elimination of Δ^3- and Δ^2-carenes from the RO–B(4-^{d}Icr$_2$) and RO–B(2-^{d}Icr$_2$) intermediates (such as **6b** and **6c**) to the RO–B(OEt)$_2$ stage.

Consequently, we examined the elimination of various terpene chiral auxiliaries from model borinate esters **6a–6c** (Table I). We found that α-pinene can be cleanly eliminated from **6a** in 24 h using acetaldehyde and 1 mol % BF$_3$·OEt$_2$ (eq 5, entry 1, Table I):[9]



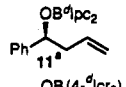
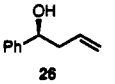
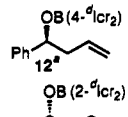
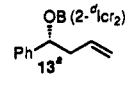
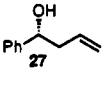
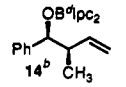
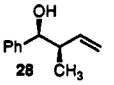
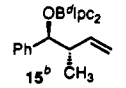
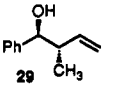
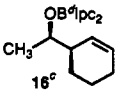
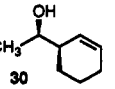
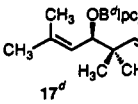
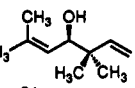
However, the elimination of Δ^3- and Δ^2-carenes from **6b** and **6c**, using acetaldehyde, is exceptionally slow and incomplete (entries 2 and 3).[10]

Fortunately, we discovered an alternative. The elimination of terpenes is more efficient and perfectly general with isobutyraldehyde at 65 °C (eqs 6–8, entries 4–8):



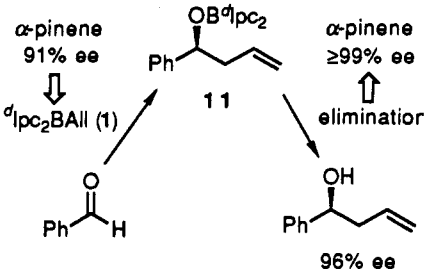
We then tested this elimination procedure with representative terpenyl borinates **11–17** (shown below), resulting from various asymmetric allyl- and crotylborations,[11] for the recovery of α-pinene and Δ^2- and Δ^3-carenes. Table II summarizes these results.

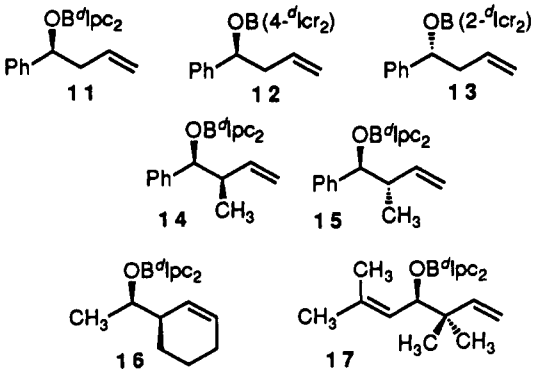
Table II. Elimination Workup with Representative Allyl- and Crotylborations

entry	substrate	elimin proced[e]	product alcohol	% isolated yield terpene	% isolated yield alcohol
1		B		α-pinene (90%)	90
2		C	26	Δ^3-carene (81%)	73
3		C		Δ^2-carene (83%)	76
4		B		α-pinene (82%)	70
5		B		α-pinene (84%)	73
6		B		α-pinene (84%)	67
7		B		α-pinene (87%)	74

[a] Synthesized according to ref 11a. [b] Reference 11b. [c] Reference 11c. [d] Reference 11d. [e] Procedure B = isobutyraldehyde (2.2 equiv), 1 mol % BF$_3$·OEt$_2$, 65 °C, 12 h; C = isobutyraldehyde (3 equiv), 1 mol % BF$_3$·OEt$_2$, 65 °C, 48 h.

Scheme II





Elimination workup achieves the liberation of α-pinene from allyl- and crotylboration products in 82–90% isolated yield (entries 1 and 4–7). Elimination of α-pinene requires 2.2 equiv of isobutyraldehyde and a reaction time of 12 h. The elimination of Δ^2- and Δ^3-carenes from hindered allylboration products is equally efficient (81–83% yield, entries 2 and 3). However, it requires a larger amount of isobutyraldehyde (3 equiv) and a longer reaction period (48 h). In all cases, isolation of the homoallylic alcohols

(8) Joshi, N. N.; Pyun, C.; Mahindroo, V. K.; Singaram, B.; Brown, H. C. *J. Org. Chem.* **1992**, *57*, 504.

