Additions of CuCN-Derived Stannylcuprates to Terminal Alkynes: A Comparative Spectroscopic and Chemical Study

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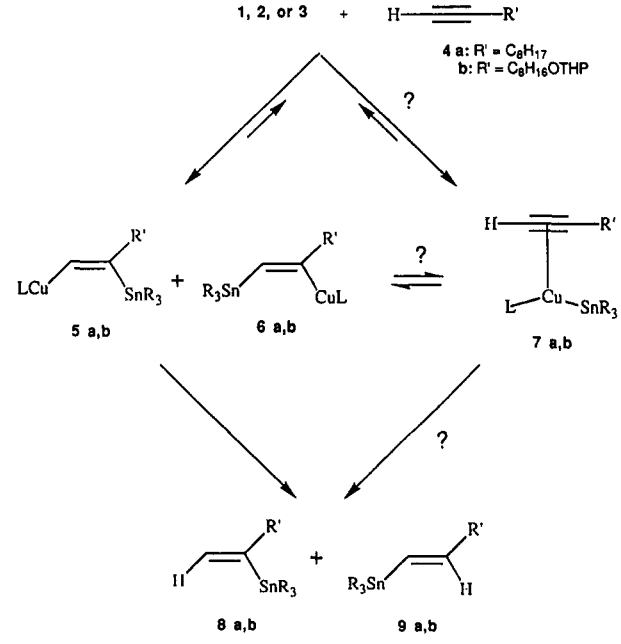
The stannylcupration of terminal alkynes **4a,b** with cuprates **1-3** proceeds rapidly and reversibly above -35 °C to afford vinylcuprate intermediates **5a,b** and **6a,b**. These intermediates have been characterized by ^{2}H and ^{13}C NMR labeling experiments. Corroborating evidence for this reversible addition comes from further chemical tests and cross-over experiments that show the thermodynamic favorability of the adducts. Further comparative study of reaction products and byproducts shows **2** to be the stannylcuprate of choice for the preparation of vinylstannanes from terminal alkynes.

The reaction of (trialkylstannyl)cuprates with terminal alkynes has been a topic of intense interest for about a decade.[1] These reactions, as well as the reactions of alkyl-[2] and silylcuprates[3] with terminal alkynes, generally proceed with high regio- and stereoselectivity providing synthetically useful routes to a wide variety of synthetic intermediates. The widely accepted hypothesis is that stannylcuprate additions to terminal alkynes proceed through vinylcopper intermediates[1,3,4] **5a,b** and **6a,b** (Scheme I), which upon quench of reaction afford products of cis addition. Another possible mechanism for addition of these cuprates to terminal alkynes involves the formation of π-copper intermediates[5] **7a,b** (Scheme I), which would afford similar products upon workup of the reaction. Careful review of the literature reveals regioselectivities and chemical yields for the stannylcupration of terminal alkynes to be variable.[1b,7]

We now wish to report that *n*-$Bu_3SnCu(CN)Li$ (**1**), (*n*-$Bu_3Sn)_2Cu(CN)Li_2$ (**2**), and *n*-Bu_3Sn(*n*-Bu)$Cu(CN)Li_2$ (**3**) react rapidly with terminal alkynes at temperatures above -35 °C to afford vinylcopper intermediates that subsequently react with a proton source to give mixtures of 2-(tributylstannyl)-1-alkenes (**8a,b**) and 1-(tributylstannyl)-1-alkenes (**9a,b**). The variable regioselectivities and chemical yields obtained in these reactions can best be explained by the intermediacy of vinylcopper intermediates as observed by ^{2}H and ^{13}C NMR spectroscopy.

Scheme I



Corroborating evidence for the presence of vinylcopper intermediates in this reversible process comes from further chemical tests and cross-over experiments.

Results and Discussion

Spectroscopic Experiments. The ^{13}C NMR spectrum of the reaction between 1 equiv of cuprate **2** and 1 equiv of 1-decyne (**4a**) with or without excess methanol revealed that no reaction takes place between these species at temperatures below -35 °C. Those signals attributed to **4a** remain while no other signals are visible in the vinyl region. When the solution is warmed above -35 °C in the presence of excess methanol, four signals attributable to 2-(tributylstannyl)-1-decene (**8a**) and (*E*)-1-(tributylstannyl)-1-decene (**9a**) are the only signals visible in the vinyl region of the ^{13}C NMR spectrum. In the absence of methanol, four somewhat obscure signals attributable to vinylcopper intermediates **5a** and **6a** become visible[6] while the alkynyl carbon signals disappeared.

The ^{13}C NMR spectrum of the reaction of 10-(tetrahydropyranyloxy)-1-decyne (**4b**) labeled with ^{13}C at C-1 and C-2,[8] with 1 equiv of **2** at -20 °C in the absence of methanol clearly shows two pairs of doublets attributable

(1) (a) Westmijze, H.; Ruitenberg, K.; Meijer, J.; Vermeer, P. *Tetrahedron Lett.* **1982**, *23*, 2797-2798. (b) Piers, E.; Chong, J. M. *J. Chem. Soc., Chem. Commun.* **1983**, 934-935. (c) Cox, S. D.; Wudl, F. *Organometallics* **1983**, *2*, 184-185. (d) Piers, E.; Chong, M. J. *Can. J. Chem.* **1988**, *66*, 1425-1429. (e) Piers, E.; Morton, H. E.; Chong, M. J. *Can. J. Chem.* **1983**, *65*, 78-87. (f) Zweifel, G.; Leong, W. *J. Am. Chem. Soc.* **1987**, *109*, 6409-6412.

(2) (a) Normant, J. F., Bourgain, M. *Tetrahedron Lett.* **1971**, 2583-2586. (b) Normant, J. F.; Cahiez, G.; Bourgain, M.; Chuit, C.; Villieras, J. *Bull. Soc. Chim. Fr.* **1974**, 1656-1660. (c) Marfat, A.; McGuirk, P. R.; Helquist, P. *J. Org. Chem.* **1979**, *44*, 3888-3901 and references cited therein.

(3) (a) Fleming, I.; Newton, T. W.; Roessler, F. *J. Chem. Soc., Perkin Trans 1* **1981**, 2527-2532. (b) Fleming, I.; Roessler, F. *J. Chem. Soc. Chem. Commun.* **1980**, 276-277. (c) Sharma, S.; Oehlschlager, A. C. *Tetrahedron* **1989**, 557-568.

