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Organoboranes for Synthesis. 13. Simple, Efficient Syntheses of Long-chain Alcohols and Carboxylic Acids.

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Abstract : General, convenient and simple syntheses of long straight chain alcohols and carboxylic acids were developed utilizing organoborane chemistry. One of the methods entails the thermal isomerization of long-chain alkyldicyclohexylboranes, followed by oxidation. An alternative procedure for the preparation of long-chain alcohols involves the KAPA isomerization of internal alkynes to the terminal derivative, followed by dihydroboration with 9-BBN and oxidation. Alternatively, the terminal alkyne can be oxidised directly to the carboxylic acid. In another strategy, the C_{30}-alcohol triacontanol was prepared by employing high pressure carbonylation of a borane intermediate.

The importance of long-chain alcohols and carboxylic acids is well documented in the literature.[1] Normal primary aliphatic alcohols with an even number (16-36) of carbon atoms are found in waxes. Several of these alcohols have functional activity. To a significant extent, C_{22}, C_{24} and C_{26} acids produce the restorative effect of sea buckthorn oil, while C_{26}, C_{28} alcohols are responsible for the restorative effect of plaintain extract.[2,3] 1-Triacontanol is a potential plant growth stimulant[4], while the C_{26} and C_{28} alcohols, when administered to humans, increase endurance, reaction speed, stress resistance and cardiac muscle function and reduce blood pressure.[6]

Several syntheses of long-straight and branched alcohols have been reported.[7-10] The facile and selective acylation of alkyl substituted thiophenes in the 2- and 5- positions affords a convenient synthetic route for the preparation of a variety of 2,5-diacylalkylthiophene derivatives, which upon desulfurization with Raney nickel, yield long-straight and branched-chain fatty acids, esters and alcohols. This approach has been employed by Tilak and coworkers for the syntheses of long-chain alcohols and carboxylic acid esters.[11-13] The synthesis of odd and even numbered fatty acid esters and alcohols with chain length ranging from C_{25} to C_{35} employing thiophene as a chain extender[13] has been achieved. Although there are many reports[7-17] in the literature for the syntheses of long-chain alcohols and acids, many of the syntheses so far reported involve a sequence of reactions with expensive reagents. We herein report the results of our studies on the truly general syntheses of long-chain alcohols and carboxylic acids utilizing promising organoborane procedures previously applied only for the synthesis of short-chain compounds.

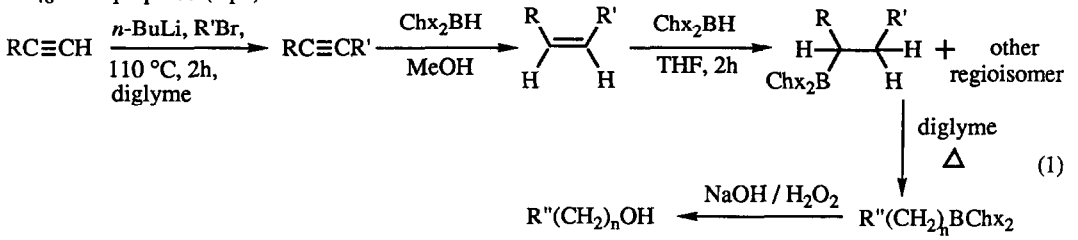
A) Thermal Isomerization Method

The thermal isomerization of organoboranes is a potentially useful synthetic route for the contrathermodynamic conversion of acyclic internal olefins into terminal olefins or their derivatives.

In the past, although the synthetic importance of the thermal isomerization was established, its application in organic synthesis to long-chain derivative remained limited due to the lack of exclusive migration of boron to the terminal position.

Previous studies[18] from our laboratories indicate that the greater the steric crowding in the trialkylborane, the faster will be its rate of isomerization and the better would be the boron distribution in favor of the terminal isomer. In our isomerization studies for the preparation of long-chain compounds, we decided to compare the rates of both dicyclohexylboron and bis-2,5-dimethylcyclohexylboron as the migrating boron moieties. Surprisingly, the rates for both the dicyclohexyl and the bis-2,5-dimethylcyclohexyl were nearly the same.

Accordingly, we decided to use dicyclohexylborane as the hydroborating agent since cyclohexene is considerably more economical than 1,4-dimethylcyclohexene. A series of long-chain alcohols ranging from C_{24} to C_{48} were prepared (eq 1).