(9) BF$_3$·OEt$_2$ catalyzes the elimination of α-pinene. See ref 8.

(10) ^{11}B NMR analysis showed that one of the two terpenyl groups on boron undergoes rapid elimination while the second elimination is very difficult, under these conditions. In fact, the reaction does not proceed to completion even in 5 days.

(11) (a) **11–13** were prepared according to ref 2v; (b) **14** and **15** were prepared according to ref 2e. (c) **16** was prepared according to ref 2t. (d) For the preparation of **17** see: Brown, H. C.; Jadhav, P. K. *Tetrahedron Lett.* **1984**, *25*, 1215.

Table III. Ethanolamine Workup with Model Borinate Esters

Ter_2*BOR″ $\xrightarrow{EA^a}$ EA–BTer_2* ↓ + R″OH

entry	model borinate	reactn condns	% isolated yield: EA adduct	% isolated yield: alcohol
1	6a	EA, pentane, 0 °C, 1 h; 25 °C, 1 h	18[b]	23
2	6a	EA, pentane, 0 °C, 1 h; 25 °C, 16 h	18[b]	40
3	6a	EA, Et_2O, 0 °C, 1 h; 25 °C, 16 h	18[b]	60
4	6a	EA, Et_2O, 0 °C, 1 h; 25 °C, 72 h	18 (90%)	93
5	6b	EA, Et_2O, 0 °C, 1 h; 25 °C, 72 h	no adduct[c]	
6	24	EA, Et_2O, 0 °C, 1 h; 25 °C, 72 h	no adduct[c]	
7	6c	EA, Et_2O, 0 °C, 1 h; 25 °C, 72 h	19 (85%)	89

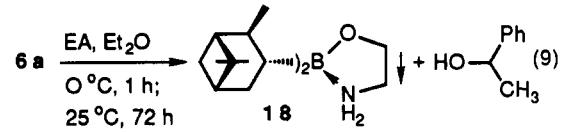
[a] Ethanolamine. [b] The formation of the EA adduct was confirmed by ^{11}B NMR (δ 9.98 ppm), but the yield of adduct was not determined. [c] There was no formation of the 1,3,2-oxazaborolidine.

by distillation proved to be simple, efficient, and convenient.

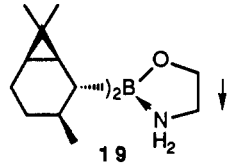
The elimination workup is perfectly general. It works for both allyl- and crotylborations and for the liberation of α-pinene, Δ^2-carene, and Δ^3-carene. In the elimination workup of **11** and **14–17**, the optical purity of the liberated α-pinene is higher than that of the starting material. Scheme II shows an example.

(b) Ethanolamine Workup. In the past, we utilized the ethanolamine workup for the asymmetric synthesis of 1-(2-cycloalkenyl)-1-alkanols.[2t] In that study, formation of the insoluble EA–B^{d}Ipc$_2$ adducts had been achieved in pentane. However, in the present study, we found that these conditions are not ideal for the formation of EA–B^{d}Ipc$_2$ adducts from hindered borinates. In the past, the ethanolamine workup had also not been applied for 4-^{d}Icr$_2$BOR and 2-^{d}Icr$_2$BOR intermediates (such as **6b** and **6c**). Therefore, we decided to establish a general experimental procedure for the precipitation of various EA adducts (EA–BTer_2*) from **6a–6c** to permit extending this procedure later to representative allyl- and crotylborations with these chiral auxiliaries.

In the present study, we found that EA adduct formation with **6a** is very slow in pentane (entries 1 and 2, Table III). We also found that EA adduct formation is considerably faster in Et_2O than in pentane (entry 3). The optimum conditions for the EA adduct formation from **6a** are as shown below (eq 9, entry 4):

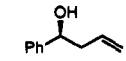
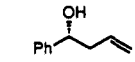
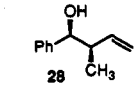
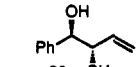
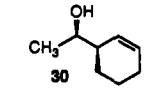
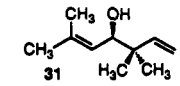


Under identical conditions, formation of the corresponding EA–B(2-^{d}Icr$_2$) adduct **19** with **6c** is also conveniently achieved (entry 7).



