Because of the sterically crowded environment about the hexasubstituted benzene ring, **1** is likely to exist predominantly in the all-anti conformation (D_{3d}). On the assumption that the vicinal coupling constants $J_{AB'}$ and J_{AB} of **1** represent the unaveraged $^3J_{anti}$ and $^3J_{gauche}$ couplings in the CH_2CH_2 fragment of a 1-methyl-2-aryl-substituted ethane, the observed values of the vicinal coupling constants of **2** correspond to a slight preponderance of the anti conformer.[8]

Acknowledgment. We thank the National Science Foundation (CHE-8009670) for support of this work.

Registry No. 1, 2456-68-0; 2, 103-65-1.

(7) In compounds of the type XCH_2CH_2Y, the vicinal coupling constants $J_{AB'}$ and J_{AB} remain nonequivalent (anisogamous) even under conditions of rapid internal rotation.[3] Barring accidental equivalence, $J_{AB'} \approx J_{AB}$ only when $p = {}^1/_3$, where p is the mole fraction of anti conformer.[4]

(8) In previous studies, the ^1H NMR spectrum of **2** was analyzed under the simplifying assumption that the seven propyl protons could be treated as an $A_2B_2C_3$ spin system. See: Cavanaugh, J. R.; Dailey, B. P. *J. Chem. Phys.* **1961**, *34*, 1094. Chamberlain, N. F. "The Practice of NMR Spectroscopy"; Plenum Press: New York, 1974; p 367.

An Important Limitation in the Reactions of 1-Chloro-1-alkenes with *n*- or *sec*-Butyllithium

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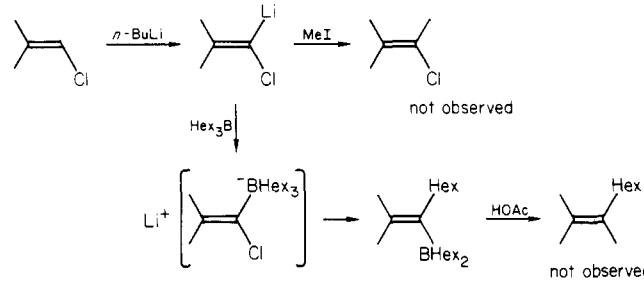
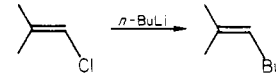
It has been reported that the low-temperature reaction of *n*-butyllithium with 1-chloro-1-alkenes yields stable lithium derivatives that can then be converted into a variety of compounds with overall retention of stereochemistry.[1-3] Often, it was stated that the reaction takes place for R = R^1 = alkyl.[2,4] However, a thorough literature

search reveals that these reactions have been reported only for the compounds in which one or both of R and R^1 are groups capable of conjugating with the double bond (such as Ar, Ph, and Cl),[1,2,4,5] and not for compounds in which both R and R^1 are typical alkyl groups. Thus, the literature is somewhat misleading for one desiring to carry out this reaction with compounds in which R and R^1 are aliphatic. Therefore, we report our results for the reactions of representative compounds of this type with *n*- or *sec*-BuLi in order to identify an important limitation of this reaction.

On the basis of statements in the literature,[2,4] one might predict that the reaction of 1-chloro-2-methyl-1-propene (**1**) with *n*- or *sec*-butyllithium would yield a lithium derivative stable at low temperatures and useful in succeeding reaction steps. However, we find no evidence for that stable intermediate in this reaction over a wide range of temperatures (−110 °C to room temperature).



At 0 °C, equimolar amounts of **1** and *n*- or *sec*-BuLi followed by addition of either methyl iodide or trihexylborane as electrophile do not lead to the products one might predict. Instead, both reactions give 2-methyl-2-heptene in low yields.[6] Thus, while these electrophiles



quench apparently stable anions of 1-chloro-1-alkenes bearing groups such as phenyl (vide supra), they fail in our system. To ascertain whether there was any involvement of the added electrophiles in formation of the 2-methyl-2-heptene, we ran a blank reaction. This reaction of equimolar amounts of **1** and *n*-BuLi also produced 2-methyl-2-heptene. Evidently, if any of the lithium derivative is formed, it reacts relatively rapidly with a second equivalent of *n*-BuLi.

