Factors Controlling Regioselectivity in Deprotonations of Unsymmetrical Ketimines

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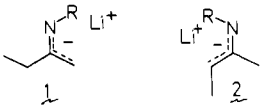
Abstract: The regioselectivity of deprotonation of equilibrium *E*-*Z* mixtures of the benzyl, *n*-butyl, cyclohexyl, phenyl, and *tert*-butyl imines of 2-butanone by lithium diisopropylamide (LDA) in tetrahydrofuran has been shown to be a function of both the nitrogen substituent and the temperature of the deprotonation reaction. High regioselectivity at either the methyl or methylene substituent could be obtained for all imines except the benzyl and *n*-butyl imines. Pure (*Z*)-2-butanone imines (R = *n*-C_4H_9, c-C_6H_{11}, *t*-C_4H_9), prepared by LDA deprotonation of acetone imines followed by methylation, were deprotonated by LDA at the methyl position at −78 °C and at 0 °C. Studies of the rates of deprotonation of the *E* and *Z* isomers of *n*-butyl, cyclohexyl, and *tert*-butyl imines of 2-butanone and of the rates and mechanisms of isomerizations of these isomeric ketimines were performed. Temperature dependent deprotonation regioselectivity was also observed in lithium diethylamide deprotonations of the benzyl, cyclohexyl, phenyl, and *tert*-butyl imines of 2-butanone. A general scheme accounting for these results and other accounts of variable regioselectivity in ketimine deprotonation is presented.

Regioselectivity in deprotonation of carbonyl compounds is important both for the synthetic utilization of the resulting enolates and because of the mechanistic implications of such selectivity.[2] In principle, azaallyllithium reagents formed from derivatives of carbonyl compounds could prove to be more useful than enolates since the substituent on the nitrogen could influence the regioselectivity of the deprotonation reaction resulting in deprotonation either syn or anti to the nitrogen substituent. In fact, deprotonation of oximes has been reported to occur with high selectivity syn to the nitrogen substituent[3] while unsymmetrical ketone dimethylhydrazones generally deprotonate on the less substituted α-carbon regardless of the C=N geometry.[4] Recently we have shown that dimethylhydrazones and imines of 3-pentanone which are unsymmetrical only by viture of the position of the nitrogen substituent relative to a ^{13}C-labeled methyl group are deprotonated with low, mixed regioselectivity.[6,7] Recent studies of ketimine deprotonations in which hindered lithium dialkylamide bases deprotonate ketimines at the less substituted carbon of cyclic ketimines and alkyllithium reagents deprotonate cyclic and acyclic ketimines at the more substituted α-carbon suggest regioselectivity in ketimine deprotonation is a complex phenomenon.[8,9] Here we report our studies of deprotonation of unsymmetrical ketimines derived from 2-butanone using lithium diisopropylamide (LDA) and lithium diethylamide (LDEA). These studies show that regioselectivity in these deprotonations varies with the nature of the imine nitrogen substituent, the experimental conditions, and the structure of the dialkylamide base and that deprotonation and alkylation can occur with high yield at either the CH_3 or the CH_2 position. In addition, studies of rates of LDA deprotonation reactions and the rates of *E* to *Z* isomerization of 2-butanone imines have enabled us to construct an interpretative mechanistic scheme to account for these results.

Results and Discussion

We have studied the regioselectivity of LDA deprotonations of the *n*-butyl, benzyl, cyclohexyl, phenyl, and *tert*-butyl imines of 2-butanone by GC analysis of the 3-methyl-2-butanone or 3-pentanone imines formed after methylation (iodomethane, −78 °C, THF) of the intermediate azaallyllithium reagents. Deprotonation of the *tert*-butyl imine of 2-butanone (equilibrium mixture of 85% *E* and 15% *Z* stereoisomers) provides an example of the effects of temperature on deprotonation regioselectivity. At −78 °C LDA deprotonation of this imine is relatively slow with a 22-h half-life. Methylation of the intermediate azaallyllithium reagent formed under these conditions gave as essentially the only product *N*-*tert*-butyl-3-pentanone imine (cf. Figure 1). In contrast, deprotonation of this equilibrium mixture of *N*-*tert*-butyl-2-butanone imines at 0 °C followed by methylation (−78 °C) yielded the imine of 3-methyl-2-butanone as the predominant product. Thus, it is possible to use the temperature of the deprotonation reaction to afford either possible regioisomeric azaallyllithium reagent **1** or **2** (R = *tert*-butyl).



Deprotonation of equilibrium *E*-*Z* mixtures of the *n*-butyl, cyclohexyl, phenyl, and benzyl imines of 2-butanone with LDA at varying temperatures between −78 and 25 °C followed by −78 °C methylation of the resulting mixtures of regioisomeric azaallyllithium reagents **1** and **2** (R = *n*-C_4H_9, c-C_6H_{11}, C_6H_5, and $CH_2C_6H_5$) yielded the results shown in Figure 1. In all cases higher deprotonation temperature favored increased amounts of methylene deprotonation leading in four of the five cases to a reversal of deprotonation regioselectivity.

