Organoboron Compounds in Organic Synthesis. 1. Asymmetric Hydroboration†

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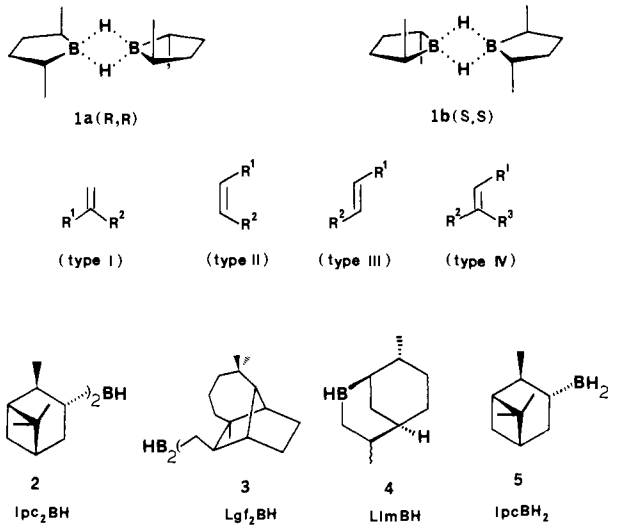
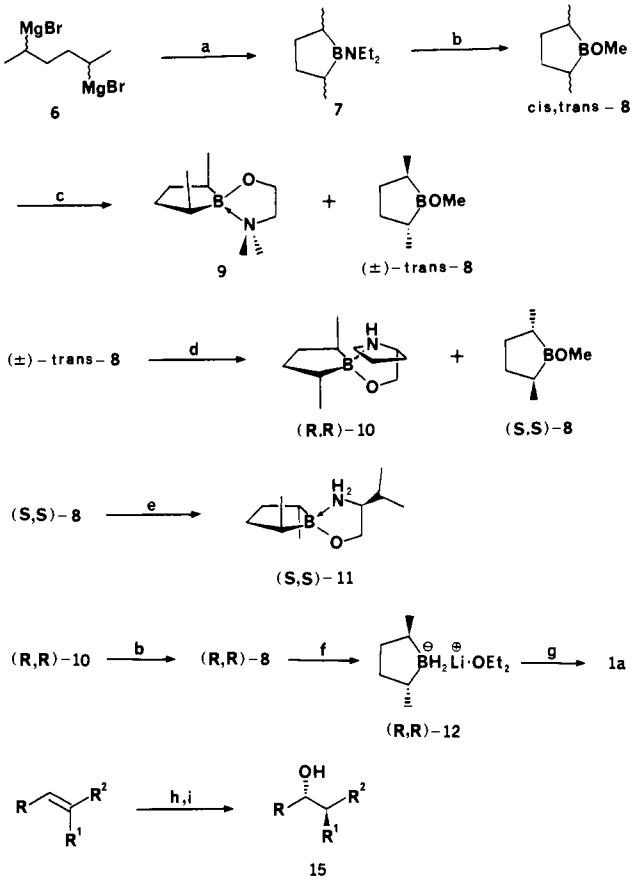
One of the most fundamental processes encountered in natural product synthesis is the stereoselective construction of a new chiral center or centers on a chiral substrate. By adoption of the strategy based on the rule of double-asymmetric synthesis, this process can be executed in a predictable and controlled manner with a homochiral reagent that is capable of achieving a (single) asymmetric induction of 98% ee or higher.[1] Our continuing efforts to develop this strategy have thus far covered the aldol reaction,[2] the Diels–Alder reaction,[3] and the epoxidation of allylic alcohols[4] and are now focused on hydroboration.[5] The enantiomeric pair of borane reagents[6] we disclose herein have the simple, aesthetically pleasing structures **1a** and **1b** of C_2 symmetry and meet the requirement of 98% ee in reactions with all types of representative achiral alkenes except for type I shown below. The borolanes



1a,b are superior to the existing chiral boranes such as **2**–**5**[7] in terms of chiral induction (Table I), and thus the *diastereoselective* synthesis of numerous *homochiral* compounds is, in principle, possible through double-asymmetric synthesis.[8] Most importantly, **1a,b** provide valuable information as to the transition-state geometry of the reaction, as its course is readily analyzed with the conformationally fixed chiral reagents (cf., **2**, **3**, and **5**).