(4) (a) Westmijze, H.; Meijer, J.; Bos, H. J. T.; Vermeer, P. *Rec. Trav. Chim. Pays-Bas* **1976**, *95*, 299-303. (b) Westmijze, H.; Meijer, J.; Bos, H. J. T.; Vermeer, P. *Rec. Trav. Chim. Pays.-Bas* **1976**, *95*, 304-307.

(5) It is possible that the first step in the reaction involves frontier orbital interactions in which there is an initial d-π *complex* formation. This would be analogous to that complex that is formed in the reaction of cuprates with α,β-enones. See: Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1984**, 3063-3066 and references cited therein.

(6) Hutzinger, M. W.; Singer, R. D.; Oehlschlager, A. C. *J. Am. Chem. Soc.* **1990**, *112*, 9397-9398.

(7) (a) Sharma, S.; Oehlschlager, A. C. *J. Org. Chem.* **1991**, *56*, 770-776. (b) Lipshutz, B. H.; Ellsworth, E. L.; Dimock, S. H.; Reuter, D. C. *Tetrahedron Lett.* **1989**, *30*, 2065-2068.

(8) Brandsma, L. *Preparative Acetylenic Chemistry*; Elsevier: New York, 1971.

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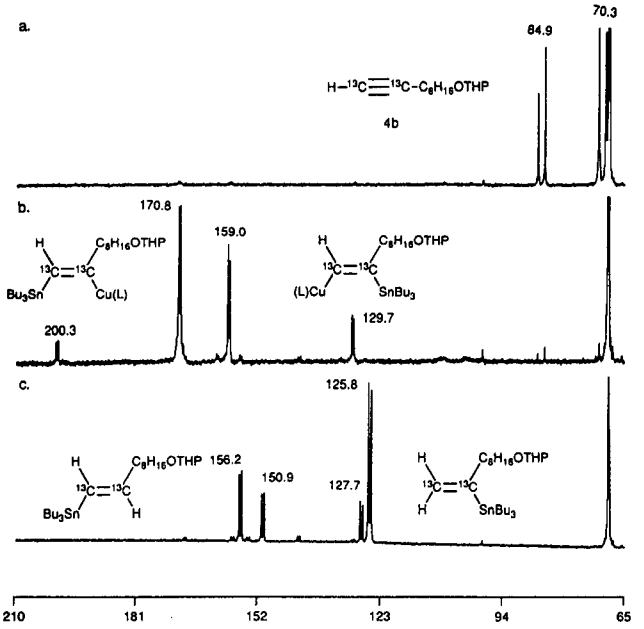


Figure 1. ^{13}C NMR spectra of (a) **2** + [1,2-^{13}C]-10-(tetrahydropyranyloxy)-1-decyne at −35 °C in THF, (b) **2** + [1,2-^{13}C]-10-(tetrahydropyranyloxy)-1-decyne at −20 °C in THF, and (c) **2** + [1,2-^{13}C]-10-(tetrahydropyranyloxy)-1-decyne + excess CH_3OH at −20 °C in THF.

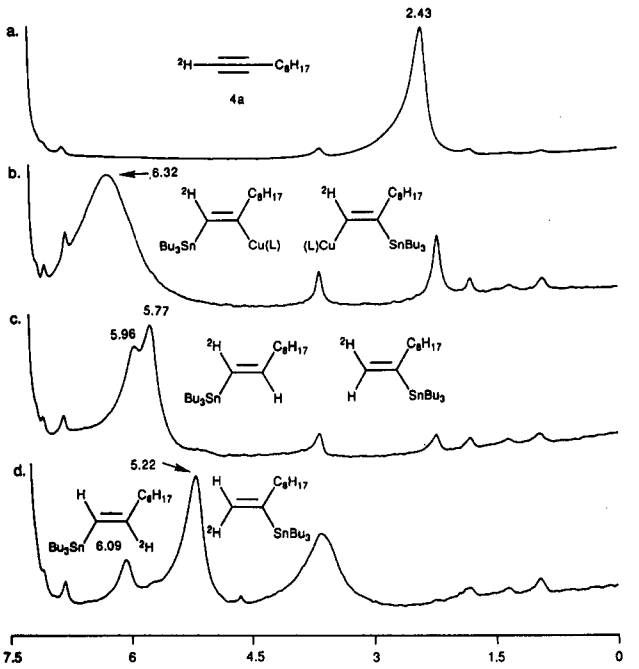


Figure 2. ^2H NMR spectra of (a) **2** + [1-^2H]-1-decyne at −35 °C or **2** + [1-^2H]-1-decyne + 1 equiv of CH_3OH at −35 °C, (b) **2** + [1-^2H]h1-decyne at 0 °C, (c) **2** + [1-^2H]-1-decyne + 1 equiv of CH_3OH at 0 °C, and (d) **2** + 1-decyne + CD_3OD at 0 °C.

to the two regioisomeric vinylcopper intermediates **5b** and **6b** (Figure 1b) whereas at −35 °C no reaction has taken place (Figure 1a). The two most intense doublets centered at δ 170.8 (d, J_{C-C} = 40.1 Hz) and 159.0 (d, J_{C-C} = 40.1 Hz $J_{^{119}Sn-C}$ = 560.9 Hz, $J_{^{117}Sn-C}$ = 544.2 Hz) can be attributed to the major vinylcopper adduct **5b**. The doublet at δ 159.0 displays ^{117}Sn and ^{119}Sn satellites, indicating that in this species (**5b**)mC-2 is bonded directly to the tri-*n*-butyltin moiety.[9] The two less intense doublets centered at δ 200.3 (d, J_{C-C} = 50.3 Hz) and 129.7 (d, J_{C-C} = 50.3 Hz, $J_{^{119}Sn-C}$ = 473.4 Hz, $J_{^{117}Sn-C}$ = 435.6 Hz) are attributed to the minor regioisomeric vinylcoppr adduct **6b**. The ^{117}Sn and ^{119}Sn satellites flanking the doublet at δ 129.7 allow assignment of this signal as C-1 in **6b** since it is bonded directly to the tri-*n*-butyltin moiety. Addition of excess methanol to this solution at −20 °C resulted in the immediate disappearance of signals due to the regioisomeric vinylcopper intermediates with concomitant emergence of signals due to the two vinyltins **8b** and **9b**. The doublets at δ 125.8 and 156.2 can be attributed to the major regioisomer **8b**,[10] whereas the doublets at δ 127.7 and 150.9 can be attributed to the minor regioisomer **9b** (Figure 1c). It is noteworthy that the signals attributed to those carbon atoms previously bonded to copper in the vinylcopper adducts undergo upfield shifts, δ 170.8 → 125.8 and δ 200.3 → 150.9, respectively, for **8b** and **9b** when the adducts are hydrolyzed to the vinylstannanes. Presumably, this is due to the greater electrophilic character of the copper cation compared to hydrogen. Also noteworthy are the observed ^{117}Sn and ^{119}Sn satellites in the vinylcopper adducts. Their presence confirms that the tri-*n*-butyltin moiety is covalently bonded to the vinyl carbon, resulting in $^{13}C-^{117}Sn$ and $^{13}C-^{119}Sn$ couplings. Had the intermediate in this reaction been a π-copper complex[5] **7a,b** then these satellites would not have been expected.

