Mechanistic Study of the Reactions of 1,1-Dihalo-2-methyl-2-phenylpropanes with LDA. Evidence for Radical and Carbene Pathways

E. C. Ashby,* Ali Mehdizadeh, and Abhay K. Deshpande

School of Chemistry and Biochemistry, Georgia Institute of Technology, Atlanta, Georgia 30332

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An attempt was made to determine the mechanisms involved in the reactions of the model systems 1,1-dichloro-2-methyl-2-phenylpropane (**1**) and 1,1-diiodo-2-methyl-2-phenylpropane (**2**) with LDA. These systems were chosen as ones capable of providing evidence for the formation of radical as well as carbene products. The techniques employed in investigating the mechanistic features of these reactions involved studying the effect of the leaving group, the effect of radical and carbene trapping agents on the product distribution, and isotopic tracer experiments using labeled solvent (THF-d_8) and nucleophile (LDA-d_2). The major product of the reaction of the geminal dichloride (**1**) is thought to be derived from a chlorocarbene, whereas the geminal diiodide (**2**) appears to form products derived from both carbene and radical intermediates. On the basis of the results of radical trapping experiments and those of deuterium-labeling experiments, evidence is presented to support the notion that products **A**, **E**, and **H** are derived from a radical precursor. In addition, products **A** and **H** are also believed to be formed from the vinylic halide **D** (or **B**) and the monoiodide **E**, respectively. Reasonable mechanisms for the formation of the other products formed in these reactions have been proposed on the basis of the available data.

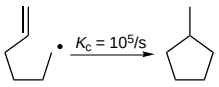
Introduction

Nucleophilic aliphatic substitution reactions of the S_N1 and S_N2 type involving aliphatic halides (RX) and nucleophiles (Y^-) have been widely studied (eq 1). However,

$$RX + Y^- \rightarrow RY + X^- \qquad (1)$$

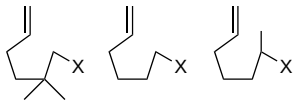
we have been able to demonstrate that some of these reactions can also proceed via competing carbene, carbanion, and single electron transfer (SET) pathways depending upon the particular halide leaving group, as well as the nature of the nucleophile.[1]

Since 1960, when Arai[2] reported cyclization of the 5-hexenyl radical to the methyl cyclopentyl radical (eq 2), cyclizable radical probes have been used for synthetic or mechanistic purposes, initially by Beckwith,[3a] Garst,[3b] Ingold,[3c] and more recently in this laboratory.[1,3d,4]



(2)

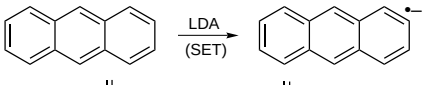
In order to verify a radical pathway, the reactions of certain alkyl halide "cyclizable radical probes", such as the ones shown below, with such nucleophiles as lithium aluminum hydride,[4a] sodium trimethyltin,[4b,c] and lithium diisopropylamide (LDA)[1a,g] have been studied extensively by this group.



a **b** **c**

where X = Cl, Br, I, OTs

LDA has been categorized as a hindered, non-nucleophilic strong base;[5] however, work carried out by this group has provided evidence for radical involvement in the reactions of LDA with polynuclear hydrocarbons (eq 3),[6] with aromatic ketones,[7] and with the cyclizable probe, 6-iodo-5,5-dimethyl-1-hexene (eq 4).[1a,g,6]



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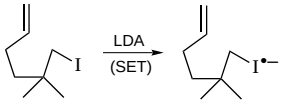

(4)

In addition to these reactions, other reactions have also shown that LDA can function as a one-electron donor toward heterocyclic compounds,[8] α-bromo imines,[9] some conjugated acetylenic compounds,[10] and benzophenone.[11]

[⊗] Abstract published in *Advance ACS Abstracts,* February 1, 1996.

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(11) (a) Kowalski, C.; Creary, X.; Rollins, A. J.; Burke, M. C. *J. Org. Chem.* **1978**, *43*, 3101. (b) Kimpe, N. D.; Palamarera, M.; Schamp, N. *J. Org. Chem.***1985**, *50*, 2993.

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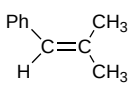
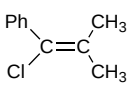
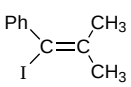
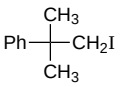
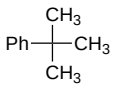
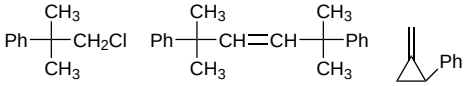
Table 1. Effect of Stoichiometry in the Reactions of 1,1-Dichloro-2-methyl-2-phenylpropane (1) and 1,1-Diiodo-2-methyl-2-phenylpropane (2) with LDA at 0 °C in THF[a]

				% yield of products[b]				
exp no.	dihalide	ratio dihalide:LDA	dihalide recovered	 **A**	 **B**	 **D**	 **E**	 **H**
1[c]	1	1:5		5.5	5.8			
2	1	1:2	9.6	trace	69			
3	1	1:1	19	trace	67			
4[d]	2	1:5		15			12	7.6
5[d]	2	1:2		6.7		15	32	1.3
6[d]	2	1:1	39	trace		24	17	

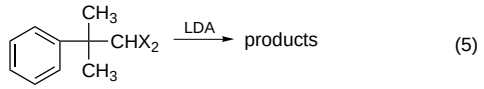
[a] Reaction times were 10 min. [b] Trace amount of **C** was formed in experiments 1−3. [c] Product **G** was also formed in 3.7% yield in experiment 1. [d] Dimer **F** was formed in experiments 4, 5 and 6 in yields of 7.2, 7.8, and 4.5%, respectively.



C **F** **G**

LDA has also been shown to form carbenes on reaction with benzylic halides.[12]

In one of our recent works,[1a] we observed that alkyl monochlorides react very slowly with LDA by a carbene pathway, whereas alkyl monoiodides afford products derived from radical intermediates. It was, therefore, of interest to determine if introduction of a second halogen atom on the carbon bearing the first halogen atom would have an effect on the mechanistic course of the reaction, especially for the chloride. We decided to employ for our studies a system (**1** and **2**) where cyclization of an intermediate radical (if formed) would not be very likely (eq 5). In addition, the phenyl group was expected to facilitate detection of carbene-derived products considering the relative ease with which phenyl migration occurs in carbenes.



