The unsaturated aldehyde 1, prepared from 5 by the protocol outlined above, was compared to that obtained from the optically active VUL 3. Both aldehyde samples were found to be idential with respect to optical rotation and the retention time using chiral stationary-phase HPLC analysis. Racemic 1 was prepared from the pyrrolidine analogue of 3, again by the same experimental protocol as used for the conversion of either 5 or 3.[1] This racemic substance was used as a standard for the HPLC evaluations of optical purity of 1 as obtained from either 5 or 3—in both of these cases the optical purity of 1 was greater than 99:1. Lastly, a single-crystal X-ray determination of 9 was carried out, and its structure demonstrated to be that as shown in 9.

Acknowledgment. Financial support from the NIH and the Merck Sharp and Dohme Corp. is gratefully acknowledged.

Supplementary Material Available: Experimental procedures, compound characterization data, and X-ray data (14 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(9) The low-yield step in this two reaction sequence is the amine elimination—a subject of further experimental effort.
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(11) Pasto, D. J.; Johnson, C. R. Organic *Structure Determination*; Prentice-Hall: Englewood Cliffs, NJ, 1989; p 72.
(12) Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification Of Organic Compounds*, 4th ed.; John Wiley: New York, 1981; p 190.

Cyclizations of 3,4-Pentadien-1-yllithium Reagents

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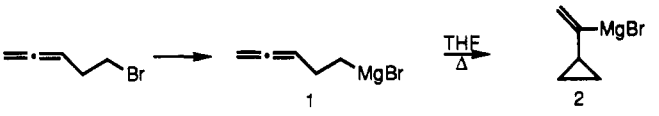
Summary: A number of 3,4-pentadien-1-yllithium reagents were obtained by metal–halogen exchange. Certain of these intermediates undergo facile cyclization to the isomeric 1-cyclobutenylmethyllithium derivatives.

Recent advances in the methodology for lithium–iodine exchange[1] have enabled the smooth formation and subsequent cyclization of a number of olefinic[2] and acetylenic[3] organolithium derivatives without interference from competing radical processes. Our long-standing interest in the utilization of the allene function as a site for intramolecular reactions of organometallic and radical intermediates[4–6] has prompted an examination of this potential route to allenic alkyllithiums.[7] We describe herein the chemistry of 3,4-pentadien-1-yllithium intermediates.[8] The only prior report in the literature on a homoallenyl main-group organometallic concerns the formation of the parent Grignard reagent 1 from the corresponding bromide in modest yield and the slow, but complete conversion of this species into its cyclopropyl isomer 2 upon heating in THF.[9] For comparison, the analogous 3-butenyllithium reagents interconvert with the isomeric cyclopropylcarbinyl species in a number of instances, although the acyclic form is ordinarily favored at equilibrium owing to the strain associated with the cyclopropyl ring in the cyclic isomer.[10]

Table I. Reactions of Organolithium Reagents 4 and 6 with Electrophiles

RI	*t*-BuLi equiv	E	additive	products[a] (%) 5	7	8
3a	1.6[b]	CHOHPh		92		
3a	2.05	$COHBu_2$	TMEDA		62	
3a	2.05	$SnPh_3$				59[c]
3a	2.05	CHOHPh	TMEDA		70[d]	30[d]
3a	2.05	CHOHPh	$Ti(O\text{-}i\text{-}Pr)_4$		68	
3b	1.6[b]	CHOHPh		82		
3b	2.05	$COHEt_2$			61	16
3b	2.05	CHOHPh	$Ti(O\text{-}i\text{-}Pr)_4$		82	
3c	2.05	CHOHPh		75		
3d	1.6[b]	TMS		80		
3e	2.05	$COHBu_2$			39	

[a] Isolated yields based on iodide. [b] Reaction not warmed to room temperature. [c] 4:1 mixture of 8:7 in crude product. [d] Not isolated, product ratio.