When solutions of kinetic azaallyllithium reagents (R = *n*-C_4H_9, c-C_6H_{11}, C_6H_5, and *t*-C_4H_9) prepared at 25 °C by LDA deprotonation of the corresponding 2-butanone imines were allowed to stand for several days at room temperature, isomerization of the initial mixture of regioisomeric azaallyllithium reagents (predominantly **2**) occurred to form the thermodynamically favored azaallyllithium reagents **1**. Although the mechanism for this isomerization is unclear,[10] the results demonstrate that the mixtures

(1) Camille and Henry Dreyfus Teacher-Scholar, 1980-1985.
(2) Substituents on ketones and the identity of the base can affect both the stereoselectivity and regioselectivity of ketone enolate formation; cf. Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066-1081. Posner, G. H.; Lentz, C. M. *J. Am. Chem. Soc.* **1979**, *101*, 934-946.
(3) Kofron, W. G.; Yeh, M.-K. *J. Org. Chem.* **1976**, *41*, 439-442. Lyle, R. E.; Fribush, H. M.; Lyle, G. G.; Saavedra, J. E. *Ibid.* **1978**, *43*, 1275-1276.
(4) Corey, E. J.; Enders, D. *Chem. Ber.* **1978**, *111*, 1337-1361, 1362-1383.
(5) In this study and in previous work[6,7] we have observed qualitatively that LDEA deprotonates imines and ketone dimethylhydrazones faster than does LDA. Since isomerization reactions we propose in eq 2 and 3 are not dependent on the identity of the base, our observations suggest that LDEA deprotonations of (*E*)-2-butanone imines above −78 °C occur with more syn selectivity than do the LDA deprotonations.
(6) Bergbreiter, D. E.; Newcomb, M. *Tetrahedron Lett.* **1979**, 4145-4148. Ludwig, J. E.; Newcomb, M.; Bergbreiter, D. E. *J. Org. Chem.*, **1980**, *45*, 4666-4669.
(7) Smith, J. K.; Bergbreiter, D. E.; Newcomb, M. *J. Org. Chem.* **1981**, *46*, 3157-3158.
(8) Meyers, A. I.; Williams, D. R.; Erickson, G. W.; White, S.; Druelinger, M. *J. Am. Chem. Soc.*, **1981**, *103*, 3081-3087.
(9) Hosomi, A.; Araki, Y.; Sakurai, H. *J. Am. Chem. Soc.* **1982**, *104*, 2081-2083.

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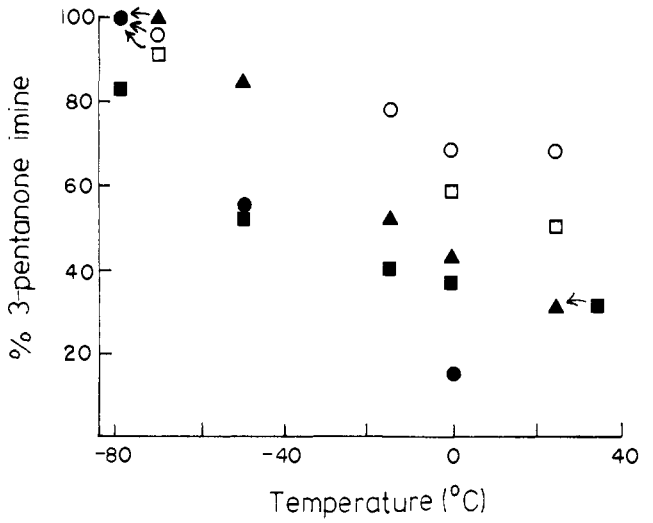


Figure 1. Percentage of 3-pentanone imine formed by LDA deprontation of *E*–*Z* equilibrium mixtures of 2-butanone imines at various temperatures followed by methylation at −78 °C. Legend [R in imine (symbol)]: *t*-C_4H_9 (●); c-C_6H_{11} (▲); C_6H_5 (■); $CH_2C_6H_5$ (○); *n*-C_4H_9 (□).

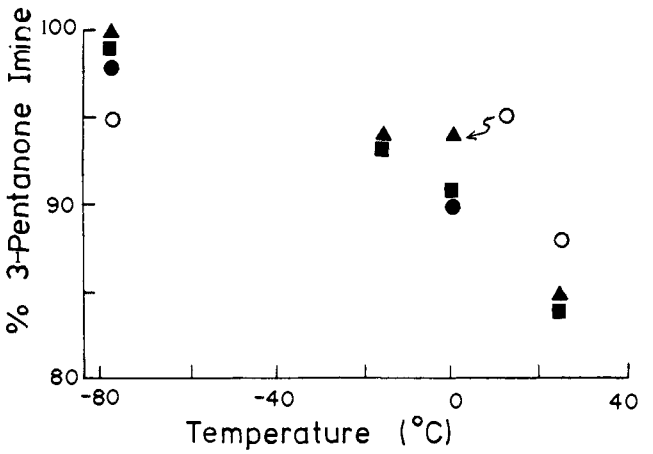


Figure 2. Percentage of 3-pentanone imine formed by LDEA deprotonation of *E*–*Z* equilibrium mixtures of 2-butanone imines at various temperatures followed by methylation at −78 °C. Legend [R in imine (symbol)]: *t*-C_4H_9 (●); c-C_6H_{11} (▲); C_6H_5 (■); $CH_2C_6H_5$ (○).