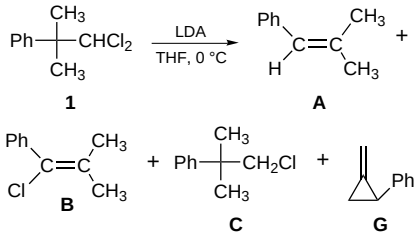
1, X = Cl
2, X = I

(5)

The advantages of this system, as well as the neopentyl system **a**, are that the complication of an unwanted dehydrohalogenation pathway is eliminated and the possibility of a S_N2 or S_N1 pathway is lessened because of the primary nature of the alkyl group and the steric hindrance of the neopentyl system. As a result, the SET pathway has a better chance of being observed in reactions of such probes with nucleophiles.

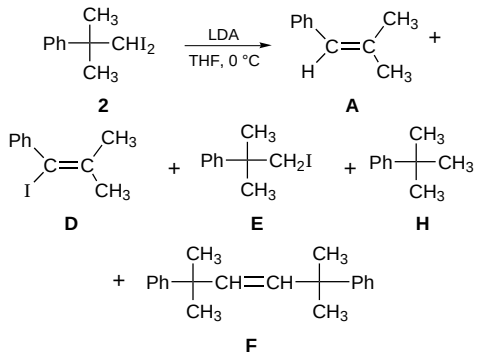
Results and Discussion

The products formed in the reactions of LDA with the dihalides 1,1-dichloro-2-methyl-2-phenylpropane (**1**) and 1,1-diiodo-2-methyl-2-phenylpropane (**2**) are given in eqs 6 and 7 and the results of varying the reactant stoichiometries are shown in Table 1. As the data in Table 1 indicate, poor material balances are observed at reactant ratios of 1:5 and 1:2 for both dihalo substrates. One might speculate that the reason for such low material balances is that excess LDA converts the radical probe dihalides, and/or the products formed initially, to some high molecular weight polymers or other products not detectable by GC. Thus, during this work, the reactions extensively studied were those in experiments 3 and 6, where the material balances were satisfactory enough to enable one to evaluate the reactions mechanistically. In all cases, experiments were carried out in duplicate and repeated if the duplicate results were not within 10%.



1 **A** **B** **C** **G**

(6)



2 **A** **D** **E** **H** **F**

(7)

Initially, it seems reasonable to categorize the products of experiments 3 and 6 into two classes: carbene products (products **B** and **D**) and reduction products coming from either single electron transfer (SET) or polar routes (products **A**, **C**, **E**, and **F**).

Effect of Leaving Group. The results in Tables 1 and 2 (experiments 1−8) indicate a significant effect of the leaving halide on the product distribution. The only important product in experiment 3 (product **B**) appears to be a carbene product, whereas in experiment 6 both carbene product (**D**) and reduction product (**E**) are present in substantial amounts. The ratio of the carbene product **D** to the SET or polar reduction products **A**, **E**, and **F** in experiment 6 is approximately 1. Furthermore, there is only a trace amount of monochloride **C** formed in experiment 3, while experiment 6 affords a significant

(12) (a) Dougherty, C. M.; Olofson, R. A. *Org. Synth.* **1978**, *58*, 37. (b) Creary, X. *J. Am. Chem. Soc.* **1977**, *99*, 7632.

Table 2. Reactions of 1-Halo-2-methyl-1-phenyl-1-propenes (B and D) with LDA at 0 °C in THF[a]

			% yield of products	
exp no.	**B** or **D**	halide recovered	**A**	**G**
7	**B**, X = Cl	77	1.5	3.2
8	**D**, X = I	9.3	87	trace

[a] The ratio of **B** or **D** to LDA was 1:2, and the reaction time was 10 min.

Table 3. Reactions of 1-Halo-2-methyl-2-phenylpropanes (C and E) with LDA at 0 °C in THF[a]

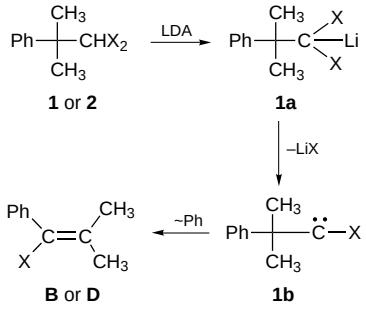
			% yield of products	
exp no.	**C** or **E**	halide recovered	**A**	**H**
9	**C**, X = Cl	100	0	0
10	**E**, X = I	71	7.5	12

[a] The ratio of **C** or **E** to LDA was 1:2, and the reaction time was 10 min.

amount of monoiodide **E**. These observations are consistent with the order of ease of reduction of halo compounds, i.e., I > Br > Cl.[13] In addition, as the results in Table 2 (experiments 7 and 8) indicate, when the vinylic halides **B** and **D** were independently allowed to react with LDA, reduction product **A** was formed in greater amount from the vinylic iodide **D** than from the corresponding vinylic chloride **B** (87% vs 1.5%). This observation is again in agreement with the trend of reduction potential of the halo compounds. Finally, the monochloride **C** is essentially unreactive toward LDA while its monoiodide counterpart **E** reacts with LDA to form *tert*-butylbenzene (**H**) (experiments 9 and 10, Table 3).

Products Suggested To Be Formed from Carbenoid/Carbene Intermediates. The major product formed in the reaction of **1** with LDA is **B** (experiment 3), and the major product formed in the reaction of **2** with LDA is **D** (experiment 6). Both products vary only in the nature of the halogen and appear to be formed by a mechanism illustrated in Scheme 1.

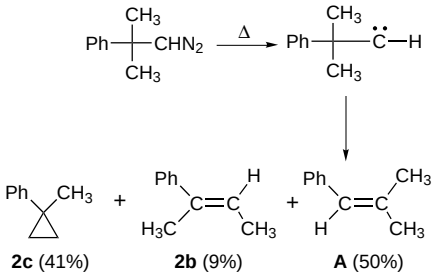
Scheme 1



According to this proposed mechanism, LDA acts as a strong base and abstracts the α-proton of the dihalo compound to form the carbenoid intermediate **1a**, which then generates the carbene intermediate **1b** by the loss of lithium halide. The carbene intermediate subsequently undergoes a phenyl migration to form the vinylic halide **B** or **D**.