The ^2H NMR spectrum of the reaction of [1-^2H]-1-decyne (**10**) with 1 equiv of **2** at −35 °C in the presence or absence of 1 equiv of methanol displayed one singlet at δ 2.43,[11] corresponding to the single alkynyl-^2H in the starting material. This indicates that no reaction takes place between the cuprate and terminal alkyne at temperatures below −35 °C even in the presence of a proton source (Figure 2a).[12] When warmed above −35 °C in the absence of methanol, a broad singlet in the vinyl region centered at δ 6.32 appears. This is attributed to the deuterated regioisomeric vinylcopper intermediates **5a** and **6a** (Figure 2b). When the same reaction containing 1 equiv of methanol was warmed above −35 °C, two overlapping singlets at δ 5.96 and 5.77 were observed in the ^2H NMR spectrum. These were attributed to the vinylstannane regioisomers (Figure 2c).

If solutions above −35 °C containing vinylcopper intermediates **5a** and **6a**, as observed by ^{13}C and ^2H NMR, were recooled below −35 °C (i.e., −78 °C) the spectra did not change. Of particular note, there were no increases in the intensities of those signals attributed to starting alkyne upon cooling. This observation indicates the vinylcopper adducts are thermodynamically favored over the starting materials over a wide temperature range.

The ^2H NMR spectrum of the reaction of 1-decyne (**4a**) with 1 equiv of **2** at −35 °C in the presence of 1 equiv of CD_3OD displayed only one very broad singlet centered at δ 3.57;[11] once again no reaction had taken place. When warmed above −35 °C, two singlets attributable to the vinylstannane **8a** and **9a** were observed at δ 6.09 and 5.22, respectively (Figure 2d). That no signals are observed in the hydride region below −35 °C indicates no reaction between the cuprate and the proton source takes place to produce tri-*n*-butyltindeuteride.

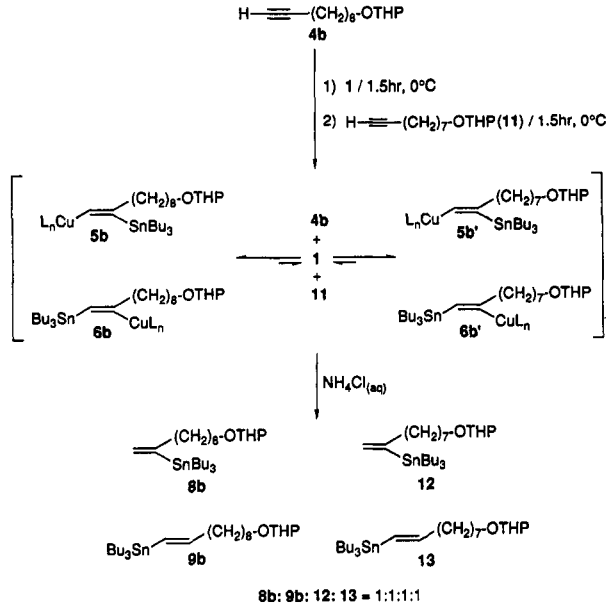
(9) Similar alkenyl $^1J_{^{119}Sn-^{13}C}$ values have been reported previously: Mitchell, T. N.; Amamria, A.; Killing, H.; Rutschow, D. *J. Organomet. Chem.* **1986**, 257–265.

(10) Determined by gas chromatographic analysis of an aliquot removed from the reaction mixture. The **8b**:**9b** GC ratio of 4:1 under these conditions agrees accurately with the ratio obtained through integration of the ^1H NMR of the reaction mixture.

(11) Relative to a benzene-$^2H_6$ internal reference.

(12) Here the proton source is not sufficiently acidic to quench the stannylcuprate. However, there is evidence that methanol does change the composition of the stannylcuprate in solution. Unpublished results.

Scheme II

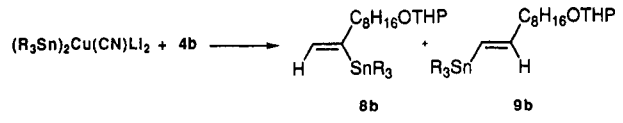


The reaction of 1 equiv of **1** with **4a** or **4b** displayed similar behavior when observed by ^{13}C and ^{2}H NMR spectroscopy. No reaction was observed between the stannylcuprate and alkyne below −35 °C even in the presence of methanol. Only when warmed above −35 °C was reaction observed when employing **1**. The vinylcopper intermediates observed in this reaction exhibited the same ^{13}C and ^{2}H NMR chemical shifts and coupling patterns as observed when they were generated in the reaction using higher order cuprate **2**. This was also true for the vinylstannane products. It was observed that the lower order cuprate **1** reacted with the alkynes **4a,b** more slowly than did the higher order cuprate **2**.

