Enantioselective Synthesis of Disubstituted Alkynes via Organoboranes

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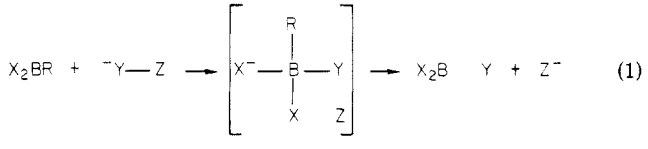
Iodine-induced rearrangement of the "ate" complex derived from diisopinocampheylalkylborane and various lithium acetylides furnishes optically active disubstituted alkynes with an enantiomeric excess comparable to that of the diisopinocampheylborane used in the initial asymmetric hydroboration. In the present investigation *sec*-butyldiisopinocampheylborane, prepared by assymetric hydroboration of *cis*-2-butene with chiral diisopinocampheylborane of high enantiomeric excess, is used to yield *sec*-butyl-substituted alkynes in excellent (≥95%) enantiomeric excess. Despite the statistical disadvantage of a 1:2 ratio of *sec*-butyl:isopinocampheyl groups, the desired alkyne is formed in 58% yield by GLPC, compared to 38% for the product derived from the migration of the isopinocampheyl group, thus suggesting low migratory aptitude for the latter. The iodine-induced rearrangement is highly stereospecific in nature and proceeds with complete retention of configuration at the migrating terminus. The method is capable of producing both enantiomers.

In recent years development of highly stereoselective reactions has become one of the most attractive field in organic syntheses, and several efficient methods have already been devised.[1] Largely due to the efforts by Brown and co-workers, diisopinocampheylborane (Ipc_2BH) and monoisopinocampheylborane ($IpcBH_2$) have found wide application in asymmetric organic synthesis.[2] Both of them are readily prepared from borane–dimethyl sulfide (BMS) and α-pinene, which is available in both enantiomeric forms; Ipc_2BH hydroborates *cis*-alkenes at low temperature (−25 °C) to give mixed trialkylborane in excellent purities.[3] Most importantly, these chiral trialkylboranes and dialkylboranes, obtained by asymmetric hydroboration of prochiral alkenes with $IpcBH_2$ in molar ratio of 1:1, have been used in the asymmetric synthesis of boranates,[4] borinates,[5] ketones,[5] and aldehydes[6] in high enantiomeric purity.

Achiral organoboranes, prepared by the hydroboration of appropriate alkenes by borane reagents, are versatile intermediates in organic synthesis.[7] They react spontaneously with nucleophiles to form thermally stable organoborates. When the nucleophiles are appropriately substituted—e.g., with an α-halogen—1,2-migration of alkyl from boron to carbon follows borate formation. Migration reactions also can be brought about by the addition of organic or inorganic electrophiles to α,β-unsaturated organoborates (eq 1–3). The product of these 1,2-



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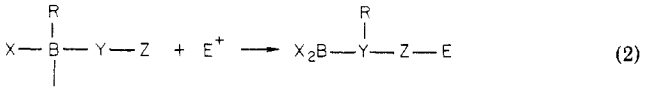

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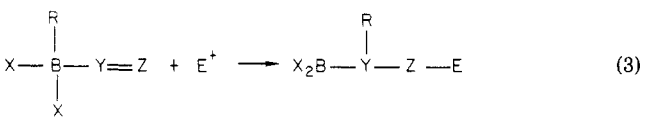

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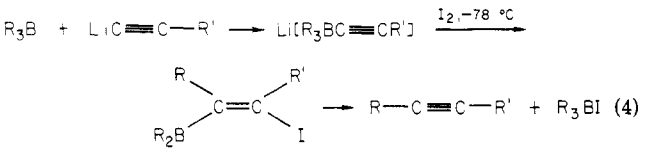
migration reactions are new organoboranes which often can be converted into various organic compounds by oxidation, protonolysis, or β-elimination. Using this 1,2-migration approach, a variety of routes to ketones, esters, acetylenes, and alkenes have been developed.[7b]

Ten years ago, Suzuki, Brown, and co-workers[8] first described convenient synthesis of acetylenes using organoborane chemistry (eq 4). Trialkylboranes react rapidly



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with lithium acetylides to produce corresponding lithium 1-alkynyltrialkylborates, which react rapidly with iodine at −78 °C. The reaction appears to involve electrophilic attack of iodine on the triple bond and rapid 1,2-migration of alkyl group from boron to acetylide carbon. The β-iodovinylboranes spontaneously undergo β-elimination of B–I to form acetylene in excellent yield (>90%, eq 4). Recently, Nozaki[9] found that the rearrangement can also be induced by methanesulfenyl chloride. Suzuki[10] has developed a related electrochemical alkylation of 1-alkynes with organoboranes for the synthesis of disubstituted acetylenes.

In connection with our studies on the isomerization of acetylenes[11] with potassium 3-aminopropylamide (KAPA)

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(3) Brown, H. C.; Jadhav, P. K.; Desai, M. C. *J. Org. Chem.* **1982**, *47*, 5065.
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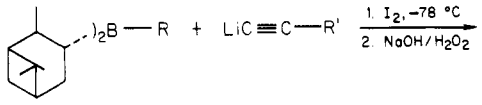
in 3-aminopropylamine (APA),[12] we needed optically active acetylenes having chiral center α to the triple bond. To provide these substrates, we have developed a convenient new route to α-chiral alkynes from optically active trialkylboranes. These trialkylboranes are synthesized in situ by asymmetric hydroboration of alkenes with Ipc_2BH. The details of this investigation is summarized here; the isomerization studies will be reported separately.