Carbene rearrangements involving hydrogen, methyl, or phenyl migration to form olefins have previously been reported by several groups, and the order of migratory aptitude is reported to be H > Ph > Me.[14] Phillip and co-workers, for instance, have reported the formation of **A**, **2b**, and **2c** (Scheme 2) in the thermal decomposition of 2-methyl-2-phenyl-1-diazopropane.[15] The two major

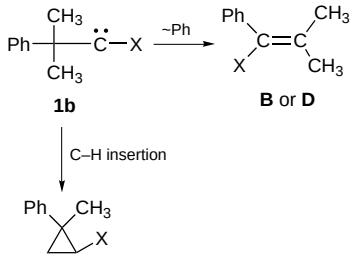
Scheme 2



products **A** and **2c** are phenyl migration and carbene insertion products, respectively, while product **2b** is the methyl migration product.

On the basis of the results reported by Phillip,[15] one might also expect cyclopropane formation from similar carbenes such as **1b** (Scheme 3). However, no cyclopropane was formed from **1** or **2** in their reactions with LDA. This can be explained by arguing that the carbene precursor to **B** or **D** is a halocarbene, whereas in Scheme 2 the carbene is a protiocarbene (we have recently observed that the halocarbene generated in the reactions of 6,6-dihalo-5,5-dimethyl-1-hexenes with LDA preferentially adds intramolecularly across the terminal C=C bond, and there is no product derived from insertion of the halocarbene into a C–H bond[1b]). Also, one cannot be certain as to whether the reactive intermediate here is the carbenoid **1a** or the free carbene **1b** (Scheme 1). Therefore, the ambiguity associated with the carbenoid/carbene mechanism shown in Scheme 1 makes it problematical to expect the products that would normally be formed when a free carbene is present. One might also argue that even if the free carbene **1b** existed as the reactive intermediate the rate of phenyl migration in this carbene to form the vinylic halides **B** or **D** could be greater than that of C–H insertion to form the cyclopropane compared to the carbene formed in Scheme 2, and hence, one would not see any cyclopropane.

Scheme 3

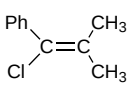
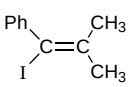
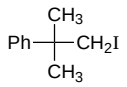
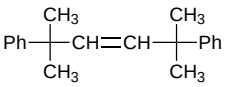


In order to trap the carbene intermediate believed to be involved (**1b**), a 10-fold excess of a known carbene

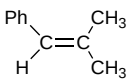
(13) Pine, S. H.; Hendrickson, J. B.; Cram, D. J.; Hammond, G. S. *Organic Chemistry*, 4th ed.; McGraw Hill: New York, 1980; p 379.

(14) Sargeant, P. B.; Shechter, H. *Tetrahedron Lett.* **1964**, 3957.
(15) Phillip, B. H.; Keating J. *Tetrahedron Lett.* **1961**, *15*, 523.

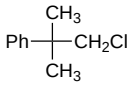
Table 4. Effect of Additives in the Reactions of 1,1-Dihalo-2-methyl-2-phenylpropanes (1 and 2) with LDA at 0 °C in THF, Ether, and TMEDA[a]

				% yield of products[c]			
							
exp no.	dihalide	solvent/additive[b]	dihalide recovered	**B**	**D**	**E**	**F**
11	1	THF/DMB[d]	19	67			
12	1	ether/DMB	51	31			
13	1	TMEDA/DMB	72	14			
6	2	none	39		24	17	4.5
14	2	THF/DBNO[e]	50		24	9.6	1.8

[a] Ratio of the dihalide to LDA was 1:1. [b] DMB = 2,3-dimethyl-2-butene, DBNO = di-*tert*-butyl nitroxide. [c] Trace amounts of **A** were also formed in all these experiments, and a trace amount of **C** was formed in experiments 11−13. [d] Ratio of **1** to DMB was 1:10. [e] Ratio of **2** to DBNO was 1:0.1.



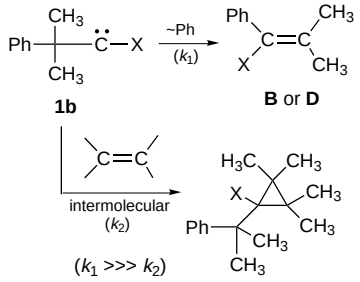
A



C

trapping agent, 2,3-dimethyl-2-butene,[16,17] was used in the reaction of **1** with LDA under normal experimental conditions (experiment 11, Table 4). However, no trace of the expected cyclopropane that would have provided evidence for the existence of carbene **1b** was found (Scheme 4). Given the result of experiment 11, it seems

Scheme 4

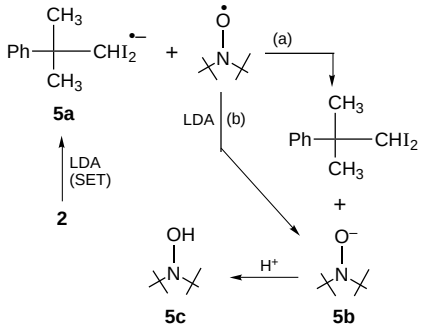


that if indeed such a free carbene exists, the rate of its intramolecular reaction (k_1) to form the olefin must be much faster than that of intermolecular trapping of the carbene (k_2) due to the steric hindrance involved in forming the product. Also, the possibility exists that a carbenoid intermediate (**1a**) rather than a free carbene (**1b**) is involved as an intermediate, and therefore, the formation of **4a** would not be expected.

The carbene trapping experiment was also attempted in two additional solvents, namely ether and TMEDA (experiments 12 and 13, Table 4), in the hope that the free carbene **1b** would be more readily formed from the carbenoid **1a** in these solvents. Once again, no cyclopropane was found and the rate of reaction decreased.