When the reaction of 1 equiv of **3** with 1 equiv of **10** in the absence of methanol was observed by ^{2}H NMR at −35 °C no reaction was observed and only one singlet corresponding to **10** at δ 2.43 was evident. When this reaction was warmed above −35 °C, a broad singlet centered at δ 6.19 attributed to deuterated vinylcopper intermediates **5a** and **6a** was observed. Surprisingly, the singlet at δ 2.43 was still present to an appreciable extent indicating incomplete reaction of **10**. The presence of another singlet at δ 0.93 attributable to [1-^{2}H]butane[13] provides an explanation for the observation of only partial consumption of **10**. When (n-Bu_3Sn)(n-Bu)Cu(CN)Li_2 (**3**) is reacted with terminal alkynes above −35 °C the alkylcopper moiety is evidently sufficiently basic to remove the acidic ^{2}H from the terminal position of the alkyne. Thus, generally lower yields are obtained in the reactions of mixed (trialkylstannyl)alkyl cuprates with terminal alkynes (Table II). Similarly, when this reaction was conducted in the presence of methanol no reaction took place below −35 °C. When warmed above this temperature, signals at δ 5.96 and 5.77 were observed and were attributed to the vinylstannane products **8a** and **9a**.

Chemical Experiments. As evidenced by the ^{13}C and ^{2}H NMR studies, the vinylcopper adducts **5a,b** and **6a,b** are thermodynamically favored over the starting materials **1**, **2**, or **3** and **4a** or **4b** in the addition of stannylcuprates to terminal alkynes. To establish that these processes are highly reversible, cross-over experiments were conducted. The addition of 1 equiv of 9-(tetrahydropyranyloxy)-1-nonyne (**11**) to a solution containing an equimolar mixture of n-$Bu_3SnCu(CN)Li$ (**1**) and 10-(tetrahydropyranyloxy)-1-decyne (**4b**, 0 °C/1.5 h) resulted in a 1:1:1:1 mixture of vinylstannane products **8b**, **9b**, **12** and **13** after 1.5 h at 0 °C followed by aqueous workup (Scheme II). This indicates an equilibrium is present between the thermodynamically favored vinylcopper adducts **5b** and **6b** and the starting materials **1** and **4b**.

Table I



entry	cuprate	conditions[a]	8b:9b[b]
1	(n-Bu_3Sn)$_2$Cu(CN)Li_2	kinetic	91:9
2		thermodynamic	15:85
3	(Me_3Sn)$_2$Cu(CN)Li_2	kinetic	86:14
4		thermodynamic	82:18

[a] Kinetic conditions: cuprate + alkyne, −78 °C, 2 h then 60 equiv of MeOH, −78 → 0 °C. Thermodynamic conditions: cuprate + alkyne, 0 °C, 2 h then 60 equiv of MeOH, 70 °C. [b] Ratios determined by GC analysis and/or ^{1}H NMR.

Further evidence for the reversibility of the stannylcupration of terminal alkynes is demonstrated through the reaction sequence shown in Scheme III. When 10-(tetrahydropyranyloxy)-1,2-bis(tri-n-butylstannyl)-1-decene (**14**) was transmetalated with 1 equiv of n-butyllithium followed by the addition of CuCn·2LiCl, vinylcuprate **5a** was formed. Even when formed by this alternate route, reaction with 1 equiv of 9-(tetrahydropyranyloxy)-1-nonyne (**11**) at 0 °C resulted in a nearly equimolar mixture of the vinylstannane products **8b**, **9b**, **12**, and **13**. Quenching of the vinylcuprate **5a** prepared by this alternate route at −35 °C with excess methanol gave a 85:15 ratio of the vinylstannanes **8b** and **9b**.

Reaction of 1 equiv of $Me_3SnCu(CN)Li$ (**15**) with 6-(tetrahydropyranyloxy)-1-hexyne (**16**) at 0 °C for 1.5 h followed by addition of a second alkyne gave no cross-over products, even after extended reaction times. Thus, the initial vinylcopper intermediates reacted to eventually produce only 6-(tetrahydropyranyloxy)-1,2-bis(trimethylstannyl)-1-hexene (**17**; 30% yield) and no equilibrium with a second alkyne could be established. The outcome of this reaction demonstrates the tendancy of the stable vinylcopper intermediates to undergo reductive coupling with **15** to afford **17** as the only product.

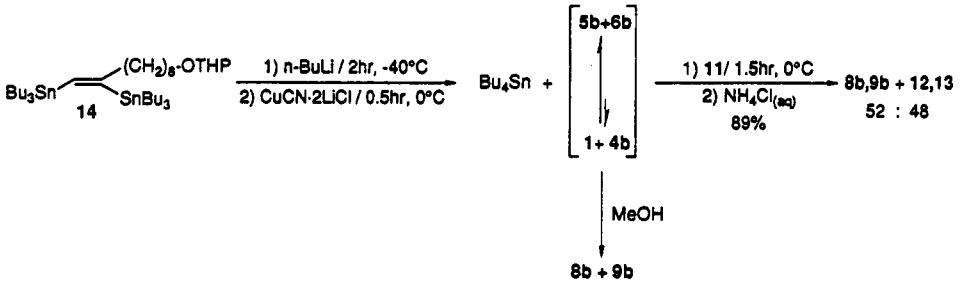
Another crossover experiment involving the reaction of (n-Bu_3Sn)$_2$Cu(CN)Li_2 (**2**) with 10-(tetrahydropyranyloxy)-1-decyne (**4b**) at 0 °C for 1.5 h followed by addition of 6-(tetrahydropyranyloxy)-1-hexyne (**16**) at 0 °C and stirring overnight gave virtually no cross-over products (i.e., less than 2%). However, if the reaction of 1 equiv of **2** with **4b** at 0 °C was allowed to proceed at this temperature for extended reaction times (i.e., overnight) variable regiochemistry was observed with essentially no change in chemical yield. Although variable regiochemistry also indicates the presence of an equilibrium process it is likely that the chemical process here is different from that in the reaction with the lower order cuprate.[14]

It was of interest to examine the outcome of the stannylcupration of terminal alkynes using (Me_3Sn)$_2$Cu(CN)Li_2 (**18**) or **2** under thermodynamic and under kinetic control

(13) Gas chromatographic head space analysis of the reaction mixture employing selected ion monitoring for [1-^{2}H]butane confirmed this.

(14) Recent results in our laboratory indicate that variable reactivity of the different cuprate species (or aggregates) present in higher order cuprates may have an effect on the observed regiochemistry as temperature is varied.