(1)

Long-chain alkynes, prepared by Eiter's[19] procedure by metalating 1-alkyne, followed by treatment with alkyl halide, gave the corresponding disubstituted alkynes. Hydroboration[20] of the alkyne with dicyclohexylborane, followed by protonolysis, furnished the desired (Z)-alkene. The (Z)-alkene was then treated with dicyclohexylborane in THF for 2 h. THF was then pumped off and the reaction mixture was diluted with diglyme. Then the reaction mixture was heated under reflux (~160 °C) for 48-72 h. Alkaline hydrogen peroxide oxidation provided the desired alcohols in 65-82% yields (Table I).

Table I : Long-chain alcohols *via* thermal isomerization method

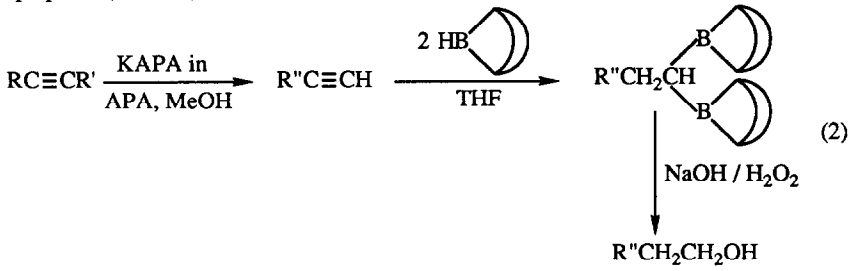
alcohols	no. of carbon atoms	yield[a], %	mp °C
1-Tetracosanol	24	82	74-76[b]
1-Triacontanol	30	78	86-88[b]
1-Hexatriacontanol	36	77	90-92[b]
1-Dotetracontanol	42	70	96-98
1-Octatetracontanol	48	65	102-104

[a]All of the reactions were performed on a 5 mmol scale and the yields are based on the starting long-chain internal alkynes. [b]All of the compounds were crystallized from *n*-hexane and the mp values agree with the literature[21] values.

(B) The KAPA Method

Potassium 3-aminopropylamide (KAPA)[22], a readily prepared difunctional "superbase" , exhibits exceptional activity in prototropic reactions. KAPA is readily formed by the quantitative reaction of potassium hydride with excess 1,3-diaminopropane (APA, trimethylenediamine). KAPA produces exceptionally rapid migrations of the triple bonds from the interior to the terminus of the carbon chain. The reaction is complete in seconds at 0 °C.

We thought of extending this reaction for the preparation of long-chain alcohols and carboxylic acids. Long-chain internal alkynes prepared by Eiter's procedure were treated with KAPA in APA and the terminal alkynes were isolated in good yields. These alkynes were subjected to dihydroboration[23] with two equivalents of 9-BBN. Oxidation of the dihydroborated product in tetrahydrofuran with alkaline hydrogen peroxide provided the corresponding alcohols in 61-80% yields (eq 2). A series of long-chain alcohols ranging from C_{24} to C_{48} were prepared (Table II).



(2)

Table II : Long-chain alcohols *via* the KAPA method

alcohols	no. of carbon atoms	yield[a], %	mp °C
1-Tetracosanol	24	80	74-76[b]
1-Triacontanol	30	76	86-88[b]
1-Hentriacontanol	31	74	84-86[b]
1-Tritriacontanol	33	73	86-88[b]
1-Hexatriacontanol	36	76	90-92[b]
1-Dotetracontanol	42	68	96-98
1-Octatetracontanol	48	61	102-104

[a]All of the reactions were performed on a 5 mmol scale and the yields are based on the starting internal alkynes. [b]All of the compounds were crystallized from *n*-hexane and the mp values agree with the literature[21] values.

The above terminal alkynes were oxidized to long-chain carboxylic acids containing one less carbon atom with potassium permanganate under phase transfer conditions (eq 3). These carboxylic acids acids were obtained in moderate yields (Table III).

$$RC{\equiv}CH \xrightarrow[\text{Adogen, AcOH, } CH_2Cl_2\text{, Reflux, 12h}]{KMnO_4 / H_2O_2} RCOOH \qquad (3)$$

