have observed that lactonization of the all-trans **15** is much faster than that of its C-1 epimer **14**. The melting point[12] (258 °C) and infrared spectrum[10] of **16** established its identity and the ^1H NMR spectrum at 360 MHz was identical with one previously described.[12]

The process described above is adaptable to the synthesis of (±)-deoxypodophyllotoxin deuterated (or tritiated) specifically at C-3, -3a, -5, and/or -2'(-6') as desired. 2-Deuteriopiperonal and 2(6)-deuteriotrimethoxybenzaldehyde are readily available by our acetal deprotonation procedure.[13] Such labeled analogues might be useful in metabolic studies.

The instability of podophyllic acid[14] is probably a major factor in the failure of our efforts to lactonize methyl epipodophyllate in satisfactory yield. Modifications of the synthesis designed to overcome this problem are currently being explored and will be reported later.[15]

(12) Ziegler, F. E.; Schwartz, J. A. *J. Org. Chem.* **1978**, *43*, 985. Brown, E.; Robin, J.-P.; Dhal, R. *J. Chem. Soc. Chem. Commun.* **1976**, 556. Decoupling experiments permitted the following additional assignments for **16**: 4.05 (d, H-1), 4.52 (q, H-3a equatorial), 3.90 (q, H-3a axial), $J_{1,2}$ = 10, $J_{3a(gem)}$ = 8, $J_{3,3a(ax\text{-}eq)}$ = 6, and $J_{3,3a(diax)}$ = 9 Hz.

(13) Plaumann, H. P.; Keay, B. A.; Rodrigo, R. *Tetrahedron Lett.* **1979**, 4921.

(14) Renz, J.; Kuhn, M.; von Wartburg, A. *Justus Liebigs Ann. Chem.* **1965**, *681*, 207. The hydrolysis of the methyl ester moiety of **13** is unfortunately not a trivial problem. Epimerization at C-2 (base), extensive decomposition (acid), or aromatization (lithium iodide/DMF) were some of the consequences. The "unnecessary" removal of the C-4 hydroxyl group was therefore undertaken to confirm the stereochemical outcome and to gain one of the desired objectives of the synthesis, (±)-deoxypodophyllotoxin.

(15) Support of this work by the Natural Sciences and Engineering Research Council of Canada and Wilfrid Laurier University is gratefully acknowledged.

Russell Rodrigo

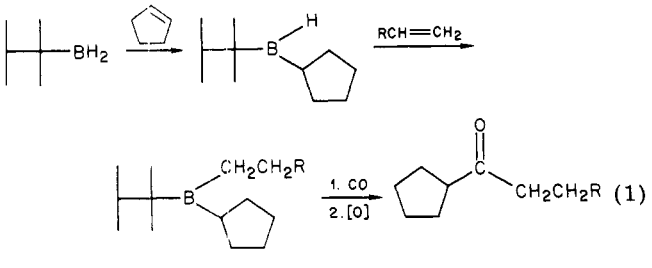
Department of Chemistry
Wilfrid Laurier University
Waterloo, Ontario, Canada

Received July 15, 1980

Thexylchloroborane-Methyl Sulfide. A Selective Monohydroborating Agent with Exceptional Regioselectivity

Summary: Thexylchloroborane, readily prepared from 2,3-dimethyl-2-butene and monochloroborane–methyl sulfide in dichloromethane solution, hydroborates representative alkenes with excellent regioselectivity to afford thexylalkylchloroboranes.

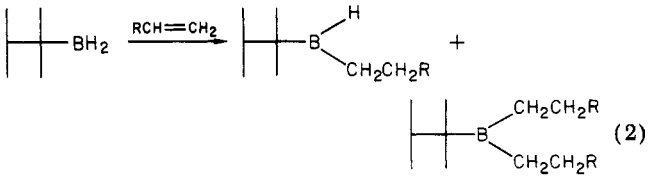
Sir: Thexylborane is an exceptionally valuable reagent which can be used to stitch two olefins together either by carbonylation or by cyanidation to form the corresponding ketone[1] (eq 1).