Scheme III



(Table I). Thus, reaction of 1 equiv of **2** with **4b** in THF at −78 °C for 2 h followed by addition of excess MeOH at −78 °C and warming to 0 °C afforded a 91:9 ratio of **8b** to **9b** with an overall chemical yield of 85%. This reaction is considered to be under kinetic control and shows a preference for formation of regioisomer **8b**. However, reaction of 1 equiv of **2** with **4b** in THF at 0 °C for 2 h followed by addition of excess MeOH at 0 °C afforded a 15:85 of **8b** to **9b** with an overall chemical yield of 95%. This reaction, presumably under thermodynamic control, indicates the position of the equilibrium in the addition of **2** to terminal alkynes when compared to the same reaction under kinetic control. A more remote possibility is that a different cuprate species is formed at elevated temperatures and gives rise to different regioselectivity.

Kinetic and thermodynamic preference for **8b** was observed when $(Me_3Sn)_2Cu(CN)Li_2$ (**18**) was reacted with **4b** in THF under both kinetic and thermodynamic control (Table I).

In an attempt to determine the most synthetically useful stannylcuprate a comparative study of the reactions of **1–3** with **4b** was undertaken. It was considered unnecessary to react the cuprates under conditions of thermodynamic control because the regioselectivity under such conditions is highly variable. The reaction of **4b** with **2** gave the most acceptable regioselectivity with a good chemical yield. Reaction of **4b** with mixed cuprate **3** under any of the conditions tried gave poorer regioselectivity with mediocre chemical yields. Although the stannyl impurities present in the presents of **4b** with **2** were greater than in the reactions of **4b** with **3**, if a polar group is present in the substrate, as in **4b**, the nonpolar impurities can be easily separated from the products by chromatography. Reactions of **4b** with **1** gave comparable regioselectivity and chemical yields accompanied by lower amounts of stannyl impurities than was the case in the reaction of **4b** with **2**, but due to the requirement for longer reaction times, cuprate **1** is less synthetically useful.

Conclusions

Low-temperature ^{13}C and ^{2}H NMR spectroscopy unequivocally establishes the presence of vinylcopper intermediates **5a,b** and **6a,b** in the reactions of **1–3** with terminal alkynes. Corroborating evidence for the existence of such intermediates is found in cross-over experiments with the same reagents. π-Complexation between the cuprate and the alkyne as an initial step leading to the formation of the vinylcopper intermediates cannot be ruled out. The experiments also show that the equilibria established in stannylcuprations favor the vinylcopper intermediates and are only established at temperatures above −35 °C.

Experimental Section

General Methods. All glassware and syringes were dried in an oven overnight at 120 °C, and glassware was flame-dried and flushed with argon immediately prior to use. Syringes were flushed with argon and kept under positive argon pressure until use. Transfer of reagents was performed with syringes equipped with stainless-steel needles. All reactions were carried out under argon. Transfer of CuCN took place in a glove bag. All alkyllithiums were freshly titrated before use.[15] Tetrahydrofuran was freshly distilled over potassium benzophenone ketyl. Unless otherwise stated, other chemicals obtained from commercial sources were used without further purification.

Low-temperature ^{13}C and ^{2}H NMR spectra were recorded at 100.62 and 61.43 MHz, respectively. The spectra were recorded on THF solutions in 10-mm NMR tubes and were referenced to THF, α 26.7 ppm, β 68.6 ppm for the ^{13}C NMR spectra and referenced to deuteriobenzene, 7.40 ppm (C_6D_6), for the ^{2}H NMR spectra. The ^{13}C and ^{1}H NMR spectra of synthesized starting materials and isolated vinylstannanes were recorded at 100.62 and 400.13 MHz, respectively, in $CDCl_3$ unless otherwise stated.

Typical Procedure for Sample Preparation. The cuprate solution was transferred via cannula to a 10-mm NMR tube equipped with a septum under argon at −78 °C to minimize warming during transfer. The terminal alkyne (and MeOH where applicable) was then added neat via syringe to the NMR tube at −78 °C to prevent any reaction. The sample was vortex stirred at this temperature for 10 min before recording ^{13}C or ^{2}H NMR spectra.

Preparation of *n*-$Bu_3SnCu(CN)Li$ (1) or $Me_3SnCu(CN)Li$ (15). To hexa-*n*-butylditin (0.23 mL, 0.45 mmol) in 2.59 mL THF under argon at −30 °C was added *n*-butyllithium (0.18 mL, 0.45 mmol, 2.5 M/hexanes) dropwise via syringe. After stirring at this temperature for 1 h, CuCN (0.040 g, 0.45 mmol) was added at −30 °C in one portion under a steady stream of argon and stirred an additional 1 h to afford a turbid orange-red (~0.15 M) solution of cuprate **1**. Cuprate **15** was prepared in a similar fashion using hexamethylditin and methyllithium.

Preparation of $(n\text{-}Bu_3Sn)_2Cu(CN)Li_2$ (2) or $(Me_3Sn)_2Cu(CN)Li_2$ (18). To hexa-*n*-butylditin (0.45 mL, 0.90 mmol) in 2.19 mL of THF under argon at −30 °C was added *n*-butyllithium (0.36 mL, 0.90 mmol, 2.5 M, hexanes) dropwise via syringe. After the mixture was stirred at this temperature for 1 h, CuCN (0.040 g, 0.45 mmol) was added at −30 °C in one portion under a steady stream of argon and stirred an additional 1 h to afford a clear yellow (~0.15 M) solution of cuprate **2**. Cuprate **18** was prepared in a similar fashion using hexamethylditin and methyllithium.

Preparation of $(n\text{-}Bu_3Sn)(n\text{-}Bu)Cu(CN)Li_2$ (3). To a hexa-*n*-butylditin (0.23 mL, 0.45 mmol) in 2.41 mL of THF under argon at −30 °C was added *n*-butyllithium (0.18 mL, 0.45 mmol, 2.5 M/hexanes) dropwise via syringe. After the mixture was stirred at this temperature for 1 h, CuCN (0.040 g, 0.45 mmol) was added at −30 °C in one portion under a steady stream of argon and stirred an additional 1 h to afford a turbid orange-red solution. To the solution was added *n*-butyllithium (0.18 mL, 0.45 mmol, 2.5 M/hexanes) dropwise via syringe at −30 °C and stirred for an additional 1 h to afford a clear light yellow (~0.15 M) solution of cuprate **3**.