Results and Discussion

The stoichiometric limitation imposed by the very nature of the iodine-induced rearrangement of unsaturated organoborates (eq 2) allows the transfer of only one of the three alkyl groups of trialkylborane. It is obvious that the use of symmetrical trialkylborane (R_3B) will give only one acetylene. However, when using unsymmetrical trialkylborane ($R^1R^2R^3B$) in the reaction (eq 4), competitive migration of all three groups is possible and consequently three acetylenes may be formed. The relative yields of products will depend on the migratory aptitude of the three alkyl groups. Migratory aptitude for a few alkyl groups have been determined by Slayden[13] in the iodine-induced rearrangement of lithium ethynyltrialkylborates. After statistical correction, an overall migratory optitude of bicyclooctyl > *n*-butyl > cyclohexyl ≃ isobutyl ≃ *sec*-butyl > thexyl was found. When the secondary and primary migrating carbon series were considered separately, the orders were bicyclooctyl > cyclohexyl > *sec*-butyl, and *n*-butyl > isobutyl. These results suggested a significant influence of steric hindrance.

We were interested in using chiral unsymmetrical trialkylborane 1 obtained by the hydroboration of prochiral alkene with Ipc_2BH. Our obvious concern was the statistical disadvantage (33%) for the migration of chiral alkyl group (R) in the alkynylborate formed from 1. Examination of models suggested that migration of the isopinocampheyl group would be rather more restricted than that of simple *sec*-alkyl groups such as *sec*-butyl. We then undertook to establish the relative migratory aptitudes of various alkyl groups (R) in preference to the isopinocampheyl group using 1-decynyl (R′ = C_8H_{17}, eq 5) as the



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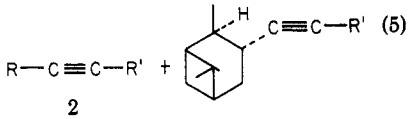

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migration terminus. The mixed trialkylboranes 1 were prepared by hydroboration of alkenes (Table I) with Ipc_2BH at 0 °C. Lithium acetylide, derived from 1-decyne and *n*-BuLi, was then added to form "ate" complex, which was treated with iodine at −78 °C to effect migration. Following oxidation ($NaOH-H_2O_2$) the alkynes formed were analyzed by GLPC. The experimental results are reported in Table I. Similarly, various trialkylboranes were synthesized by the hydroboration of alkenes with disiamylborane[14]—an acyclic analogue of Ipc_2BH—and reacted sequentially with decynyl lithium, iodine, and alkaline hydrogen peroxide (eq 6). The results are summarized in Table II.

Table I. Relative Alkyl Group Migratory Aptitude (*M*) in the Iodination of Lithium Decynyldiisopinocampheylalkylborate (eq 5)

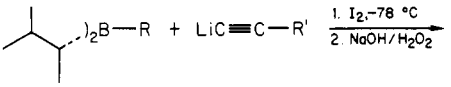
S no.	alkene	% of alkyne products[a] 2[b]	3[b]	ratio of products %2/%3	*M*[c]
1	1-hexene	76.8	23.8	3.23	6.46
2	2-methyl-1-butene	64.2	35.8	1.79	3.58
3	2,3-dimethyl-1-butene	63.6	36.4	1.75	3.50
4	styrene	70.1	29.9	2.34	4.68
5	*cis*-2-butene	57.6	42.4	1.36	2.72
6	cyclopentene	45.3	54.7	0.83	1.66

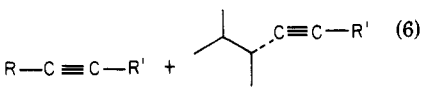
[a] Determined by GLPC analysis using internal standard. [b] Percentages are reported as the average of at least two experiments. [c] Taking isopinocampheyl group as 1.0.

Table II. Relative Alkyl Group Migratory Aptitude (*M*) in the Iodination of Lithium Decynyldisiamylalkylborate (eq 6)

S no.	alkene	% of alkyne products[a] 4[b]	5[b]	ratio of products %4/%5	*M*[c]
1	1-hexene	55.2	44.8	1.23	2.46
2	2-methyl-1-butene	38.2	61.8	0.62	1.24
5	*cis*-2-butene	33.6	66.4	0.51	1.02

[a] Determined by GLPC analysis using internal standard. [b] Percentages are reported as the average of at least two experiments. [c] Taking siamyl group as 1.0.





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Since only one alkyl group is transferred during the reaction, relative migratory aptitude dictates the relative amount of alkyne products formed. From the inspection of Tables I and II, the following points stands out immediately. (i) In accord with Slayden's study,[13] a primary alkyl group migrates in preference to secondary groups. (ii) Among the secondary alkyl groups, the isopinocampheyl group has a very low migratory aptitude, e.g., *sec*-butyl and cyclopentyl groups, after statistical correction, migrates 2.72 and 1.66 times as fast as the isopinocampheyl group. (iii) Comparison of last column of Tables I and II reveals that the siamyl group migrates 2.7 times as fast as the isopinocampheyl group.

It is very interesting to notice that trialkylborane 1 (R = *sec*-butyl) has all secondary groups, yet the migratory aptitude of *sec*-butyl overcomes a 1:2 statistical disadvantage to yield the corresponding alkyne in 58% yield.

Alkyl migrations from boron to carbon are known to occur stereospecifically with regard to the migrating center in a variety of reactions. Chirality induced in formation of 1 should be directly transferred to the product alkyne; in the case of *sec*-butyl groups, the induced chirality can exceed 98%. Consequently, the ability to selectively transfer the *sec*-butyl group from 6 to an alkyne via iodination of the alkynyl borate suggested a new route to structures with a triple bond attached directly to a chiral secondary saturated carbon, structures which are not readily accessible by other means. To confirm the antic-

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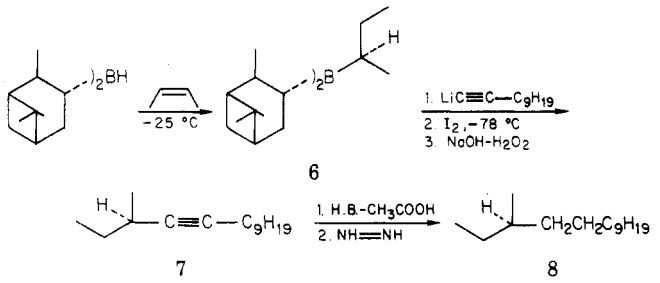
ipated stereospecificity, we used alkynyl borate iodination in a reaction sequence to prepare (*R*)-(−)-3-methyltetradecane **8**, for which rotation of 95% ee (minimum) material is reported.[15]