We observe such formation of 2-methyl-2-heptene at temperatures as low as −23 and −45 °C. At lower temperatures (−78 or −110 °C) where the lithium derivative should be more stable, the reaction of equimolar amounts of **1** and *n*- or *sec*-BuLi followed by addition of 1 equiv of the electrophile yields predominantly polymerization products.

One might argue that the failure of the use of MeI to yield 2-chloro-3-methyl-2-butene could be due to problems inherent in the reactivity of MeI toward organolithiums, although this is unlikely since the use of 1 equiv of this electrophile has been shown to give good results in such cases.[7] However, the failure of Hex_3B to quench the anion is not due to any such problems with the electrophile, since the spontaneous rearrangement undergone by such borate complexes has been well-demonstrated.[8] This reaction probably involves initial metalation α to chlorine, similar to the *cis*- or *trans*-1-chloro-2-methylstyrene system.[9] However, at any of the temperatures investigated, the anion of the aliphatic system evidently is not sufficiently long-lived to be useful in succeeding reaction steps, as is that of the aromatic system. We find no evidence for deprotonation γ to chlorine which has been reported to be the major reaction of some 1-chloro-2-methylcycloalkenes.[10]

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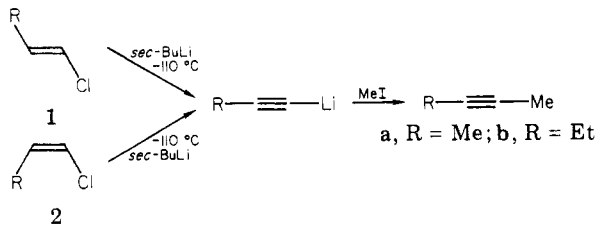
Table I. Products and Conditions of the Reactions of 1-Chloro-1-alkenes with *n*- or *sec*-Butyllithium Followed by the Addition of Methyl Iodide

reactant				products	
no.	compd	base[a]	temp, °C	compd	%[b]
1	1-chloro-2-methyl-1-propene	*n*-BuLi	−110	1	34
				polymerization	
		n-BuLi	0	1	8
				2-methyl-2-heptene	13
				2-butyne	<1
2a	*trans*-1-chloropropene	*sec*-BuLi	−110	**2a**	36
				2-butyne	50
		sec-BuLi (2 equiv)	−110	2-butyne	20
3a	*cis*-1-chloropropene	*sec*-BuLi	−110	**3a**	36
				2-butyne	49
		sec-BuLi (2 equiv)	−110	2-butyne	32
2b	*trans*-1-chloro-1-butene	*sec*-BuLi	−110	**2b**	40
				2-pentyne	43
3b	*cis*-1-chloro-1-butene	*sec*-BuLi	−110	**3b**	52
				2-pentyne	42

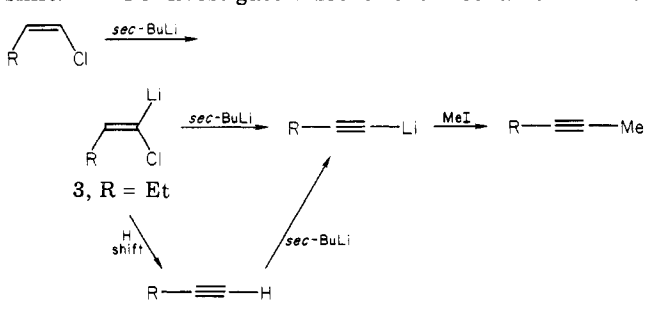
[a] One equivalent unless indicated otherwise. [b] Yields are an average of at least three runs.

Because the results for **1** were so different from those for 1-chloro-2-methylstyrene, we thought it desirable to determine whether the results for simple vinyl chlorides, such as 1-chloro-1-propene and -butene, would also be different from those for 1-chlorostyrene. Therefore, we investigated the reactions of these representative vinyl chlorides with *n*- or *sec*-butyllithium. Here, the results for the alkenyl systems (Table I) were essentially analogous to those reported for the styryl systems.[1] The reaction of *cis*- or *trans*-1-chloro-1-alkenes with equimolar amounts of *sec*-BuLi followed by addition of MeI yields a 2-alkyne and starting chloroalkene (Table I). No propyne or 1-butyne was observed. Increasing the amount of *sec*-BuLi



to 2 equiv depleted the chloroalkene, but there was no corresponding increase in the alkyne yield. Instead, the yield dropped, possibly due to an increase in dimerization and trimerization reactions.[11,12a]