10-(Tetrahydropyranyloxy)-1-decyne (4b). To a cooled solution (0 °C) of 9-decyn-1-ol[16] (5 g, 32.5 mmol) in CH_2Cl_2 (20 mL) was added an excess of 3,4-dihydro-2*H*-pyran (3 mL, 51 mmol) followed by several crystals (ca. 5 mg) of *p*-toluenesulfonic

(15) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165–168.
(16) Abrams, S. R. *Can. J. Chem.* **1984**, *62*, 1333–1334.

Table II. Reactions of Cuprates 1–3 with 4b under Various Conditions

entry	cuprate	method[a]	product: stannyl byproducts[b]	2-stannyl: 1-stannyl	yield (%)
1	2	A	1:3.7	75:25	78
2		B	1:4.1	77:23	73
3		C	1:3.4	91:9	85
4	0.5 equiv of 2	C	1:2.6	90:10	50
5	1	C	1:1.9	87:13	70
6	3	A	1:2.4	68:32	56
7		B	1:2.6	60:40	53
8		C	1:2.7	72:28	53
9	1.33 equiv of 3	C	1:2.8	66:34	63
10	2 equiv of 3	C	1:4.0	69:31	73

[a] Method A: cuprate + 1 equiv of MeOH, −78 °C min then **4b**, −78 °C, 1 h followed by aqueous workup. Method B: cuprate + **4b**, −78 °C, 1 h then 1 equiv of MeOH, −78 °C, 1 h followed by aqueous workup. Method C: cuprate + **4b**, −78 °C, 1 h then 60 equiv of MeOH, −78 °C, 1 h followed by aqueous workup. [b] Stannyl byproducts are n-Bu_4Sn and n-Bu_6Sn_2 with each equivalent of n-Bu_6Sn_2 byproduct expressed as 2 equiv of stannyl byproduct.

acid. After 10 min, the flask was removed from the ice bath and stirring continued for 1 h at room temperature. Solvent and unreacted 3,4-dihydro-2*H*-pyran were removed in vacuo, and the remaining oil was purified by column chromatography (19:1/hexanes/ethyl acetate) to yield 7 g (91%) of **4b**: ^{1}H NMR δ 4.58–4.55 (1 H, m), 3.90–3.83 (1 H, m), 3.72 (1 H, dt, J = 9.5, 7 Hz), 3.53–3.46 (1 H, m), 3.37 (1 H, dt, J = 9.5, 7 Hz), 2.17 (2 H, dt, J = 7, 2.6 Hz), 1.93 (1 H, t, J = 2.6 Hz), 1.89–1.78 (1 H, m), 1.75–1.67 (1 H, m), 1.63–1.47 (8 H, m), 1.43–1.26 (8 H, m). Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 10.92. Found: C, 75.30; H, 11.19.

10-(Tetrahydropyranyloxy)-2-(tri-*n*-butylstannyl)-1-decene (8b): ^{1}H NMR δ 5.65 (1 H, dt, J = 2.9, 1.4 Hz, J_{Sn-H} = 140 Hz), 5.08 (1 H, d, J = 2.9 Hz; J_{Sn-H} = 65 Hz), 4.59–4.55 (1 H, m), 3.90–3.83 (1 H, m), 3.72 (1 H, dt, J = 9.5, 7 Hz), 3.53–3.46 (1 H, m), 3.37 (1 H, dt, J = 9.5, 7 Hz), 2.22 (2 H, t, J = 7 Hz), 1.87–1.78 (1 H, m), 1.75–1.66 (1 H, m), 1.63–1.43 (14 H, m), 1.39–1.24 (14 H, m), 0.91–0.76 (15 H, m).

(*E*)-10-(Tetrahydropyranyloxy)-1-(tri-*n*-butylstannyl)-1-decene (9b): ^{1}H NMR δ 5.94 (1 H, dt, J = 19, 6 Hz), 5.84 (1 H, d, J = 19 Hz), 4.95–4.55 (1 H, m), 3.90–3.83 (1 H, m), 3.72 (1 H, dt, J = 9.5, 7 Hz), 3.53–3.46 (1 H, m), 3.37 (1 H, dt, J = 9.5, 7 Hz), 2.11 (2 H, q, J = 7 Hz), 1.87–1.78 (1 H, m), 1.75–1.67 (1 H, m), 1.63–1.43 (14 H, m), 1.43–1.25 (14 H, m), 0.92–0.76 (15 H, m).

[1,2-^{13}C]-10-(Tetrahydropyranyloxy)-1-decyne. A solution of [1,2-^{13}C]acetylene was prepared by transferring the gas from an ampule (0.1 L, 4.09 mmol) via cannula to a cooled flask containing THF (20 mL, −78 °C). The tip of the cannula was submerged into the solvent, which aided in controlling the flow rate and ensured maximum dissolution of acetylene. Subsequent preparation of the lithium monoacetylide was achieved by slow addition of n-BuLi (1.64 mL, 4.09 mmol) to the reaction flask at −78 °C.[17] After 30 min, a solution of 1-bromo-8-(tetrahydropyranyloxy)octane (1.2 g, 4.1 mmol) in THF (2 mL) was transferred to the reaction via cannula followed by addition of HMPA (5 mL) and this mixture was warmed to room temperature overnight. The quenched (H_2O) reaction was extracted with brine (3 × 100 mL), and the combined aqueous fractions were back-extracted with diethyl ether (2 × 50 mL). Removal of solvent in vacuo from the combined organic layers yielded a crude oil consisting of an unseparable mixture of [1,2-^{13}C]-10-(tetrahydropyranyloxy)-1-decyne and unreacted 1-bromo-8-(tetrahydropyranyloxy)octane. Final purification was accomplished by conversion of 1-bromo-8-(tetrahydropyranyloxy)octane to its corresponding phosphonium salt (PBu_3/acetone, reflux 4 h), which was easily removed by flash chromatography (19:1 hexanes/ethyl acetate) to yield 0.98 g (76%) of uncontaminated [1,2-^{13}C]-10-(tetrahydropyranyloxy)-1-decyne as a liquid: ^{1}H NMR δ 4.59–4.54 (1 H, m), 3.90–3.82 (1 H, m), 3.72 (1 H, dt, J = 9.5, 7 Hz), 3.53–3.45 (1 H, m), 3.37 (1 H, dt, J = 9.5, 7 Hz), 2.19–2.12 (2 H, m), 1.92 (1 H, dt, J = 298, 2.5 Hz), 1.87–1.77 (1 H, m), 1.74–1.46 (9 H, m), 1.43–1.26 (8 H, m); ^{13}C NMR δ 98.84, 84.73 (d, J_{C-C} = 170.1 Hz), 68.07, 67.96 (d, J_{C-C} = 170.1 Hz), 67.62, 62.31, 30.79, 29.72, 29.30, 29.01, 28.74, 28.40, 26.18, 25.52, 19.69. Anal. Calcd for $^{13}C_2C_{13}H_{56}O_2$: C, 75.00; H, 10.83. Found: C, 75.34; H, 10.90.