Hydroboration of *cis*-butene with Ipc_2BH derived from (+)-α-pinene has been shown to yield **6** possessing the *R* configuration[4,21] from which (*R*)-**8** is related by substituted



of alkynyl carbon for boron with retention. Ipc_2BH was prepared[3] in THF from (+)-α-pinene and BMS; reaction with *cis*-2-butene at −25 °C afforded *R*-**6**. Lithium acetylide, derived from 1-undecyne, and *n*-BuLi was added to **6** to form the "ate" complex. Treatment with iodine at −78 °C gave, after oxidative workup ($NaOH/H_2O_2$), (*R*)-(−)-3-methyltetradecyne (**7**) which could be isolated in 48% yield by distillation. Conversion of **7** to **8** for confirmation of stereospecifically required reduction of the triple bond by unambiguous means. However, the proximity of the chiral center to the center of unsaturation restricts the use of catalytic hydrogenation. Catalytic hydrogenation of alkynes proceeds via alkenes,[16] and substantial racemization has been observed[17] during the hydrogenation of several optically active alkenes. To avoid any ambiguity this transformation was achieved in two steps by reduction of the triple bond to olefin by hydroboration and protonolysis (Sia_2BH, CH_3COOH)[18] and further hydrogenation to the saturated derivative by diimide.[19] Thus (*R*)-(−)-3-methyl-4-tetradecyne (**7**) afforded *cis*-3-methyl-4-tetradecene, and (*R*)-(−)-3-methyl-4-tetradecane (**8**) $[\alpha]_D^{23}$ −6.53° (neat), corresponding to a minimum of 95% ee for **8**. Since both hydroboration–protonolysis and diimide reduction of olefins proceed without racemization,[19a,b] it is apparent that **7** is also at least 95% optically pure. The maximum enantiomeric excess which has been achieved in hydroboration of *cis*-2-butene with Ipc_2BH is 98.1%, using carefully controlled equilibration of Ipc_2BH with excess pinene for several days. Under the somewhat less rigorous conditions employed in this study (see Experimental Section), the enantiomeric excess of Ipc_2B–*sec*-butyl would be ca. 96% and the same enantiomeric excess would be expected for **7**. Thus the transfer of the *sec*-butyl group is confirmed to proceed without racemization. Any apparent minor loss of optical purity reflects the uncertainty in the enantiomeric excess of the Ipc_2B–*sec*-butyl and/or of **7**.[20]

This indicates that the iodine-induced 1,2-migration reaction of lithium alkynyltrialkylborates is highly stereospecific and proceeds with retention of configuration at the migrating center. The alkynes are thus produced with a configuration which is induced in the asymmetric hydroboration step with Ipc_2BH. Configuration of the alkyl group introduced in hydroboration of alkenes with Ipc_2BH has been shown to be related consistently to the configuration of the pinene initially use to prepare the R_2BH. Therefore, use of (−)-α-pinene in place of (+)-α-pinene would yield alkynes with the *S* configuration.

Similar reactions with the lithium acetylides obtained from 1-pentyne, 1-hexyne, 1-octyne, and 1-nonyne afforded (*R*)-(−)-3-methyl-4-octyne, (*R*)-(−)-3-methyl-4-nonyne, (*R*)-(−)-3-methyl-4-undecyne, and (*R*)-(−)-3-methyl-4-dodecyne in 43–52% yield.

Optically pure Ipc_2BH used during the hydroboration always has 15% excess α-pinene.[3] In most cases, the pinene was separated from the final product by fractional distillation, after oxidation of all remaining boron species. However, the boiling point of 3-methyl-4-octyne is relatively low and is close to that of α-pinene. To avoid problems during isolation, two modifications in procedure were made. First, excess α-pinene was removed under vacuum (0.2 mmHg, 25 °C, 12 h) after hydroboration of *cis*-2-butene with Ipc_2BH. Second, the reaction mixture was not oxidized after iodination; instead solvents (cyclohexane, THF, Et_2O) were removed and the product was collected in cold trap (−78 °C) under vacuum (0.5 mmHg, 25 °C, 12 h). Redistillation of trap material gave pure (*R*)-(−)-3-methyl-4-octyne (43%), $[\alpha]_D^{23}$ −33.2° (*c* 3.1, $CHCl_3$).

Phenyl, cycloalkyl, and *tert*-alkyl substituents on the alkyne could be used in place of *n*-alkyl groups. Thus, treatment of **6** with the lithium acetylides of phenylethyne, cyclohexylethyne, and 3,3-dimethyl-1-butyne followed by iodination gave (*R*)-(−)-1-phenyl-3-methyl-1-pentyne, (*R*)-(−)-3-methyl-1-cyclohexyl-1-pentyne, and 2,2,5-trimethyl-3-pentyne, respectively.

The optical purity for all the *sec*-butyl-substituted alkynes synthesized above from **6** is presumed to be ≥95% by analogy with that determined for (*R*)-(−)-3-methyl-4-tetradecyne.

Apart from *cis*-2-butene, diisopinocampheylborane hydroborates various other *cis*-alkenes—e.g., *cis*-3-hexene, norbornene—with very high induction of chirality. Logically, the present method can be extended for the synthesis of various substituted alkynes from such alkenes in high enantiomeric excess.

In summary, the present investigation indicates that the isopinocampheyl group has low migratory aptitude. The migratory aptitude order, determined by Slayden[13] for secondary migrating alkyl groups, can be extended as follows: bicyclooctyl > cyclohexyl > *sec*-butyl, 3-methyl-2-butyl (siamyl) > isopinocampheyl. We have established that the iodine-induced rearrangement of lithium alkynyl trialkylborates is highly stereospecific in nature and proceeds with essentially complete retention of configuration at the migrating center. Chiral alkynes are produced with configuration and enantiomeric excess determined in the highly stereoselective initial asymmetric hydroboration. Utilization of the alkyl group R in Ipc_2BR is relatively efficient. Finally, the accessibility of both enantiomeric forms of α-pinene—and thus of diisopino-

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(20) Subsequently, hydrogenation of this type of alkyne to saturated derivatives was found to proceed with ≤2% racemization at 0 °C in presence of 5% platinum on carbon. Brown, C. A.; Desai, M. C., unpublished observations.