Reduction Products. Products **A**, **C**, **E**, and **F** appear to be reduction products. Compared to products **A** and **C** in experiments 3 and 6, products **E** and **F** are formed in considerably large amounts in experiment 6. It is possible for **E** and **F** to be formed from either a polar or a radical intermediate. A preliminary investigation employing a known radical scavenger[16] provided some evidence for the involvement of a radical precursor in the formation of **E** and **F**. When 10 mol % of di-*tert*-butyl nitroxide (DBNO) was added to the reaction mixture of **2** with LDA in THF at 0 °C (experiment 14, Table 4), the yield of product **E** dropped 44% and the yield of **F** dropped 60%. Furthermore, a new product, which was determined to be the corresponding hydroxide of the radical scavenger as judged by its molecular ion and mass spectral fragmentation pattern, was also formed. As Scheme 5 below shows, this hydroxide could have been

Scheme 5



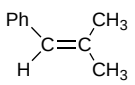
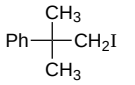
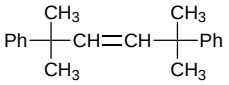
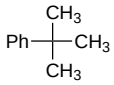
formed by electron transfer from the radical anion (**5a**) to DBNO (pathway **a**) to form the anion (**5b**) or by electron transfer from LDA to DBNO (pathway **b**) to form **5b**, followed by subsequent abstraction of a proton from the medium. The first suggestion assumes that the radical anion (**5a**) has sufficient lifetime to transfer its electron to the radical scavenger (it was not possible to isolate **5c** and further characterize it by NMR spectroscopy because it was formed in such small quantity). The conclusion of this trapping experiment (experiment 14, Table 4) is that products **E** and **F** are formed from radical precursors.

As far as the formation of **E** is concerned, the mechanism in Scheme 6 is proposed which involves a SET route. There are two places from which a hydrogen atom can be abstracted by the radical intermediate **6b**, namely the solvent and the amide. By use of the solvent THF-d_8 and analysis of the deuterium content of the product, it was determined that there was no deuterium incorporation in any of the products in the reaction of **2** with LDA in THF-d_8 (experiment 15, Table 5). However, since C−H bonds in THF are strengthened by replacing the hydrogen atoms with deuterium in THF-d_8, one cannot rule out, with absolute certainty, the possibility that THF is the hydrogen atom source. This point will be established later.

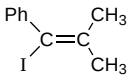
(16) Goldstein, M. J.; Dolbier, W. R. *J. Am. Chem. Soc.* **1965**, *87*, 2293.

(17) Kirmse, W. *Carbene Chemistry*, 2nd ed.; Academic Press: New York, 1971; p 294.

Table 5. Effect of Isotopically Labeled Solvent and Nucleophile in the Reaction of 1,1-Diiodo-2-methyl-2-phenylpropane (2) with LDA at 0 °C

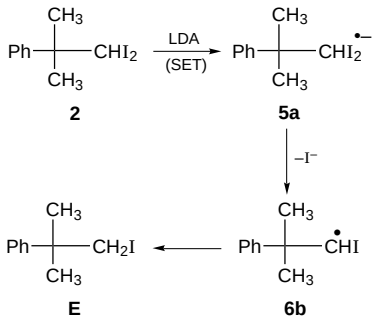
				% yield of products[c] (% d_1 incorporation)			
							
exp no.	solvent	amide[a,b]	dihalide recovered	**A**	**E**	**F**	**H**
6	THF	LDA	39	trace	17	4.5	
15	THF-d_8	LDA	40	trace	14	3.6	
				(0)	(0)	(0)	
16	THF	LDA-d_2	45	trace	8.8	2.0	
				(0)	(70)	(0)	
17	THF-d_8	LDA-d_2	47	trace	7.3	1.8	
				(0)	(81)	(0)	
4	THF	LDA		15	12	7.2	7.6
18	THF	LDA-d_2		18	7.6	3.3	6.4
				(39)			(42)
19	THF-d_8	LDA-d_2		16	8.1	3.6	5.9
				(42)			(43)

[a] The ratio of **2** to LDA was 1:1 in experiments 6, 15, 16, and 17. [b] The ratio of **2** to LDA was 1:5 inexperiments 4, 18, and 19. [c] Product **D** was also formed in experiments 6, 15, 16, and 17 in yields of 24, 28, 28, and 22%, respectively.



D

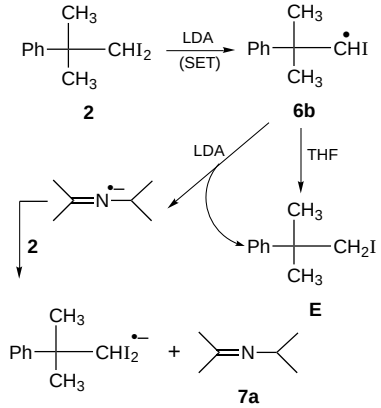
Scheme 6



When the ^{1}H NMR spectrum of the product mixture in experiment 15 was evaluated, the signals corresponding to isopropylideneisopropylamine were detected. This imine is a byproduct of either a polar reduction pathway such as the one reported in the reduction of benzophenone by LDA[7] or one formed by SET reduction. The observation in experiment 14 that the formation of reduction products **E** and **F** was inhibited by using a radical scavenger leads one to believe that a radical pathway is operative in the formation of **E** and **F**. In such SET reductions, the α-hydrogens of LDA are the more probable source of hydrogen atoms.

In order to confirm that the α-hydrogens of LDA are the major source of hydrogen atoms in the reaction of **2** with LDA in THF, LDA-d_2 was prepared from diisopropylamine-d_2 which had been found to contain 94% deuterium by ^{1}H NMR analysis. This labeled amide was then allowed to react with **2** using protio THF (experiment 16, Table 5) and THF-d_8 (experiment 17) as the solvent. The percentages of deuterium incorporated in product **E** in experiments 16 and 17 were 70% and 81%, respectively. The yield of **E** decreased as did the rate of reaction in both experiments. These results are not too surprising since LDA and LDA-d_2 should not be expected to have identical one-electron donor capabilities, and indeed the rate decrease involving LDA-d_2 was small. In addition, the yield of **F** decreased by a factor of 2, and there was no deuterium incorporation in this product in either experiment 16 or 17. A suggested mechanism in full accord with such high deuterium incorporation in product **E** and that is also consistent with the results obtained from experiments 14 and 15 is shown in Scheme 7.

