Carboxylation of 2,2-Difluorovinyllithium: A New General Synthesis of α,β-Unsaturated β-Fluoro-alcohols, -ketones, and -acids

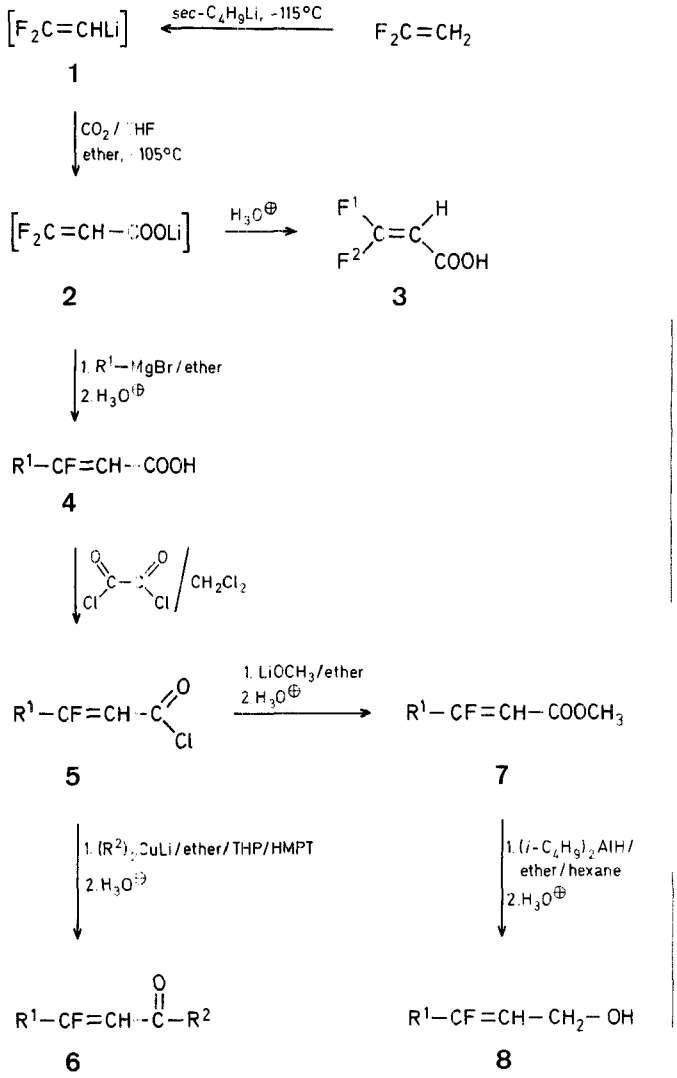
J. P. Gillet, R. Sauvêtre, J. F. Normant*

Laboratoire de Chimie des Organo-Éléments, Université P. et M. Curie, Tour 44, 4, place Jussieu, F-75230 Paris Cédex 05, France

We have recently described a simple preparation of 2,2-difluorovinyllithium **(1)** via metal/hydrogen exchange[1]. We have now extended the scope of this reaction to the preparation of α,β-unsaturated β-fluoro-alcohols, -ketones, and -acids; hitherto, only a few special examples of this class of compounds have been described[2-11].

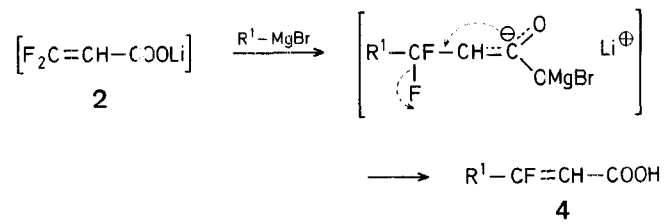
Carboxylation of **1** using carefully dried carbon dioxide in tetrahydrofuran/ether (80/20) at −105 °C affords 3,3-difluoro-

0039-7881/82/0432-0297 $ 03.00

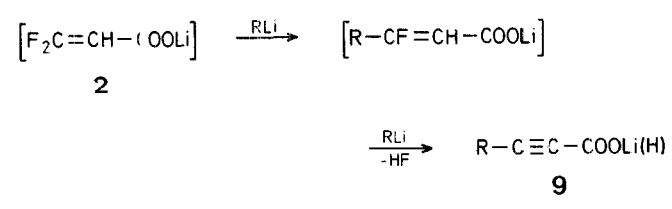


acrylic acid **(3)**. Isolation of **3** is difficult because this compound is easily hydrolyzed to malonic acid at room temperature.