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Table III. Asymmetric Synthesis of Disubstituted Alkynes by Iodination of Lithium Alkynyldiisopinocampheylalkylborates[a,b]

acetylene	alkene	alkyne	product alkynes: % yield (isolated)	product alkynes: $[\alpha]^{23}_D$, deg	config	ee, %
1-pentyne	*cis*-2-butene	3-methyl-4-octyne	43	−33.2 (*c* 2.1, $CHCl_3$)	*R*	≥95[d]
1-hexyne	*cis*-2-butene	3-methyl-4-nonyne	52	−32.0 (neat)	*R*	≥95[d]
1-octyne	*cis*-2-butene	3-methyl-4-undecyne	43	−24.4 (*c* 2.95, $CHCl_3$)	*R*	≥95[d]
1-nonyne	*cis*-2-butene	3-methyl-4-dodecyne	45	−21.1 (*c* 3.9, $CHCl_3$)	*R*	≥95[d]
1-undecyne	*cis*-2-butene	3-methyl-4-tetradecyne	48	−20.0 (*c* 4.02, $CHCl_3$)	*R*	≥95[c]
phenylethyne	*cis*-2-butene	3-methyl-1-phenyl-1-pentyne	47	−43.8 (*c* 6.8, $CHCl_3$)	*R*	≥95[d]
cyclohexylethyne	*cis*-2-butene	3-methyl-1-cyclohexyl-1-pentyne	41	−26.6 (*c* 3.84, CH_3)	*R*	≥95[d]
3,3-dimethyl-1-butyne	*cis*-2-butene	2,2,5-trimethyl-3-pentyne	27	−26.2 (*c* 2.3, $CHCl_3$)	*R*	≥95[d]

[a] Various lithium alkynyldiisopinocampheylalkylborates were prepared by adding lithium acetylides (derived from acetylene and *n*-BuLi) to chiral trialkylboranes (synthesized by asymmetric hydroboration of alkenes with Ipc_2BH). [b] Ipc_2BH was prepared from (+)-α-pinene, $[\alpha]^{23}_D$ +47.1° (neat), 92%, ee. Note that the procedure contains an equilibration and crystallization and results Ipc_2BH^2 with ee of 96–99%. [c] Optical purity was determined by reduction to (*R*)-(−)-3-methyltetradecane, $[\alpha]^{23}_D$ −6.53° (neat). For (*S*)-3-methyltetradecane with *minimum* 95% ee Lardicci et al. (Lardicci, L.; Salvadori, P.; Pino, P. *Ann. Chim. (Rome)* **1952**, *52*, 652) report $[\alpha]^{25}_D$ +6.56° (neat). [d] Enantiomeric excess considered to be ≥95% based on analogy with the preparation of (*R*)-(−)-3-methyltetradecane by the same procedure. Subsequent to completion of this study, we have used this procedure in preparation of similar structures with ee confirmed to be ≥95%.[11]

campheylborane (Ipc_2BH)—provides a single route to both enantiomers of α-chiral alkynes. Additional studies are underway in our laboratories to further extend the scope of the reaction and to implement this method for the synthesis of chiral lipids, e.g., insect pheromones.[11]

Experimental Section

The reaction flask and other glass equipment were dried in an oven and assembled in a stream of dry nitrogen gas. Special experimental techniques used in handling air-sensitive materials are described in detail elsewhere.[22]

Materials. $BH_3{\cdot}SMe_2$ and (+)-α-pinene of 92% ee was purchased from Aldrich Chemical Company. Tetrahydrofuran (THF) and (+)-α-pinene were purified by distillation from a small excess of lithium aluminum hydride (LAH) and stored under nitrogen. The alkynes used for this study were commercial products of the highest purity available from Farchan Laboratories and were distilled before use.

Physical Methods. ^{11}B NMR and ^{13}C NMR were recorded with Varian FT 80A instrument. The chemical shifts of ^{11}B NMR are relative to $BF_3{\cdot}Et_2O$. GC analyses were carried out with Hewlett-Packard 5750 and 5734A chromatographs using 6 ft × 0.25 in. columns packed with either SE-30 or Carbowax 20M on Chromosorb W. Unless otherwise specified, starting materials and distilled products appeared ≥98% pure by GLPC. For preparative GLPC, a 6 ft × 0.5 in. column packed with 20% SE-30 on Chromosorb W (60–80 mesh) was used. Optical rotations were measured on a Rudolph Autopol II polarimeter.

Synthesis of Trialkylboranes. The following standard experimental setup was used for the synthesis of trialkylboranes needed for the determination of migratory aptitude of alkyl groups (Tables I and II).

A dry, 50-mL, round-bottomed flask equipped with a septum covered side arm, a magnetic bar, and a glass inlet adaptor connected to a mercury bubbler were assembled hot and cooled under a stream of nitrogen. The flask was cooled in a 0 °C bath and charged with the reagents. *cis*-2-Butene was condensed at −78 °C (dry ice–acetone) in a dried, septum-capped graduated test tube and was delivered via a double-ended needle to the hydroborating solution by pressurized nitrogen.

(A) Diisopinocampheylalkylboranes. The usual experimental setup was employed. Ip_2BH was prepared[3] by mixing at 0 °C $BH_3{\cdot}SMe_2$ (0.5 mL, 5 mmol), 5 mL of THF, and (+)-α-pinene (1.9 mL, 12 mmol); the mixture was then stirred at 0 °C for 3 h and left in cold room at 0 °C overnight. The appropriate alkene (20% excess) was added and the solution was stirred at 0 °C for a further 3 h. In case of *cis*-2-butene, hydroboration was carried out at −25 °C for 6 h.

(B) Disiamylalkylboranes. Disiamylborane (5 mmol) was synthesized according to a standard procedure.[14] The appropriate alkene (20% excess) was added and the solution was stirred at 0 °C for 6 h and at room temperature for 0.5 h.