of **1** and **2** formed in the other experiments are not thermodynamic mixtures. It is also noteworthy that the less substituted azaallyllithium reagent is the thermodynamically favored regioisomer unlike the case for analogous lithium enolates.[11]

Deprotonation of the benzyl, cyclohexyl, phenyl, and *tert*-butyl imines of 2-butanone using lithium diethylamide (LDEA) was also studied to determine what effect the structure of the dialkylamide base has on deprotonation regioselectivity and to determine if the temperature dependence of deprotonation observed in LDA deprotonations is a general phenomenon. As is shown in Figure 2, deprotonation of these 2-butanone imines at various temperatures between −78 °C and 25 °C followed by −78 °C methylation yields products derived from both **1** and **2**. In these LDEA deprotonation reactions, **1** is always the major species present as indicated by the predominance of the 3-pentanone imine products after methylation. However, there is a clear trend leading to more **2** as the temperature of the deprotonation reaction increases, a trend which parallels the LDA results discussed above. Because we have not investigated the rate of isomerizations in these LDEA deprotonation reactions (vide infra), we cannot be certain

(10) Equilibration mechanisms for these species involving proton transfer or oxygen-catalyzed isomerization have precedence: cf. Lee, J. Y.; Lynch, T. J.; Mao, D. T.; Bergbreiter, D. E.; Newcomb, M. *J. Am. Chem. Soc.* **1981**, *103*, 6215–6217 and references therein.

(11) See: House, H. O. "Modern Synthetic Reactions", 2nd ed.; W. A. Benjamin: Menlo Park, CA, 1972; pp 558–560.

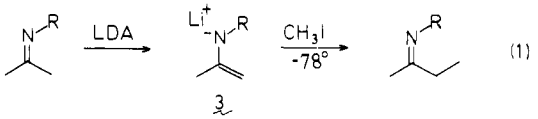
Table I. Half-Lives for Deprotonation of 2-Butanone Imines by LDA in THF at −78 °C[a]

R in imine	*E*–*Z*	imine concn, M	LDA concn, M	$t_{1/2}$,[c] h
t-C_4H_9	85:15	0.30	0.40	22.5
	85:15	0.24	0.60	22.0
	0:100[b]	0.14	0.21	<1
c-C_6H_{11}	80:20	0.13	0.17	2.7
	80:20	0.055	0.44	2.8
	80:20	0.085	0.17	2.9
	80:20	0.064	0.48	3.3
	80:20	0.043	0.69	~4
	0:100[b]	0.06	0.07	0.62
	0:100[b]	0.07	0.13	0.25
	0:100[b]	0.05	0.40	<0.08
	0:100[b]	0.09	0.50	<0.08
C_6H_5	80:20	0.15	0.22	0.33
	80:20	0.11	0.33	0.30
	0:100[b]	0.08	0.24	<0.08
n-C_4H_9	85:15	0.10	0.80	0.10
	85:15	0.10	0.50	0.25
	85:15	0.10	0.25	0.58
	0:100[b]	0.01	0.05	0.30
	0:100[b]	0.10	0.40	<0.02

[a] Solutions of 2-butanone imines in THF containing an internal standard were treated with LDA at −78 °C. Aliquots were removed periodically and added to THF solutions of iodomethane at −78 °C. The resulting mixtures were analyzed by GC. [b] 2-Butanone imines prepared in an analogous reaction which contained a $^{13}CH_3$ label contained no detectable *E* ketimine by ^{13}C NMR spectroscopy. [c] Time at which 50% conversion of the 2-butanone imine to a mixture of azaallyllithium reagents occurred.

if these differences reflect a greater preference by LDEA for syn deprotonation of (*E*)-2-butanone imines than is seen with LDA at temperatures above −78 °C.[5] Minor differences have been noted previously in deprotonation regioselectivity with LDEA as compared to LDA.[6,7] However, these previous results show in one case more anti deprotonation with LDEA and in another case no effect on changes in base identity, suggesting that any explanation of the subtle effects of changes in lithium dialkylamide base structure on deprotonation regioselectivity will require further study.

The complex results shown in the figures suggested that the origins of the regioselective preferences could only be understood by kinetic studies of stereochemically pure imines. These kinetic studies have been performed by using LDA as a base since the most dramatic changes in deprotonation regioselectivity were observed with this hindered lithium dialkylamide base. Since the equilibrium mixtures of 2-butanone imines were all ca. 80:20 *E*–*Z*, we used these mixtures for studies of rates of deprotonation of *E* imines. Stereochemically pure (>95%) *Z* imines were prepared by the sequence of reactions shown in eq 1 by using the azaallyllithium reagents **3** derived from acetone imines. When the reaction sequence of eq 1 was carried out with $^{13}CH_3I$, we obtained species readily studied by ^{13}C NMR spectroscopy.