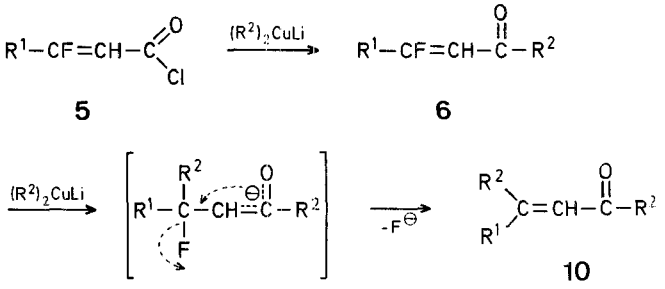
The addition of alkyl- or arylmagnesium halides to lithium 2,2-difluoroacrylate **(2)** proceeds at low temperature; elimination of fluoride anion from the intermediate anion gives the 3-fluoro-2-alkenoic acid **4**.



Organolithium compounds react with **2** in a similar manner; however, they promote elimination of hydrogen fluoride from the lithium 3-fluoro-2-alkenoate to give the corresponding lithium 2-alkynoate **(9)**.

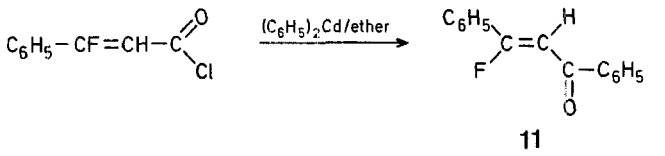


Oxalyl chloride reacts readily with acids **4** in dichloromethane at 20 °C to give the sensitive acid chlorides **5** in high yield and purity. Compounds **5** can be used in further reactions without previous purification. Thus, the reaction of crude **5** with lithium dialkylcuprates at very low temperature (−110 °C for R^1, R^2 = alkyl) in ether/tetrahydropyran/hexamethylphosphoric triamide (60/20/20)[13] affords ketones **6** which to a minor extent undergo a 1,4-addition with further cuprate to give ketone **10** (5%) with elimination of fluoride ion.



If only tetrahydrofuran is used in place of tetrahydropyran and HMPT, a 55% yield of **6** and an 11% yield of **10** is obtained.

The reaction of β-fluorocinnamoyl chloride (**5**, $R^1 = C_6H_5$) with diphenylcadmium in ether at room temperature yields, after distillation, pure (*Z*)-β-fluorochalcone **(11)**.



Methyl 3-fluoro-2-alkenoates **(7)** are prepared by stirring a mixture of acid chlorides **5** and lithium methoxide in ether. 3-Fluoro-2-alkenols **(8)** are conveniently obtained by reduction of esters **7** with diisobutylaluminum hydride; in this reaction, the ester function is selectively reduced; not even traces of the corresponding saturated alcohol can be detected in the reduction product.

In the reactions leading to compounds **4–8**, the (*E*)-isomers are formed predominantly.

Configurations were determined by ^{1}H- and ^{19}F-N.M.R. spectrometry; the greater coupling constant $^3J_{HF}$ was assigned to the (*Z*)-isomers and the smaller coupling constant $^3J_{HF}$ to the (*E*)-isomers.

The purity of the liquid products was determined by G.L.C. analysis (Carbowax 20 M 10%, 3 m) and ^{1}H-N.M.R. spectrometry. The I.R. spectra were recorded on a Perkin-Elmer 157 G apparatus. The ^{1}H- and ^{19}F-N.M.R. spectra were recorded on a JEOL MH 100 instrument and the ^{13}C-N.M.R. spectra on a JEOL FX 60 Q instrument.

All reactions are carried out under dry argon.

3,3-Difluoroacrylic Acid (3):

A stream of carbon dioxide (dried by passing through a column packed with calcium chloride and then through conc. sulfuric acid) is passed over a stirred solution of 2,2-difluorovinyllithium[1] (**1**; 50 mmol) in tetrahydrofuran (120 ml)/ether (30 ml) at −105 °C. The reaction is complete after 10 min. The temperature is then raised to −60 °C for 15 min, the mixture is diluted with 6 normal sulfuric acid (50 ml), extracted with ether (4 × 50 ml), and dried with magnesium sulfate. The solvent is removed on a rotary evaporator to give crude **3**.