Surprisingly, however, precipitation of the EA adduct is not observed with **6b**. ^{11}B NMR examination of the EA reaction of **6b** and **24** revealed that the formation of the 1,3,2-oxazaborolidine does not take place, presumably because of high steric crowding (entries 5 and 6, Table III).

Table IV. Ethanolamine Workup[a] with Representative Allyl- and Crotylborations

entry	substrate	product alcohol	% isolated yield: EA adduct	% isolated yield: alcohol
1	11[b]	 26	18 (81%)	65
2	12[b]		no adduct	
3	13[b]	 27	19 (78%)	62
4	14[c]	 28	18 (83%)	75
5	15[c]	 29	18 (80%)	73
6	16[d]	 30	18 (76%)	63
7	17[e]	 31	18 (82%)	81

[a] Reaction conditions: ethanolamine, ether, (i) 0 °C, 1 h; (ii) 25 °C, 72 h. [b] Prepared according to ref 11a. [c] Reference 11b. [d] Reference 11c. [e] Reference 11d.

Scheme III

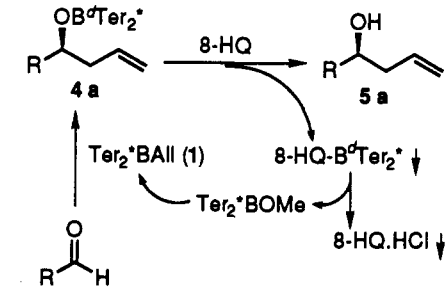


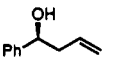
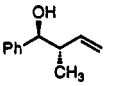
Table IV summarizes the results of the EA workup procedure for **11–17** resulting from representative allyl- and crotylborations. Clearly, the procedure works for borinates derived from ^{d}Ipc$_2$B and 2-^{d}Icr$_2$B (entries 1, 3–7). However, it is not general and cannot be applied to 4-^{d}Icr$_2$BOR intermediates, such as **12** (entry 2). The isolated yields of the product alcohols range, in general, from 62 to 81%. The isolated yields of the EA–BTer_2* adducts also range from 75 to 86%. The EA–BTer_2* adducts are air- and moisture-sensitive, and so appropriate precautions must be taken during filtration.

(c) 8-Hydroxyquinoline Workup. As pointed out above, although the EA workup works well with ^{d}Ipc$_2$BOR and 2-^{d}Icr$_2$BOR intermediates, it fails to provide crystalline adducts with 4-^{d}Icr$_2$BOR derivatives. This is indeed a serious setback considering the importance of the Δ^3-caranyl chiral auxiliary for asymmetric allyl- and crotylboration. Consequently, we decided to explore a workup involving 8-hydroxyquinoline (8-HQ), in the hope of achieving significantly better results for the separation of the chiral auxiliary from the product (Scheme III).

Accordingly, the reaction of 8-hydroxyquinoline (8-HQ) was systematically explored with the model borinates **6a–6c**. Table V summarizes these results. It was indeed

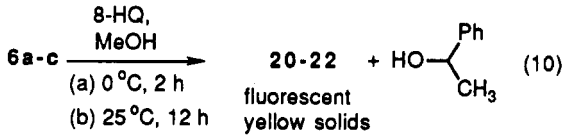
Table V. 8-Hydroxyquinoline Workup with Representative Borinate Esters

Ter_2*BOR″ $\xrightarrow{8\text{-HQ}}$ 8-HQ–BTer_2* ↓ + R″OH

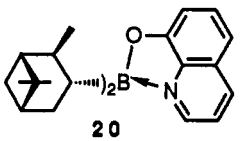
entry	borinate	reactn condns	% isolated yield: 8-HQ adduct	% isolated yield: product alcohol
1	**6a**	8-HQ, methanol, 0 °C, 2 h; 25 °C, 24 h	**20** (80)	1-phenylethanol (85)
2	**6b**	8-HQ, methanol, 0 °C, 2 h; 25 °C, 24 h	**21** (82)	1-phenylethanol (86)
3	**6c**	8-HQ, methanol, 0 °C, 2 h; 25 °C, 24 h	**22** (86)	1-phenylethanol (88)
4	**12**[a]	8-HQ, methanol, 0 °C, 2 h; 25 °C, 24 h	21 (74)	 **26** (80)
5	**15**[b]	8-HQ, methanol, 0 °C, 2 h; 25 °C, 24 h	**20** (84)	 **29** (83)

