+9.6° (c 0.94, EtOH). The ^{1}H NMR spectrum of **19** was identical with that of **17**.

(*R*)-1,2-*O*-Benzylidene-3-*O*-hexadecylglycerol (20). Sodium hydride (0.13 g, in 50% mineral oil, 2.7 mmol) was washed three times with hexane and suspended in dry DMF (10 mL). To this suspension was added a solution of **9b** (0.31 g, 1.7 mmol) in dry DMF (5 mL) over a period of 5 min, and the reaction mixture was stirred at room temperature for 10 min. Hexadecyl mesylate (0.59 g, 1.8 mmol) was then added, and the reaction mixture was stirred at 70 °C for 2.5 h. After cooling, excess NaH was destroyed by careful addition of water (0.5 mL), and the product was extracted with Et_2O. The organic layer was washed with water (7 × 25 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness to give the crude product as an oil. Purification by column chromatography on silica gel, eluting with hexane/EtOAc (9:1, v/v), furnished **20** (0.49 g, 72%): mp 42–45 °C; ^{1}H NMR ($CDCl_3$) δ 0.83 (t, 3, J = 6 Hz), 1.23 (br s, 28), 3.35–3.65 (m, 4), 3.66–4.5 (m, 3), 5.75 and 5.86 (s, 1), 7.15–7.6 (m, 5). Anal. Calcd for $C_{26}H_{44}O_3$: C, 77.18; H, 10.96. Found: C, 77.03; H, 11.03.

(*R*)-1-*O*-Benzyl-3-*O*-hexadecylglycerol (21). Method A. This compound was prepared from **24b** via the same procedure used to obtain compound **11** by method A, in 77% yield: mp 36–38 °C; $[\alpha]_D$ −0.84° (c 1.91, EtOH); ^{1}H NMR ($CDCl_3$) δ 0.83 (t, 3, J = 6 Hz), 1.23 (s, 28), 2.76 (d, 1, J = 4.5 Hz, D_2O exchangeable), 3.3–3.67 (m, 6), 3.8–4.1 (m, 1), 4.5 (s, 2), 7.26 (s, 5). Anal. Calcd for $C_{26}H_{46}O_3$: C, 76.80; H, 11.40. Found: C, 77.02; H, 11.12.

Method B: LAH/$AlCl_3$. To a stirred solution of compound **20** (0.25 g, 0.6 mmol) in Et_2O:CH_2Cl_2 (10 mL, 1:1) was added LAH (0.12 g, 3.2 mmol), and the mixture was heated to boiling. To this solution $AlCl_3$ (0.34 g, 2.5 mmol) in Et_2O (5 mL) was slowly added over a period of 15 min. Refluxing was continued for 2 h. After cooling, excess LAH was decomposed by the addition of EtOAc (4 mL) followed by water (5 mL). Alumina was filtered off, and the ether solution was washed with water (3 × 5 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness to give the crude product 0.23 g. Filtration on silica gel with $CHCl_3$ provided **21** (0.22 g, 84%).

(*R*)-1,2-*O*-Isopropylidene-3-*O*-hexadecylglycerol (22b). This compound was prepared from **9a** via the same procedure used to obtain **20** from **9b**, in 89% yield as an oil: $[\alpha]_D$ −7.34° (c 3.89, EtOH); ^{1}H NMR ($CDCl_3$) δ 0.86 (t, 3, J = 6 Hz), 1.23 (s, 28), 1.3 (s, 3), 1.4 (s, 3), 3.35–4.35 (m, 7). Anal. Calcd for $C_{22}H_{44}O_3$: C, 74.10; H, 12.44. Found: C, 74.09; H, 12.43.

(*S*)-1-*O*-Hexadecylglycerol (23b). This was obtained from **22b** via the same procedure used to obtain **16** from **10a**, in 74% yield: mp 64 °C (lit.[6b] mp 62.5–63.5 °C); $[\alpha]_D$ +2.83° (c 0.6, $CHCl_3$) [lit.[6b] $[\alpha]_D$ +3.1° (c 1.0, $CHCl_3$)].

(*S*)-1-*O*-Benzylglycidol (24a). This compound was obtained from **23a** via the same procedure used to obtain **17** from **16**, in 72.3% yield: $[\alpha]_D$ +11.8° (neat) [lit.[26] $[\alpha]_D$ +13.9° (neat)].

(*S*)-1-*O*-Hexadecylglycidol (24b). The same procedure for obtaining **17** was applied to **24b**. However this product was obtained by filteration of the crude reaction mixture on a silica gel column with hexane/EtOAc (9:1, v/v) in 72% yield: mp 37 °C; $[\alpha]_D$ +4.96° (c 1.74, EtOH); ^{1}H NMR ($CDCl_3$) δ 0.86 (t, 3, J = 6 Hz), 1.25 (s, 28), 2.53 (dd, 1, J = 2.5 and 5.0 Hz), 2.83 (dd, 1, J = 4.2 and 5.0 Hz), 3.0–3.23 (m, 1), 3.25–3.8 (m, 4). Anal. Calcd for $C_{19}H_{38}O_2$: C, 76.45; H, 12.83. Found: C, 76.68; H, 12.61.