Scheme I



[a] (a) Cl_2BNEt_2, ether–THF, −78 °C; (b) HCl/ether, MeOH, pentane, 0 °C; (c) $Me_2NCH_2CH_2OH$, pentane, room temperature; (d) (*S*)-prolinol, pentane, 0 °C; (e) (*S*)-valinol, pentane, 0 °C; (f) $LiAlH_4$, MeOH, ether, 0 °C; (g) MeI, ether, room temperature; (h) (*R,R*)-**12**, MeI, ether, room temperature; (i) $HOCH_2CH_2OH$, 2 or 6 N NaOH/MeOH, THF, 30% H_2O_2, 40–50 °C.

Preparation of Stable, Crystalline Precursors (*R,R*-10, *S,S*-11) for 1a,b (scheme I).[9] Reaction of (diethylamino)dichloroborane (Et_2NBCl_2)[10] with the Grignard reagent **6**[11] prepared from 2,5-dibromohexanes[12] yielded (56–61%) a cis and trans mixture of 2,5-dimethylborolanes (**7**) which were converted with ethereal HCl and methanol into the corresponding methoxyl derivatives **8** in 82–86% yield (cis/trans ratio, 47:53).[13] Addition of 0.45 equiv of *N,N*-dimethylethanolamine to **8** in pentane followed by equilibration at room temperature and vacuum transfer of the remaining uncomplexed **8** (fraction A) left the crystalline amine complex **9** of the essentially pure-cis isomer. Repetition of this

† The authors wish to dedicate this communication to Professor Koji Nakanishi on the occasion of his 60th birthday.

(1) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew Chem., Int. Ed. Engl.* **1985**, *24*, 1. The phrase "double-asymmetric synthesis" and the word "homochiral" are defined in this article.

(2) (a) Masamune, S.; Choy, W.; Kerdesky, F. A. J.; Imperiali, B. *J. Am. Chem. Soc.* **1981**, *103*, 1566. (b) Masamune, S.; Hirama, M.; Mori, S.; Ali, Sk. A.; Garvey, D. S. *Ibid.* **1981**, *103*, 1568.

(3) Masamune, S.; Reed, L. A., III; Davis, J. T.; Choy, W. *J. Org. Chem.* **1983**, *48*, 4441.

(4) In corroboration with Professor Sharpless' group. (a) Lee, A. W. M.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Walker, F. J. *J. Am. Chem. Soc.* **1982**, *104*, 3515. (b) Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Reed, L. A., III; Sharpless, K. B.; Walker, F. J. *Science (Washington, D.C.)* **1983**, *220*, 949.

(5) (a) Mikhailov, B. M.; Bubnov, Y. N. "Organoboron Compounds in Organic Synthesis"; OPA: Amsterdam B. V., 1984. (b) Koster, R. In "Methoden der Organische Chemie"; Houben-Weyl, Georg Thieme Verlag: New York, 1983; Vol. 13/3. (c) Brown, H. C. "Organic Synthesis via Boranes"; Wiley: New York, 1975. (d) Brown, H. C. "Boranes in Organic Chemistry"; Cornell University Press: New York, 1972.

(6) All the dialkylboranes described herein almost certainly exist in a dimeric form. However, the nomenclature for monomers is used for simplicity.

(7) For a recent review of asymmetric hydroboration, see: Brown, H. C.; Jadhav, P. K. In "Asymmetric Synthesis"; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2, Chapter 1.

(8) Many dialkylboranes resulting from the reaction of type IV olefins with **5** are highly crystalline and can be recrystallized to "achieve products of essentially 100% optical purity" [(a) Brown H. C.; Singaram, B. *J. Am. Chem. Soc.* **1984**, *106*, 1797; (b) *Chem. Eng. News* **1984**, *62*, 28]. This procedure owes its success to the *efficient resolution technique*. Therefore, **5** is inapplicable in double-asymmetric synthesis or cannot be used with costly olefins (such as those very often encountered in multistep syntheses) without a substantial loss.

(9) Full details of all crucial experiments are described in the supplementary material.

(10) Niedenzu, K.; Dawson, J. W. *J. Am. Chem. Soc.* **1959**, *81*, 3561.

(11) Using a procedure modified from that reported by: McDermott, J. X.; White, J. F.; Whitesides, G. M. *J. Am. Chem. Soc.* **1976**, *98*, 6521.