(1)

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The results in Table I show that at −78 °C, the rates of LDA deprotonation of (*E*)-2-butanone imines containing bulky R groups (R = cyclohexyl or *tert*-butyl) were essentially independent of base concentration! In contrast, LDA deprotonations of the corresponding (*Z*)-2-butanone imines under these conditions were both faster and base dependent. One explanation for this observation would be that the *E* imines in fact were not deprotonated under these conditions but first underwent rate-limiting isomerization to *Z* imines which rapidly deprotonated anti to the R group to give azaallyllithium reagents **1** (Scheme I). In accord with this mechanism, deprotonation of the (*Z*)-cyclohexyl imine at −78 or 0 °C followed by methylation gave the 3-pentanone product unlike

Scheme I

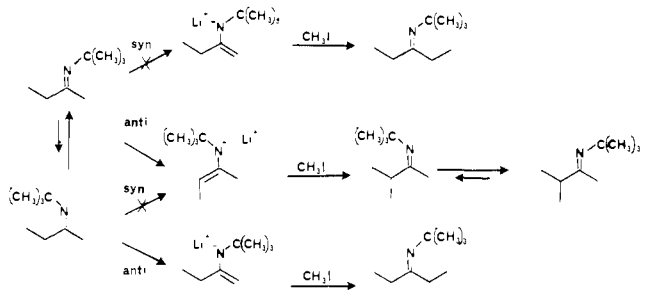


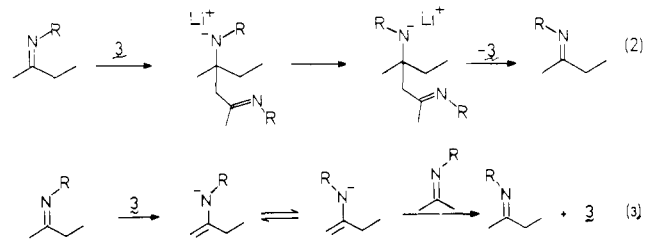
Table II. Isomerization of (*Z*)-2-butanone Imines to (*E*)-2-Butanone Imines[a]

R in imine	temp, °C	imine concn,[b] M	3 concn,[c] M	$t_{1/2}$,[d] h
t-C_4H_9	0	0.83	0	0.22
c-C_6H_{11}	−20	0.87	0	1.67
	−20	0.87	0.1	0.68
	−20	0.87	0.36	0.21
C_6H_5	−20	0.87	0.14	0.58
n-C_4H_9	0	0.78	0	0.75
	0	0.78	0.34	0.28
	0	0.78	0.57	0.28

[a] (*Z*)-2-Butanone imines were prepared in THF by deprotonation of the appropriate acetone imine with 1.1 molar equiv of LDA at 0 °C followed by alkylation of the resulting azaallyllithium reagents **3** with ^{13}C iodomethane at −78 °C. The resulting mixtures were warmed in a thermostated probe of an NMR spectrometer, and the ^{13}C NMR spectra were recorded periodically. The extent of formation of the *E* imine was determined by measurement of the area of the signal resulting from the $^{13}CH_3$ group of the respective imine. [b] The total estimated concentration of imine and azaallyllithium reagent **3**. [c] Azaallyllithium reagent **3** was present in solutions alkylated with a deficient amount of iodomethane; on the basis of the errors accumulated in successive volumetric transfers, the concentrations of **3** listed may be inaccurate by as much as 0.1 M. [d] The time at which a 1:1 mixture of *E* and *Z* imines was observed.

the case with the E–Z mixture (Figure 1). On the basis of the data of Table I, the minor *Z* component of 2-butanone imines must be deprotonated much faster than the *E* component in deprotonations of ca. 80:20 E–Z mixtures of 2-butanone imines. In accord with this expectation, qualitative rate studies show that deprotonation of *E*–*Z* mixtures of 2-butanone imines appears to be faster for the first 5–15% of the reaction. However, experimental difficulties made quantitative measures of this phenomenon unfeasible. The independence of $t_{1/2}$ for the deprotonations of *E*–*Z* mixtures of 2-butanone imines thus reflects the rate of deprotonation of the predominant *E* isomer.

To correlate Scheme I, the rates of isomerization of (*Z*)-[4-^{13}C]-2-butanone imines were studied (Table II). The uncatalyzed rates of isomerization were found to be too slow to be accommodated by Scheme I. However, when a deficiency of iodomethane was employed in the alkylation reaction used to prepare the ^{13}C-labeled butanone imines, the rates of isomerization were clearly accelerated. This isomerization could occur either by the mechanism of eq 2 or by the mechanism of eq 3. Thus, for LDA

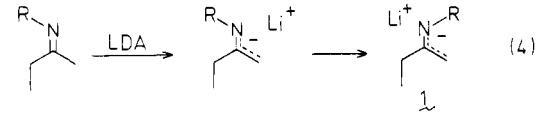


deprotonations of (*E*)-2-butanone imines with bulky R groups, azaallyllithium reagents like **1**, **2**, or **3** apparently can serve as either nucleophilic or base catalysts for the isomerization process which would occur by pathways directly analogous to, but in the reverse direction of, the reactions shown in eq 2 or 3.[12]

As the temperature of the deprotonation reaction increases, LDA deprotonation of the methylene position anti to the R group apparently begins to compete effectively with *E*–*Z* isomerization and mixtures of **1** and **2** form. Eventually, the ratio of **1**–**2** reflects the initial ratio of *E*–*Z* isomers of the starting ketimine.