(*S*)-1-*O*-Benzyl-3-*O*-hexadecylglycerol (25). Epoxide **24a** was ring opened with sodium hexadecylate as outlined for obtaining compound **11** from **17** by method A. The product was obtained in 69% yield: mp 36–38 °C; $[\alpha]_D$ +0.95° (c 2.95, EtOH). The ^{1}H NMR spectrum of **25** was identical with that of **21**.

Acknowledgment. This work was partially supported by U.S. Army Contract No. DAMD-86-C-6012 and by a program project grant from NCI to the Roger Williams Cancer Center (No. P01 CA 20892-11). We are thankful to Drs. Leon Goodman and Raymond P. Panzica for helpful suggestions and discussions and to Dr. Michael McGregor for the high-resolution NMR studies. The technical assistance of H. El-Subbsagh is also acknowledged.

Vinylic Organoboranes. 11. A Highly Stereospecific and Regiospecific Synthesis of Trisubstituted Alkenes via Organoboranes

Herbert C. Brown* and Narayan G. Bhat[1]

H. C. Brown and R. B. Wetherill Laboratories of Chemistry, Purdue University, West Lafayette, Indiana 47907

Received May 23, 1988

A highly stereospecific synthesis of trisubstituted alkenes using (*E*)- and (*Z*)-2-(1-substituted-1-alkenyl)-1,3,2-dioxaborinanes is presented. (*E*)-2-(1-Substituted-1-alkenyl)-1,3,2-dioxaborinanes (**1**), as described previously, readily react with organolithium or Grignard reagents in diethyl ether at −78 °C to form the corresponding "ate" complexes. Treatment of these "ate" complexes with iodine in methanol induces the migration of the alkyl group from boron to the adjacent carbon, followed by a base-induced deiodoboronation to afford stereodefined trisubstituted alkenes in good yields (50–82%) and in excellent stereochemical purities (≥97%). Similarly, (*Z*)-2-(1-substituted-1-alkenyl)-1,3,2-dioxaborinanes (**2**), easily obtainable by a previous procedure, react with organolithium or Grignard reagents, followed by treatment with iodine and base, to produce the stereoisomeric trisubstituted alkenes in good yields (65–82%) and in excellent isomeric purities (≥97%). These two procedures provide a convenient route to any of the six possible trisubstituted alkenes, $R^1CH{=}CR^2R^3$.

Introduction

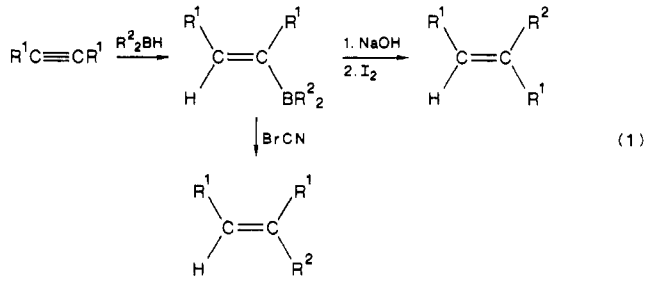
The synthesis of trisubstituted alkenes of defined stereochemistry has attracted considerable attention in recent years because many biologically active compounds occurring in nature possess the structural skeleton of trisubstituted alkenes.[2] Application of organoboranes to the stereospecific synthesis of (*Z*)-disubstituted[3] and

(1) Postdoctoral research associate on National Science Foundation Grant CHE 8706102.

(2) (a) Marfat, A.; McGuirk, P. R.; Helquist, P. J. *J. Org. Chem.* **1979**, *44*, 3888. (b) Obayashi, M.; Utimoto, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1760. (c) Masaki, Y.; Sakuma, K.; Kaji, K. *J. Chem. Soc., Chem. Commun.* **1980**, 434.

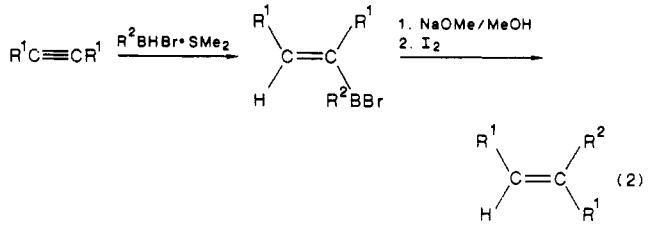
0022-3263/88/1953-6009$01.50/0

(*E*)-disubstituted[4] alkenes are well documented in the literature. An elegant approach to the synthesis of trisubstituted alkenes[3a,5] has been reported by G. Zweifel (eq 1).



(1)

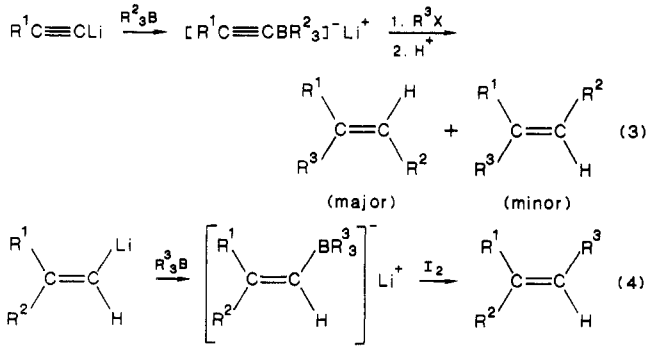
However, these procedures have been severely handicapped by the limited availability of dialkylboranes. Another disadvantage of this procedure is that one of the two alkyl groups (R^2) from the dialkylboranes is not utilized. Such a loss is undesirable when the alkyl group is derived from an expensive or difficultly synthesized alkene. Recently, we have surmounted these difficulties by utilizing haloboranes,[6] particularly, monoalkylbromoboranes,[6b] as hydroborating agents for the stereospecific syntheses of trisubstituted alkenes (eq 2).