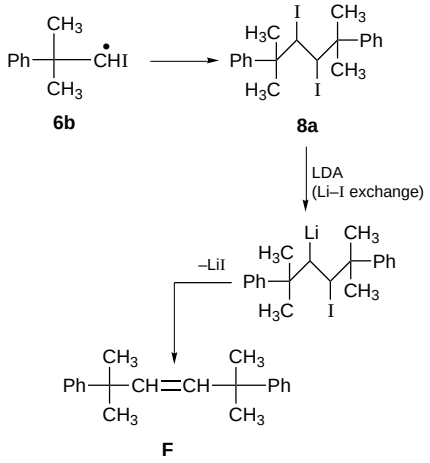
Scheme 7



It is proposed that, in the formation of **E**, the hydrogen atom comes from both the LDA and the THF. In experiment 16, the LDA-d_2 is preferred over the protio THF. However, the 30% protium in product **E** (experiment 16) can originate from THF or the 6% hydrogen contained in the LDA-d_2. On labeling both the solvent and the LDA with deuterium (experiment 17), there was an 11% increase in the deuterium content of **E** compared to when only the LDA was labeled, thus showing that hydrogen can also be abstracted from THF to form **E**. The 19% protium content of **E** (experiment 17) can again be attributed to the 6% protium in the LDA-d_2. Thus, it appears that even though both sources of hydrogen atom are labeled here, the radical intermediate **6b** preferentially abstracts a hydrogen atom from LDA.

The following mechanism (Scheme 8) is proposed for the formation of **F** on the basis of the results of experiments 14−17 (Tables 4 and 5), whereby **F** seems to be

Scheme 8



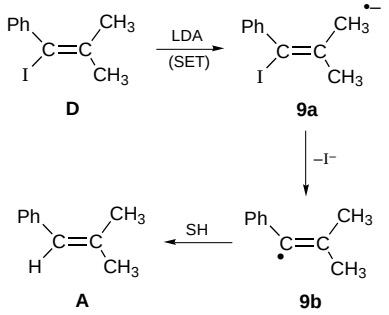
formed by a radical mechanism that does not involve hydrogen atom abstraction. In this proposed mechanism, the radical intermediate **6b** dimerizes to form the vicinal diiodide (**8a**) which undergoes iodine−lithium exchange followed by loss of lithium iodide to form **F**.

It was not possible to isolate the vicinal diiodide **8a**. However, evidence supporting the last step in this mechanism was provided by the reaction of the simplest vicinal diiodide, 1,2-diiodoethane, with LDA. When 1 equiv of LDA was treated with 1,2-diiodoethane at 0 °C in THF, a gas was generated which was shown to be ethylene. The reaction was instantaneous and the yield quantitative.

Proposed Mechanisms for the Formation of Minor Products A and H. The results of experiments 7 and 8 (Table 2), 10 (Table 3), and 18−20 (Tables 5 and 6) provide evidence that supports reasonable mechanisms for the formation of **A** and **H**. The observation that the reduction of the vinylic iodide **D** with LDA in experiment 8 (Table 2) gives an almost quantitative yield of product **A** indicates that **D** is the precursor to **A** in the reactions of **2** with LDA. This conclusion is further supported by the fact that **D**, which is a major product in exp 6 (Table 1), is not observed when **2** is treated with excess LDA (experiment 4, Table 1) and that there was 15% of **A** formed in exp 4. Even though the vinylic chloride **B** is not quite as reactive with LDA as the corresponding iodide, it seems reasonable to assume that it is reactive enough to yield small quantities of **A** in experiments 1−3 (Table 1).

The observation that no deuterium was incorporated in product **A** in experiments 15−17 (Table 5) can be explained by considering that, in these experiments, product **A** is formed only in trace quantities so that it becomes very difficult to obtain an accurate analysis for the deuterium incorporation in this product. On the other hand, when 5 equiv of LDA-d_2 (prepared from diisopropylamine-d_2, 94% deuterium content) was allowed to react with **2** in protio THF (experiment 18, Table 5) and THF-d_8 (experiment 19, Table 5), 39% and 42% deuterium, respectively, was incorporated in product **A**. Consequently, on the basis of these results, it is reasonable to assume that the α-hydrogen atoms of LDA are the only source of hydrogen. However, whether the reduction of **D** to **A** occurs via a radical pathway (Scheme 9) or a polar one cannot be verified on the basis of the results of experiments 18 and 19 since both radical and polar pathways would utilize the same hydrogen atom in LDA.

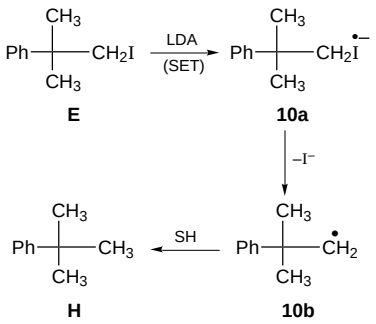
Scheme 9



The low deuterium content of product **A** in experiments 18 and 19 (Table 5) can partly be explained by the same reasons previously discussed for the formation of product **E**, namely that the LDA-d_2 is only 94% d_2, and since the LDA-d_2 is employed in 5:1 ratio with respect to **2**, there is sufficient protium present to give a high protium content because of the primary deuterium kinetic isotope effect.

Combining the results of experiments 10, 18, and 19 (Tables 3 and 5) suggests that product **H** is a product of further reduction of the monoiodide **E** with LDA (Scheme 10) in which the α-hydrogens of LDA are almost the

Scheme 10



exclusive source of hydrogen. Furthermore, the low deuterium content of **H** (42% in experiment 18 and 43% in experiment 19, Table 5) can be partly accounted for by the same arguments as those presented for the formation of **A**.