1 2

Fortunately, the rapid metal–halogen exchange induced by treating allenic iodides 3 with *t*-BuLi was not usually complicated by direct metalation of the allene function, which is also a facile process.[11] Thus, the parent iodide

(1) Bailey, W. F.; Punzalan, E. R. *J. Org. Chem.* **1990**, *55*, 5404. Negishi, E.; Swanson, D. R.; Rousset, C. J. *J. Org. Chem.* **1990**, *55*, 5406. Bailey, W. F.; Patricia, J. J. *J. Organomet. Chem.* **1988**, *352*, 1.
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(5) Apparu, M.; Crandall, J. K. *J. Org. Chem.* **1984**, *49*, 2125.
(6) Crandall, J. K.; Mualla, M. *Tetrahedron Lett.* **1986**, *27*, 2243.
(7) For a study involving the reaction of lithium metal with 6-halo-1,2-hexadienes, see: Arseniyadis, S.; Gore, J.; Laurent, A.; Roumestant, M.-L. *J. Chem. Res., Synop.* **1978**, 416. Roumestant, M.-L.; Arseniyadis, S.; Gore, J.; Laurent, A. *J. Chem. Soc., Chem. Commun.* **1976**, 479.
(8) A report describing the reactivity of homologous organolithium reagents is in preparation; presented at the 203rd National American Chemical Society Meeting, San Francisco, CA, April 5–10, 1992; American Chemical Society: Washington DC, 1992; Abstr. Orgn 299.
(9) Richey, H. G.; Kossa, W. C. *Tetrahedron Lett.* **1969**, 2313.
(10) Hunter, D. H.; Stothers, J. B.; Warnhoff, E. W. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic: New York, 1980; Vol. 1, pp 391–470. Hill, E. A. *J. Organomet. Chem.* **1975**, *91*, 123. For related radical systems, see: Surzur, J.-M. In *Reactive Intermediates*; Abramovitch, A. R., Ed.; Plenum: New York, 1982; Vol. 2, Chapter 2. Beckwith, A. L. J.; Ingold, K. U. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic: New York, 1980; Vol. 1, pp 162–283.
(11) Brandsma, L.; Verkruijsse, H. D. *Synthesis of Acetylenes, Allenes, and Cumulenes*; Elsevier: New York, 1981. Linstrumelle, G.; Michelot, D. *J. Chem. Soc., Chem. Commun.* **1975**, 561.

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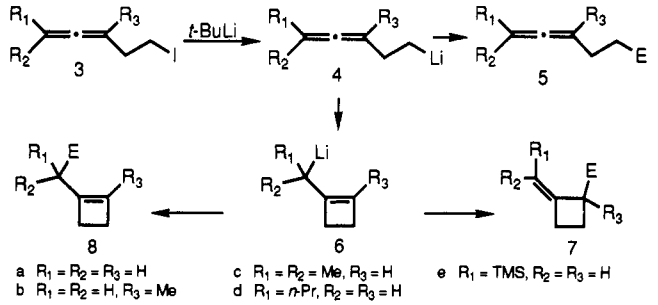
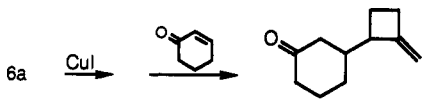
3a was readily converted to 3,4-pentadien-1-yllithium (4a) by adding 1.6 equiv of t-BuLi in pentane to a solution of 3a in ether at −78 °C. The efficient formation of 4a was demonstrated by trapping after 5 min with an excess of benzaldehyde to give allenic alcohol 5a (E = CHOHPh) in excellent isolated yield (92%). However, an isomeric organolithium species was generated when a similar reaction of 3a with 2.05 equiv[12] of t-BuLi was subsequently warmed to room temperature for 30 min. Cyclic structure 6a[13] was assigned to this intermediate by characterization of its adduct with 5-nonanone as methylenecyclobutane 7a (E = $COHBu_2$).[14] Although cyclization of 4a was anticipated on the basis of earlier work with related radicals,[4] the regioselective conversion of 4a to its cyclobutyl isomer 6a was totally unexpected given the cyclizations to cyclopropane derivatives observed with homoallenyl radicals,[4] Grignard reagent 1,[9,15] and related homoallyl derivatives.[10]