(1)

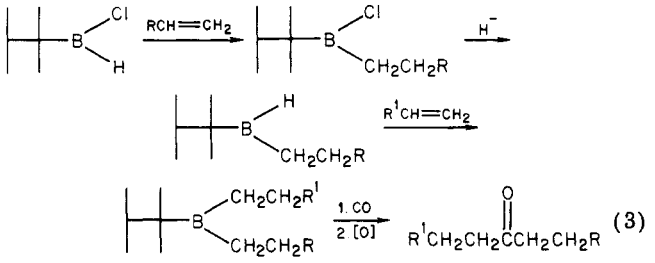
(1) Brown, H. C.; Negishi, E. *J. Am. Chem. Soc.* **1967**, *89*, 5285. Pelter, A.; Smith, K.; Hutchings, M. G.; Rowe, K. *J. Chem. Soc., Perkin Trans. 1*, **1975**, 129. For a review of application of thexylborane, see: Negishi, E.; Brown, H. C. *Synthesis* **1974**, 77.

Unfortunately, the synthesis fails in attempting to stitch together two monosubstituted vinyl derivatives[2] (eq 2). It



(2)

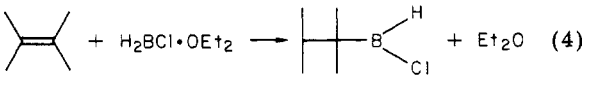
occurred to us that this problem might be solved by the use of thexylchloroborane (ThBHCl) (eq 3). However, we



(3)

encountered a number of difficulties in its synthesis and utilization. The reaction of monochloroborane–THF[3] with 2,3-dimethyl-2-butene in THF proceeds to form thexylchloroborane, stabilized as a THF adduct (ThBHCl·THF). However, the reaction of this derivative with olefins at 0 °C was sluggish and higher temperatures appeared undesirable,[4] both because of the known disproportionation in the hydroboration of olefins with monochloroborane in THF[5] and because of the facile cleavage of THF by chloroborane derivatives, such as boron trichloride[6] and dialkylchloroboranes.[7]

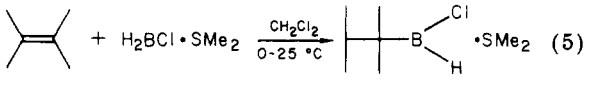
Accordingly, we undertook to synthesize thexylchloroborane in ethyl ether,[4] a solvent much more resistant to boron trichloride and dialkylchloroboranes.[5] In this solvent the initial hydroboration proceeds nicely (eq 4). However,



(4)

the subsequent hydroboration of 1-hexene with this reagent did not proceed cleanly, yielding mixtures of $ThBCl_2$, $ThBR_2$, and ThBRCl. Spectroscopic examination revealed that the reagent corresponds to a rapidly equilibrating mixture of $ThBH_2$, ThBHCl, and $ThBCl_2$.[4]

Accordingly, we shifted to the use of $H_2BCl{\cdot}SMe_2$ as the hydroborating agent.[8] Indeed, this solved the problem. The hydroboration in methylene chloride proceeded smoothly, forming 98% pure $ThBHCl{\cdot}SMe_2$ (eq 5). This



(5)

reagent is remarkably stable at room temperature and hydroborates representative olefins rapidly and cleanly to give pure thexylmonoalkylchloroborane (eq 6).

(2) Katz, J.-J. Ph.D. Thesis, Purdue University, 1974.

(3) (a) Brown, H. C.; Tierney, P. A. *J. Inorg. Nucl. Chem.* **1959**, *9*, 51. (b) Zweifel, G. *J. Organomet. Chem.* **1967**, *9*, 215. (c) Pasto, D. J.; Balasubramaniyan, P. *J. Am. Chem. Soc.* **1967**, *89*, 295.