Our proposed mechanism for deprotonation of imines of 2-butanone depicted in Scheme I assumes that the R group on nitrogen of the imine directs attack of a hindered lithium dialkylamide base to the acidic C–H anti to this R group at 0 °C. At lower temperatures, both deprotonation at the anti CH_2 site and deprotonation at the CH_3 syn to the R group are slower than isomerization by either or both of the mechanisms described by eq 2 and 3. As the imine isomerizes, the *Z* isomer that contains an anti CH_3 group is formed and rapid deprotonation of this anti CH_3 group then ensues ultimately producing the isomerized *syn*-azaallyllithium reagent. Scheme I suggests that deprotonation regiochemistry is dominated by steric effects associated with the R group on the imine nitrogen with the imposition of other effects due to the differences between the kinetic acidity of CH_2 and CH_3 groups under some conditions. When the size of the R group on nitrogen is altered from a *tert*-butyl group to a smaller *n*-butyl group, the effectiveness of the R group on nitrogen as a steric block of syn deprotonation at CH_3 at low temperature should decrease. The results of studies of the rates of deprotonation of the *n*-butyl imine of 2-butanone at −78 °C confirm this hypothesis. While the *tert*-butyl and cyclohexyl imines of 2-butanone deprotonate at this temperature without a kinetic dependence on the LDA concentration, the rate of *n*-butyl imine deprotonation is dependent on the concentration of LDA. The azaallyllithium reagent **1** is still formed under these conditions, showing that CH_3 deprotonation is occurring. Separate experiments (see Table II) show that isomerization of this sterically unencumbered *n*-butyl imine at −78 °C would be too slow to precede deprotonation even in the presence of catalytic amounts of **3**. Thus, deprotonation regioselectivity is affected by the nature of the R group on ketimines as well as by temperature and the structure of the base used for deprotonation.

One conclusion from our studies deserves special comment. In the case of low-temperature LDA deprotonation of ketimines with bulky (R = *tert*-butyl, cyclohexyl) substituents on nitrogen, deprotonation anti to the substituent must give as the first formed azaallyllithium reagent the anti anionic species (eq 4). This first formed intermediate would then rapidly isomerize to the syn species **1** which is known to be substantially more stable.[13] Thus, the steric effects of the R group can evidently override any electronic preference for syn anionic species which might be manifested in the transition state for deprotonation.



Overall, our experiments provide a detailed rationale for the regiochemistry observed in deprotonation reactions of simple acyclic ketimines carried out by lithium dialkylamide bases. The studies reported here demonstrate the various factors which are

(12) The azaallyllithium reagent **1** formed by deprotonation of the starting 2-butanone imine can catalyze the isomerization of the butanone imine, thus making this isomerization and subsequent deprotonation an autocatalytic process. Initially, this autocatalysis should produce a rate acceleration in this deprotonation reaction. However, in the range of 25–75% conversion, this bimolecular isomerization reaction in which the catalyst is being formed at the same rate as the substrate is being consumed will appear to behave in a nearly first-order manner. For example, the rate will vary from a relative rate of 1 at 25% conversion to 1.33 at 50% conversion and then back to 1 at 75% conversion. Although our GC data which measure the rate of formation of **1** and **2** do have some scatter, a first-order plot of these data did show this expected initial rate acceleration and final rate deceleration.

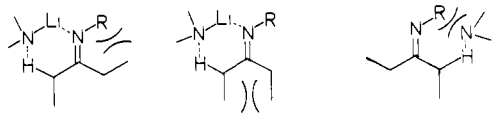
(13) Regardless of the regioselectivity in the deprotonation step, *syn*-azaallyllithium reagents are thermodynamically favored: cf. Houk, K. N.; Stozier, R. W.; Rondan, N. G.; Fraser, R. R.; Chauqui-Offermanns, N. *J. Am. Chem. Soc.* **1980**, *102*, 1426–1429 and references therein.