The observation that the deuterium incorporated in products **A** and **H** is almost the same in experiments 18 and 19 (Table 5) speaks against a radical intermediate abstracting a hydrogen atom from the solvent. In order to provide evidence for the involvement of radical intermediates in the conversion of **D** to **A** (Scheme 9) or **E** to **H (**Scheme 10**)**, a known radical scavenger was employed. In the reaction of **2** with LDA in a 1:1 ratio, in the presence of 10 mol % of DBNO, the formation of products **E** and **F** was greatly reduced (Table 4, experiment 14); however, when 10 mol % of DBNO was added to the reaction of **2** with LDA in a 1:5 ratio in THF at 0 °C (experiment 20, Table 6), there was no significant change in the yield of any of the products except that of the dimeric radical product **F** which dropped 60% as it had in experiment 14 (Table 4). The reason why the yield of products **A**, **E**, and **H** did not change in experiment 20 (Table 6) could be that LDA is present in a much greater amount than the radical trap. This causes the radical intermediates **6b** (Scheme 6), **9b** (Scheme 9), and **10b** (Scheme 10) to be preferentially trapped by LDA than by the radical scavenger. Also, it is possible that the excess LDA reacts with the radical scavenger, DBNO.

Table 6. Effect of Radical Trap DBNO in the Reaction of 1,1-Diiodo-2-methyl-2-phenylpropane (2) with LDA in a 1:5 Ratio at 0 °C

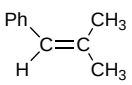
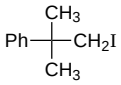
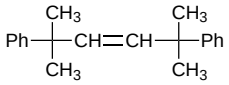
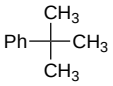
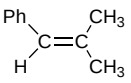
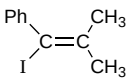
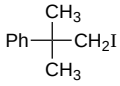
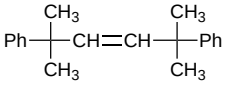
		% yield of products			
					
exp no.	additive	**A**	**E**	**F**	**H**
4	none	15	12	7.2	7.6
20	DBNO (10 mol%)	14	14	4.4	8.3

Table 7. Reaction of 1,1-Diiodo-2-methyl-2-phenylpropane (2) with Lithium Tetramethylpiperidide in a 1:1 Ratio at 0 °C

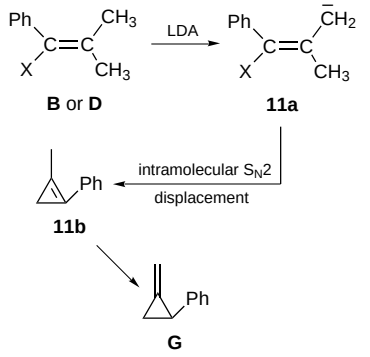
		% yield of products (% deuterium incorporation)			
					
exp no.	condns	**A**	**D**	**E**	**F**
21[a]	LTMP/THF	2.3	9.5	6.5	21
22[b]	LTMP/THF-d_8	2.1	22	1.4	10
		(20)	(0)	(14)	(0)

[a] In experiment 21, 47% of **2** was recovered after 10 min. [b] In experiment 22, 55% of **2** was recovered after 10 min.

By using a lithium amide with no α-hydrogen atoms such as lithium tetramethylpiperidide (LTMP), the radical intermediates **6b**, **9b**, and **10b** were expected to abstract hydrogen atoms from the solvent. When **2** was allowed to react with 1 equiv of LTMP in THF-d_8 at 0 °C (experiment 22, Table 7), the deuterium incorporation in products **A** and **E** was 20% and 14%, respectively. This result provides strong evidence for the involvement of radical intermediates in the formation of **A** and **E**. However, since **H** was not formed as a product of the reaction of **2** with LTMP, data are not available to support a radical mechanism for the formation of **H**.

Proposed Mechanisms for the Formation of Minor Products C and G. Product **C** can arise via SET or polar reduction of **1** by LDA. The available results do not allow one to differentiate between these two pathways. Product **G** is only formed when an excess of LDA is used (experiment 1, Table 1) or when products **B** or **D** are allowed to react with LDA (experiments 7 and 8, Table 2). **G** is thought to be formed from **B** or **D** via a mechanism (Scheme 11) in which LDA abstracts the allylic hydrogen of the vinylic halide to form the carbanion **11a**.

Scheme 11



This carbanion then cyclizes by an intramolecular S_N2 process to form the strained three-membered ring **11b** which subsequently isomerizes rapidly to form **G**. Since **G** was not formed from **D** (Table 2) and since **D** is more likely to undergo a SET process than **B**, it is unlikely that **G** was formed by the reaction of LDA with **B** by a SET process. **G** could not have originated from **C** or **E** since reaction of **C** or **E** with LDA did not produce product **G** (Table 3).[18]

Effect of Solvent. When **2** was allowed to react with LDA at 0 °C in diethyl ether, there was no appreciable change in the product distribution or the reaction rate compared to the same reaction in THF (experiments 6 and 23, Table 8). However, when **1** was allowed to react with LDA in diethyl ether at 0 °C, the rate of the reaction decreased substantially compared to the same reaction in THF (experiments 3 and 24, Table 8). The lower rate of the reaction of **1** with LDA in diethyl ether compared to THF can be explained by the lower solvating power of diethyl ether compared to THF. As a result of this, the lithium in LDA is not as strongly coordinated to diethyl ether as it is to THF; therefore, LDA is expected to be less ionic and more sterically hindered in diethyl ether than in THF. This result should cause LDA to be a weaker base in removing the α-hydrogen atoms of the probe compounds. The same solvent effect was studied concerning the reactions of **2** with LDA; however, in this case, the reduction potential of **2** is so much more favorable to electron transfer from LDA than **1** that SET is the major reaction pathway that is not very sensitive to steric effects. On the other hand, the reaction of **1** with LDA proceeds predominantly through a carbene intermediate that proceeds initially by a proton abstraction reaction which is sensitive to steric effects.