It has been determined that in the reactions of the chlorostyrenes, the intermediate lithium phenylacetylide is formed from the initial anion via a reaction with a second equivalent of organolithium base rather than by an H shift.[1,13] To investigate whether the mechanism of the



analogous aliphatic system is similar, we carried out a simple test for the H-shift mechanism. If the reactions of **2** and **3** did involve the H shift, this would necessitate that the 1-alkyne formed react with *sec*-BuLi much faster than do the starting materials. Otherwise, some 1-alkyne would be observed. To test this, we ran a competitive reaction of **3b** vs. 1-pentyne with *sec*-BuLi at −110 °C and determined the relative reaction rate, $k_{\mathbf{3b}}/k_{\text{1-pentyne}} = 1.22$. Since the relative reactivity of the two compounds is so close to unity, the H shift is ruled out in this system. Thus, the mechanism for this reaction appears analogous to that of the β-chlorostyrenes.[1] It probably involves a reaction of the initial anion with a second equivalent of *n*- or *sec*-BuLi to give a lithium alkynide, which then reacts with methyl iodide to yield the 2-alkyne.

Experimental Section

General Comments. Standard techniques for handling air- and moisture-sensitive compounds were used.[14] THF was distilled over LAH. The chloroalkenes (Albany International) were distilled over CaH_2. *n*-Nonane (Phillips) was used as received for the internal standard.

Reactions of 1, 2, or 3 with *n*- or *sec*-BuLi. In all cases the reactions were carried out on a 10.0-mmol scale in 10 mL of THF solvent. The appropriate chloroalkene, *n*-nonane, and THF were transferred via syringe to a 25-mL round-bottom flask equipped with a magnetic stirring bar. The solution was then cooled to the desired temperature by use of a slush bath: 100% ethanol/liquid N_2, −110 °C; dry ice/acetone, −78 °C; chlorobenzene/liquid N_2, −45 °C; CCl_4/liquid N_2, −23 °C; ice, 0 °C. One equivalent of either *n*- or *sec*-BuLi was slowly added via syringe to the reaction flask. Maintaining both the reaction temperature and the stirring, 1 equiv of MeI was added. The results were independent of whether the MeI was added immediately or after 30 min. After stirring for another 30 min, the contents of the flask were warmed to room temperature, and the products were analyzed.

When Hex_3B was used as the electrophile in the reactions of **1** with *n*-BuLi, the reaction temperatures used were −110 and 0 °C, and these reactions were carried out in a manner analogous to that described above for MeI. In the latter instance, *n*-BuLi was added to the reaction mixture at −110 °C. After 30 min of stirring, the flask was warmed to 0 °C, and 1 equiv of Hex_3B was added. When Hex_3B was used as the electrophile, a ^{11}B NMR

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spectrum was taken 30 min after addition of the Hex_3B; in no case was there a signal corresponding to a vinylborane or a vinylborate complex. To effect protonolysis, the flask was warmed to 0 °C after 30 min or kept at 0 °C for 30 min, and 1 equiv of HOAc was added. The contents were analyzed by GC, and no 2-methyl-2-nonene was detected.

Competitive Reaction. *cis*-1-Chloro-1-butene and 1-pentyne (10.0 mmol each) were added via syringe to a round-bottom flask containing *n*-nonane (4 mmol) and THF (10 mL) and equipped with a magnetic stirring bar. The flask was then cooled to −110 °C, and *sec*-BuLi (10.0 mmol) was slowly added via syringe. After 30 min of stirring at low temperature, the reaction mixture at −110 °C was quenched with MeI. The contents of the flask were then warmed to room temperature and analyzed by GC for residual reactants. The relative reactivities were calculated by using the Ingold–Shaw equation.[15]

Instrumentation. All products were identified by GC coinjection with an authentic sample using a variety of columns and by GC/MS. GC data was obtained by using a Varian 1200 instrument equipped with a $^1/_8$ in column. Columns used were as follows: 6 ft 10% SP2100 on 100/120 Supelcoport, 18 ft 30% adiponitrile on 60/80 mesh Firebrick, 6 ft 0.15% picric acid on 80/100 Carbopack in series with 9 ft 30% adiponitrile on 60/80 mesh Firebrick. Mass spectra data were obtained with a Finnigan 4000 GC/MS equipped with a 6 ft × $^1/_4$ in. 3% OV-1 on 80/100 mesh Chromosorb W or an 18 ft × $^1/_8$ in. 30% adiponitrile column. ^{11}B NMR spectra were obtained with a Varian FT80A.