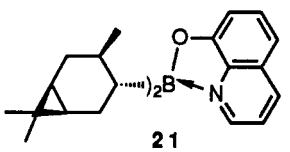
[a] Prepared according to ref 11a. [b] Reference 11b.

gratifying to observe that 8-HQ reacts equally well with all of the model borinates (**6a–6c**) in methanol at 25 °C and affords highly crystalline 8-HQ–BTer_2* adducts **20–22** (eq 10, entries 1–3).



(10)


20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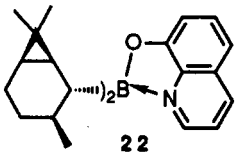
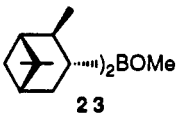
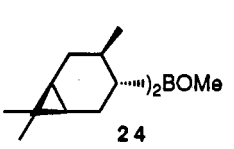
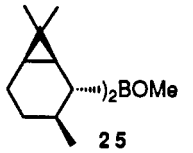

22

It is noteworthy that, 8-HQ reacts readily with ***6b*** *and cleanly affords a crystalline adduct* ***21****.* There are many significant advantages to the 8-HQ workup. It works equally well for both allyl- and crotylborations. The formation of 8-HQ adducts is remarkably smooth and efficient (74–86%) in every case examined. The 8-HQ–BTer_2* adducts (**20–22**) are exceptionally air-stable and are not hygroscopic. Therefore, unlike the EA adducts, filtration of the 8-HQ adducts from the reaction mixture can be performed in open air, which greatly facilitates the isolation of the homoallylic alcohols. The isolated yields of the product alcohols are generally excellent, in the range of 80–88%.[12]

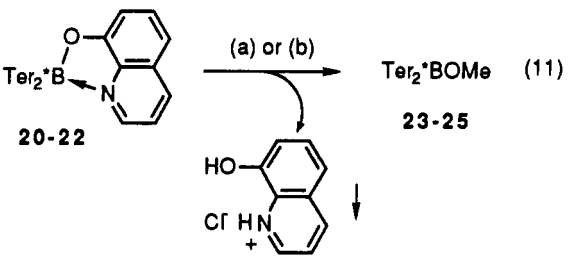
(d) Recovery of Ter_2*BOMe. The transformation of EA–BTer_2* adducts (**18,19**) and 8-HQ–BTer_2* adducts (**20–22**) to the Ter_2*BOMe (**23–25**) is an important step for recycling the various chiral auxiliaries.


23


24


25

The 8-HQ–BTer_2* adducts (**20–22**) are easily converted into the corresponding Ter_2*BOMe (**23–25**) by treatment with HCl (1 M in Et_2O) or H_2SO_4 (concd) in methanol at 0 °C for 0.5 h, in essentially quantitative yields (eq 11):



(11)

(a) HCl inEt_2O, MeOH, 0 °C, 0.5 h

(b) H_2SO_4 (conc.), MeOH, 0 °C, 0.5 h

The isolation of different Ter_2*BOMe derivatives from the reaction mixture is very simple because 8-hydroxyquinoline forms an insoluble hydrochloride which easily precipitates out of the solution. In the same manner, the EA–BTer_2* adducts (**18** and **19**) also liberate the Ter_2*BOMe derivatives.