(4) (a) Sikorski, J. A. M.S. Thesis, Purdue University, 1976. (b) However, by operating at a higher temperature, 25 °C, Zweifel and Pearson have successfully hydroborated olefins in THF with ThBHCl without concurrent attack on the solvent (*J. Am. Chem. Soc.* **1980**, *102*, 5919).

(5) Brown, H. C.; Ravindran, N. *J. Am. Chem. Soc.* **1976**, *98*, 1785.

(6) Garrard, W.; Lappert, M. F. *Chem. Rev.* **1958**, *58*, 1081.

(7) Bhatt, M. V. *J. Organomet. Chem.* **1978**, *156*, 221.

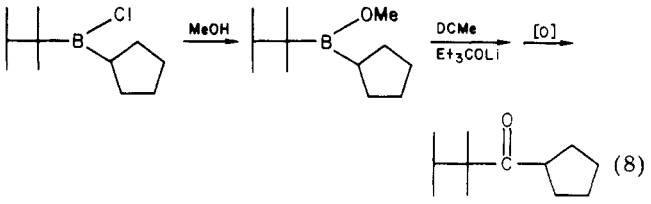
(8) Brown, H. C.; Ravindran, N.; Kulkarni, S. U. *J. Org. Chem.* **1979**, *44*, 2417.

0022-3263/80/1945-4540$01.00/0

Table I. Hydroboration of Representative Alkenes with ThBHCl·SMe_2 in CH_2Cl_2 at 25 °C[a]

alkene	reaction time,[b] h	oxidation products,[c] % ThOH	ROH
1-hexene	1.0	89	100
1-octene	1.0	91	88
cis-2-pentene[d]	2.0		
cyclopentene	2.0	91	89
2-methyl-1-pentene	3.0	94	91
1-methylcyclopentene	5.0	98	89
4-pentenyl acetate[d]	1.5		
styrene	6.0	92	94

[a] Reactants were mixed at 0 °C and then brought to 25 °C. [b] Determined by ^{11}B NMR. [c] Determined by GC, using a suitable internal standard. [d] Oxidation products not analyzed.



(8)

We then examined the regioselectivity of this new reagent. Indeed, it exhibits highly promising characteristics. Hydroboration of 1-hexene proceeds to place 99% of the boron at the terminal position. Hydroboration of

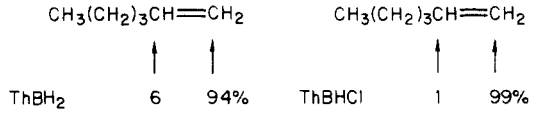
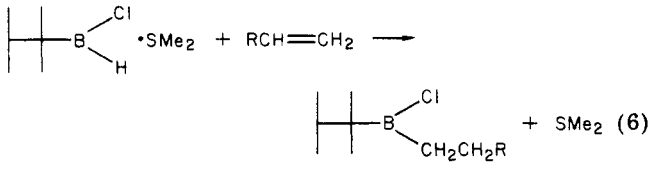


Table II. Directive Effects in the Hydroboration of Representative Alkenes with ThBHCl·SMe_2[a]

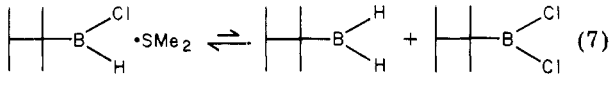
alkene	isomeric alcohols	relative yields,[b] % BH_3·SMe_2[c]	$ThBH_2$[d]	H_2BCl·SMe_2[e]	ThBHCl·SMe_2
1-hexene	1-hexanol	93.6	94	99.2	99
	2-hexanol	6.4	6	0.8	1
2-methyl-1-butene	2-methyl-1-butanol	99[f]		99.9	99
	2-methyl-2-butanol	1		0.1	1
2-methyl-2-butene	3-methyl-2-butanol	98[f]		99.5	99
	2-methyl-2-butanol	2		0.5	1
cis-2-pentene	2-pentanol	55[f]		63[g]	76
	3-pentanol	45		37	24
cis-4-methyl-2-pentene	4-methyl-2-pentanol	57[f]	66	60[h]	97
	2-methyl-3-pentanol	43	34	40	3
styrene	2-phenylethanol	86.3	94	93	>99
	1-phenylethanol	13.7	6	7	<1