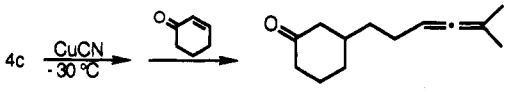


The easy generation of 6a from an acyclic allenic precursor permitted a study of its reaction with various electrophiles (see Table I). Trapping of 6a with Ph_3SnCl gave stannylation mainly at the exocyclic carbon leading predominantly to 8a (E = $SnPh_3$; 4:1 ratio of 8a:7a). Unlike its reaction with 5-nonanone, the reaction of benzaldehyde with 6a led to a mixture of regioisomers 7a and 8a (E = CHOHPh; 2.3:1 ratio). This type of product mixture is often found in the reactions of carbonyl compounds with unsymmetrically substituted allyllithium reagents.[16] However, preliminary conversion of 6a to an "ate" complex[17] by the introduction of $Ti(O\text{-}i\text{-}Pr)_4$ resulted in the exclusive formation of regioisomer 7a with benzaldehyde. Interestingly, the diasteriomers of 7a were produced in a stereorandom manner (1:1 ratio). Finally, 6a could be converted to an allylic organocopper reagent by the addition of CuI; subsequent reaction of this modified organometallic reagent with 2-cyclohexenone in the presence of TMSCl yielded ketone 9.[18] Once again, the new bond is formed with high selectivity for the more substituted, endocyclic carbon of the allylic organometallic reagent, although a 2:1 mixture of diastereomers of 9 was generated.



Similar chemistry was observed with iodide, 3b, which possesses a methyl substituent at the internal allenic carbon. Thus, reaction with t-BuLi at −78 °C gave acyclic organolithium 4b, which was smoothly converted to its cyclic isomer 6b upon warming to room temperature for 30 min. Trapping of acyclic 4b with benzaldehyde gave allenic alcohol 5b (E = CHOHPh; 82% yield), whereas the addition of 3-pentanone to cyclic 6b generated a mixture of 7b (E = $COHEt_2$; 61% isolated yield) and 8b (16% yield). Once again prior transformation of 6b to the "ate" complex with $Ti(O\text{-}i\text{-}Pr)_4$ resulted in highly regioselective addition of benzaldehyde to the tertiary center to form 7b (E = CHOHPh; 1.1:1 ratio of diastereomers) exclusively.

Unfortunately, iodides 3c and 3d with alkyl substitution at the remote end of the allene did not lead to cyclic products, even though the acyclic lithium derivatives were readily generated. Prolonged standing of the dimethyl-substituted alkyllithium 4c at room temperature resulted in uncharacterized decomposition; the addition of TMEDA (essential for the cyclization of certain olefinic alkyllithiums[2]) did not improve this situation. Nonetheless, 4c could be utilized for synthetic transformations as shown by the formation of 5c (E = CHOHPh) with benzaldehyde and the generation of substituted cyclohexanone 10 upon transmetalation with CuCN at −30 °C, followed by the addition of 2-cyclohexenone. Monosubstituted organolithium 4d likewise resisted cyclization, but was converted to silane 5d (E = TMS) with TMSCl.