Experimental Section

Materials. Reagent grade diethyl ether, dimethoxyethane (DME), tetrahydrofuran (THF), and *p*-xylene were purchased

(18) A reviewer has suggested a reasonable alternate pathway for the formation of **G** from anion **11a** in **Scheme 11,** as follows:

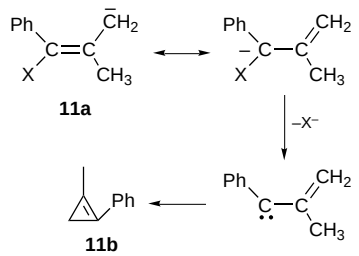
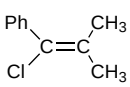
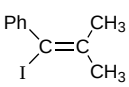
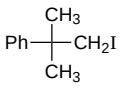
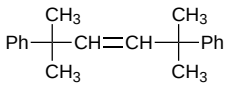
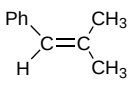


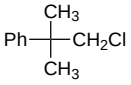
Table 8. Role of Ether and THF as Solvents in the Reactions of 1,1-Dihalo-2-methyl-2-phenylpropanes (1 and 2) with LDA at 0 °C in THF[a]

				% yield of products[b,c]			
							
exp no.	dihalide	solvent	dihalide recovered	**B**	**D**	**E**	**F**
6	2	THF	39		24	17	4.5
23	2	ether	43		22	14	7.3
3	1	THF	19	67			
24	1	ether	51	31			

[a] The ratio of the dihalide to LDA was 1:1. [b] A trace amount of **A** was also formed in all experiments. [c] A trace amount of **C** was also formed in experiments 3 and 24.



A



C

from Fisher and distilled from a deep blue solution of sodium benzophenone ketyl under N_2 prior to use. Chloroform, methanol, and absolute ethanol were purchased from Fisher and used as received. Diisopropylamine, cyclohexylamine, triethylamine, and 2,3-dimethyl-2-butene were purchased from Aldrich and distilled from CaH_2. Cumene, *dl*-2-phenylpropanal, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), and 2-butanol were purchased from Aldrich and distilled from CaH_2 at reduced pressure. Iodomethane was purchased from Aldrich and distilled from $CaCl_2$. Methyllithium was purchased as a 1.30 M solution in ether from Aldrich. 2-Methyl-1-phenyl-1-propene (**A**), *tert*-butylbenzene (**H**), 1-chloro-2-methyl-2-phenylpropane (**C**), triethylbenzylammonium chloride, hydrazine hydrate, iodine, sodium cyanoborodeuteride, 1,2-diiodoethane, ammonium acetate, CH_3OD, di-*tert*-butyl nitroxide, and acetone were also purchased from Aldrich and used without further purification. The integrity of all starting materials was checked by GLC prior to use.

General Procedures. All glassware was dried in an oven at 150 °C and cooled under N_2 before use. Glassware in which the reactions were carried out were flame dried under vacuum and cooled under N_2 three times prior to use.

^1H and ^{13}C NMR spectra were recorded on a Varian Gemini 300 MHz instrument using tetramethylsilane (TMS) as reference (0.0 δ). Mass spectral analyses were performed using a VG 70-SE mass spectrometer. Gas liquid chromatographic (GLC) analyses were performed using a Varian Model 3700 instrument equipped with a flame ionization detector (FID) and a fused silica DB5 (30 m) column. The conditions for analyses were as follows: 70 °C for 3 minutes, followed by 10 °C per minute to 250 °C for 15 min. Preparative GLC separations were performed using an F & M Model 720 instrument equipped with a thermal conductivity detector (TCD) and a Carbowax 20 M (6 ft) column under the following conditions: column temperature, isothermal at 100 °C; He flow rate of 50 mL/min. Separations by flash column chromatography employed silica gel 200-400 mesh, 60 Å (Aldrich), as the stationary phase and hexane (Fisher) as the mobile phase.

Characterization of Products. Products 2-methyl-1-phenyl-1-propene (**A**), 1-chloro-2-methyl-2-phenylpropane (**C**), and *tert*-butylbenzene (**H**) were identified by matching their mass spectra with those of commercially available authentic samples.

1-Chloro-2-methyl-1-phenyl-1-propene (B). This compound was isolated from the product mixture of the reaction of LDA with 1,1-dichloro-2-methyl-2-phenylpropane (**1**) by preparative GLC according to the conditions described under General Procedures (t_R = 56 min), and its mass spectral data were matched with literature values.[19]

1-Iodo-2-methyl-1-phenyl-1-propene (D). This compound was isolated from the product mixture of the reaction of LDA with 1,1-diiodo-2-methyl-2-phenylpropane (**2**) by flash column chromatography according to the conditions described under General Procedures, and its mass spectral data were matched with literature values.[20]

1-Iodo-2-methyl-2-phenylpropane (E). This compound was synthesized and purified according to a literature method[21] in 24% yield, and its mass spectral data were matched with those reported.

2,5-Dimethyl-2,5-diphenyl-3-hexene (F). This compound was isolated from the product mixture of the reaction of LDA with **2** by flash column chromatography, and its mass spectral data were matched with those reported.[22]

2-Phenylmethylenecyclopropane (G). This compound was isolated from the product mixture of the reaction of LDA with **1** by preparative GLC (t_R = 28 min), and its mass spectral data were matched with those reported.[23]

Ethylene. This compound was generated quantitatively in the reaction of 1,2-diiodoethane with LDA under the usual experimental conditions and its spectral data were matched with those reported.[24] IR: 946, 1418, 1461, 1868, 1888, and 3084 cm^{-1}. High resolution mass spectrum: obsd 28.031 479, calcd 28.031 300 2.

Preparations. 1,1-Dichloro-2-methyl-2-phenylpropane (1). This compound was prepared and purified according to a literature method[25] in 25% yield, and its spectral data were matched with those reported. ^1H NMR ($CDCl_3$): δ 7.4 (5 H, m), 5.95 (1 H, s), and 1.56 (6 H, s). Mass spectrum: (relative intensity) 202 (M^+, 3), 167 (7), 119 (100), and 91 (30).

2-Methyl-2-phenylpropanal. This compound was prepared by a literature method reported for a similar compound.[26] To a three-necked round-bottom flask equipped with a reflux condenser and dropping funnel was added cyclohexylamine (44.6 g, 0.5 mol). Next, *dl*-2-phenylpropanal (67.1 g, 0.5 mol) was added dropwise, with stirring, over a period of 1 h. The temperature rose during the addition, and a cloudy mixture formed. The organic layer was separated from the aqueous layer and treated with 7.5 g of anhydrous K_2CO_3, stirred at room temperature for 17 h, and decanted into 6.0 g of BaO. The mixture was stirred for 10 h, and the organic layer was filtered to give 96.1 g (89% yield) of the crude imine which was used in the subsequent step without purification. Mass spectrum of the imine: *m*/*e* (relative intensity) 215 (M^+, 9), 133 (13), 91 (20), 83 (40), and 40 (100).