(12) Kornblum, N.; Eicher, J. H. *J. Am. Chem. Soc.* **1949**, *71*, 2259.

(13) For the manipulation of functional groups on the boron atom, see ref 5b.

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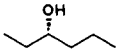
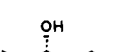
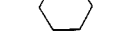
Table I. Asymmetric Hydroboration with Achiral Olefins with **1a**, **2**, **3**, **4**, and **5**

		With 1a of 96.5% or 97.5% ee [a]						% ee of 15 corrected for the enantiomeric purity of each chiral borane used				
entry	olefin	olefin type	reaction time, h, (temp.)	alcohol 15	% yield of 15 [b]	$[\alpha]_D^{21}$ of 15 [c]	% ee of 15 obtained	1a	$(Ipc)_2BH$ (2) (config.) [d]	(Lgf)$_2$BH (3) (config.) [d]	LimBH (4) (config.) [d]	IpcBH$_2$ (5) (config.) [d]
1		I [e]	1		85	+0.25° (c 1.18, $CHCl_3$) [f]	1.4 [g]	1.5 (S)	32 (R) [h]			
2		II [i]	1 36 (4°C) 2		75	−13.3° (c 0.63, CH_3OH) [j]	95.2 [k]	97.6 (S)	99.1 (R)	78 (R)	55.0 (R)	24 (S)
3		III [e]	6.5		83	+8.86° (c 0.93, C_2H_5OH) [l]	96.4 [m]	99.9 (S)	94.1 (R)	71 (R)		
4		II [i]	12 (−20°C) 48 (4°C) 6		71	+13.4° (c 0.71, CH_3OH) [j]	97.0 [k]	99.5 (S)	14 (R) [h]	25 (S)	58.6 (R)	73 (S)
5		III [e]	10		83	+8.83° (c 1.05, C_2H_5OH) [l]	96.0 [m]	99.5 (S)				75 (S)
6		IV [e]	15		90	+5.04° (c 1.13, C_2H_5OH) [n]	94.2 [k]	97.6 (S)	15 (R) [h]	70 (R)	66.5 (R)	53 (S)
7		IV [e]	9.5		89	+46.6° (c 1.13, CH_3OH) [o]	97.0 [m]	100 (S,S)	24 (S,S)	63 (R,R)	45.0 (R,R)	66 (S,S)
8		I [e]	1V		60 (69) [p]	+37.8° (c 1.16, CH_3OH) [q]	93.2 [k]	95.6 (S,S)				77 (S,S)
9		IV [e]	12		97	−10.6 (c 1.36, CCl_4) [r]	95.8 [k]	99.3 (S)		52 (R)		

[a] Reaction in ethyl ether using 1.2 equiv of (*R*,*R*)-**12** and 2.4 equiv of CH_3I at room temperature (21–23 °C) unless otherwise noted. [b] Determined by GC analysis after acetylation [$(CH_3CO)_2O$–C_5H_5N-4-$(CH_3)_2NC_5H_4N$]. [c] All optical rotations were measured at the alcohol stage except entry 9 (acetate). [d] Data from Brown's reports (ref 7 and the following: Brown, H. C.; Ayyangar, N. R.; Zweifel, G. *J. Am. Chem. Soc.* **1964**, *86*, 1071). All numbers are corrected for the optical purity of the starting material. [e] (*R*,*R*)-**12** of 96.5% ee was used for hydroboration. [f] *R* alcohol $[\alpha]^{28}_D$ −2.95° (*c* 60.521, $CHCl_3$): Tsuda, K.; Kishida, Y.; Hayatsu, R. *J. Am. Chem. Soc.* **1960**, *82*, 3396. [g] Based on ^1H NMR of the MTPA ester. [h] (+)-$(Ipc)_2BH$ derived from (−)-α-pinene was used. [i] (*R*,*R*)-**12** of 97.5% ee was used. [j] Commercially available *S* alcohol (81.6% ee HPLC analysis of MTPA ester, Aldrich Chemical Co.) $[\alpha]^{21}_D$ +12.0° (*c* 1.12, CH_3OH). [k] HPLC analysis of the derived MTPA esters: Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543. [l] *S* alcohol $[\alpha]^{20}_D$ +8.0 (*c* 0.6, C_2H_5OH): Davies, J.; Jones, J. B. *J. Am. Chem. Soc.* **1979**, *101*, 5405. [m] HPLC analysis of the Pirkle's carbamates: Pirkle, W. H.; Hoekstra, M. S. *J. Org. Chem.* **1974**, *39*, 3904. [n] *S* alcohol $[\alpha]^{25}_D$ +5.34° (*c* 5.0, C_2H_5OH): Pickard, R. H.; Kenyon, J. *J. Chem. Soc.* **1913**, *103*, 1923. [o] 1*S*,2*S* alcohol $[\alpha]^{25}_D$ +43.9° (*c* 1.00, CH_3OH): Partridge, J. J.; Chadha, N. K.; Uskokovič, M. R. *J. Am. Chem. Soc.* **1973**, *95*, 532. [p] Yield in parenthesis is based on consumed starting material. [q] 1*S*,2*S* alcohol $[\alpha]^{20}_D$ +42.9° (*c* 1, CH_3OH): Bäckström, R.; Sjöberg, B. *Ark. Kemi* **1967**, *26*, 549. [r] (*S*)-1-Acetoxy-1-cyclohexylethane of 32 ± 6% ee shows $[\alpha]^{25}_D$ −1.6° (*c* 1.1, CCl_4): This (−)-isomer was erroneously recorded as having an *R* configuration (personal communication from Professor Meyers): Meyers, A. I.; Ford, M. E. *J. Org. Chem.* **1976**, *41*, 1735.