(2)

However, a still more serious disadvantage may be pointed out. The procedure requires a symmetrical alkyne for the hydroboration stage (eq 1), providing only trisubstituted olefins with two of the substituents being identical. We wanted a truly general procedure in which three different substituents could be introduced to give any one of the six possible stereoisomers.

Other methods reported for the synthesis of trisubstituted alkenes via organoboranes employ either trialkyl-1-alkynylborates[7] (eq 3) or trialkylvinylborates[8] (eq 4).

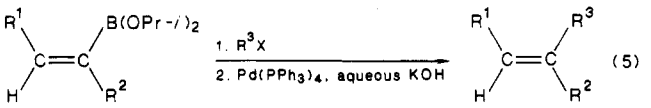


(3)

(major) (minor)

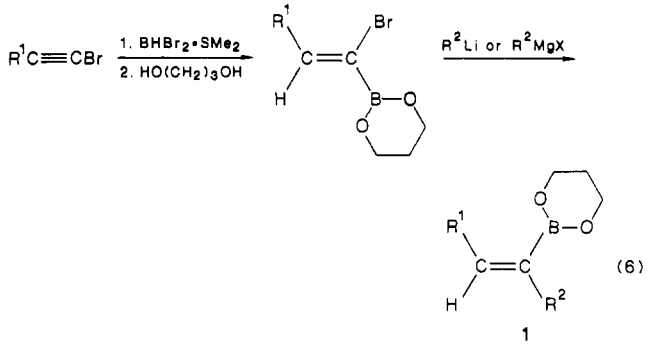
(4)

Recently, A. Suzuki and his co-workers have described an elegant, highly regio- and stereospecific synthesis of trisubstituted alkenes via the palladium-catalyzed cross-coupling reaction of alkenylboronic esters with organic halides[9] (eq 5).



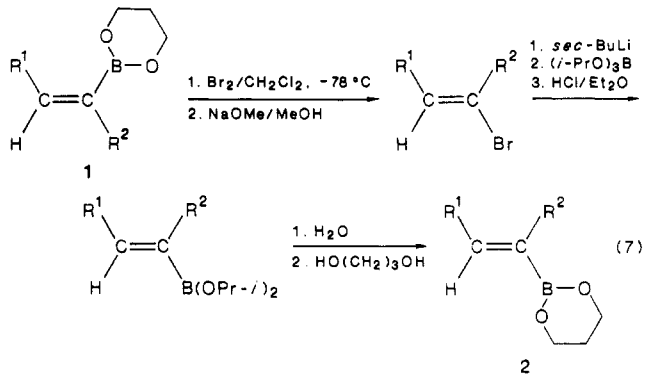
(5)

We have developed simple, convenient procedures for preparing both (*E*)- and (*Z*)-2-(1-substituted-1-alkenyl)-1,3,2-dioxaborinane derivatives,[10] viz., **1** and **2** (eq 6 and 7).



(6)

1



(7)

2

The increasing importance of trisubstituted alkenes as valuable structural units in various natural products makes desirable simple, efficient, and stereospecific methods for the synthesis of such structures. Consequently, we undertook a study to explore the synthesis of trisubstituted alkenes of defined stereochemistry via **1** and **2**, utilizing organolithium or Grignard reagents (eq 8 and 9).

Results and Discussion

The boron intermediates **1** and **2** were prepared as described previously.[10] We selected **1** and **2** for the present study because of the relative stability of the cyclic ester group.[10a] The intermediates **1A–G** were treated with alkyllithiums or Grignard reagents in diethyl ether at −78 °C. In a typical experiment, the boron intermediate, (*E*)-2-(1-butyl-1-hexenyl)-1,3,2-dioxaborinane (**1A**), was

(3) (a) Zweifel, G.; Arzoumanian, H.; Whitney, C. C. *J. Am. Chem. Soc.* **1967**, *89*, 3652. (b) Brown, H. C.; Basavaiah, D.; Kulkarni, S. U.; Bhat, N. G.; Vara Prasad, J. V. N. *J. Org. Chem.* **1988**, *53*, 239.

(4) (a) Zweifel, G.; Arzoumanian, H. *J. Am. Chem. Soc.* **1967**, *89*, 5086. (b) Brown, H. C.; Basavaiah, D.; Kulkarni, S. U.; Lee, H. D.; Negishi, E.; Katz, J.-J. *J. Org. Chem.* **1986**, *51*, 5270.

(5) (a) Zweifel, G.; Fisher, R. P.; Snow, J. T.; Whitney, C. C. *J. Am. Chem. Soc.* **1972**, *94*, 6560. (b) Zweifel, G.; Fisher, R. P. *Synthesis* **1975**, 376.