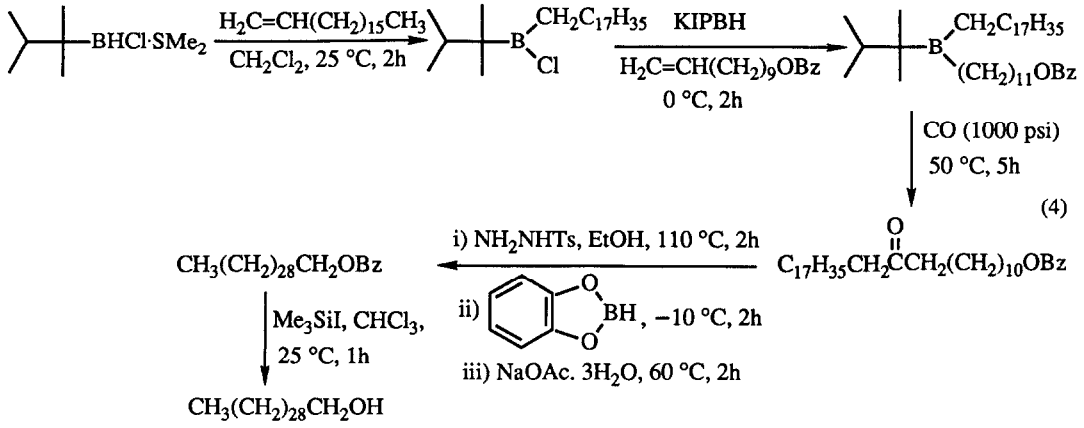
Table III : Long-chain carboxylic acids *via* $KMnO_4$ oxidation of terminal alkynes

alkyne	no. of carbon atoms	carboxylic acid	no. of carbon atoms	yield[a], %	mp°C
1-Triacontyne	30	nonacosanoic acid	29	68	89-90[b]
1-Hentriacontyne	31	triacontanoic acid	30	67	91-93[b]
1-Tritriacontyne	33	dotriacontanoic acid	32	69	92-94[b]
1-Hexatriacontyne	36	pentatriacontanoic acid	35	55	96-98[b]

[a]All of the reactions were performed on a 3 mmol scale and the yields are based on the starting long-chain terminal alkynes. [b]All of the compounds were crystallized from toluene and the mp values agree with literature[21] values.

C) CARBONYLATION METHOD

n-Triacontanol has attracted considerable attention from synthetic chemists because of its promise as a potential plant growth stimulant. However, many of the syntheses reported so far suffer from a long sequence of chemical operations or low overall yields. We devised a novel and highly efficient synthesis of *n*-triacontanol. Hydroboration of 1-octadecene with thexylchloroborane followed by hydridation in the presence of 1-benzyloxy-10-undecene, by potassium triisopropoxyborohydride[24] furnished the corresponding trialkylborane. High pressure carbonylation[25] of the mixed trialkylborane followed by oxidation produced 1-benzyloxy-12-oxotriacontane in excellent yield. Conversion of the ketone into its tosylhydrazone,[26] followed by reduction with catecholborane,[27] gave 1-benzyloxytriacontane, which upon treatment with iodotrimethylsilane[28] afforded 1-triacontanol in 84% overall yield (eq 4).



EXPERIMENTAL

All glassware and syringes were dried in an oven at 150 °C for several hours prior to use and assembled while hot, cooling under a stream of nitrogen. The manipulations involving air-sensitive substances were carried out by standard procedures.[29] The ^{11}B and ^{1}H - NMR were recorded on a multiprobe varian FT-300 spectrometer. Mass spectra were recorded on a Finnegan GC / mass spectrometer.

Materials. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Anhydrous diethyl ether (EE) was purchased from Mallinckrodt, Inc., and used directly. Dodecyne, 10-undecen-1-ol, catecholborane and iodotrimethylsilane were purchased from Aldrich Chemical Company. Thexylchloroborane - methylsulfide and potassium triisopropoxyborohydride were prepared according to the reported procedures.[24b,30]

Preparation of long-chain internal acetylenes

The following procedure for 13-triacontyne is representative. In a 250 mL round-bottom flask fitted with a nitrogen inlet tube and a reflux condenser was placed a solution of the 1-octadecyne (30.1 mL, 100 mmol) in dry diglyme (50 mL). The solution was cooled to 0 °C and treated with *n*-butyllithium (50 mL, 100 mmol) over a period of 15 min. The reaction mixture was stirred at room temperature for 2 h and then at 50 °C for an additional 1 h. 1-Bromododecane(24 mL, 100 mmol) in diglyme (20 mL) was then added and the reaction mixture was stirred at 110 °C for a period of 2 h. The reaction mixture was then diluted with water (200 mL) and extracted with ether (4 x 50 mL). The ether extract was washed with water, brine and dried. Removal of solvent followed by crystallization of the residue from acetone afforded the desired 13-triacontyne in 70% yield (29.2g), mp 38-40 °C. ^{1}H - NMR ($CDCl_3$) : δ 1.1 (bt, 6H), 1.8 (bs, 48H), 2.37 (bt, 4H).