Table 1. 3-Fluoro-2-alkenoic Acids (**4**)

R^1	Yield[a] [%]	b.p./torr [°C]	*E/Z* Ratio	Molecular formula[b]	I.R. (neat) ν [cm^{-1}]	^{1}H-N.M.R. (CCl_4/TMS) δ [ppm], *J* [Hz]	^{19}F-N.M.R. (CCl_4/C_6H_5—CF_3) δ [ppm], *J* [Hz]
C_2H_5	60	60–74°/0.1	87/13	$C_5H_7FO_2$ (118.1)	1700 (C=O); 1665 (C=CF)	*E:* 2.8 (d of q, 2H, $^3J_{HH}$=7.5, $^3J_{FH}$=24); 5.45 (d, 1H, $^3J_{FH}$=19) *Z:* 2.3 (d of q, 2H, $^3J_{HH}$=7.5, $^3J_{FH}$=14); 5.1 (d, 1H, $^3J_{FH}$=32)	*E:* −10.2 (d of t, $^3J_{FH}$=19, $^3J_{FH}$=24) *Z:* −11.4 (d of t, $^3J_{FH}$=32, $^3J_{FH}$=14)
n-C_4H_9	70	67–87°/0.05	82/18	$C_7H_{11}FO_2$ (146.2)	1695 (C=O); 1655 (C=CF)	*E:* 2.85 (d of t, 2H, $^3J_{HH}$=7, $^3J_{FH}$=25); 5.6 (d, 1H, $^3J_{FH}$=19) *Z:* 2.35 (d of t, 2H, $^3J_{HH}$=7, $^3J_{FH}$=17); 5.25 (d, 1H, $^3J_{FH}$=32)	*E:* −7.8 (d of t, $^3J_{FH}$=19, $^3J_{FH}$=25) *Z:* −10.8 (d of t, $^3J_{FH}$=32, $^3J_{FH}$=17)
C_6H_5	51	oil	87/13	$C_9H_7FO_2$ (166.1)	1695 (C=O); 1640 (C=CF)	*E:* 5.75 (d, 1H, $^3J_{FH}$=20) *Z:* 5.75 (d, 1H, $^3J_{FH}$=33)	*E:* −13.1 (d, $^3J_{FH}$=20) *Z:* −32.4 (d, $^3J_{FH}$=33)

[a] Yields are based on the starting *sec*-butyllithium[1].
[b] Limits of error of microanalyses: C, ±0.42; H, ±0.20.

Table 2. 3-Fluoro-2-alkenoyl Chlorides (**5**)

R^1	Yield [%]	b.p./torr [°C]	*E/Z* Ratio	Molecular formula[c]	I.R. (neat) ν [cm^{-1}]	^{1}H-N.M.R. (CCl_4/TMS) δ [ppm], *J* [Hz]	^{19}F-N.M.R. (CCl_4/C_6H_5—CF_3) δ [ppm], *J* [Hz]
n-C_4H_9	95[a] 80[b]	55–58°/11	87/13	$C_7H_{10}ClFO$ (164.6)	1765 (C=O); 1635 (C=CF)	*E:* 2.75 (d of t, 2H, $^3J_{HH}$=7.5, $^3J_{FH}$=26); 6.0 (d, 1H, $^3J_{FH}$=16) *Z:* 2.25 (d of t, 2H, $^3J_{HH}$=7.5, $^3J_{FH}$=17); 5.6 (d, 1H, $^3J_{FH}$=30)	*E:* −3.4 (d of t, $^3J_{FH}$=16, $^3J_{FH}$=26) *Z:* −4.7 (d of t, $^3J_{FH}$=30, $^3J_{FH}$=17)
C_6H_5	92[a] 60[b]	59–60°/0.1	85/15	C_9H_6ClFO (184.6)	1765 (C=O); 1620 (C=CF)	*E:* 6.10 (d, 1H, $^3J_{FH}$=18) *Z:* 6.15 (d, 1H, $^3J_{FH}$=30)	*E:* −5.7 (d, $^3J_{FH}$=18) *Z:* −23.8 (d, $^3J_{FH}$=30)

[a] Yields are based on the starting acids **4** without distillation.
[b] Yields after distillation.
[c] Limits of error of microanalyses: C, ±0.43; H, ±0.09; Cl, ±0.38.