procedure to fraction A using 0.08 equiv of the same ethanolamine followed by distillation of the volatile fraction provided an 86% yield of the racemic methoxyborolane (±)-*trans*-**8** which was contaminated with 2% of the cis isomer.[13] This surprisingly clean, high-yield separation is due to the thermodynamic stability of **9** relative to that of the corresponding complex derived from the trans isomer.[14] Furthermore, (±)-*trans*-**8** was found to be readily resolvable. Thus, in a manner similar to that described above, complexation of (±)-*trans*-**8** with 0.45 equiv of (*S*)-prolinol led to the predominant formation of the *R*,*R* precursor **10** (*R*,*R* 97%, *S*,*S* 1%, *R*,*S* 2%)[15] and the uncomplexed volatile fraction B. After removal of the remaining, small amount of the *R*,*R* isomer with an additional 0.1 equiv of (*S*)-prolinol, fraction B consisted of essentially pure (*S*,*S*)-**8** which was transformed into its (*S*)-valinol complex (*S*,*S*)-**11** (*S*,*S* 97%, *R*,*R* 1%, *R*,*S* 2%)[15] for the purpose of purification and storage. *This appears to be the first report of the resolution of a racemic borane.* Both (*R*,*R*)-**10** and (*S*,*S*)-**11** which are obtainable in >98% purity upon recrystallization are stable to air and moisture at room temperature for at least 6 months. All steps in the preparation are executable on a practical laboratory scale (0.1–1.0 mol).

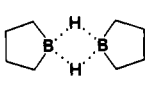
Generation of 1a and 1b and hydroboration (Scheme I).[9] The amine complex (*R*,*R*)-**10** can be directly converted to the borate ethereate (*R*,*R*)-**12** with lithium aluminum hydride or indirectly through (*R*,*R*)-**8**. The latter indirect route offers the advantage that (*R*,*R*)-**12** is obtainable in higher purity and has been used in this work. Thus, the generation of (*R*,*R*)-**8** (see the conversion of **7** to *cis*,*trans*-**8**) followed by reduction with lithium aluminum hydride provided (*R*,*R*)-**12**. In the same manner, valinol complex (*S*,*S*)-**11** was converted to (*S*,*S*)-**12**. These borates **12**'s are crystalline compounds which were dissolved in ether and used to generate in situ a known amount of the chiral borolanes **1a** and **1b** through the reaction with excess iodomethane (2 equiv).[16]

The parent borolane **13** is known to be thermally unstable and to isomerize easily to yield 1,6-diboracyclodecane **14** (which does

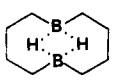
(14) The equilibrium constant [*cis*-**8** complex][*trans*-**8**]/[*cis*-**8**][*trans*-**8** complex] is approximately 100.