Reaction of Diisopinocampheylboranes and Disiamylalkylboranes with Lithium Octylacetylide and Iodine. Lithium octylacetylide (5 mmol), prepared by adding 2.1 M *n*-BuLi in hexane (2.4 mL, 5 mmol) to a stirred solution of 1-decyne in THF (5 mmol, 8 mL), was added to the flask containing the trialkylborane (5 mmol). The mixture was then stirred for 0.5 h at room temperature; a clear solution formed. After the lithium decynyltrialkylborate solution was cooled to −78 °C and a solution of iodine (1.27 g, 5 mmol) in ethyl ether (13 mL) was added slowly to the vigorously stirred solution. After 3 h at −78 °C, the solution was warmed to room temperature and then was washed with 3 M aqueous sodium hydroxide (2 × 5 mL). The organic phase was then oxidized with 3 M sodium hydroxide (3.4 mL, 10 mmol), followed by of 30% hydrogen peroxide (1.6 mL, 15 mmol). The reaction mixture was maintained at 55 °C for 1 h to ensure completion of oxidation. The aqueous layer was saturated with potassium carbonate and the organic layer was analyzed by GLPC on an SE-30 column. The results are summarized in Tables I and II.

Illustrative Procedure for the Synthesis of Alkynes (Table III). Synthesis of (*R*)-(−)-3-Methyl-4-tetradecyne. For convenience, the synthesis of (*R*)-(−)-3-methyl-4-tetradecyne is divided into two stages: (A) preparation of *sec*-butyldiisopinocampheylborane (6) and (B) iodination of lithium undecynyl-*sec*-butylidiospinocampheylborate.

(A) Preparation of *sec*-Butyldiisopinocampheylborane. Ipc_2BH (99.1 % ee) in THF was prepared according to the published procedure from (+)-α-pinene (92% ee) and BMS.[3] To a stirred suspension of Ipc_2BH (50 mmol) in THF at −25 °C was added *cis*-2-butene (4.5 mL, 50 mmol). After 6 h at −25 °C the formation of trialkylborane (^{11}B NMR δ 87) was complete. The *sec*-butyldiisopinocampheylborane thus prepared was used for the synthesis of *sec*-butyl-substituted alkyne summarized in Table III.

(B) Formation and Iodination of Lithium Undecynyl-*sec*-butyldiisopinocampheylborate. A dry, 100-mL flask, equipped with a septum inlet, magnetic stirring bar, and mercury bubbler was purged with nitrogen and maintained under a static pressure of gas until oxidation of the organoborane was complete. The flask was charged with *sec*-butyldiisopinocampheylborane (50 mmol) and cooled to 0 °C. In a 250-mL flask was placed (under nitrogen) 100 mL of THF and (7.6 g, 50 mmol) of 1-undecyne. The flask was cooled in an ice bath, and 2.1 M *n*-butyllithium in hexane (23.8 mL, 50 mmol) was added to form the lithium acetylide. The acetylide mixture was then transferred to a 1000-mL flask containing *sec*-butyldiisopinocampheylborane (50 mmol) in THF at 0 °C. The reaction mixture was stirred for 0.5 h at 0 °C to form the "ate" complex which was cooled to −78 °C. A solution of (12.7 g, 50 mmol) of iodine in 130 mL of ethyl ether was then added dropwise via a double-ended needle over a period of 40 min. After stirring for an additional 8 h at −78 °C, aqueous sodium thiosulfate solution (7.0 g in 10 mL) was added

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

to discharge the iodine color, and the content of the flask was brought to room temperature by replacing the cooling bath by a water bath. While maintaining the nitrogen atmosphere, the solution was then washed twice with a mixture of 40 mL of 3 M sodium hydroxide and 2 mL of saturated aqueous solution of sodium thiosulfate. The organic phase was oxidized by adding 3 M aqueous sodium hydroxide (33 mL) followed by dropwise addition of 30% hydrogen peroxide (15.0 mL) (exothermic!). The reaction mixture was further stirred at 55 °C for 1 h, cooled, and extracted with ethyl ether (3 × 100 mL). The extract was washed successively with water (3 × 75 mL) and brine (1 × 100 mL), and dried over anhydrous magnesium sulfate. The solvents were removed on rotary evaporator and residue was fractionated to furnish a mixture of isopinocampheol and 3-methyl-4-tetradecyne which were separated by flash column chromatography on silica gel. Elution with pentane afforded (*R*)-(−)-3-methyl-4-tetradecyne (5.0 g, 48%): bp 90 °C (0.4 mmHg); ^{13}C NMR (neat) δ 84.5, 80.3, 31.9, 30.2, 29.5, 29.2, 29.1, 28.8, 27.6, 22.6, 21.0, 18.7, 13.9, 11.5. Prior to determination of optical rotation, it was purified by preparative GLPB: $[\alpha]_D^{23}$ −20.0° (*c* 4.02, $CHCl_3$).

Hydroboration–Protonolysis of (*R*)-(−)-3-Methyl-4-tetradecyne. Disiamylborane (10 mmol) was prepared according to the published procedure[14] using 2-methyl-2-butene and BMS. Disiamylborane was added to the rapidly stirred solution of (*R*)-(−)-3-methyl-4-tetradecyne (2.1 g, 10 mmol) in THF (5 mL) at −10 °C. The solution was brought to room temperature and was further stirred for 2 h to ensure completion of the hydroboration. Protonolysis was accomplished by adding anhydrous acetic acid (10 mL) and allowing the mixture to stir for 2 h at room temperature. The entire mixture was poured into ice water and taken up in ether. The disiamylboronic acid in ether–THF mixture was oxidized by the addition of 3 M aqueous sodium hydroxide (10 mL) and 30% hydrogen peroxide (3 mL). The reaction mixture was maintained at 55 °C for 1 h, cooled, and extracted with ethyl ether (3 × 30 mL). The extract was washed successively with water (3 × 30 mL) and brine (1 × 20 mL) and dried over anhydrous magnesium sulfate. The solvents were removed under reduced pressure and the residue distilled to give (*R*)-(−)-3-methyl-4-tetradecene (1.5 g, 70%): bp 85–89 °C (0.4 mmHg); ^{13}C NMR ($CDCl_3$) δ 136.0, 128.6, 33.4, 32.0, 30.3, 30.0, 29.6, 29.4, 28.8, 27.5, 22.7, 21.0, 20.9, 14.0, 11.8. After purification by preparative GLPC, it showed $[\alpha]_D^{23}$ −13.0° (*c* 3.5, $CHCl_3$).