Table 3. 2-Fluoro-1-alkenyl Ketones (**6**)

R^1	R^2	Yield[a] [%]	b.p./torr or m.p. [°C]	*E/Z* Ratio	Molecular formula[b]	I.R. (neat) ν [cm^{-1}]	^{1}H-N.M.R. (CCl_4/TMS) δ [ppm], *J* [Hz]	^{19}F-N.M.R. (CCl_4/C_6H_5—CF_3) δ [ppm], *J* [Hz]
n-C_4H_9	C_2H_5	70	b.p. 69–95°/11	73/27	$C_9H_{15}FO$ (158.2)	1705 (C=O); 1675, 1640 (C=CF)	*E,Z:* 2.4 (q, 2H, $^3J_{HH}$=7) *E:* 2.8 (d of t, 2H, $^3J_{HH}$=7, $^3J_{FH}$=26); 5.95 (d, 1H, $^3J_{FH}$=21) *Z:* 2.5 (d of t, 2H, $^3J_{HH}$=7, $^3J_{FH}$=18); 5.30 (d, 1H, $^3J_{FH}$=40)	*E:* −14.4 (d of t, $^3J_{FH}$=21, $^3J_{FH}$=26) *Z:* −19.0 (d of t, $^3J_{FH}$=40, $^3J_{FH}$=18)
C_6H_5	C_6H_5	45[c]	m.p. 59°[c]	[c]	$C_{15}H_{11}FO$ (226.2)	1670 (C=O); 1615 (C=CF)	*Z:* 6.75 (d, 1H, $^3J_{FH}$=35)	*Z:* −34.9 (d, $^3J_{FH}$=35)

[a] Yields are based on the starting acid chlorides **5**.
[b] Limits of error of microanalyses: C, ±0.09; H, ±0.10.
[c] *Z*-Isomer, recrystallized from hexane.

Sublimation into a cold trap under reduced pressure gives crystalline **3**; *yield:* 3.3 g (61%); m.p. 20–21°C; purity (^{1}H-N.M.R.): ~95%.

$C_3H_2F_2O_2$ (108.0) calc. C 33.33 H 1.85 found 33.75 1.88

I.R. (neat): ν = 2500–3100 (—COOH); 1720 (F_2C=CH—); 1680 cm^{-1} (C=O).

^{1}H-N.M.R. (CCl_4/TMS): δ = 5.0 ppm (d of d, 1H, $^3J_{F,H}$ = 2 Hz, $^3J_{F,H}$ = 21 Hz).

Table 4. Methyl 3-Fluoro-2-alkenoates (**7**)

R^1	Yield[a] [%]	b.p./torr [°C]	*E/Z* Ratio	Molecular formula[b]	I.R. (neat) ν [cm^{-1}]	^{1}H-N.M.R. (CCl_4/TMS) δ [ppm], *J* [Hz]	^{19}F-N.M.R. (CCl_4/C_6H_5—CF_3) δ [ppm], *J* [Hz]
n-C_4H_9	77	69–85°/11	90/10	$C_8H_{13}FO_2$ (160.2)	1725 (C=O); 1675 (C=CF)	*E,Z:* 3.70 (s, 3H) *E:* 2.85 (d of t, 2H, $^3J_{HH}$ = 7.5, $^3J_{FH}$ = 26); 5.55 (d, 1H, $^3J_{FH}$ = 20) *Z:* 2.25 (d of t, 2H, $^3J_{HH}$ = 7.5, $^3J_{FH}$ = 16); 5.15 (d, 1H, $^3J_{FH}$ = 33)	*E:* −13.1 (d of t, $^3J_{FH}$ = 20, $^3J_{FH}$ = 26) *Z:* −16.2 (d of t, $^3J_{FH}$ = 33, $^3J_{FH}$ = 16)
C_6H_5	80	63–72°/0.05	87/13	$C_{10}H_9FO_2$ (180.2)	1730 (C=O); 1660 (C=CF)	*E:* 3.5 (s, 3H); 5.70 (d, 1H, $^3J_{FH}$ = 21) *Z:* 3.6 (s, 3H); 5.75 (d, 1H, $^3J_{FH}$ = 33)	*E:* −15.1 (d, $^3J_{FH}$ = 21) *Z:* −33.4 (d, $^3J_{FH}$ = 33)

[a] Yields are based on the starting acids **4**.
[b] Limits of error of microanalyses: C, ±0.37; H, ±0.29.