[a] Hydroboration by standard procedure followed by oxidation with alkaline H_2O_2 and GC analysis on 14 ft × 1/8 in. column packed with 5% Carbowax 20M on Varaport-30. [b] Total yields 90 ± 5%. [c] Reference 13. [d] Reference 14. [e] Reference 8. [f] Values for BH_3·THF taken from ref 12. [g] Values for H_2BBr·SMe_2 from ref 8. [h] Values for H_2BCl·OEt_2 taken from ref 5.



(6)

Evidently the difference in the results between those realized in ethyl ether solution and in the present experiments is the result of the formation of a relatively stable dimethyl sulfide adduct which does not undergo significant equilibration[9] (eq 7). The greater reactivity of this adduct

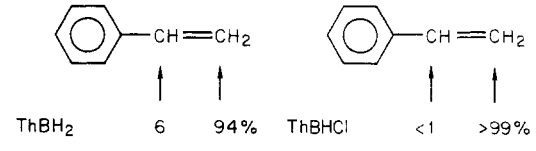


(7)

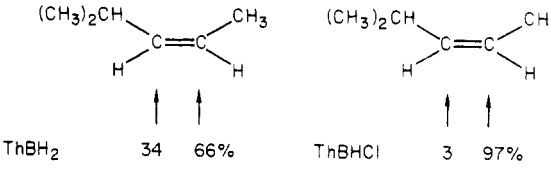
over that realized in THF must be attributed both to weaker bonding and to lower concentration of the donor species.

Oxidation of ThBRCl with alkaline hydrogen peroxide affords the corresponding alcohols (ROH) along with 2,3-dimethyl-2-butanol (Table I). A further proof for the formation of reasonably pure ThBRCl is provided by examination of the product produced after the usual replacement of boron by carbon[10] (eq 8) in the borane formed by reaction of the reagent with cyclopentene. Isomerically free thexylcyclopentyl ketone was formed in a yield of 82% (GC).[11]

styrene also exhibits much higher regioselectivity than borane[12,13] or thexylborane.[14] Finally, *cis*-4-methyl-2-



pentene yields 97% attachment of the boron to the less hindered carbon of the double bond. Data for a com-



parison of the more powerful directive effects of ThBHCl·SMe_2 with those of BH_3·SMe_2,[13] $ThBH_2$,[14] and H_2BCl·SMe_2[8] are summarized in Table II.

A stock solution of ThBHCl·SMe_2 was prepared by adding 330 mmol (10% excess) of 2,3-dimethyl-2-butene to a mixture of 300 mmol of H_2BCl·SMe_2 and 60 mmol of SMe_2 in 72 mL of CH_2Cl_2 at 0 °C. After the complete addition, the mixture was stirred for 1.5 h at 25 °C, when ^{11}B NMR indicated a single resonance at δ 7.5 (d, J_{BH} =

(9) However, in the slow hydroboration of styrene and 1-methylcyclopentene, the formation of up to 10% $ThBCl_2$·SMe_2 is detected by ^{11}B NMR.

(10) Carlson, B. A.; Brown, H. C. *J. Am. Chem. Soc.* **1973**, *95*, 6876.

(11) In the DCME reaction involving secondary alkyl groups, up to 29% internal olefins can be produced with the ketone (ref 10). In the present case, a volatile impurity, ~8%, probably such an olefin, was also formed.

(12) Brown, H. C.; Zweifel, G. *J. Am. Chem. Soc.* **1960**, *82*, 4708.