(15) The assignment of absolute stereochemistry is based on the oxidation of each complex **9**, **10**, and **11** to the known (*R*,*S*)-, (*R*,*R*)-, and (*S*,*S*)-2,5-hexanediols, respectively; see: Serck-Hannsen, K.; Ställberg-Stenhangen, S.; Stenhangen, E. *Ark. Kemi* **1953**, *5*, 203. The determination of ee's is based on HPLC analysis of the bis-MTPA esters of these diols.

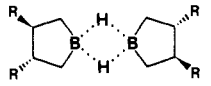
(16) (a) Singaram, B.; Cole, T. E.; Brown, H. C. *Organometallics* **1984**, *3*, 1520. (b) Brown, H. C.; Singaram, B.; Cole, T. E. *J. Am. Chem. Soc.* **1985**, *107*, 460.



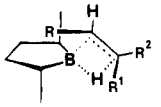
13



14



17



16a R ≠ H
b R = H

not react with olefins).[17] The borolanes **1a,b** were found to undergo the same type of isomerization only slowly (half-life times of several days, 0.5 M solution, 25 °C),[18] and this stability of **1a,b** is extremely gratifying. Thus, a variety of olefins were successfully hydroborated with **1a** and converted to the corresponding alcohols **15** in the usual manner[9] as summarized in Table I. With the exception of a type I olefin or olefins (entry 1) *all* hydroborations proceeded with excellent stereoselection, clearly meeting the criteria set above. The reagent **1a** is sufficiently reactive to hydroborate even type IV olefins as reflected by high yields (entries 6–9) and remedies the deficiencies of some of the known chiral boranes, e.g., **2**.

Brown's recent kinetic studies of hydroboration indicate that in general (mono)boranes rather than diboranes are the reacting species involved in the transition state.[19] Coupled with these kinetic data, the extent and directionality of the observed asymmetric inductions lead to the proposal of a simple transition-state model shown in **16** for the reaction of olefins with **1a**.[20] The distance between an olefinic carbon terminus and the boron atom must be quite short, and the HC=C and RC=C groupings of type II–IV olefins are clearly distinguished and afford a high degree of asymmetric induction (**16a**). The low percent ee observed for the type I olefin is also understandable (**16b**). A set of trans-3,4-disubstituted borolanes **17**, e.g., R = Et, cyclohexyl, have been prepared in optically active form and they exhibit a uniformly marginal degree of asymmetric induction (4–23% ee) with type II–IV olefins. This result is again consistent with the view that the trajectory of the olefins toward the monomer of **17** is approximated by that shown in **16** and the sp^3 hybridization of the boron atom has substantially developed in the transition state.

The major problems associated with hydroboration of type II–IV olefins are now essentially solved (except perhaps for the costliness of the reagent) but those with type I olefins remain. Indeed, highly enantioselective or diastereoselective hydroboration of type I olefins is almost without precedent.[7,21] While work is under way to solve these problems, it should be pointed out that long after the first impressive asymmetric hydroboration was observed in 1961 for bis(isopinocampheyl)borane **2**,[22] a systematic, logical step has now been taken toward the design of chiral boranes.

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Supplementary Material Available: Full details of crucial experiments (12 pages). Ordering information is given on any current masthead page.

Direct Nucleophilic 1,4-Acylation of α,β-Unsaturated Ketones and Aldehydes via Acylcuprate Reagents

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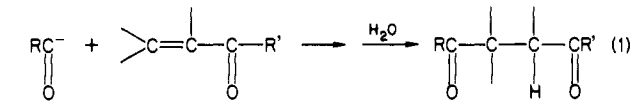
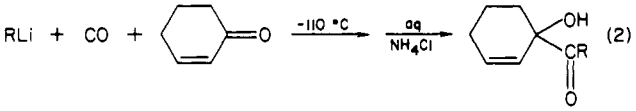
Nucleophilic 1,4-addition of an acyl anion to α,β-unsaturated ketones and aldehydes (eq 1) is a reaction of great potential interest



(1)

to organic chemists. The resulting 1,4-diketones or 1,4-keto aldehydes are useful intermediates in the synthesis of either furan or cyclopentenone systems.[1] In the absence of a useful acyl anion reagent, previous workers have carried out extensive, only partially successful investigations of the applicability of "masked acyl anion equivalents" in 1,4-addition to α,β-unsaturated systems.[2] Noteworthy as a pioneering effort to effect direct nucleophilic acylation of conjugated enones was the reaction of Corey and Hegedus[2e] in which an excess of the 1:1 $RLi/Ni(CO)_4$ reagent was used at −50 °C. Although good yields of 1,4-dicarbonyl products were obtained, this procedure had limited appeal due to the high toxicity of $Ni(CO)_4$.