Diimide Reduction of (*R*)-(−)-*cis*-3-Methyl-4-tetradecene. In a 200-mL round-bottom flask equipped with a magnetic bar, an efficient condenser, and an air inlet tube were placed (*R*)-(−)-*cis*-3-methyl-4-tetradecene (1.0 g, 4.7 mmol), 97% hydrazine (1.5 g, 47 mmol), absolute ethanol (40 mL), and copper(II) sulfate pentahydrate (0.15 g). Air was bubbled through the reaction mixture with vigorous stirring for 6 h; then the flow of air was stopped, the mixture was filtered, and the filtrate was extracted with pentane (2 × 50 mL). The combined organic phases were washed successively with 2 N hydrochloric acid (1 × 30 mL), water (2 × 30 mL), and brine (1 × 25 mL), and dried over anhydrous magnesium sulfate. The solvents were removed on a rotary evaporator and the residue was distilled to afford (*R*)-(−)-3-methyl-4-tetradecane (0.6 g, 60%): bp 87–88 °C (0.4 mmHg); ≥95% pure by GLPC; ^{13}C NMR ($CDCl_{13}$) δ 36.6, 34.5, 32.0, 30.1, 29.7, 29.5, 29.4, 24.2, 22.7, 19.2, 14.0, 11.3; rotation (after preparative GLPC) $[\alpha]_D^{23}$ −6.53° (neat).

Synthesis of (*R*)-(−)-3-Methyl-4-octyne. It was synthesized according to the illustrative procedure described for the synthesis of (*R*)-(−)-3-methyl-4-tetradecyne, using of 1-pentyne (3,4 g, 50 mmol). However, two modifications were followed: (1) After the synthesis of *sec*-butyldiisopinocampheylborane, THF, and then (+)-α-pinene were removed under reduced pressure (25 °C, 30 mmHg for 1 h and 0.5 mmHg for 12 h, respectively). Then, trialkylborane was redissolved in THF (18 mL). (2) Iodination of lithium pentynyl-*sec*-diisopinocampheylborate was done exactly under the same conditions as that illustrated for the synthesis of (*R*)-(−)-3-methyl-4-tetradecyne. However, after washing the reaction mixture from iodination with aqueous sodium hydroxide, solvents were removed under reduced pressure (30 mm, 25 °C) and the product was isolated cold trap (−78 °C) under vacuum (0.2 mmHg, 25 °C, 12 h). Redistillation of trap material furnished (*R*)-(−)-3-methyl-4-octyne (3.0 g, 43%): bp 74 °C (85 mmHg); ≥95% pure by GLPC; ^{13}C NMR ($CHCl_3$) δ 84.7, 80.1, 30.2, 27.5, 22.6, 21.0, 20.6, 13.2, 11.5; rotation (after preparative GLPC) $[\alpha]_D^{23}$ −33.2° (*c* 3.1, $CHCl_3$).

Synthesis of 3-Methyl-4-nonyne. It was synthesized exactly according to the procedure described for the synthesis of (*R*)-(−)-3-methyltetradecyne using 1-hexyne (5.7 mL, 50 mmol) of 1-hexyne. The final isolation was done by fractional distillation of the residue obtained after usual workup, using a Widmer column (12 in.) to yield pure (*R*)-(−)-3-methyl-4-tetradecyne (3.53 g, 52%): bp 68 °C (14 mmHg); ^{13}C NMR ($CDCl_3$) δ 84.0, 80.1, 31.4, 30.3, 27.6, 21.9, 18.4, 13.5, 11.6; rotation (after preparative GLPC) $[\alpha]_D^{23}$ −31.99° (neat).

Synthesis of 3-Methyl-4-undecyne. It was synthesized by following the illustrative procedure described for the synthesis of (*R*)-(−)-3-methyl-4-tetradecyne using 1-octyne (5.5 g, 50 mmol). The distillation of the residue obtained after usual workup gave a mixture of isopinocampheol and alkyne which was separated by flash column chromatography on silica gel. Elution with pentane afforded (*R*)-(−)-3-methyl-4-undecyne (3.57 g, 43%): bp 103 °C (30 mmHg); ^{13}C NMR ($CDCl_3$) δ 84.4, 80.1, 31.3, 30.2, 29.1, 28.4, 27.5, 22.5, 21.0, 18.6, 13.7, 11.5; rotation (after preparative GLPC) $[\alpha]_D^{23}$ −24.4° (*c* 2.95, $CHCl_3$).

Synthesis of (*R*)-(−)-3-Methyl-4-dodecyne. It was synthesized by the method described for the preparation of (*R*)-(−)-3-methyl-4-tetradecyne using the lithium acetylide derived from 1-nonyne (8.2 mL, 50 mmol). The residue obtained after oxidative workup and solvent removal was subjected to flash column chromatography on silica gel. Elution with pentane separated the mixture of 3-methyl-4-dodecyne and 1-isopinocampheyl-1-nonyne from isopinocampheol. Fractional distillation using a Widmer column (12 in.) furnished (*R*)-(−)-3-methyl-4-dodecyne (4.05 g, 45%): bp 88 °C (4 mmHg); ≥95% pure by GLPC); ^{13}C NMR ($CDCl_3$) δ 84.8, 80.5, 31.8, 30.4, 29.4, 28.9, 27.7, 22.7, 21.2, 18.8, 14.1, 11.8; rotation (after preparative GLPC) $[\alpha]_D^{23}$ −21.1° (*c* 3.9, $CHCl_3$).