(13) Lane, C. F. *J. Org. Chem.* **1974**, *39*, 1437.

(14) Zweifel, G.; Brown, H. C. *J. Am. Chem. Soc.* **1963**, *85*, 2066.

128 Hz). The IR spectrum exhibited a strong absorption at 2450 cm^{-1}, indicating the presence of nonbridged B–H species.

The following procedure is representative for the hydroboration reaction. To a solution of 1-hexene (20 mmol) in CH_2Cl_2 was added ThBHCl·SMe_2 (20 mmol) at 0 °C and the mixture was stirred for 1 h at 25 °C, when ^{11}B NMR showed a single resonance at δ 80, as expected for a dialkylchloroborane. Some hindered and less reactive alkenes require somewhat longer reaction times (Table I).

In conclusion, thexylchloroborane–methyl sulfide, conveniently prepared from the readily available monochloroborane–methyl sulfide, is a new reagent with exceptionally high regioselectivity. The thexylalkylchloroboranes, produced in such hydroborations, are valuable new intermediates which make possible an exceptionally general synthesis of ketones.[15]

Registry No. 1-Hexene, 592-41-6; 1-octene, 111-66-0; *cis*-2-pentene, 627-20-3; cyclopentene, 142-29-0; 2-methyl-1-pentene, 763-29-1; 1-methylcyclopentene, 693-89-0; 4-pentenyl acetate, 1576-85-8; styrene, 100-42-5; 2,3-dimethyl-2-butanol, 594-60-5; 2-methyl-1-butene, 563-46-2; 2-methyl-2-butene, 513-35-9; *cis*-4-methyl-2-pentene, 691-38-3; 1-hexanol, 111-27-3; 2-hexanol, 626-93-7; 2-methyl-1-butanol, 137-32-6; 2-methyl-2-butanol, 75-85-4; 3-methyl-2-butanol, 598-75-4; 2-pentanol, 6032-29-7; 3-pentanol, 584-02-1; 4-methyl-2-pentanol, 108-11-2; 2-methyl-3-pentanol, 565-67-3; 2-phenylethanol, 60-12-8; 1-phenylethanol, 98-85-1; 2,3-dimethyl-2-butene, 563-79-1; H_2BCl·SMe_2, 63348-81-2; ThBHCl·SMe_2, 75067-06-0.

(15) Kulkarni, S. U.; Lee, H. D.; Brown, H. C. *J. Org. Chem.*, following paper in this issue.
(16) Graduate research assistant on Grant GP 41169X from the National Science Foundation.
(17) Postdoctoral research associate, Purdue University.
(18) Postdoctoral research associate on a grant from Albany International Chemicals Division.

Herbert C. Brown,* James A. Sikorski[16]
Surendra U. Kulkarni,[17] Hsiupu D. Lee[18]

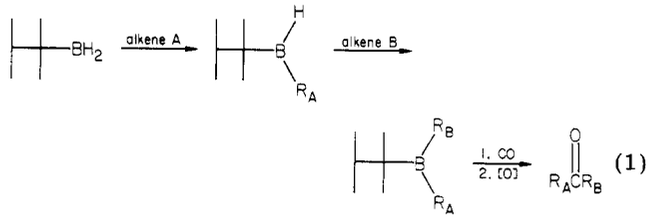
Richard B. Wetherill Laboratory
Purdue University
West Lafayette, Indiana 47907

Received June 27, 1980

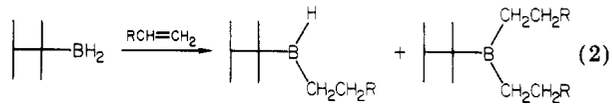
A General Synthesis of Ketones from Alkenes via Stepwise Hydroboration with Thexylchloroborane

Summary: Thexylalkylchloroboranes, reduced in the presence of a second alkene, produced mixed thexyldialkylboranes in high purity. These derivatives are readily transformed into the corresponding ketones by carbonylation or cyanidation, providing for the first time a general conversion of two different olefins into the corresponding ketone.