Conclusion

Asymmetric allyl-/crotylboration of aldehydes with terpenyl-based reagents **1–3** is exceptionally enatio- and diastereoselective (90–≥99% ee; ≥99% de). In the past, isolation of the products in these reactions was achieved via oxidative workup which destroys the chiral auxiliary and produces a large amount of the undesirable terpenol byproduct. To recycle the precious chiral starting materials and circumvent the problems occasionally encountered in the isolation of homoallylic alcohols in oxidation, we have developed three alternative procedures: (1) the elimination workup, (2) the EA workup, and (3) the 8-HQ workup. The elimination workup achieves liberation of the enantiomerically pure (≥99% ee) terpenes (α-pinene and Δ^2- and Δ^3- carenes), in excellent isolated yields. While the EA workup has a relatively limited success in the recovery of chiral auxiliaries, the 8-HQ workup is completely general and makes possible the recovery of all the Ter_2*BOMe (Ter = Ipc, 4-Icr, and 2-Icr) intermediates in excellent isolated yields. These procedures are especially valuable when separation of the homoallylic alcohols from the terpenols, by distillation, is very difficult. Undoubtedly, the 8-hydroxyquinoline workup is the most efficient and perfectly general method for product isolation as well as chiral auxiliary recovery. We believe that these procedures will significantly enhance the scope of the asymmetric allyl- and crotylboration of aldehydes and will serve as powerful alternatives for any catalytic versions of the future.

Experimental Section

All reaction flasks and equipment were dried at 150 °C for several hours prior to use and assembled hot under a stream of nitrogen. Special techniques for handling air-sensitive materials

(12) For additional examples of 8-HQ workup, see the following paper.

(13) One of the reviewers has recommended giving a reference to a very recent application of 8-hydroxyquinoline (published after the submission of the present manuscript) for the conversion of boroxazolidones to the corresponding amino acids: Legters, J.; Thijs, L.; Zwanenburg, B. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 211. The use of 8-hydroxyquinoline to precipitate borinic esters has been reported in the past: Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1971**, *93*, 2802.

are described elsewhere.[14] All ^{11}B and ^{1}H NMR spectra were recorded on a Gemini-300 BB NMR spectrometer. ^{13}C NMR spectra were recorded on a Gemini-200 BB spectrometer. Optical rotation measurements were conducted on a Rudolph Autopol III automatic polarimeter. The preparations of 11–17 were all performed according to the literature procedures.[11]

Preparation of 6a–6c. The procedure described below for **6a** is representative. To a stirred suspension of $^{d}Ipc_2BH$ (**7a**, 14.3 g, 50 mmol) in anhydrous ether(44 mL) at 0 °C was added 1-phenylethanol (6.11 g, 50 mmol) dropwise, over a period of 0.5 h. Following addition, the reaction mixture was stirred at 0 °C for 1 h and 25 °C for an additional hour. The completion of the reaction was confirmed by the appearance of a single peak (δ 52 ppm) in ^{11}B NMR spectrum, corresponding to **6a**. The solution of **6a** (approximately 1.0 M) was used in all subsequent experiments.

The preparation of **6b** was done exactly as described above, starting from 4-$^{d}Icr_2BH$ (**8**). However, the preparation of **6c** was performed in dichloromethane instead of Et_2O from 2-$^{d}Icr_2BH$ (**9**) as the reaction proceeded much faster in the former solvent.

Elimination Workup of 6a Using Acetaldehyde. Procedure A. To a mixture of neat **6a** (10.15 g, 25 mmol), obtained by stripping Et_2O from the solution of **6a** (25 mL, 1.0 M, 25 mmol), and $BF_3{\cdot}OEt_2$ (0.03 g, 0.25 mmol) was added acetaldehyde (2.64 g, 60 mmol) dropwise at 0 °C. The reaction mixture was then stirred at 25 °C for 24 h. ^{11}B NMR analysis indicated 100% completion of the elimination by the disappearance of the original peak at δ 52 (**6a**) and the appearance of a new peak at δ 17, corresponding to the $(EtO)_2BOR$ species (eq 5). Next, water (20 mL) was added and the reaction mixture heated at 65 °C for 2 h. The aqueous mixture, cooled to 25 °C, was then extracted with ether (2 × 25 mL). Concentration of the etheral solution followed by careful fractional distillation afforded α-pinene (3.13 g, 92%, bp 60 °C (25 Torr)) and 1-phenylethanol (2.63 g, 86%, bp 110 °C (25 Torr)).

Under the conditions described above for **6a**, the elimination of **6b** and **6c** with acetaldehyde does not proceed to completion. ^{11}B NMR analysis shows that while the elimination of one of the two terpene moieties is facile, the second elimination is quite difficult.