Table 5. 3-Fluoro-2-alkenols (**8**)

R^1	Yield[a] [%]	b.p./torr [°C]	*E/Z* Ratio	Molecular formula[b]	I.R. (neat) ν [cm^{-1}]	^{1}H-N.M.R. (CCl_4/TMS) δ [ppm], *J* [Hz]	^{19}F-N.M.R. (CCl_4/C_6H_5—CF_3) δ [ppm], *J* [Hz]
n-C_4H_9	70	82–84°/11	90/10	$C_7H_{13}FO$ (132.2)	3330 (OH); 1700 (C=CF)	*E:* 2.30 (d of t, 2H, $^3J_{HH}$ = 7, $^3J_{FH}$ = 23); 4.0 (d, 2H, $^3J_{HH}$ = 8); 5.25 (d of t, 1H, $^3J_{HH}$ = 8, $^3J_{FH}$ = 21)	*E:* −36.4 (d of t, $^3J_{FH}$ = 23, $^3J_{FH}$ = 21) *Z:* −42.5 (d of t, $^3J_{FH}$ = 37, $^3J_{FH}$ = 17)
C_6H_5	80	84°/0.1	87/13	C_9H_9FO (152.2)	3300 (OH); 1680 (C=CF)	*E:* 4.05 (d, 2H, $^3J_{HH}$ = 7.5); 5.45 (d of t, 1H, $^3J_{HH}$ = 7.5, $^3J_{FH}$ = 20) *Z:* 4.25 (d of d, 2H, $^3J_{HH}$ = 8, $^4J_{FH}$ = 2); 5.40 (d of t, 1H, $^3J_{HH}$ = 8, $^3J_{FH}$ = 35)	*E:* −35.0 (d, $^3J_{FH}$ = 20) *Z:* −54.8 (d, $^3J_{FH}$ = 35)

[a] Yields are based on the starting esters **7**.
[b] Limits of error of microanalyses: C, ±0.33; H, ±0.15.

^{19}F-N.M.R. (CCl_4/C_6H_5—CF_3): δ = +2.2 (d of d, $^2J_{F,F}$ = 23 Hz, $^3J_{F,H}$ = 21 Hz); −3.7 ppm (d of d, $^2J_{F,F}$ = 23 Hz, $^3J_{F,H}$ = 2 Hz).

3-Fluoro-2-alkenoic Acids (4); General Procedure:
An ethereal solution of the alkyl- (or aryl-)magnesium bromide (100 mmol) is added dropwise over 30 min to a stirred solution of lithium 3,3-difluoroacrylate (**2**; 50 mmol; prepared as in the preceding procedure and freed from carbon dioxide by bubbling argon through the solution for 60 min at 20°C) at −80°C. The temperature of the mixture is gradually raised to −40°C during 40 min. The resultant solution is hydrolyzed with 6 normal sulfuric acid (50 ml), extracted with ether (3 × 50 ml), and dried with magnesium sulfate. The solvent is removed under reduced pressure. If the corresponding 2-alkynoic acid **9** is present (2–5%), a solution of bromine (1 mmol of bromine per 1 mmol of **9**) in dichloromethane is added to the crude mixture with stirring (*decoloration of the bromine solution*) and the mixture is distilled in vacuo to give the pure acid **4**.

3-Fluoro-2-alkenoyl Chlorides (5); General Procedure:
A solution of oxalyl chloride (40 mmol) in dichloromethane (15 ml) is added over 10 min to a stirred solution of the 3-fluoro-2-alkenoic acid **4** (20 mmol) in dichloromethane (30 ml) at 20°C. The reaction is complete after 2 h. The solvent is removed under reduced pressure and the product **5** used directly in a subsequent reaction. For analytical purposes, the highly hydrolysis-sensitive products **5** may be distilled in vacuo.

2-Fluoro-1-alkenyl Ketones (6); General Procedure:
A solution of the 3-fluoro-2-alkenoyl chloride **5** (25 mmol) in ether (15 ml) is added dropwise at −110°C to a stirred solution of the lithium dialkylcuprate (or diarylcuprate) (25 mmol) in ether/tetrahydropyran/HMPT (60+20+20 ml)[13]. Stirring is continued for 10 min at −110°C, the temperature then allowed to rise to −70°C, and the mixture hydrolyzed with 6 normal sulfuric acid (50 ml). It is then filtered through Hyflosel® and extracted with ether (3 × 50 ml). The organic layer is successively washed with water, saturated sodium hydrogen carbonate solution, 3 normal sodium thiosulfate solution, and water. It is then dried with magnesium sulfate and distilled under reduced pressure to give the ketone **6**.