In anticipation that substitution of stabilizing groups on the allene would facilitate cyclization, silyl allene 3e was exchanged with t-BuLi, warmed to room temperature, and then reacted with 5-nonanone. This gave cyclic alcohol 7e (E = $COHBu_2$) in modest yield, but regioselectively and exclusively as the E isomer.[19]

A completely different result was obtained with highly substituted sulfone 11a. In this case, reaction with t-BuLi, even at −100 °C, followed by methanol quenching after 1 h, gave a 1:4:5 mixture of reduced allene 11b, rearranged sulfone 12b and bicyclic sulfone 13. The structure of 13 was suggested by detailed 2D-NMR studies and subsequently confirmed by an X-ray structure.[20] Thus, the initially formed organolithium 11c appears to undergo a facile 1,3-transfer of the phenylsulfonyl group[21] to generate

(12) The typical cyclization procedure involved the addition of 2.05 equiv of t-BuLi to an etheral solution of 3 at −78 °C followed by warming to room temperature for 30 min prior to the addition of an electrophile at −78 °C.[1] In experiments using the initially formed acyclic reagents 4, only 1.6 equiv of t-BuLi was required for complete conversion of 3 at −78 °C, and contamination with t-BuLi adducts to added electrophiles was minimized. TMEDA was utilized in several early experiments, but was subsequently found not to be beneficial in these cyclizations.[2]

(13) 1-Cyclobutenylmethyllithium (6a) has also been prepared by metalation of methylenecyclobutane: Wilson, S. R.; Phillips, L. R.; Natalie, K. J. *J. Am. Chem. Soc.* **1979**, *101*, 3340. Wilson, S. R.; Phillips, L. R. *Tetrahedron Lett.* **1975**, 3047.

(14) Compound 7a (E = $COHBu_2$) showed: ^1H NMR δ 4.88 (m, 2), 3.12 (m, 1), 2.51 (m, 2), 1.62–1.12 (m, 15), 0.92 (t, 3, J = 7 Hz), 0.91 (t, 3, J = 7 Hz); ^{13}C NMR δ 151.1, 106.8, 74.7, 51.9, 37.3, 34.9, 29.1, 26.0, 25.6, 23.3 (2), 18.2, 14.1 (2); IR 3490, 1664 cm^{-1}.

(15) Repetition of the Grignard cyclization of 1, followed by trapping with 5-nonanone, gave the adduct of 2 as the major cyclic product as reported,[9] but minor amounts of 7a (E = $COHBu_2$) were also present (ca. 4:1 ratio).

(16) For leading references discussing allyllithium reagents, see: Fraenkel, G.; Chow, A.; Winchester, W. R. *J. Am. Chem. Soc.* **1990**, *112*, 2582. Courtois, G.; Miginiac, L. *J. Organomet. Chem.* **1974**, *69*, 1.

(17) Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer-Verlag: Berlin, 1986. Seebach, D.; Wilder, L. *Helv. Chim. Acta* **1982**, *65*, 1972.

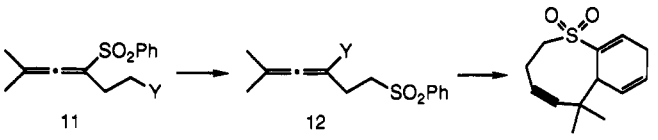
(18) The Lipshutz protocol for allylic copper reagents was used: Lipshutz, B. H.; Ellsworth, E. L.; Dimock, S. H.; Smith, R. A. *J. Am. Chem. Soc.* **1990**, *112*, 4404.

(19) The stereochemical assignment is based on an NOE experiment involving irradiation of the TMS group, which gave a 5% enhancement of the signal corresponding to the allylic methylene group.

(20) Details of the X-ray crystallographic determination are presented in the supplementary material.

(21) This particular transfer is not common; a few examples involving strained sulfonyl systems have been reported: Chou, T.; Chang, L.-J. *J. Org. Chem.* **1985**, *50*, 4998. Meinwald, J.; Knapp, S.; Obendorf, S. K.; Hughes, R. E. *J. Am. Chem. Soc.* **1976**, *98*, 6643. Yoshida, Y.; Komatsu, M.; Ohshiro, Y.; Agawa, T. *J. Org. Chem.* **1979**, *44*, 830.