Elimination Workup of 6a with Isobutyraldehyde. Procedure B. To a neat mixture of **6a** (10.15 g, 25 mmol) and $BF_3{\cdot}OEt_2$ (0.03 g, 0.25 mmol) was added isobutyraldehyde (3.96 g, 55 mmol) dropwise at 0 °C. The reaction mixture was then refluxed at 65 °C for 12 h. The completion of the reaction was confirmed by ^{11}B NMR spectroscopy by the disappearance of the peak at δ 52 (**6a**) and the appearance of a new peak at δ 18, corresponding to the $(i\text{-}BuO)_2BOR$ species (eq 6). Next, water (20 mL) was added, and the reaction mixture was heated at 65 °C for 4 h. The aqueous mixture, cooled to 25 °C, was then extracted with ether (2 × 25 mL). As described above, concentration of the etheral solution followed by careful fractional distillation afforded α-pinene (3.06 g, 90%) and 1-phenylethanol (2.50 g, 82%). The recovered α-pinene (≥99% chemical purity) showed $[\alpha]^{23}_D$ +50.7° (neat).

Elimination Workup of 6b and 6c with Isobutyraldehyde. Procedure C. The procedure C is exactly the same as procedure B but involves the use of a greater amount of isobutyraldehyde (5.41 g, 75 mmol) and a longer reaction period (48 h) for the elimination of Δ^3- or Δ^2-carenes from neat **6b** (10.2 g, 25 mmol) or **6c** (10.2 g, 25 mmol).

General Elimination Workup for 11–17 with Isobutyraldehyde. The following procedure, described for the elimination of α-pinene from **11** with isobutyraldehyde, is representative. This is essentially procedure B with minor modifications.

To a neat mixture of **11**[11a] (4.32 g, 10 mmol) and $BF_3{\cdot}OEt_2$ (0.01 g, 0.1 mmol) was added isobutyraldehyde (1.58 g, 22 mmol) in a dropwise manner at 0 °C. Following completion of the addition, the reaction mixture was refluxed at 65 °C for 12 h. The completion of the reaction was confirmed by ^{11}B NMR spectroscopy, as described above. The liberated α-pinene and excess isobutyraldehyde were then collected into a cold trap (at −78 °C) under aspirator vacuum (15 Torr). The residual borate ester was hydrolyzed with 3 N NaOH (20 mL) for 4 h. Following hydrolysis, the reaction mixture was extracted with Et_2O (3 × 20 mL), and the extract was washed with dilute HCl (2 × 15 mL) and brine (2 × 15 mL). Drying of the extract ($MgSO_4$), concentration, and distillation furnished 1-phenyl-3-buten-1-ol (1.33 g, 90%, bp 84 °C (1 mm)). The mixture collected in the trap was washed with 10% aqueous $NaHSO_3$ (2 × 15 mL) and brine (2 × 15 mL) and distilled to obtain pure α-pinene (2.45 g, 90%). The recovered α-pinene (≥99% chemical purity) showed $[\alpha]^{23}_D$ +50.7° (neat).

The elimination workup employed for **12** and **13** was essentially the same as described above for **11**, except that it required a larger amount of isobutyraldehyde (3 equiv. per equiv. of the substrate) and a longer reaction period (48 h).

Ethanolamine Workup for 6a. (a) In Pentane. Neat **6a** (10.15 g, 25 mmol), obtained by stripping Et_2O from the solution of **6a** (25.0 mL, 1.0 M, 25 mmol) under aspirator vacuum (20 mm), was dissolved in pentane (25 mL), and the solution was cooled to 0 °C. Ethanolamine (1.53 g, 25 mmol), prechilled to 0 °C, was added dropwise. The reaction mixture was stirred at 0 °C for 1 h and at 25 °C for 1 h. After 0.5 h, however, the precipitation of EA-$BIpc_2$* (**18**) was observed. The reaction mixture was then diluted with chilled pentane (50 mL) and the reaction mixture was allowed to settle. The clear pentane layer was decanted via a Kramer filter[14] into another flask, and the operation was repeated. The combined pentane extracts were concentrated, and 1-phenylethanol was isolated by distillation: yield 0.24 g (23%).

When this reaction was repeated for a longer reaction period (0 °C, 1 h; 25 °C, 16 h), the isolated yield of 1-phenylethanol had improved. Yield: 1.03 g (40%).