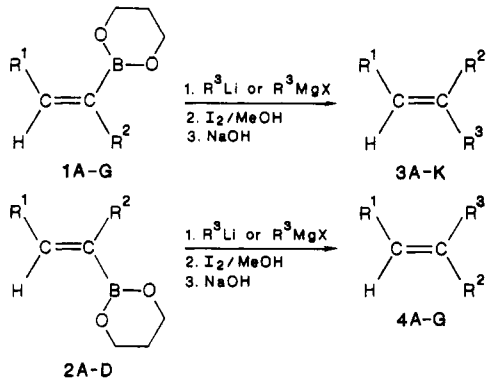
(6) (a) Brown, H. C.; Basavaiah, D.; Kulkarni, S. U. *J. Org. Chem.* **1982**, *47*, 171. (b) Brown, H. C.; Basavaiah, D. *Ibid.* **1982**, *47*, 5407.

(7) (a) Pelter, A.; Bentley, T. W.; Harrison, C. R.; Subrahmanyam, C.; Laub, R. J. *J. Chem. Soc., Perkin Trans 1*, **1976**, 2419. (b) Pelter, A.; Gould, K. J.; Harrison, C. R. *Ibid.* **1976**, 2428. (c) Pelter, A.; Harrison, C. R.; Subrahmanyam, C.; Kirkpatrick, D. *Ibid.* **1976**, 2435. (d) Pelter, A.; Subrahmanyam, C.; Laub, R. J.; Gould, K. J.; Harrison, C. R. *Tetrahedron Lett.* **1975**, 1633.

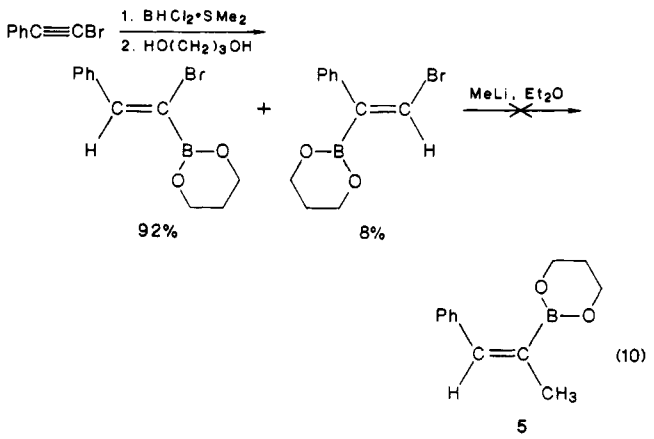
(8) (a) LaLima, N. J.; Jr.; Levy, A. B. *J. Org. Chem.* **1978**, *43*, 1279. (b) Levy, A. B.; Angelastro, R.; Marinelli, E. R. *Synthesis* **1980**, 945.

(9) (a) Satoh, M.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1986**, 1329. (b) Satoh, Y.; Serizawa, H.; Miyaura, N.; Hara, S.; Suzuki, A. *Tetrahedron Lett.* **1988**, *29*, 1811.

(10) (a) Brown, H. C.; Imai, T.; Bhat, N. G. *J. Org. Chem.* **1986**, *51*, 5277. (b) Brown, H. C.; Bhat, N. G. *Tetrahedron Lett.* **1988**, *29*, 21.



treated with phenyllithium at −78 °C in diethyl ether, stirred for 0.5 h at −78 °C, and then brought to 0 °C. After removal of the solvent, the residue was dissolved in methanol at 0 °C. The ^{11}B NMR spectrum showed a broad single peak at δ +5.70, indicative of an "ate" complex. Iodination in methanol at −78 °C, followed by treatment with a base, produced 5-phenyl-(*E*)-5-decene (**3A**) in 80% yield. Better results were also realized when **1A** was treated with 2-lithiothiophene or 2-lithiofuran, followed by iodination and treatment with a base. When **1G** was treated with ethylmagnesium bromide, followed by treatment with iodine, a relatively poor yield (50%) of 1-cyclopentyl-2-ethyl-(*E*)-1-propene (**3K**) was obtained. GC analysis of the reaction product indicated the presence of alkenyl iodides (~30–35%), presumably arising from the electrophilic attack of iodine on the boron-sp^2-carbon bond. Although the great majority of the reactions examined proceeded nicely to the desired products in yields of 50–82%, one significant difficulty was encountered. When methyllithium was used, relatively poor yields of methyl-substituted alkenes resulted. This indicates that the methyl group has a relatively poor migratory aptitude in these reactions. Consequently, we were unsuccessful in our attempts to prepare (*E*)-2-(1-methyl-2-phenylethenyl)-1,3,2-dioxaborinane (**5**) (eq 10).[11] As a result, in



this system only four of the six possible stereoisomers of phenyldialkyl-substituted alkenes could be prepared by the present procedure. However, many other representative trisubstituted alkenes (**4A–K**) were prepared by using this reaction sequence (eq 8). The results are summarized in Table I.

Similarly, treatment of the boron intermediates **2** with an alkyllithium or a Grignard reagent produced "ate" complexes which, upon treatment with iodine in methanol at −78 °C, followed by a base, afforded the corresponding stereoisomeric trisubstituted alkenes (**4A–G**) in good yields. Following the reaction sequence shown in Eq 9, we prepared a representative selection of trisubstituted alkenes. The results are summarized in Table II.