Synthesis of (*R*)-(−)-3-Methyl-1-phenyl-1-pentyne. It was synthesized by following the illustrative procedure described for the synthesis of (*R*)-(−)-3-methyl-4-tetradecyne using phenylethyne (5.5 mL, 50 mmol). The residue obtained after oxidative workup and solvent removal was distilled to provide a mixture isopinocampheol and alkynes which was separated by flash column chromatography on silica gel with pentane and distilled to yield (*R*)-(−)-3-methyl-1-phenyl-1-pentyne (3.73 g, 47%): bp 116° (4 mmHg); >98% GLPC pure; one spot on TLC; ^{13}C NMR (neat) δ 131.1, 127.6, 126.9, 124.1, 93.8, 80.9, 29.7, 27.8, 20.2, 11.3; rotation (after preparative GLPC) $[\alpha]_D^{23}$ −43.8° (*c* 6.8, $CHCl_3$).

Synthesis of (*R*)-(−)-3-Methyl-1-cyclohexyl-1-pentyne. It was synthesized by the method described for preparation of (*R*)-(−)-3-methyl-4-tetradecyne using the lithium acetylide derived from cyclohexylethyne (5.4 g, 50 mmol). The residue, obtained after oxidative workup and solvent removal, was distilled to give a mixture of isopinocampheol, 1-isopinocampheyl-2-cyclohexylethyne, and the desired alkyne. Flash column chromatography of the mixture on silica gel with pentane removed isopinocampheol from the mixture of alkynes. Fractional distillation afforded (*R*)-(−)-3-methyl-1-cyclohexyl-1-pentyne (3.36 g, 41%): bp 100 °C (1 mmHg); ≥95% pure by GLPC; ^{13}C NMR ($CDCl_3$) δ 84.5, 78.7, 33.2, 30.3, 29.1, 27.5; 26.1, 24.8, 21.1, 11.6; rotation (after preparative GLPC) $[\alpha]_D^{23}$ −16.6° (*c* 3.84, $CHCl_3$).

Synthesis of (*R*)-(−)-2,2,5-Trimethyl-3-pentyne. It was synthesized by following the illustrative procedure described for the synthesis of (*R*)-(−)-3-methyl-4-tetradecyne using the acetylide derived from 3,3-dimethyl-1-butyne (4.1 g, 50 mmol). Careful fractionation of product obtained after usual workup gave (*R*)-(−)-2,2,5-trimethyl-3-pentyne (1.85 g, 27%): ≥95% pure by GLPC; bp 33–35° (40 mmHg); ^{13}C NMR (neat) δ 89.0, 82.7, 31.4, 30.3, 27.2, 21.1, 11.4; rotation (after preparative GLPC) $[\alpha]_D^{23}$ −26.2° (*c* 3.32, $CHCl_3$).

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Registry No. 1 (R = $(CH_2)_5CH_3$), 90791-90-5; 1 (R = $CH_2CH(CH_3)CH_2CH_3$), 90791-91-6; 1 (R = $CH_2CH(CH_3)CH(CH_3)_2$), 90791-92-7; 1 (R = CH_2CH_2Ph), 90791-93-8; 1 (R = *c*-C_5H_9), 90791-94-9; 2 (R = $(CH_2)_5CH_3$, R′ = $(CH_2)_7CH_3$), 74685-28-2; 2 (R = $CH_2CH(CH_3)CH_2CH_3$, R′ = $(CH_2)_7CH_3$),

90791-86-9; **2** (R = $CH_2CH(CH_3)CH(CH_3)_2$, R′ = $(CH_2)_7CH_3$), 90791-87-0; **2** (R = CH_2CH_2Ph, R′ = $(CH_2)_7CH_3$), 90791-88-1; (*R*)-**2** (R = $CH(CH_3)CH_2CH_3$, R′ = $(CH_2)_3CH_3$), 90791-97-2; (*R*)-**2** (R = $CH(CH_3)CH_2CH_3$, R′ = $(CH_2)_5CH_3$), 90791-98-3; (*R*)-**2** (R = $CH(CH_3)CH_2CH_3$, R′ = $(CH_2)_6CH_3$), 90791-99-4; (*R*)-**2** (R = $CH(CH_3)CH_2CH_3$, R′ = $(CH_2)_8CH_3$), 90792-00-0; (*R*)-**2** (R = $CH(CH_3)CH_2CH_3$, R′ = Ph), 90898-31-0; (*R*)-**2** (R = $CH(CH_3)CH_2CH_3$, R′ = c-C_6H_{11}), 90792-01-1; **2** (R = c-C_5H_9, R′ = $CCH_2)_7CH_3$), 90791-89-2; (*R*)-**2** (R = $CH(CH_3)CH_2CH_3$, R′ = $(CH_2)_2CH_3$), 90822-56-3; (*R*)-**2** (R = $CH(CH_3)CH_2CH_3$, R′ = $C(CH_3)_3$), 90792-02-2; **3** (R′ = $(CH_2)_7CH_3$), 90791-85-8; **6**, 90865-48-8; **7**, 90822-55-2; Ipc_2BH, 21947-87-5; $CH_2{=}CH(CH_2)_3CH_3$, 592-41-6; $CH_2{=}C(CH_3)CH_2CH_3$, 563-46-2; $CH_2{=}C(CH_3)CH(CH_3)_2$, 563-78-0; $C_6H_5CH{=}CH_2$, 100-42-5; *cis*-$CH_3CH{=}CHCH_3$, 590-18-1; $CH{\equiv}C(CH_2)_7CH_3$, 764-93-2; I_2, 7553-56-2; $CH{\equiv}C(CH_2)_2CH_3$, 627-19-0; $CH{\equiv}C(CH_2)_4CH_3$, 693-02-7; $CH{\equiv}C(CH_2)_5CH_3$, 629-05-0; $CH{\equiv}C(CH_2)_6CH_3$, 3452-09-3; $CH{\equiv}C(CH_2)_8CH_3$, 2243-98-3; $C_6H_4C{\equiv}CH$, 536-74-3; $CH{\equiv}CC(CH_3)_3$, 917-92-0; $LiC{\equiv}C(CH_2)_7CH_3$, 21433-46-5; (*R*)-$CH_3CH_2CH(CH_3)(CH_2)_{10}CH_3$, 55253-05-9; (*R*)-$CH_3CH_2CH(CH_3)CH{=}CH(CH_2)_8CH_3$, 90792-03-3; disiamylborane, 1069-54-1; cyclopentene, 142-29-0; cyclohexylethyne, 931-48-6; lithium 1-decynyldiisopinocampheylhexylborate, 90822-39-2; lithium 1-decynyldiisopinocampheyl-2-methylbutylborate, 90791-72-3; lithium 1-decynyldiisopinocampheyl-2,3-dimethylbutylborate, 90791-73-4; lithium 1-decynyldiisopinocampheylphenethylborate, 90791-74-5; lithium 1-decynyldiisopinocampheyl-2(*R*)-butylborate, 90822-40-5; lithium 1-decynyldiisopinocampheylcyclopentylborate, 90791-75-6; disiamylhexylborane, 16413-17-5; disiamyl-2-methylbutylborane, 90791-95-0; disiamyl-2-butylborane, 90791-96-1; lithium 1-decynyldisiamylhexylborate, 90791-76-7; lithium 1-decynyldisiamyl-2-methylbutylborate, 90791-77-8; lithium 1-decynyldisiamyl-2-butylborate, 90791-78-9; lithium 1-pentynyldiisopinocampheyl-2(*R*)-butylborate, 90791-79-0; lithium 1-hexynyldiisopinocampheyl-2(*R*)-butylborate, 90791-80-3; lithium 1-octynyldiisopinocampheyl-2(*R*)-butylborate, 90791-81-4; lithium 1-nonynyldiisopinocampheyl-2(*R*)-butylborate, 90791-82-5; lithium 1-undecynyldiisopinocampheyl-2(*R*)-butylborate, 90791-83-6; lithium phenylethynyldiisocampheyl-2(*R*)-butylborate, 90822-41-6; lithium cyclohexylethynyldiisocampheyl-2(*R*)-butylborate, 90822-42-7; lithium 1-(3,3-dimethylbutynyl)diisocampheyl-2(*R*)-butylborate, 90791-84-7.