In recent papers we have described how acyllithium reagents, generated in situ at low (−110 to −135 °C) temperatures by the RLi + CO reaction, may be used to effect direct nucleophilic acylation of diverse organic electrophiles.[3-11] In these reactions, a solution of the organic electrophile was cooled to the appropriate low temperature and saturated with carbon monoxide at atmospheric pressure, and then the organolithium reagent was added very slowly at a constant rate while the CO stream was continued. Such a procedure, when applied to the nucleophilic acylation of cyclohexen-2-one and cyclopenten-2-one, gave only products of 1,2-addition, e.g., eq 2. A similar reaction of the *t*-BuLi/CO



(2)

R = *n*-Bu, 68%
R = *t*-Bu, 80%

(17) (a) Brown, H. C.; Negishi, E. *Tetrahedron* **1977**, *33*, 2331. (b) Brown, H. C.; Negishi, E. *J. Am. Chem. Soc.* **1971**, *93*, 6682.
(18) This dimerization appears to proceed with retention of the stereochemistry at the 2,5-positions of **1a,b**.
(19) (a) Brown, H. C.; Chandrasekharan, J.; Nelson, D. J. *J. Am. Chem. Soc.* **1984**, *106*, 3768. (b) Chandrasekharan, J.; Brown, H. C. *J. Org. Chem.* **1985**, *50*, 518 and references quoted therein.
(20) Cf.: (a) Houk, K. N.; Rondan, N. G.; Wu, Y.-D.; Metz, J. T.; Paddon-Row, M. N. *Tetrahedron* **1984**, *40*, 2257. (b) Paddon-Row, M. N.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 7162.
(21) For exceptions, see: (a) Masamune, S.; Lu, L. D.-L.; Jackson, W. P.; Kaiho, T.; Toyoda, T. *J. Am. Chem. Soc.* **1982**, *104*, 5523. (b) Evans, D. A.; Bartroli, J. *Tetrahedron Lett.* **1982**, *23*, 807.
(22) Brown, H. C.; Zweifel, G. *J. Am. Chem. Soc.* **1961**, *83*, 486.

(1) (a) Ellison, R. A. *Synthesis* **1973**, 397. (b) Ho, T. L. *Syn. Commun.* **1974**, *48* 265. (c) Ellison, R. A. *Tetrahedron Lett.* **1975**, 499.
(2) See the leading reviews of masked acyl anion equivalents for examples and references: (a) Hase, T. A.; Koskimies, J. K. *Aldrichimica Acta* **1981**, *14*, 73; **1982**; *15*, 35. (b) Lever, O. W., Jr. *Tetrahedron* **1976**, *32*, 1943. (c) Albright, J. D. *Tetrahedron* **1983**, *39*, 3207. (d) Gröbel, B.-T.; Seebach, D. *Synthesis* **1977**, 357. (e) Corey, E. J.; Hegedus, L. S. *J. Am. Chem. Soc.* **1969**, *91*, 4926.
(3) Seyferth, D.; Weinstein, R. M.; Wang, W.-L.; Hui, R. C. *Tetrahedron Lett.* **1983**, *24*, 4907.
(4) Seyferth, D.; Weinstein, R. M.; Wang, W.-L. *J. Org. Chem.* **1983**, *48*, 1144.
(5) Weinstein, R. M.; Wang, W.-L.; Seyferth, D. *J. Org. Chem.* **1983**, *48*, 3367.
(6) Seyferth, D.; Hui, R. C. *Tetrahedron Lett.* **1984**, *25*, 5251.
(7) Seyferth, D.; Hui, R. C. *J. Org. Chem.* **1985**, *26*, 1985.
(8) Seyferth, D.; Hui, R. C. *Tetrahedron Lett.* **1984**, *25*, 2623.
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(10) Seyferth, D.; Weinstein, R. M. *J. Am. Chem. Soc.* **1982**, *104*, 5534.
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