Conclusion

In summation, we have now developed a practical, general procedure for the preparation of trisubstituted olefins containing three different alkyl substituents of defined stereochemistry. With rare exception, the present methodology works very well for arylated and heterocyclic substituted alkenes. The present procedure is also useful for introducing organyl groups not available via hydroboration, and the substitution of the alkyl group proceeds with inversion. The methodology also expands the synthetic utility of the alkenylboronic esters, viz., **1** and **2**, and overcomes the difficulties associated with Zweifel's procedure for preparing trisubstituted olefins.

Experimental Section

General. All of the boiling points are uncorrected. GC analyses were carried out on a Varian 1400 gas chromatograph (column 12 ft × $^1/_8$ in. packed with 10% SE-30 on Chromosorb W AW DMCS). ^1H NMR and ^{11}B NMR spectra were recorded on Varian T-60 and FT-80A spectrometers, respectively.

Materials. The boron compounds **1A–G** and **2A–D** were prepared as described in the literature.[10] All of the organolithium reagents were purchased and titrated with 1,3-diphenyl-2-propanone (*p*-tolylsulfonyl)hydrazone.[12] All of the Grignard reagents were purchased from Aldrich. Ether (Mallinckrodt, anhydrous) and *n*-pentane (Phillips) were further dried over molecular sieves, 4 Å. 1-Alkynes were obtained from Farchan Laboratories. 2-Lithiothiophene and 2-lithiofuran were prepared by the action of *n*-butyllithium on thiophene and furan, respectively, in diethyl ether at 0 °C for 0.5 h. All manipulations of the boron compounds were done under nitrogen by using standard procedures.[13]

The preparation of 5-phenyl-(*E*)-5-decene (3A) is representative. In a dry 100-mL flask equipped with a magnetic stirring bar and septum inlet were placed (*E*)-2-(1-butyl-1-hexenyl)-1,3,2-dioxaborinane (**1A**, 10 mmol, 2.43 mL) and diethyl ether (20 mL). It was then cooled to −78 °C, and phenyllithium in a cyclohexane–diethyl ether mixture (10 mmol, 5 mL) was added dropwise. The reaction mixture was stirred for 0.5 h at −78 °C and at 0 °C for 1 h. The solvents were then pumped off, and methanol (10 mL) was added at 0 °C. Iodine (10 mmol, 2.54 g) in methanol (40 mL) was then added slowly at −78 °C, and the reaction mixture was stirred at −78 °C for 3 h. It was then allowed to come to room temperature, and sodium hydroxide (10 mL of a 3 M solution) was added. After being stirred for 15 min, the reaction mixture was diluted with water (150 mL) and extracted with *n*-pentane (3 × 25 mL). The combined pentane extract was washed with an aqueous 1 M solution of sodium thiosulfate (25 mL) and water (2 × 50 mL) and then dried over anhydrous potassium carbonate. Evaporation of the solvent gave a crude product, which was purified by distillation to afford 5-phenyl-(*E*)-5-decene (**3A**, 1.73 g, 80%): bp 75–77 °C/0.01 mm; n^{20}_D 1.5082; GC analysis showed >99% stereochemical purity; IR (neat) ν 1598, 850, 760, and 696 cm^{-1}; ^1H NMR ($CDCl_3$/TMS) δ 0.73–1.53 (m, 14 H), 2.10–2.53 (m, 4 H), 5.60 (t, J = 6 Hz, 1 H), and 7.03–7.36 (m, 5 H); mass spectrum, m/e (M^+) 216.

(11) Hydroboration of 1-bromo-2-phenylethyne with $Cl_2HB{\cdot}SMe_2$ gives a 92:8 mixture of the regioisomers, shown in eq 10: Bhat, N. G.; Brown, H. C., unpublished results.

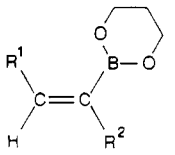
(12) Lipton, M. F.; Sorenson, C. M.; Sadler, A. C.; Shapiro, R. H. *J. Organomet. Chem.* **1980**, *186*, 155.

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

(14) Both *E* and *Z* isomers cleanly separate on a 10% SE-30 column on Chromosorb W (12 ft × $^1/_8$ in.) programmed at 50–250 °C (10 °C/min).

(15) In the case of phenyl-substituted and heterocyclic substituted alkenes, the vinylic proton is more deshielded in the *E* compound (δ 5.53–5.86) than in its *Z* isomer (δ 5.40–5.46).