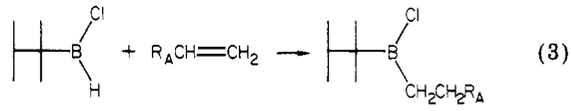
Sir: Thexylborane provides an elegant route for the conversion of two olefins into the corresponding ketone[1] (eq 1). Unfortunately, the reaction is not general. R_A must be an olefin with significant steric hindrance, one that is capable of reacting with thexylborane to give the thexylmonoalkylborane derivative.[2] Simple terminal olefins,



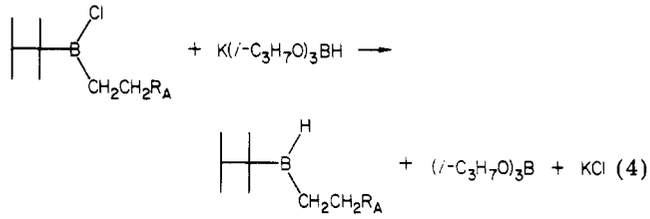
such as $RCH{=}CH_2$, cannot be utilized[2] (eq 2). This



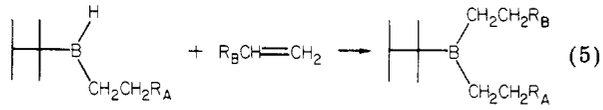
limitation can now be circumvented by applying the new reagent, thexylchloroborane–methyl sulfide.[3] This reagent reacts cleanly with essentially all common structural types of olefins, including simple terminal alkenes (eq 3). The



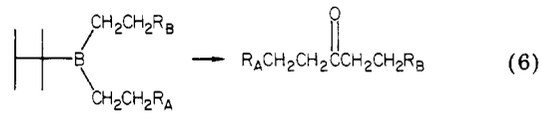
product, thexylalkylchloroborane, is readily reduced by the reagent potassium triisopropoxyborohydride (KIPBH)[4-6] (eq 4). The resulting thexylalkylborane readily hydro-



borates a second mole of olefin (eq 5). Carbonylation[1] or



cyanidation[7] then provides the desired ketone (eq 6).



Although we have emphasized the application of this new synthetic route to the conversion of two terminal olefins into the corresponding ketone (eq 3–6), it should be noted that the synthesis appears to be general, with no limitation now known as to the nature of the two olefins which can be introduced or the order in which they need be introduced. (This contrasts with the earlier, less general synthesis where it was necessary to use a more hindered olefin for the first step (eq 1).[1])

Fortunately, KIPBH is a very gentle reducing agent, one which tolerates many functional groups.[6] Consequently, it is possible to apply this synthesis to alkenes containing many different substituents.

In order to minimize the anticipated redistribution re-

(1) Brown, H. C.; Negishi, E. *J. Am. Chem. Soc.* **1967**, *89*, 5285.
(2) Brown, H. C.; Negishi, E.; Katz, J.-J. *J. Am. Chem. Soc.* **1975**, *97*, 2791.
(3) Brown, H. C.; Sikorski, J. A.; Kulkarni, S. U.; Lee, H. D. *J. Org. Chem.*, preceding paper in this issue.
(4) Brown, C. A. *J. Am. Chem. Soc.* **1973**, *95*, 4100.
(5) KIPBH is available as a 1.0 M solution in THF from the Aldrich Chemical Co.
(6) Brown, C. A.; Krishnamurthy, S.; Kim, S. C. *J. Chem. Soc., Chem. Commun.* **1973**, 391.
(7) Pelter, A.; Smith, K.; Hutchings, M. G.; Rowe, K. *J. Chem. Soc., Perkin Trans. 1* **1975**, 129.

0022-3263/80/1945-4542$01.00/0