Isomerization of the C_{30} - internal acetylene to C_{30}-terminal acetylene by KAPA

The following procedure for the preparation of 1-triacontyne is representative. In a 100 mL round bottom flask fitted with the usual accessories was placed a dispersion of KH (0.900g dispersion in mineral oil, 22.5 mmol). The dispersion was washed with pentane three times to remove the mineral oil. The flask containing KH was then dried under vacuum. To this was then added 1,3-diaminopropane (2 mL) at 25 °C and the reaction mixture was stirred at room temperature for 30 min.. To this was then added 13-triacontyne (6.27g, 15 mmol) rapidly. The reaction mixture darkened and the precipitate of potassium acetylide was observed. It was then stirred for a period of 0.5 h. The reaction mixture was then quenched by the addition of methanol followed by water. It was then extracted with ether, backwashed with 10% HCl, water, brine and dried. Removal of solvent followed by crystallization of the residue from hexane:acetone afforded the desired 1-triacontyne in 80% yield (5.0g), mp 62-64 °C. ^{1}H - NMR ($CDCl_3$) : δ 1.0 (bt, 3H), 1.71 (bs, 52H), 2.4 (b, 1H).

Hydroboration of terminal alkyne with 9-BBN followed by subsequent alkaline hydrogen peroxide oxidation

The following procedure for the preparation of *n*-triacontanol is representative. In a 100 mL round bottom flask fitted with a stirring bar and a nitrogen inlet was placed 1-triacontyne (2.1g, 5 mmol). To this was then added 9-BBN in THF (10 mL, 1 M solution, 10 mmol). The reaction mixture was stirred overnight (10 h). Oxidation of the reaction mixture with H_2O_2 and NaOH provided the desired *n*-triacontanol. This was purified

by repeated crystallization from hexane to afford the pure *n*-triacontanol in 70% yield (1.53g), mp 86-88 °C. ^1H - NMR ($CDCl_3$) : δ 1.0 (bt, 3H), 1.5 (bs, 56H), 3.8 (bt, 3H).

Conversion of 13-triacontyne to 13-(*Z*)-triacontene

The following procedure for the preparation of 13-(*Z*)-triacontene is representative. In a 100 mL round bottom flask fitted with the usual accessories was placed a solution of borane-methylsulfide (1.53 mL, 15 mmol) in THF (15 mL). The reaction flask was cooled to 0 °C, followed by the dropwise addition of cyclohexene (3 mL, 30 mmol). The precipitate of dicyclohexylborane thus formed was stirred for a further period of 1 h at 0 °C. To this was then added 13-triacontyne (6.27g, 15 mmol) and the reaction mixture was stirred at room temperature for a period of 2 h. Methanol (1.2 mL, 30 mmol) was added and the reaction mixture was heated under reflux for a period of 4 h. The usual work-up, followed by distillation of the residue under reduced pressure, afforded the desired (*Z*)-alkene in 80% yield (1.68g), bp 180-184 °C/0.01mm Hg. ^1H - NMR ($CDCl_3$) : δ 1.0 (bt, 6H), 1.57 (bs, 38H), 2.1 (b, 4H), 5.35 (bt, 2H).

Hydroboration of 13-(*Z*)-triacontene with dicyclohexylborane followed by isomerization and oxidation

The following procedure for the preparation of *n*-triacontanol is representative. Dicyclohexylborane (5 mmol) was prepared using the same procedure as described above. To a solution of dicyclohexylborane (5 mmol) in THF (5 mL) was added 13-(*Z*)-triacontene (2.1g, 5 mmol) and the reaction mixture was stirred at room temperature for a period of 2 h. THF was then pumped off from the reaction mixture and diglyme (5 mL) was added. The reaction mixture was then heated under reflux for a period of 48 h. The flask was then cooled to 0 °C and then subjected to alkaline hydrogen peroxide oxidation to afford the desired alcohol. This was purified by repeated crystallization from hexane to afford the pure *n*-triacontanol in 75% yield (1.6g).