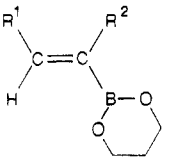
Table I. Stereospecific Synthesis of Trisubstituted Alkenes via



R^1	R^2	R^3Li or R^3MgX	product[a]	yield,[b] %	bp, °C/mm	n^{20}_D
n-C_4H_9	n-C_4H_9	PhLi	5-phenyl-(*E*)-5-decene (**3A**)	80	75–77/0.01	1.5082
n-C_4H_9	n-C_4H_9		5-(2-thiophene-yl)-(*E*)-5-decene (**3B**)	81	76–78/0.01	1.5216
n-C_4H_9	n-C_4H_9		5-(2-furanyl)-(*E*)-5-decene (**3C**)	78	58–60/0.01	1.4892
n-C_4H_9	CH_3	PhLi	2-phenyl-(*E*)-2-heptene (**3D**)	76	50–52/0.01	1.5232
c-C_6H_{11}	CH_3	PhLi	1-cyclohexyl-2-phenyl-(*E*)-1-propene (**3E**)	74	74–76/0.01	1.5438
$(CH_2)_3Cl$	CH_3	PhLi	2-phenyl-6-chloro-(*E*)-2-hexene (**3F**)	76	72–74/0.01	1.5497
n-C_6H_{13}	n-C_4H_9	PhLi	5-phenyl-(*E*)-5-dodecene (**3G**)	82	82–84/0.01	1.5056
C_2H_5	CH_3	PhLi	2-phenyl-(*E*)-2-pentene (**3H**)	76	66–68/9.50	1.5395
n-C_6H_{13}	CH_3	PhLi	2-phenyl-(*E*)-2-nonene (**3I**)	79	70–72/0.01	1.5185
n-C_4H_9	n-C_4H_9	$(CH_3)_2CHMgCl$	5-isopropyl-(*E*)-5-decene (**3J**)	64	66–68/1.50	1.4442
c-C_5H_9	CH_3	C_2H_5MgBr	1-cyclopentyl-2-ethyl-(*E*)-1-propene (**3K**)	(50)[c]		

[a] All reactions were carried out on a 10-mmol scale, and the stereochemical purity (≥97%) of the products was determined by GC analysis[14] and ^1H NMR spectral data.[15] [b] Yields are based on the starting boronate esters, viz., **1**. [c] The value in parentheses is the GC yield, with n-hexadecane as an internal standard.

Table II. Stereospecific Synthesis of Trisubstituted Alkenes via



R^1	R^2	R^3Li or R^3MgX	product[a]	yield,[b] %	bp, °C/mm	n^{20}_D
n-C_4H_9	n-C_4H_9		5-(2-furanyl)-(*Z*)-5-decene (**4A**)	80	54–56/0.01	1.4816
n-C_4H_9	n-C_4H_9	PhLi	5-phenyl-(*Z*)-5-decene (**4B**)	82	72–74/0.01	1.4987
n-C_4H_9	n-C_4H_9		5-(2-thiophene-yl)-(*Z*)-5-decene (**4C**)	78	72–74/0.02	1.5130
n-C_6H_{13}	n-C_4H_9	PhLi	5-phenyl-(*Z*)-5-dodecene (**4D**)	77	81–83/0.01	1.4930
n-C_6H_{13}	CH_3	PhLi	2-phenyl-(*Z*)-2-nonene (**4E**)	75	68–70/0.01	1.5039
n-C_4H_9	$CH(CH_3)_2$	PhLi	2-methyl-3-phenyl-(*Z*)-3-octene (**4F**)	78	48–50/0.01	1.4998
n-C_4H_9	n-C_4H_9	$(CH_3)_2CHMgCl$	5-isopropyl-(*Z*)-5-decene (**4G**)[c]	65	70–72/1.70	

[a] All of the reactions were carried out on a 10-mmol scale, and the stereochemical purity (≥97%) was established by GC analysis[14] and ^1H NMR spectral data.[15]. [b] Isolated yields based on the starting boronate esters, viz., **2**. [c] GC analysis on a 10% SE-30 column showed only 85% stereochemical purity.

5-(2-Thiophene-yl)-(*E*)-5-decene (3B): IR (neat) ν 1631, 1578, 817, and 690 cm^{-1}; ^1H NMR ($CDCl_3$/TMS) δ 0.76–1.53 (m, 14 H), 2.00–2.60 (m, 4 H), 5.86 (t, J = 7 Hz, 1 H), and 6.76–7.10 (m, 3 H); mass spectrum, m/e (M^+) 222.

5-(2-Furanyl)-(*E*)-5-decene (3C): IR (neat) ν 1558, 790, and 726 cm^{-1}; ^1H NMR ($CDCl_3$/TMS) δ 0.83–1.56 (m, 14 H), 2.00–2.50 (m, 4 H), 5.83–6.40 (m, 3 H), and 7.23 (unresolved d, 1 H); mass spectrum, m/e (M^+) 206.

2-Phenyl-(*E*)-2-heptene (3D): IR (neat) ν 1641, 1596, 850, 754, and 694 cm^{-1}; ^1H NMR ($CDCl_3$/TMS) δ 0.86–1.50 (m, 7 H), 2.00 (s, 3 H), 2.06–2.26 (m, 2 H), 5.76 (t, J = 6.20 Hz, 1 H), and 7.10–7.36 (m, 5 H); mass spectrum, m/e (M^+) 174.

1-Cyclohexyl-2-phenyl-(*E*)-1-propene (3E): IR (neat) ν 1594, 753, and 693 cm^{-1}; ^1H NMR ($CDCl_3$/TMS) δ 1.06–1.90 (m, 10 H), 2.00 (s, 3 H), 2.30–2.46 (m, 1 H), 5.60 (d, J = 8 Hz, 1 H), and 7.10–7.40 (m, 5 H); mass spectrum, m/e (M^+) 200.