Table III. Properties of Imines

imine	bp, °C (torr)	lit. bp, °C (torr)	ref
$(CH_3)_2C{=}N(CH_2)_3CH_3$	47 (24)	127 (760)	17
$(CH_3)_2C{=}NCH_2Ph$	62–64 (0.04)	107 (13)	18
$(CH_3)_2C{=}NPh$	38 (0.08)	65–66 (7)	19
$(CH_3)_2C{=}N\text{-}c\text{-}C_6H_{11}$	38 (1.5)	181 (760)	20
$(CH_3)_2C{=}N\text{-}t\text{-}C_4H_9$	110–115 (760)	38–39 (44)	21
$CH_3CH_2C(CH_3){=}N(CH_2)_3CH_3$	35–36 (0.2)	42–44 (15)	22
$CH_3CH_2C(CH_3){=}NCH_2Ph$	56–58 (0.01)	74–80 (0.7)	22
$CH_3CH_2C(CH_3){=}NPh$	37 (0.02)	107–108 (27)	23
$CH_3CH_2C(CH_3){=}N\text{-}c\text{-}C_6H_{11}$	48 (0.2)	79–80 (16)	24
$CH_3CH_2C(CH_3){=}N\text{-}t\text{-}C_4H_9$ (a)[a]	126–129 (760)		
$(CH_3CH_2)_2C{=}N(CH_2)_3CH_3$	38–39 (0.15)	64 (16)	25
$(CH_3CH_2)_2C{=}NCH_2Ph$	62–65 (0.15)	134 (20)	22
$(CH_3CH_2)_2C{=}NPh$	55 (0.02)	97–98 (11)	23
$(CH_3CH_2)_2C{=}N\text{-}c\text{-}C_6H_{11}$	55–56 (0.06)	102–104 (26)	24
$(CH_3CH_2)_2C{=}N\text{-}t\text{-}C_4H_9$ (b)[a]	151–153 (760)		
$(CH_3)_2CHC(CH_3){=}N(CH_2)_3CH_3$ (c)[a]	39–40 (0.15)		
$(CH_3)_2CHC(CH_3){=}NCH_2Ph$ (d)[a]	126–127 (12)	not reported	26
$(CH_3)_2CHC(CH_3){=}NPh$	55–60 (0.05)	54–56 (0.3)	27
$(CH_3)_2CHC(CH_3){=}N\text{-}c\text{-}C_6H_{11}$	62–64 (0.1)	81–84 (13)	28
$(CH_3)_2CHC(CH_3){=}N\text{-}t\text{-}C_4H_9$	133–135 (760)	56–59 (55)	29

[a] ^1H-decoupled ^{13}C NMR spectra (δ, $CDCl_3$) for the (*E*) isomers: a, 169.2, 54.4, 37.6, 30.5, 19.9, 11.6; b, 172.5, 54.2, 32.7, 31.1, 26.6, 12. 12.1, 11.6; c, 170.3, 50.0, 39.0, 32.9, 20.2, 19.0, 14.0, 13.2; d, 174.7, 140.7, 128.2, 127.4, 126.2, 54.6, 40.1, 19.8, 15.0.

important in determining deprotonation regiochemistry and illustrate in a qualitative sense the relative magnitude of these various effects. Scheme I for LDA deprotonation is in accord with the results of regioselectivity studies of LDA deprotonations of cyclic ketimines[8] (which could be interpreted as rate-limiting isomerization followed by anti deprotonation to give the less substituted azaallyllithium reagent) and with the regioselectivity seen in alkyllithium deprotonations of cyclic and acyclic ketimines[9] (which could be interpreted as fast anti deprotonation to give a mixture of regioisomeric azaallyllithium reagents whose composition reflects the *E*–*Z* ratio of the starting ketimine). However, it is important to emphasize that such regioselective control is only expected in methyl ketones or cyclic ketones; in more highly substituted ketimines low regioselectivity may often be observed as shown by our results for 3-pentanone imines.[7] This expectation is based on consideration of the strained transition states **4**–**6** which



4 **5** **6**

must obtain in an acyclic ketimine deprotonation in which neither substituent is a methyl group. High regioselectivity in deprotonation of more highly substituted ketimines could be expected only through judicious choice of the R group on nitrogen in the ketimine, the identity of the hindered lithium dialkylamide base, and the conditions used for the deprotonation reaction. High regioselectivity in deprotonation of more substituted ketimines should nevertheless be possible.[30]

Experimental Section

General Procedures. All reactions involving organometallic species were run under an inert atmosphere of nitrogen or argon by using routine procedures.[14] ^1H NMR spectra were recorded either on a Varian T-60 or EM-390 NMR spectrometer using Me_4Si as an internal standard. ^1H-decoupled ^{13}C NMR spectra were recorded at 25 MHz on a JEOL PFT-100 NMR spectrometer equipped with a low-temperature apparatus; benzene-d_6 was used for a lock signal; chemical shifts were measured relative to the upfield signal of THF which we defined as δ 25.0. Probe temperatures in ^{13}C NMR experiments were measured by using a digital thermometer with a copper–constantan thermocouple in a nonspinning NMR tube containing THF inserted into the probe of the NMR spectrometer; the thermocouple was kept above the level of the coils. GC analyses were performed on either a Hewlett-Packard Model 5880A or Varian 2440 chromatograph using capillary columns (38-m Carbowax or 25-m SE-30). Imine syntheses employed reagent quality ketones and amines obtained from Aldrich Chemical Co.

The preparation of "clean" LDA solutions in THF which were suitable for ^{13}C NMR spectroscopy has been described.[15]

Imine Syntheses. Imines were synthesized from ketones by conventional procedures. Representative procedures are described below. Boiling points of the imines and ^{13}C NMR spectral data for the new imines prepared in this paper are presented in Table III.