1-Benzyloxy-12-oxotriacontane

To 1-octadecene (5.05g, 20 mmol) was added thexylchloroborane-methylsulfide (10 mL, 2.0 M, 20 mmol) in CH_2Cl_2 at 0 °C in a dropwise manner. After the addition, the reaction mixture was stirred for 2 h at 25 °C. 1-Benzyloxy-10-undecene (5.44g, 20 mmol) was added to the reaction mixture at 0 °C, followed by dropwise addition of triisopropoxyborohydride (16 mL, 1.25 M, 20 mmol) in THF. The reaction mixture was stirred at 0 °C for 2 h and then distilled water (1.0 mL) and THF (30 mL) were added. After centrifuging, the supernatant liquid was separated, transferred into a 0.3 L Parr pressure bomb and subjected to carbonylation at 1000 psi pressure, 50 °C for 5h. The reaction mixture was then oxidized after adding ethanol (20 mL) to it by using NaOH (30 mL, 3 M, 90 mmol) and hydrogen peroxide (30 mL, 30%) at 50 °C for 6 h. After conventional workup using pentane and evaporation of volatiles, a white crystalline solid of 1-benzyloxy-12-oxotriacontane was obtained in 88% yield (9.76g). IR (Nujol) : 1710, 1150, 1070, 750, 690 cm^{-1}. ^1H - NMR ($CDCl_3$) : δ 0.90 (t, 3H), 1.25 (m, 50H), 2.40 (m, 4H), 3.50 (t, 2H), 4.50 (s, 2H), 7.35 (s, 5H). The crude ketone was used as such for the deoxygenation reaction.

1-Triacontanol

To 1-benzyloxy-12-oxotriacontane (8.13g, 15 mmol) in absolute ethanol (3 mL), *p*-toluenesulfonylhydrazide (2.98g, 16 mmol) was added and the reaction mixture refluxed at 110 °C for 4 h. The solution was then cooled to room temperature, at which time a white crystalline hydrazone derivative was obtained. The solvent ethanol was pumped off under vacuum and the solid was dissolved in $CHCl_3$ (10 mL). The solution was cooled to -10 °C and catecholborane (1.80g, 15 mmol) was added. After stirring the reaction mixture at this temperature for 1 h, $NaOAc.3H_2O$ (6.12g, 45 mmol) was added and the solution was refluxed for an additional hour. The reaction mixture was then extracted with ether and the organic layer was washed with aqueous NaOH and aqueous NaOAc. The organic layer was dried over magnesium sulfate. Evaporation of the volatiles then gave a white solid which, upon treatment with iodotrimethylsilane (3.2g, 16 mmol) by the reported procedure, followed by crystallization in hexane, provided a white crystalline solid of 1-triacontanol in 84% overall yield (6.24g).

Preparation of long-chain carboxylic acids

The preparation of nonacosanoic acid from 1-triacontyne is representative. 1-Triacontyne (4 mmol, 1.68g) was dissolved in methylene chloride (12 mL) and a solution of trialkylammonium chloride (Adogen 464, 0.5g) in methylene chloride (12 mL) was added to it. The reaction mixture was added to AcOH (2.5 mL), followed by the addition of a solution of $KMnO_4$ (10 mmol, 1.6g) in water (25 mL). The reaction mixture was stirred under reflux for 12 h and then allowed to come to room temperature. Sodium bisulfite (solid) was added in portion until the mixture became colorless. The solid, nonacosanoic acid, separated out. It was then filtered and crystallized twice from toluene to afford the pure nonacosanoic acid in 68% yield (1.2g), mp 89-90 °C.