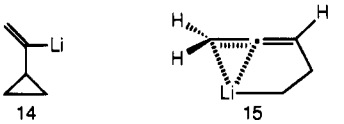
isomer **12c**, which subsequently adds its allenyllithium function to the activated aromatic ring to give an organolithium precursor of **13** in a rather novel rearrangement process.[22]



11 12 13

a Y = I; b Y = H; c Y = Li

In conclusion, appropriately substituted allenic organolithiums **4** undergo efficient cyclization to their cyclobutenylmethyl isomers **6**, which can be utilized in a variety of synthetic transformations leading to cyclobutane derivatives. The curious contrast in the intramolecular addition processes of **4** and the corresponding Grignard reagent **1** is remarkable. The preference of the more reactive lithium reagent **4** to cyclize to **6** appears to be kinetically controlled, since the isomeric cyclopropylvinyllithium **14** shows no tendency to isomerize to **6**.[23] Aggregation of the lithium reagents[24] could be an important mechanistic feature in that the availability of two or more lithium atoms in the oligomers might facilitate electronic reorganization. In the case of allenic species **4**, intramolecular complexation[25] of the more remote double bond with a lithium center as in **15** (shown as the monomer for simplicity) should be more favorable than association of the nearer double bond owing to strain considerations. Complex **15** is a likely precursor of **6** when the allene terminus is unsubstituted so that a primary organolithium is formed. Terminal substitution is expected to retard cyclization; indeed, this has also been observed with 5-hexen-1-yllithium derivatives.[2] The thermodynamic stability of cyclic form **6** over acyclic structure **4** with terminal allenes contrasts with the analogous 4-pentenyllithiums where the cyclic form, although kinetically accessible,[26] is disfavored thermodynamically relative to the acyclic isomer. The equilibrium shift towards the cyclic structure in the case of **4** ⇌ **6** is attributed to the allene "strain"[27] in **4** and the extra stabilization of the primary allylic organolithium moiety of **6**, which more than compensate for the additional strain of the cyclobutene ring. As a consequence, **6** can be conveniently obtained from acyclic precursor **4** for use in synthetic reactions.



14 15

Acknowledgment. We thank Dr. John Huffman (Indiana University, Molecular Structure Center) for the X-ray structure determination of **13** and Dr. Feng Lin for performing the 2D-NMR experiments. Departmental equipment grants aided in the purchase of the following: Varian XL-300 NMR (PHS-S10-RR-1882-01), Varian VXR 400s NMR (PHS-S10-RR-3956-01), Bruker AM-500 NMR (PHS-S10-RR-02858-01) and (NSF-CHE-85-13707), and Kratos MS 80 mass spectrometer (NSF-CHE-81-11957).

Supplementary Material Available: Experimental details including spectroscopic data for all new compounds and complete data for the X-ray structure determination of **13** (46 pages). Ordering information is given on any current masthead page.

(22) Similar transformations have been documented in abnormal Truce–Smiles rearrangements: Truce, W. E.; Madaj, E. J. *Sulfur Reports* **1983**, *3*, 259. Drozd, V. N. *Int. J. Sulfur Chem.* **1973**, *8*, 443.

(23) Mislanker, D. G.; Mugrage, B.; Darling, S. D. *Tetrahedron Lett.* **1981**, *22*, 4619.

(24) Wardell, J. L. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Ed. Pergamon: Oxford, 1982; Vol. 1, Chapter 2. Wakefield, B. J. *The Chemistry of Organolithium Compounds*; Pergamon: Oxford, 1974.

(25) Evidence for this type of main-group metal complexation with the double bond in 3-butenyl and 4-pentenyl compounds has been presented: St. Denis, J.; Oliver, J. P.; Smart, J. B. *J. Organomet. Chem.* **1972**, *44*, C32. St. Denis, J.; Dolzine, T.; Oliver, J. P. *J. Am. Chem. Soc.* **1972**, *94*, 8260.

(26) Hill, E. A.; Richey, H. G.; Rees, T. C. *J. Org. Chem.* **1963**, *28*, 2161.

(27) Jenson, J. L. *Prog. Phy. Org. Chem.* **1976**, *12*, 189.