***tert*-Butyl Imine of 3-Pentanone.** This imine and other hindered imines were prepared by using the procedures described previously by Weingarten.[16] In this procedure, 43 g of 3-pentanone (0.5 mol), 73 g of *tert*-butylamine (1 mol), and 300 mL of pentane were cooled to 0 °C in a three-necked, 1-L flask under an argon atmosphere. Then 27 mL of titanium tetrachloride (0.25 mol) was added dropwise from a pressure-equalized addition funnel to this stirring reaction mixture over a 1-h period. After an additional 0.5 h of stirring at 0 °C, IR spectroscopy of an aliquot indicated that the starting carbonyl compound had been consumed. At this point the reaction mixture was filtered. The filter cake was washed three times with 100-mL portions of pentane. The filtrates were then combined, the volatile solvents were removed by using a rotary evaporator, and the residue was distilled to yield 35 g (50% yield) of a colorless liquid.

Cyclohexyl Imine of 3-Pentanone. Less hindered ketimines were prepared in acceptable yield by using azeotropic removal of water from refluxing benzene solutions of amines and carbonyl compounds. Thus, a solution of 58 mL of 3-pentanone (0.55 mol) and 57 mL of cyclohexylamine (0.5 mol) in 300 mL of benzene was heated to reflux until the appropriate amount of water (ca. 9 mL) was collected in a Dean-Stark apparatus. Removal of the solvent by distillation at reduced pressure followed by distillation of the residue yielded 72 g of the ketimine as a colorless liquid.

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Preparation of (Z)-2-Butanone Imines. The following procedure was used for the preparation of all (Z)-2-butanone imines. To 2 mL of a solution of 1 N "clean" LDA base[15] in THF at -78 °C in an NMR tube was added 1.8 mmol of an acetone imine (vortex stirring). Benzene-d_6 (0.2 mL) was added and the deprotonation reaction was followed by ^{13}C NMR spectroscopy at ca. -80 °C. After complete deprotonation (ca. 30 min), the NMR tube was maintained at -78 °C and the mixture was treated with 0.45 mL of 5 M iodomethane in THF (for ^{13}C NMR studies 30% ^{13}C-enriched iodomethane was used). The resulting solution of (Z)-2-butanone imine was assayed by ^{13}C NMR spectroscopy at -80 °C. The solutions were maintained at -78 °C until they were used in further studies.

Regioselectivity Studies. Solutions of LDA and LDEA in THF were prepared by adding 0.9 molar equivs of *n*-butyllithium in hexane (Aldrich) to the appropriate amine (distilled from CaH_2 and stored over 4A molecular sieves under argon) in THF (freshly distilled from potassium/benzophenone) at -78 °C followed by warming to 0 °C for 10 min. The base solutions (15-18 mL) were ca. 0.1-0.5 N in lithium dialkylamide in these various studies. Base solutions were equilibrated at the appropriate temperature, and the appropriate 2-butanone imine and a hydrocarbon standard were added via syringe. Aliquots (ca. 0.5 mL) of the reaction mixtures were transferred to flasks at -78 °C and treated with excess iodomethane. Products were identified by comparison of their GC retention times to those of authentic product imines prepared separately from the appropriate amine and ketone. GC yields were high (typically 95-105%). In several cases where the 3-pentanone imine products were formed >90% yield, the reaction mixture was treated with water, the mixture was distributed between ether and water, the resulting organic phase was dried ($MgSO_4$), and the solvent was removed at reduced pressure. The resulting residue was examined by ^1H NMR spectroscopy to confirm the identity of the 3-pentanone imine products.

Rates of Deprotonation. Clean 1 N LDA solutions were prepared[15] and then diluted to the desired concentrations. The base solutions were equilibrated at the appropriate temperature, and the 2-butanone imines and a hydrocarbon standard were added via syringe. At various times aliquots of the reaction mixtures were removed and methylated, and the resulting products were analyzed by GC by the methods described above in the regioselectivity studies. In the deprotonations which occurred over several hours, relatively smooth first-order conversions were observed from at least 20-80% completion. The results of these rate studies are given in Table I.

Isomerization Studies. Clean 1 N LDA solutions were used for the preparation of 30% ^{13}C-enriched (Z)-[4-^{13}C]-2-butanone imines at -78 °C as described above. For studies of the effects of azaallyllithium reagents **3**, an insufficient amount of iodomethane was used in the alkylation reaction. The mixtures were warmed to the desired temperatures in the probe of the NMR spectrometer and ^1H-decoupled ^{13}C NMR spectra were recorded periodically. The heights of the peaks from the labeled positions of the butanone imines were compared to determine the amounts of the *E* and *Z* isomers. The results of these experiments are presented in Table II. Because of the accumulated errors of successive volumetric transfers, we estimate that the calculated concentrations of **3** may be in error by as much as 0.1 N. The $t_{1/2}$'s reported in Table II are the times at which a 1:1 mixture of *E* and *Z* isomers was present. In none of the studies was there observed a signal from the azaallyllithium reagents **1** or **2** which would form by deprotonation of the 2-butanone imines by **3**. Separate experiments however showed that this latter deprotonation reaction is facile at room temperature and thus remains a possible mechanism for the observed isomerization catalyzed by **3** at low temperatures.