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REFERENCES

1. Baumann, H.; Buhler, M.; Fochem, H.; Hirsinger, F.; Zoebelein, H.; Falbe, J. *Angew. Chem. Intl. Ed. Engl.* **1988**, *27*, 41.
2. Mironov, V. A.; Vasil'ev, G. S.; Matrosov, B. S.; Filippova, T. M.; Zamureenko, V. A.; Mishchenko, V.V.; Mairanovkii, V. G.; Kas'yanenko, M. I.; Maksimova, M. M. *Khim. Farm. Zh.* **1983**, *10*, 1242.
3. Mironov, V. A.; Vasil'ev, G. S.; Matrosov, B. S.; Filippova, T. M.; Zamureenko, V. A.; Mishchenko, V.V.; Mairanovkii, V.G.; Fel'dshtein, M.A. *Khim.-Farm.Zh.* **1983**, *11*, 1321.
4. Ries, S. K.; Wert, V.; Sweeley, C. C.; Liavitt, R. A. *Science* **1977**, *195*, 1339.
5. Mori. M. *J. Insect. Physiol.* **1982**, *28(11)*, 969.
6. Katahira, R.; Yamasita, H. *New Food Ind.* **1984**, *26(3)*, 16.
7. Jones, R. G. *J. Am. Chem. Soc.* **1947**, *69*, 2350.
8. Wymberg, H.; Logothetis, A. *J. Am. Chem. Soc.* **1956**, *78*, 1958.
9. Miller, K. E.; Hymaker, C.; Gilman, H. *J. Org. Chem.* **1959**, *24*, 622.

10. Singh, S. K.; Murthy, P. S.; Joshi, G. C. *Tetrahedron Lett.* **1992**, 2419.
11. Malte, V. M.; Tilak, B. D. *Indian J. Chem.* **1969**, *7B*, 1175.
12. Bhalerao, U. T.; Rao, S. J.; Tilak, B. D. *Tetrahedron Lett.* **1984**, 5439.
13. Rao, S. J.; Bhalerao, U. T.; Tilak, B. D. *Indian J. Chem.* **1987**, *26B*, 1987.
14. Iyer, R. R.; Mamdapur, V. R. *Indian J. Chem.* **1986**, *25B*, 1216.
15. Iyer, R. R.; Mamdapur, V. R. *Chem. Ind (London)* **1986**, 398.
16. Maruyama, K.; Terada, K.; Yamamoto, Y. *J. Org. Chem.* **1980**, *45*, 737.
17. Dhillon, R. S.; Singh, J.; Gautam, V. K. *Indian J. Chem.* **1988**, *27B*, 689.
18. (a) Brown, H. C.; Racherla, U. S.; Taniguchi, H. *J. Org. Chem.* **1981**, *46*, 4313. (b) Brown, H. C.; Racherla, U. S. *Organometallics* **1982**, *1*, 765. (c) Racherla, U. S.; Pai, G. G. *Heterocycles* **1982**, *18*, 285. (d) Brown, H. C.; Racherla, U. S. *J. Organometallic Chemistry* **1983**, 241. (e) Brown, H. C.; Racherla, U. S. *J. Org. Chem.* **1983**, *48*, 1389. (f) Brown, H. C.; Racherla, U. S. *J. Am. Chem. Soc.* **1983**, *105*, 6506.
19. Eiter, K. *Naturwissenshaften* **1972**, *59*, 468.
20. Molander, G. A.; Brown, H. C. *J. Org. Chem.* **1986**, *51*,4512.
21. (a) Watanabe, A. *Bull. Chem. Soc. Jpn.* **1960**, *33*, 531. (b) *Idem., ibid* **1961**, *34*, 398. (c) Shiina, S. *J. Soc. Chem. Ind. Jap* (*Kogyo Kwagaku Zassi*) **1936**, *39*, 345. (d) Robinson, G. M. *J. Chem. Soc.* **1934**, 1543.
22. Brown, C. A.; Yamashita, A. *J. Am. Chem. Soc.* **1975**, *97*, 891.
23. Brown, H. C.; Scouten, C. G.; Liotta, R. *J. Am. Chem. Soc.* **1979**, *101*, 96.
24. (a) Brown, C. A. *J. Org. Chem.* **1974**, *39*, 3913. (b) Brown, H. C.; Nazer, B.; Sikorski, J. A. *Organometallics* **1983**, *2*, 634.
25. Brown, H. C.; Negishi, E. *J. Am. Chem. Soc.* **1967**, *89*, 5285.
26. Hutchins, R. O.; Milewski, C. A.; Maryanoff, B. E. *J. Am. Chem. Soc.* **1973**, *95*, 3662.
27. Kabalka, G. W.; Baker, J. D. *J. Org. Chem.* **1975**, *40*, 1834.
28. Jung, M. E.; Lyster, M. A. *J. Org. Chem.* **1977**, *42*, 3761.
29. Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Syntheses via Boranes*; Wiley-Interscience : New York **1975**.
30. Brown, H. C.; Sikorski, J. A.; Kulkarni, S. U.; Lee, H. D. *J. Org. Chem.* **1982**, *47*, 863.