2-Phenyl-6-chloro-(*E*)-2-hexene (3F): IR (neat) ν 1641, 1595, 757, and 698 cm^{-1}; ^1H NMR ($CDCl_3$/TMS) δ 1.60–2.53 (m, 7 H), 3.50 (t, J = 6 Hz, 2 H), 5.66 (t, J = 6 Hz, 1 H), and 7.10–7.43 (m, 5 H); mass spectrum, m/e (M^+) 194, 196.

5-Phenyl-(*E*)-5-dodecene (3G): IR (neat) ν 1594, 760, and 696 cm^{-1}; ^1H NMR ($CDCl_3$/TMS) δ 0.73–1.40 (m, 18 H), 2.00–2.53 (m, 4 H), 5.53 (t, J = 7 Hz, 1 H), and 7.03–7.26 (m, 5 H); mass spectrum, m/e (M^+) 244.

2-Phenyl-(*E*)-2-pentene (3H): IR (neat) ν 1641, 1595, 753, and 693 cm^{-1}; ^1H NMR ($CDCl_3$/TMS) δ 0.75 (t, J = 7 Hz, 3 H), 1.90 (s, 3 H), 2.00–2.33 (m, 2 H), 5.63 (t, J = 6 Hz, 1 H), and 6.96–7.33 (m, 5 H); mass spectrum, m/e (M^+) 134.

2-Phenyl-(*E*)-2-nonene (3I): IR (neat) ν 1594, 753, and 693 cm^{-1}; ^1H NMR ($CDCl_3$/TMS) δ 0.83–1.46 (m, 11 H), 2.00 (s, 3 H),

2.06–2.26 (m, 2 H), 5.76 (t, J = 7 Hz, 1 H), and 7.10–7.36 (m, 5 H); mass spectrum, m/e (M^+) 202.

5-Isopropyl-(*E*)-5-decene (3J): ^{1}H NMR ($CDCl_3$/TMS) δ 0.83–1.40 (m, 20 H), 1.80–2.50 (m, 5 H), and 5.06 (t, J = 6 Hz, 1 H); mass spectrum, m/e (M^+) 182.

The preparation of 5-(2-furanyl)-(*Z*)-5-decene (4A) is representative. In a dry 100-mL flask were placed (*Z*)-2-(1-butyl-1-hexenyl)-1,3,2-dioxaborinane (**2A**, 10 mmol, 2.44 mL) and diethyl ether (20 mL). The flask was cooled to −78 °C, and 2-lithiofuran (prepared by treating 10 mmol of furan with 10 mmol of *n*-butyllithium in diethyl ether (10 mL) at 0 °C for 0.5 h) was added dropwise. The reaction mixture was stirred at −78 °C for 0.5 h and at 0 °C for 1 h. The solvents were then pumped off, and methanol (10 mL) was added at 0 °C. Iodine (10 mmol, 2.54 g) in methanol (40 mL) was added slowly with vigorous stirring at −78 °C. The reaction mixture was stirred at −78 °C for 3 h and then brought to room temperature. Sodium hydroxide (10 mL of a 3 M solution) was added, and the reaction mixture was stirred for 15 min. It was then diluted with water (150 mL) and extracted with *n*-pentane (3 × 25 mL). The combined pentane extract was washed with an aqueous 1 M solution of sodium thiosulfate (25 mL) and water (2 × 25 mL) and then dried over anhydrous magnesium sulfate. Evaporation of the solvent afforded a crude product, which was purified by distillation to provide 5-(2-furanyl)-(*Z*)-5-decene (**4A**, 1.64 g, 80%): bp 54–56 °C/0.01 mm; n^{20}_D 1.4816; GC analysis showed >97% stereochemical purity; IR (neat) ν 1651, 1584, 800, and 730 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS) δ 0.80–1.60 (m, 14 H), 2.16–2.38 (m, 4 H), 5.40 (t, J = 6 Hz, 1 H), 6.13–6.36 (m, 2 H), and 7.30 (unresolved d, 1 H); mass spectrum, m/e (M^+) 206.

5-Phenyl-(*Z*)-5-decene (4B): IR (neat) ν 1598, 1568, 770, and 700 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS) δ 0.70–1.46 (m, 14 H), 1.83–2.36 (m, 4 H), 5.40 (t, J = 6.20 Hz, 1 H), and 7.00–7.23 (m, 5 H); mass spectrum, m/e (M^+) 216.

5-(2-Thiophene-yl)-(*Z*)-5-decene (4C): IR (neat) ν 1644, 1578, 847, and 690 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS) δ 0.70–1.50 (m, 14 H), 2.00–2.40 (m, 4 H), 5.46 (t, J = 7 Hz, 1 H), and 6.80–7.20 (m, 3 H); mass spectrum, m/e (M^+) 222.

5-Phenyl-(*Z*)-5-dodecene (4D): IR (neat) ν 1598, 770, and 700 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS) δ 0.70–1.46 (m, 18 H), 1.83–2.46 (m, 4 H), 5.43 (t, J = Hz, 1 H), and 7.06–7.36 (m, 5 H); mass spectrum, m/e (M^+) 244.

2-Phenyl-(*Z*)-2-nonene (4E): IR (neat) ν 1598, 763, and 700 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS) δ 0.80–1.53 (m, 11 H), 1.83–2.10 (m, 5 H), 5.46 (t, J = Hz, 1 H), and 7.10–7.36 (m, 5 H); mass spectrum, m/E (M^+) 202.