Ethanolamine Workup for 6a. (b) In Ether (Standard Procedure). The following procedure is applied for both **6a** and **6b**.

To a solution of **6a** in ether (25.0 mL, 1.0 M, 25 mmol) at 0 °C was added chilled ethanolamine (1.53 g, 25 mmol) dropwise. The reaction mixture was stirred at 0 °C for 1 h and 25 °C for 72 h. At the end of the reaction, Et_2O was pumped off under aspirator vacuum (20 mm), and the dry solid was extracted with chilled pentane (3 × 50 mL). The combined pentane extract was concentrated, and 1-phenylethanol was isolated in pure form by distillation. Yield: 2.15 g (93%). The EA-$B^{d}Ipc_2$ (**18**) was also isolated in excellent yield (8.02 g, 93%).[15]

General Ethanolamine Workup for 11–17. The same standard procedure described above for **6b** was applied for all the allyl- and crotylborations. The isolated yields of the product alcohols ranged from 62 to 81%. No ethanolamine adduct formation was observed in the case of **12**.

Standard 8-Hydroxyquinoline Workup Procedure. The following is a standard procedure for 8-hydroxyquinoline workup, applicable to the model compounds as well as allyl- and crotylborations.

Neat **6a** (10.15 g, 25 mmol), obtained by stripping Et_2O from a solution of **6a** (25 mL, 1.0 M, 25 mmol), was taken into anhydrous methanol (25 mL) and the resulting emulsion cooled to 0 °C while stirring. Next, 8-hydroxyquinoline (3.63 g, 25 mmol) was dissolved in methanol (25 mL) by gentle warming in a water bath at 40 °C, and the resulting solution (cooled to 25 °C) was added to the solution of **6a**. The resulting mixture was stirred at 0 °C for 2 h and 25 °C for 12 h. After approximately 4 h, a fluorescent yellow solid of the 8-HQ–$B^{d}Ipc_2$ adduct (**20**) precipitated out. The solid was then filtered in air and washed with cold methanol to obtain a pure crystalline solid: yield 8.58 g (80%); mp 108 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.43 (d, 3 H, J = 6.9 Hz), 0.61–2.29 (m, 31 H), 6.95 (d, 1 H, J = 7.8 Hz), 7.10 (d, 1 H, J = 8.2 Hz), 7.51–7.60 (m, 2 H), 8.31 (d, 1 H, J = 8.2 Hz), 8.62 (d, 1 H, J = 4.7 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 22.60, 23.18, 24.95, 28.22, 29.88, 30.71, 32.14, 33.94, 37.60, 38.91, 39.04, 39.36, 41.94, 42.27, 48.71, 49.35, 107.95, 110.98, 121.83, 128.58, 133.08, 138.48, 139.45, 140.17, 160.27; MS (70 eV, 250 °C) m/z 430 (M + H, 100), 292 (26.68). Anal. Calcd for $C_{29}H_{40}BON$: C, 81.11; H, 9.32; N, 3.26; B, 2.16. Found: C, 81.01; H, 9.63; N, 3.22; B, 2.14. The methanolic extract was concentrated and 1-phenylethanol was isolated by distillation: yield 2.60 g (85%).

(14) Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Syntheses via Boranes*; Wiley-Interscience: New York, 1975.

(15) Brown, H. C.; Vara Prasad, J. V. N. *J. Org. Chem.* **1986**, *51*, 4526.

Recovery of Ter_2*BOMe (23-25) from EA-BTer_2* Adducts (18 and 19) and 8-HQ-BTer_2* Adducts (20-22). The following procedure is representative.

To a solution of 8-HQ-B(4-^{d}Icr_2) adduct 21 (2.15 g, 5 mmol) in a mixture of Et_2O (10 mL) and methanol (2 mL) was added anhydrous HCl in Et_2O (5.0 mL, 1.0 M, 5 mmol) at 0 °C and the reaction stirred for 0.5 h. There was an instantaneous precipitation of the 8-HQ·HCl salt. ^{11}B NMR analysis of the reaction mixture revealed a complete disappearance of the peak at δ 15 ppm, corresponding to the 8-HQ-B(4-^{d}Icr_2) adduct 21, and the appearance of a new peak at δ 53 ppm, corresponding to 4-^{d}Icr_2BOMe (24). The volatiles were then pumped off under vacuum (10 mm), and the resulting mixture was extracted with pentane (2 × 15 mL). The clear pentane extract was decanted into another flask and concentrated to obtain 4-^{d}Icr_2BOMe (24) as a colorless liquid: yield 1.48 g (94%).