(*Z*)-1-Fluoro-1,3-diphenyl-3-oxopropene (β-Fluorochalcone, 11):
A solution of 3-fluoro-3-phenylpropenoyl chloride (**5**, $R^1 = C_6H_5$; 50 mmol) in ether (15 ml) is added to a stirred solution of diphenylcadmium (50 mmol) in ether (30 ml)[12] at 20°C. Stirring is continued at 35°C for 1 h, the mixture then hydrolyzed with 6 normal sulfuric acid (50 ml), and extracted with ether (3 × 50 ml). The ether extracts are washed with saturated sodium hydrogen carbonate solution, dried with magnesium sulfate, and distilled under vacuum to give pure **11**.

$C_{15}H_{11}FO$ (226.2)

M.S.: *m/e* = 226 (M^+).

^{13}C-N.M.R. ($CDCl_3$/TMS): δ = 171.3, 159.0 (—CF=, J_{CF} = 278 Hz); 101.7, 101.4 (—CH=, J_{CF} = ? Hz); 188.5 ppm (C=O).

Methyl 3-Fluoro-2-alkenoates (7); General Procedure:
A solution of the 3-fluoro-2-alkenoyl chloride **5** (20 mmol) in ether (10 ml) is added dropwise at 0°C to a stirred solution of lithium methoxide [22 mmol; prepared from methyllithium (22 mmol) and methanol (0.9 ml) in ether (30 ml)]. The mixture is stirred for 1 h at 20°C, then hydrolyzed with 6 normal sulfuric acid (50 ml), and extracted with

ether (3 × 50 ml). The ether extracts are washed with saturated sodium hydrogen carbonate solution (50 ml), dried with magnesium sulfate, and distilled in vacuo to give the pure ester **7**.

3-Fluoro-2-alkenols (8); General Procedure:
A solution of diisobutylaluminum hydride (2 equiv) in hexane is added dropwise at 0 °C to a stirred solution of the methyl 3-fluoro-2-alkenoate **7** (20 mmol) in ether (50 ml). The temperature is then raised to 20 °C, the mixture stirred for 1 h, hydrolyzed with 6 normal sulfuric acid (50 ml), and extracted with ether (3 × 50 ml). The ether extracts are washed with saturated sodium hydrogen carbonate solution (50 ml) and evaporated. Sodium hydrogen carbonate (0.2 g) is added to the residue and the alcohol **8** purified by distillation in vacuo.

This work was supported by the C.N.R.S. We are indebted to Pechiney-Ugine-Kühlmann for a generous gift of 1,1-difluoroethylene.

Received: July 14, 1981
(Revised form: September 21, 1981)

* Address for correspondence.

[1] R. Sauvêtre, J. F. Normant, *Tetrahedron Lett.* **22,** 957 (1981).
[2] A. L. Henne, C. J. Fox, *J. Am. Chem. Soc.* **76,** 479 (1954).
[3] I. L. Knunyants, R. N. Sterlin, V. E. Bogachev, *Izvest. Akad. Nauk SSSR Otdel. Khim. Nauk* **1958,** 425; *C. A.* **52,** 17087 (1958).
[4] A. L. Henne, W. J. Zimmerschied, *J. Am. Chem. Soc.* **69,** 281 (1947).
[5] V. L. Isaev et al., *Zh. Vses. Khim. Ova.* **22,** 711 (1977); *C. A.* **88,** 89304 (1977).
[6] I. L. Knunyants et al., *Tetrahedron* **29,** 595 (1973).
[7] R. A. Bekker et al., *Otkrytia Izobret. Prom. Obraztsy Tovarnye Znaki* **50,** 88 (1973); *C. A.* **79,** 12883 (1973).
[8] V. M. Ismailov et al., *Zh. Vses. Khim. Ova* **19,** 334 (1974); *C. A.* **81,** 63105 (1974).
[9] L. A. Rozov et al., *Izv. Akad. Nauk SSSR Ser. Khim.* **1976,** 2750; *C. A.* **86,** 120902 (1977).
[10] M. Suda, *Tetrahedron Lett.* **21,** 2555 (1980).
[11] M. Suda, *Tetrahedron Lett.* **22,** 1421 (1981).
[12] *Methods of Elemento-organic Chemistry,* Vol. 3, N. I. Sheverdina, K. A. Kocheshkov, North Holland Book Co., Amsterdam, 1967.
[13] A. Alexakis, N. Jabri, J. F. Normant, unpublished results.

0039-7881/82/0432-0301 $ 03.00