A portion of the above imine (10.75 g, 50 mmol) was added to a solution of 50 mmol of LDA in 35 mL of THF in a three-

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necked round-bottom flask under a stream of N_2 at −78 °C. The resulting solution was warmed to 20 °C over a period of 1.5 h and then treated dropwise with 7.8 mL (0.125 mol) of CH_3I with stirring for 20 min while the temperature of the reaction mixture was kept in the range 20−40 °C by external cooling. At the end of this addition, the reaction mixture, which was a slurry containing solid LiBr, was stirred at room temperature for 3.5 h. Ice−water was then added to the reaction mixture, and the organic layer was extracted with ether. The ether layer was washed with saturated NaCl solution and distilled water and then dried over anhydrous $MgSO_4$. The ether was removed using a rotary evaporator to give 11.0 g (96% yield) of the dimethylimine which was used in the subsequent step without purification. Mass spectrum of the dimethylimine: m/e (relative intensity) 229 (M^+, 16), 119 (80), 110 (60), 91 (19), and 83 (100).

Hydrolysis of the dimethylimine was then carried out by stirring 9.16 g (40 mmol) in 50.0 mL of hexane at room temperature with 120 mL of 8% aqueous acetic acid under a stream of N_2 for 2 h. The aqueous layer was then separated from the hexane layer and extracted with ether several times. The combined hexane and ether extracts were then washed with saturated NaCl solution and distilled water and then dried over anhydrous $MgSO_4$. Solvents were removed using a rotary evaporator and the product distilled at reduced pressure to give 5.30 g (89% yield) of 2-methyl-2-phenylpropanal as a colorless liquid (boiling point: 80 °C at 10 mmHg). The spectral data were matched with those reported in the literature.[27] ^{1}H NMR ($CDCl_3$): δ 9.5 (1 H, s), 7.3 (5 H, m), and 1.45 (6 H, s). Mass spectrum of 2-methyl-2-phenylpropanal: *m/e* (relative intensity) 148 (M^+, 7), 119 (100) and 91 (58).

1,1-Diiodo-2-methyl-2-phenylpropane (2). This compound was prepared according to a literature method reported for the synthesis of geminal diiodides.[28] To 1.42 g (100 mmol) of 2-methyl-2-phenylpropanal, 12 mL of ethanol, and 6.0 mL of triethylamine was added 6.0 mL of hydrazine hydrate, and the reaction mixture was allowed to reflux for 1 hour. The cooled solution was extracted with $CHCl_3$, and the organic layer was washed with distilled water and finally dried over anhydrous $MgSO_4$. The hydrazone was obtained as an oil by evaporating the solvent using a rotary evaporator, and it was used in the subsequent step without purification. ^{1}H NMR ($CDCl_3$): δ 7.2 (5 H, m), 7.05 (1 H, s), 5.1 (2 H, broad s), and 1.4 (6 H, s).

The hydrazone was dissolved in 12 mL of ether and 4.0 mL of triethylamine and treated with a concentrated solution of excess iodine in ether until the evolution of N_2 gas had ceased and the iodine color persisted. The ether layer was then washed consecutively with 5% $Na_2S_2O_3$, 3 N HCl, 5% Na_2CO_3, and distilled water and then dried over anhydrous $MgSO_4$. The ether was removed using a rotary evaporator, and the crude material was purified by liquid−solid chromatography using silica gel 200−400 mesh, 60 Å to obtain 0.77 g (20% yield) of **2** as a yellow solid. ^{1}H NMR ($CDCl_3$): δ 7.32 (5 H, m), 5.7 (1 H, s), and 1.4 (6 H, s). Mass spectrum: (relative intensity) 386 (M^+, 8), 259 (27), 132 (100), 117 (49), and 91 (24).

Lithium Diisopropylamide (LDA). At −78 °C, 1.0 mL of a 1.30 M solution of MeLi (1.3 mmol) in ether was added to 0.24 mL (1.7 mmol) of diisopropylamine in 1.0 mL of dry THF in a round-bottom flask under a stream of N_2. The resulting mixture was stirred at this temperature for 30 min. At the end of this period, the mixture was warmed to 0 °C and the solvents and excess diisopropylamine were removed under reduced pressure. LDA was then obtained as a white powder which was dissolved in dry THF. The LDA solution was used immediately after standardization. The standardization was carried out by adding to the organolithium compound a standard 0.5 M solution of 2-butanol in p-xylene dropwise under nitrogen using 2,2′-bipyridyl as an indicator. The purple color of LDA in 2,2′-bipyridyl changed to pale green at the end point.[29] The yield of LDA was usually 70−90% based on MeLi.

Lithium Diisopropylaminde-d_2 (LDA-d_2). This compound was prepared and standardized using the same method as that for the protio compound employing diisopropylamine-d_2 as the starting amine.

N,N′-Bis(1-deuterio-1-methylethyl)amine (Diisopropylamine-d_2). This compound was prepared according to a reported method[30] in 20% yield based on acetone. The deuterium content of this compound was found to be about 94% by means of ^{1}H NMR. The ^{1}H NMR of this compound matched with that reported. ^{1}H NMR: δ 0.967 (12 H, s).

General Procedure for Reactions of 1,1-Dihalo-2-methyl-2-phenylpropanes and Other Alkyl Halides with LDA. To 1.5 mmol of the alkyl halide in a dry 5 mL round-bottom flask was added enough solvent to make a solution of the alkyl halide and then the flask placed in a bath at 0 °C. Unless otherwise specified, 1 equiv of cold standard LDA was usually added in a dropwise manner. All the reactions carried out were complete within 1 min, after which time there was no change in the product distribution. However, the stirring was continued for an additional 10 min, after which time the reaction mixture was quenched and the products were analyzed by GLC using *n*-dodecane as an internal standard. The quenching was usually carried out by adding an aliquot from the reaction pot to several drops of distilled water at 0 °C under N_2 and extracting the products in ether. In all the reactions carried out, the concentrations of the halide and LDA were about 0.5 M. Whenever an additive such as a radical or a carbene trap was required, the solution of the alkyl halide was prepared first and the trap was added to it before the addition of LDA.

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