An Investigation of the Intramolecular Ene Reaction of *N*-Acyl Imines[1]

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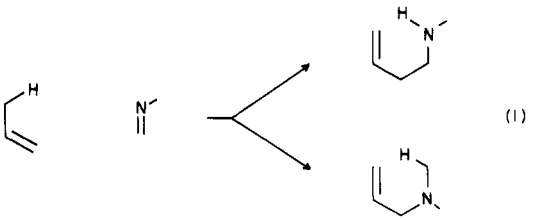
N-Acyl imines, produced by the flash vacuum thermolysis of hydroxamic acid derivatives, participate in the intramolecular ene reaction to give nitrogen heterocycles. The reaction is accelerated by carboxyl substitutents on the carbon atom of the *N*-acyl imine, and the reaction is more successful for the production of pyrrolidine rather than piperdine derivatives.

The ene reaction[2] was first described by Alder and coworkers[3] over 40 years ago. Although related to the Diels–Alder reaction, the ene reaction has been the focus of far fewer studies. Interest in the ene reaction has intensified in recent years resulting in a number of studies concerned with its mechanism[4] as well as its application to the solution of synthetic problems.[5]

The ene reaction using an imine as an enophile, in principle, has potential for the preparation of organic nitrogen compounds. It is also more complicated since there are two isomeric pathways that this reaction can follow. This is, the process can result in either the formation of a carbon–carbon or a carbon–nitrogen single bond (eq 1). From an analysis of the bond energies involved, both of these ene reactions involving imines are



(1)

predicted to be considerably less favorable than the all carbon ene reaction.[6] This situation is primarily a result of the small difference in bond strength between a C=N π bond and the nitrogen σ bonds, C–N and N–H, compared to a C=C π bond and the carbon σ bonds, C–C and C–H. Between the isomeric ene reaction of imines, bond energy data predict the pathway involving the formation of the carbon–nitrogen bond to be less favorable than formation of the carbon–carbon bond. The literature is consistent with this analysis. Simple imines, in contrast to either alkenes or even carbonyl compounds,[2,8] do not

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(5) For examples, see: (a) Ogawa, Y.; Shibasaki, M. *Tetrahedron Lett.* **1984**, 1067. (b) Wovkulich, P. M.; Batcho, A. D.; Uskokovic, M. R. *Helv. Chem. Acta* **1984**, *67*, 612. (c) Snider, B. B.; Cartaya-Marin, C. P. *J. Org. Chem.* **1984**, *49*, 1688. (d) Salomon, M. F.; Pardo, S. N.; Salomon, R. G. *J. Am. Chem. Soc.* **1984**, *106*, 3797. (e) Oppolzer, W. *Pure Appl. Chem.* **1981**, *53*, 1181.

(6) The values (kcal/mol) for the bond energies used were: C–H (98), N–H (92),[7a] and C–C (83); C–N (72.8)[7b] and C=C (59.4); C=N (74.3) (π bond strengths).[7c] Estimates in kcal/mol for the enthalpies of the ene reactions are: the all carbon (–23.6) and the imine, C–C bond formation (–3.7) and the imine, C–N bond formation (+1.5).

(7) (a) Kerr, J. A. *Chem. Rev.* **1966**, *66*, 465. (b) Sandorfy, C. In "The Chemistry of the Carbon–Nitrogen Double Bond"; Patai, S., Ed.; Wiley-Interscience: New York, 1970; p 1. (c) Shaw, R. In "The Chemistry of Double Bonded Functional Groups"; Patai, S., Ed.; Wiley: New York, 1977; p 131.

(8) This trend has also been observed in the Diels–Alder reaction; that is, compared to both alkenes and carbonyl groups, imines are reluctant to participate in this reaction. This observation is also consistent with an analysis of the bond strengths involved. Primarily, the problem is that the energy difference between the π bond and σ bonds involving nitrogen are smaller than those involving either carbon or oxygen.

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