2-Methyl-3-phenyl-(*Z*)-3-octene (4F): IR (neat) ν 1598, 763, and 700 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS) δ 0.83 (distorted t, 3 H), 1.00 (d, J = 6 Hz, 6 H), 1.13–1.53 (m, 4 H), 1.70–2.80 (m, 3 H), 5.40 (t, J = 7 Hz, 1 H), and 6.93–7.36 (m, 5 H); mass spectrum, m/e (M^+) 202.

5-Isopropyl-(*Z*)-5-decene (4G): ^{1}H NMR ($CDCl_3$/TMS) δ 0.86–1.53 (m, 20 H), 1.90–2.56 (m, 5 H), and 5.03 (t, J = 6 Hz, 1 H); mass spectrum, m/e (M^+) 182.

Acknowledgment. We are indebted to the National Science Foundation (Grant CHE 8706102) for support of this work.

Registry No. **1a**, 105763-12-0; **1g**, 117582-75-9; **1** (R^1 = *n*-C_4H_9, R^2 = CH_3), 117582-72-6; **1** (R^1 = *c*-C_6H_{11}, R^2 = CH_3), 105763-14-2; **1** (R^1 = $(CH_2)_3Cl$, R^2 = CH_3), 117582-73-7; **1** (R^1 = *n*-C_6H_{13}, R^2 = C_4H_9), 105763-13-1; **1** (R^1 = C_2H_5, R^2 = CH_3), 117582-74-8; **1** (R^1 = *n*-C_6H_{13}, R^2 = CH_3), 117582-90-8; **2a**, 105763-18-6; **2b**, 117582-76-0; **2c**, 117582-77-1; **2d**, 117605-92-2; **3a**, 66619-22-5; **3b**, 117582-78-2; **3c**, 117582-79-3; **3d**, 83021-58-3; **3e**, 117582-80-6; **3f**, 117582-81-7; **3g**, 117582-82-8; **3h**, 70303-28-5; **3i**, 62135-01-7; **3j**, 117582-83-9; **3k**, 117582-84-0; **4a**, 117582-85-1; **4b**, 110897-35-3; **4c**, 117582-86-2; **4d**, 117582-87-3; **4e**, 62135-02-8; **4f**, 117582-88-4; **4g**, 117582-89-5; PhLi, 591-51-5; $(CH_3)_2CHMgCl$, 1068-55-9; C_2H_5MgBr, 925-90-6; 2-lithiothiophene, 2786-07-4; 2-lithiofuran, 2786-02-9.

Addition of Organocuprates to Acetylenic Di- and Trifluoromethyl Ketones. Regiospecific Synthesis of β,β-Disubstituted Unsaturated Fluoro Ketones

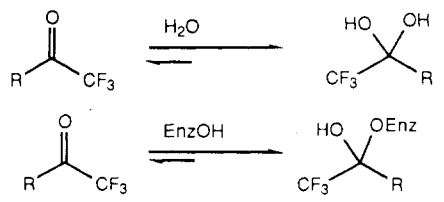
Russell J. Linderman* and Madhu S. Lonikar

Department of Chemistry, North Carolina State University, Raleigh, North Carolina 27695-8204

Received May 6, 1988

A regiospecific synthesis of β,β-disubstituted-α,β-unsaturated di- and trifluoromethyl ketones has been achieved by the conjugate addition of higher order cyano cuprate reagents to acetylenic di- and trifluoromethyl ketones. An efficient and reproducible synthesis of the acetylenic fluoro ketones required was devised by alkylation of lithio acetylides with ethyl di- or trifluoroacetate in the presence of boron trifluoride etherate. Several cuprate reagents were studied for regio- and stereoselectivity in addition reactions with the acetylenic fluoro ketones. Although complete regioselectivity was achieved, the stereochemistry of the reaction was quite variable. The *E* isomers predominated; however, the use of in situ trimethylsilyl chloride reversed the selectivity, producing the *Z* isomers as the major product. Nevertheless, stereochemically pure compounds were isolated by chromatographic separation. Reactions with organocuprate reagents derived from alkyl Grignard reagents were ineffective, producing a mixture of 1,4- and 1,2-addition products as well as the reduced fluoro ketones. Copper(I) iodide mediated Grignard additions provided only the reduction product in good yield.

Over the past several years, organofluorine compounds have gained considerable interest due to the potential to achieve enhanced biological activity for this class of molecules as compared to the nonfluorinated counterpart.[1] In particular, α-fluorocarbonyl compounds have recently been shown to function as transition state analogue inhibitors for a variety of hydrolytic enzymes due to the inherent stability of the hydrate or hemiacetal form.[2] For



(1) (a) *Biomedicinal Aspects of Fluorine Chemistry*; Filler, R., Kobayashi, Y., Eds.; Elsevier: New York, 1982. (b) Filler, R. In *Organofluorine Chemicals and their Industrial Applications*; Banks, R. F., Horwood, E., Eds.; Halstead: New York, 1979. (c) Gerstenberger, M. R. C.; Haas, A. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 647. (d) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123.

0022-3263/88/1953-6013$01.50/0