[1,2-^{13}C]-10-(Tetrahydropyranyloxy)-2-(tri-*n*-butylstannyl)-1-decene: ^{1}H NMR δ 5.64 (1 H, d, J_{C-H} = 151 Hz), 4.93 (1 H, d, J_{C-H} = 151 Hz), 4.59–4.54 (1 H, m), 3.91–3.83 (1 H, m), 3.72 (1 H, dt, J = 9.5, 7 Hz), 3.53–3.46 (1 H, m), 3.37 (1 H, dt, J = 9.5, 7 Hz), 2.22 (2 H, t, J = 7 Hz), 1.88–1.77 (1 H, m), 1.75–1.66 (1 H, m), 1.63–1.42 (14 H, m), 1.39–1.23 (14 H, m), 0.91–0.84 (15 H, m).

[1,2-^{13}C]-(*E*)-10-(Tetrahydropyranyloxy)-1-(tri-*n*-butylstannyl)-1-decene: ^{1}H NMR δ 6.16–5.98 (1 H, m), 5.79–5.61 (1 H, m), 4.59–4.54 (1 H, m), 3.91–3.83 (1 H, m), 3.72 (1 H, Dt, J = 9.5, 7 Hz), 3.53–3.46 (1 H, m), 3.37 (1 H, dt, J = 9.5, 7 Hz), 2.11 (2 H, t, J = 7 Hz), 1.88–1.77 (1 H, m), 1.75–1.66 (1 H, m), 1.63–1.42 (14 H, m), 1.39–1.23 (14 H, m), 0.91–0.84 (15 H, m).

1-Decyne-$^2H_1$ (10): ^{1}H NMR δ 2.18 (2 H, t, J = 7 Hz), 1.52 (2 H, quint, J = 7 Hz), 1.43–1.33 (2 H, m), 1.28 (8 H, b s), 0.88 (3 H, t, J = 7 Hz).

(*Z*)-10-(Tetrahydropyranyloxy)-1,2-bis(tri-*n*-butylstannyl)-1-decene (14). To a solution of (n-Bu_3Sn)$Cu(CN)Li_2$ (3.84 mmol) in THF (20 mL) was added **2** (1 mL, 3.84 mmol) at −30 °C. After being stirred at 0 °C for 1 h, the solution was cooled to −50 °C and n-Bu_3SnCl (1.36 mL, 5 mmol) added. The reaction mixture was kept at −5– °C for 30 min and then stirred at room temperature for 15 min before quenching with brine. A crude oil obtained after extraction with diethyl ether (3 × 50 mL) and subsequent solvent removal was purified by flash chromatography (19:1 hexanes/ethyl acetate) to afford 2.55 g (81%) of **7**: ^{1}H NMR δ 6.55 (1 H, s, $J_{^{119}Sn-H}$ = 192 Hz; 78 Hz; $J_{^{117}Sn-H}$ = 183, 75 Hz), 4.60–4.55 (1 H, m), 3.90–3.83 91 H, m), 3.72 (1 H, dt, J = 9.5, 7 Hz), 3.53–3.46 (1 H, m), 3.37 (1 H, dt, J = 9.5, 7 Hz), 2.27 (2 H, t, J = 7 Hz, J_{Sn-H} = 43 Hz), 1.88–1.77 (1 H, m), 1.75–1.67 (1 H, m), 1.53–1.40 (20 H, m), 1.40–1.30 (20 H, m), 0.97–0.78 (30 H, m). Anal. Calcd for $C_{39}H_{81}O_2Sn_2$: C, 57.14; H, 9.89. Found: C, 57.30; H, 9.76.

6-(Tetrahydropyranyloxy)-1-hexyne (16). This compound was prepared from 5-hexyn-1-ol (5 g, 51 mmol) in a fashion analogus to that described for the synthesis of **4b**: yield 8.1 g (87%); ^{1}H NMR δ 4.59–4.55 (1 H, m), 3.88–3.81 (1 H, m), 3.75 (1 H, dt, J = 9.5, 6.5 Hz), 3.53–3.46 (1 H, m), 3.40 (1 H, dt, J = 9.5, 6.5 Hz), 2.22 (2 H, dt, J = 7, 2.5 Hz), 1.94 (1 H, t, J = 2.5 Hz), 1.86–1.76 (1 H, m), 1.75–1.67 (1 H, m), 1.75–1.46 (9 H, m). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.53; H, 9.89. Found: C, 72.30; H, 9.96.

6-(Tetrahydropyranyloxy)-2-(tri-*n*-butylstannyl)-1-hexene (from reaction of 15 and 16): ^{1}H NMR δ 5.68–5.65 (1 H, m, J_{Sn-H} = 140 Hz), 5.11–5.08 (1 H, m, J_{Sn-H} = 65 Hz), 4.61–4.57 (1 H, m), 3.90–3.82 (1 H, m),. 3.37 (1 H, dt, J = 9.5, 7 Hz), 2.26 (2 H, t, J = 7 Hz) 1.87–1.78 (1 H, m), 1.75–1.66 (1 H, m), 1.63–1.38 (12 H, m), 1.36–1.24 (8 H, m), 0.91–0.84 (15 H, m); ^{13}C NMR δ 155.37, 124.85, 98.71, 67.36, 62.13, 41.14, 30.76, 29.41, 29.22, 29.13, 27.38, 26.27, 25.54, 19.56, 13.66, 9.58, 9.40. Anal. Calcd for $C_{23}H_{46}O_2Sn$: C, 58.35; H. 9.73. Found: C, 58.21; H, 9.66.