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Chiral Synthesis via Organoboranes. 36. Exceptionally Enantioselective Allylborations of Representative Heterocyclic Aldehydes at −100 °C under Salt-Free Conditions

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Chiral terpenyl-based allylborane reagents (Ter_2*$BCH_2CH{=}CH_2$, 1-3) undergo facile condensation with representative heterocyclic aldehydes (HetCHO) at −100 °C (in the absence of Mg^{2+} salts) and afford the corresponding homoallylic alcohols (HetCH*(OH)$CH_2CH{=}CH_2$, 12-19) in enantiomeric purities approaching 100% ee. A new workup procedure involving 8-hydroxyquinoline (8-HQ) has been utilized for the convenient isolation of the product alcohols.

Heterocyclic natural products are exceptionally valuable both as targets for total synthesis as well as for biomedical and pharmaceutical research, owing to their unique structural features and remarkably diverse medicinal value. Recently, a number of heterocyclic natural products which exhibit extremely useful biological activities have been isolated from marine and other natural sources.[1,2] A characteristic feature in the structures of these natural products is the presence of various α-heterocyclic carbinol moieties (Chart I).

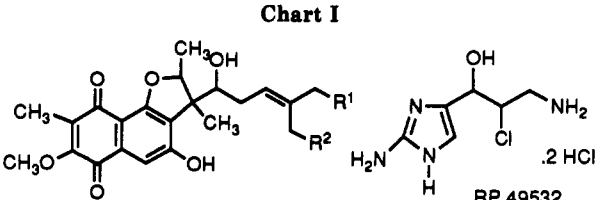
A highly stereoselective synthesis of such heterocyclic natural products requires remarkably enantioselective (≥99% ee) synthetic methods for the construction of heterocyclic carbinol moieties. To our knowledge, such truly general and perfectly enantioselective (≥99% ee) methods have not been reported in the literature for the synthesis of various heterocyclic carbinols.

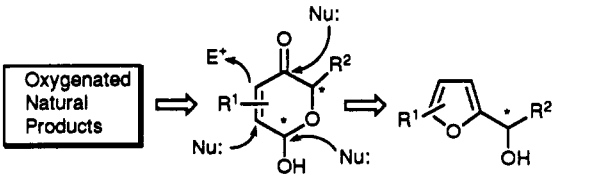
Further, it is well-known that enantiomerically pure 2-furanylcarbinols can be transformed into hydropyranone intermediates which are valuable for the asymmetric synthesis of innumerable oxygenated natural products (Scheme I).[3,4]

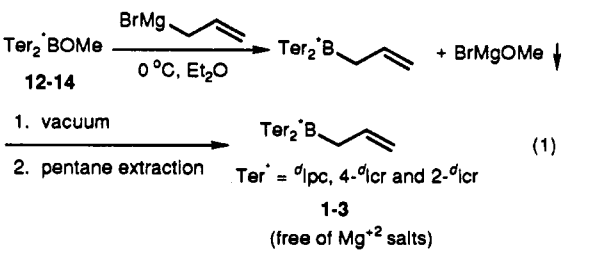
Similarly, the thiophenyl-, pyridyl-, and other heterocyclic carbinols of high optical purity are also useful for the stereoselective synthesis of many other important heterocyclic compounds.[5] Consequently, with a view to support such synthetic applications, we undertook a systematic examination of the asymmetric allylboration of representative heterocyclic aldehydes 4-11 with the diterpenylallylboranes 1-3 at −100 °C, in the absence of Mg^{2+} salts (Scheme II).[6]

Results and Discussion

B-Allyldiisopinocampheylborane (^{d}Ipc$_2$BAll, 1), *B*-allylbis(4-isocaranyl)borane (4-^{d}Icr_2BAll, 2), and *B*-allylbis(2-isocaranyl)borane (2-^{d}Icr_2BAll, 3) were prepared in chemically pure form starting from the corresponding methoxyditerpenylboranes (Ter_2*BOMe), according to the previously reported procedures (eq 1):[6]







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