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Registry No. 1, 513-37-1; **2a**, 16136-85-9; **2b**, 7611-87-2; **3a**, 16136-84-8; **3b**, 7611-86-1; *n*-BuLi, 109-72-8; *sec*-BuLi, 598-30-1; 2-methyl-2-heptene, 627-97-4; 2-butyne, 503-17-3; 2-pentyne, 627-21-4.

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Preparation of Oxygenated Phenylacetic Acids

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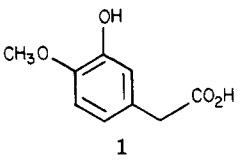
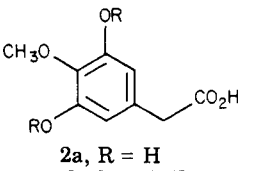
Oxygen-substituted phenylacetic acids have been employed in the synthesis of a wide variety of natural products, embracing such diverse species as flavonoids and alkaloids.[1,2] One especially important area is their use in the synthesis of the opiate alkaloids.[3,4] Rice has employed (3-hydroxy-4-methoxyphenyl)acetic acid (**1**, homoisovanillic acid) in a concise synthesis of the opiate precursor dihydrothebainone.[3a,d] In a related approach to the synthesis of the opiate skeleton, Beyerman employed [3,5-bis(benzyloxy)-4-methoxyphenyl]acetic acid (**2b**).[4a-c]



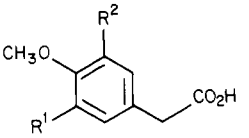
1



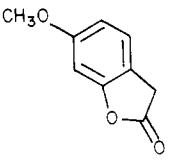
2a, R = H
b, R = C_7H_7

Finally, Schwartz demonstrated the utility of **2b** for the synthesis of thebaine using the phenolic oxidative coupling approach.[5] Due to the importance of **1** and **2a** as codeine precursors, much attention has been given to their preparation.[6] In general, the synthesis of these compounds involves the one-carbon homologation of a benzyl derivative and then manipulation of the aromatic functionality. The most convenient preparations of **1** use isovanillin as the starting material. This strategy was demonstrated by Grewe and Fischer[6f] wherein isovanillin was converted to the cyanohydrin, which was then successively hydrolyzed and reductively dehydroxylated to give **1** in greater than 80% yield. This preparation of **1**, while affording a good yield of material, suffers in that it is experimentally tedious and involves procedures during which hydrogen cyanide is evolved. To date, only one synthesis of an analogue of **2a** has been reported.[7] Gallic acid was esterified and then selectively methylated in poor yield at the 4-hydroxyl group. Benzylation of the remaining free phenols and homologation by the Arndt–Eistert procedure[8] gave **2b**.

The disadvantages noted above prompted us to devise a general method of preparation of **1** and **2a** from a common starting material. An excellent candidate for the initiation of this strategy is the relatively inexpensive and readily available (4-methoxyphenyl)acetic acid **3**.[9] Our proposed synthesis of **1** and **2a** required bromination of **3a** to **3b** and **3c** followed by displacement of the halides by hydroxide in a copper-catalyzed reaction. A previous attempt to employ this general strategy for the synthesis of **1** was performed by Hrothama.[10] In that report, the necessary ipso substitution of the halogen atom in **3d** was not observed. This compound was found to be relatively unreactive to reagents such as aqueous barium hydroxide at 170 °C and reacted via aryne mechanisms (**3d** → **4**) at higher temperatures. However the recent report of the facile substitution of 4-bromoanisole by methoxide using cuprous oxide catalysis[11] and our own success in the synthesis of catechols from *o*-bromophenols prompted us to explore the applicability of **3b** and **3c**.[12]



3a, $R^1 = R^2 = H$
b, $R^1 = H$; $R^2 = Br$
c, $R^1 = R^2 = Br$
d, $R^1 = H$; $R^2 = Cl$
e, $R^1 = Br$; $R^2 = OH$



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