(*E*)-6-(Tetrahydropyranyloxy)-1-(tri-*n*-butylstannyl)-1-hexene (from reaction of 15 and 16): ^{1}H NMR δ 5.95 (1 H, dt, J = 19, 6 Hz), 5.86 (1 H, d, J = 19 Hz), 4.95–4.55 (1 H, m), 3.90–3.83 (1 H, m), 3.37 (1 H, dt, J = 9.5, 7 Hz), 3.53–3.46 (1 H, m), 3.38 (1 H, dt, J = 9.5, 7 Hz), 2.15 (2 H, q, J = 7 Hz), 1.87–1.78 (1 H, m), 1.75–1.66 (1 H, m), 1.65–1.37 (12 H, m), 1.35–1.24 (8 H, m), 0.92–0.76 (15 H, m); ^{13}C NMR δ 149.34, 127.43, 99.82, 67.48, 62.29, 37.63, 30.78, 29.41, 29.22, 29.12, 27.26, 27.00, 25.58, 25.53, 19.67, 13.70, 9.57, 9.40. Anal. Calcd for $C_{23}H_{46}O_2Sn$: C, 58.35; H, 9.73. Found: C, 57.96; H, 9.53.

(*Z*)-6-(Tetrahydropyranyloxy)-1,2-bis(trimethylstannyl)-1-hexene (17): ^{1}H NMR δ 6.61 (1 H, T, J = 1.2 Hz; J_{Sn-H} = 197, 87 Hz), 4.60–4.50 (1 H, m), 3.90–3.82 (1 H, m), 3.37 (1 H, dt, J = 9.5, 7 Hz), 3.53–3.46 (1 H, m), 3.57 (1 H, dt, J = 9.5, 7 Hz), 2.36 (2 H, dt, J = 7, 1.2 Hz), 1.89–1.78 (1 H, m), 1.75–1.67 (1 H, m), 1.62–1.48 (6 H, m), 1.47–1.38 (2 H, m), 0.16 (9 H, s, J_{Sn-H} = 52 Hz), 0.15 (9 H, s, J_{Sn-H} = 52 Hz); ^{13}C NMR δ 168.8, 143.0, 98.8, 67.4, 62.2, 47.3, 30.8, 29.2, 26.4, 25.5, 19.6, −7.5,

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-7.7. Anal. Calcd for $C_{17}H_{36}O_2Sn_2$: C, 40.0; H, 7.06. Found: C, 40.57; H, 6.77.

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Supplementary Material Available: Experimental procedures for compounds including **4b, 8b, 9b, 10, 14, 16,** and **17** (3 pages). Ordering information is given on any current masthead page.

Complex Induced Proximity Effects: β-Lithiations of Carboxamides

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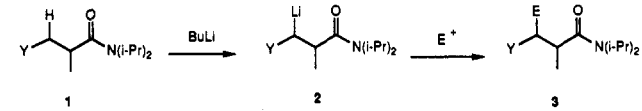
The *R*,S** and the *R*,R** diastereomers of *N,N*-diisopropyl-2,3-dideuterio-2-methyl-3-phenylpropanamide (**5, 6**) have been used to investigate the diastereoselectivity of the β-lithiation of *N,N*-diisopropyl-2-methyl-3-phenylpropanamide (**4**). The β-lithiation of **4** is highly diastereoselective with the β-proton that is in the same relative position as the β-proton of diastereomer **6** being preferentially removed. The β-lithio species derived from **4** is shown to be a pyramidal, organolithium reagent based on ^{13}C NMR. Lithiation of the *R*,S** and the *R*,R** diastereomers of *N,N*-diisopropyl-2-methyl-3-(phenylthio)butanamide (**7, 8**) and *N,N*-diisopropyl-2,3-dimethyl-4-pentenamide (**9, 10**) occur at the β-position. Lithiation of the *R*,S** and *R*,R** diastereomers of *N,N*-diisopropyl-2-methyl-3-phenylbutanamide (**11, 12**) occurs at the β-position for **11** and at the α-position for **12**. A conformational model is shown to correlate with these observations. The β-lithio species formed do not react diastereospecifically.

Reactions that involve specific removal of a proton from a carbon followed by reaction of the resulting carbanion with an electrophile are the basis for a wide range of synthetic strategies. Resonance and inductive effects typically dominate the deprotonation reaction, and thermodynamically favored carbanions are well-established synthetic intermediates. A growing number of kinetic deprotonations have been discovered, particularly for lithiations, and the carbanions that result from such reactions are useful as intermediates in innovative synthetic sequences.[1-13]

We have reported reactions in which tertiary amides that are activated by a phenyl, phenylthio, or vinyl group in the β-position undergo β-deprotonations in preference to the expected and well-precedented α-deprotonations to give an enolate. The observation is that **1**, when treated with an organolithium base, affords a lithiated intermediate, formally **2**, which on subsequent reaction with an electrophile provides the β-substituted product **3** diastereoselectively. In the present paper we address the issues of the actual structure of **2** and the regioselectivity and stereoselectivity of the lithiation. We provide direct evidence that **2** is correctly represented as a β-lithio amide, that the β-deprotonations are highly diastereoselective, and that the stereochemistry of the substituted products is dependent on the electrophile.



1 **2** **3**

Y = Ph, CH_2=CH, PhS

The overall conversion of **1** to **3** involves formation and substitution of a homoenolate carbanion, a species that has been most usually available in masked form or from a β-halo carbonyl precursor.[3-9] Approaches similar to the direct removal of a proton in the conversion of **1** to **2** have been reported by McDougal for β-lithio acetals,[10] by Tanaka for dilithiated amides,[11] and by Watt[12] and Funk[13] for β-lithio enals.

Results and Discussion

We have investigated the structure of the product of lithiation of *N,N*-diisopropyl-2-methyl-3-phenylpropanamide (**4**) and the stereochemistry of the deprotonations

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(3) These β-lithio amides provide the synthetic equivalent of a β-lithio α-alkyl carboxylic acid. Several reviews of the β-homoenolate synthon are available.[4] Transition metal promoted cyclopropane ring openings,[5] metal insertion into a carbon-halogen bond[6] or a carbon-carbon bond,[7] destannylation,[8] and halogen metal exchange[9] are examples of different routes.
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