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Registry No. (*E*)-$CH_3CH_2C(CH_3)$=N-*t*-C_4H_9, 77390-50-2; (*E*)-$CH_3CH_2C(CH_3)$=N-c-C_6H_{11}, 55969-52-3; (*E*)-$CH_3CH_2C(CH_3)$=NPh, 72037-54-8; (*E*)-$CH_3CH_2C(CH_3)$=NCH_2Ph, 72037-48-0; (*E*)-$CH_3CH_2(CH_3)$=$N(CH_2)_3CH_3$, 85629-19-2; (*Z*)-$CH_3CH_2C(CH_3)$=N-*t*-C_4H_9, 77390-51-3; (*Z*)-$CH_3CH_2C(CH_3)$=N-c-C_6H_{11}, 55969-53-4; (*Z*)-$CH_3CH_2C(CH_3)$=NPh, 75250-70-3; (*Z*)-$CH_3CH_2C(CH_3)$=NCH_2Ph, 77390-49-9; (*Z*)-$CH_3CH_2C(CH_3)$=$N(CH_2)_3CH_3$, 85629-20-5; $(CH_3)_2C$=$N(CH_2)_3CH_3$, 6700-95-4; $(CH_3)_2C$=NCH_2Ph, 1197-48-4; $(CH_3)_2C$=NPh, 1124-52-3; $(CH_3)_2C$=N-c-C_6H_{11}, 6407-36-9; $(CH_3)_2C$=N-*t*-C_4H_9, 66548-20-7; $(CH_3)_2CHC(CH_3)$=$N(CH_2)_3CH_3$, 85629-21-6; $(CH_3)_2CHC(CH_3)$=NCH_2Ph, 62453-12-7; $(CH_3)_2CHC(CH_3)$=NPh, 74265-71-7; $(CH_3)_2CHC(CH_3)$=N-c-C_6H_{11}, 39139-90-7; $(CH_3)_2CHC(CH_3)$=N-*t*-C_4H_9, 57808-25-0; LDA, 4111-54-0; LDEA, 816-43-3; 3-pentanone, 96-22-0; *tert*-butylamine, 75-64-9; cyclohexylamine, 108-91-8; *n*-butyllithium, 109-72-8; diethylamine, 109-89-7; diisopropylamine, 108-18-9.

(30) **Note Added in Proof**: Methods for obtaining high regioselectivity in deprotonations of highly substituted ketimines have been established: Smith, J. K.; Newcomb, M.; Bergbreiter, D. E.; Williams, D. R.; Meyers, A. I. *Tetrahedron Lett.*, submitted for publication.

Cyclopropylidene Rearrangement in the Reduction of 1,2:3,4-Bis(dihalomethano)-1,2,3,4-tetrahydropolymethylnaphthalenes by Naphthalenides

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Abstract: The reduction of octamethyl-substituted title compound (**1a**) with Na naphthalene in THF at -70 °C afforded 1,2:3,4-diethylideno-1,2,3,4-tetrahydro-2,3,5,6,7,8-hexamethylnaphthalene (**2a**, 75%), whereas at 25 °C a mixture of 1,2,3,4,5,7,8,9-octamethylbenzocyclooctene (**5a**) and 2,3,5,6,7,8,9-heptamethyl-1-ethylideno-1*H*-benzocycloheptene (**4a**) but not **2a** was formed. The structure of **2a** was determined by its oxidation with OsO_4 to 1,2,3,4,6,7-hexamethylnaphthalene. The formation of **2a** is explained in terms of a cyclopropylidene rearrangement. The reaction was facilitated at low temperatures by the use of Na or K naphthalene and was also dependent upon the change of solvent, halogen, and more significantly the substituents of the starting compound. Title compounds bearing methyl groups at 1,2,3,4,5,6,7,8-, 1,2,3,4,5,8-, 1,2,3,4,5,6-, and 1,2,3,4,5-positions underwent the rearrangement whereas those bearing methyl groups at 1,4,5,6,7,8-, 1,2,3,4,6,7-, 1,2,3,4-, and 1,4,5,8-positions did not. Thus, structural requisites for the rearrangement are the presence of two methyl groups at paired peri positions and also the presence of cyclopropane *cis*-dimethyl substitutents, which as discussed with the aid of crystallographic analysis, accumulate steric strain around the peri position but release it by shifting the aryl group to a carbene center. The formation of **4** and **5** is explained in terms of ring opening of the intervening α-halocyclopropyl anion followed by carbene rearrangements.

It has commonly been held that the electron-transfer reduction of organic halides RX proceeds by a stepwise mechanism via the free radical R· and its anion $R:^-$.[1] When this general mechanism is applied to *gem*-dihalides, the indispensable intermediate is an

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