Pergamon

Tetrahedron, Vol. 53, No. 44, pp. 14871-14894, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)10001-1

Hydrogen Shifts in Cyclohexylcarbenes. Spatial Dependence of Activating Power and of Primary Deuterium Isotope Effects.

James A. Kenar † and Alex Nickon*

Department of Chemistry, Johns Hopkins University, Baltimore, MD 21218-2685, USA

E-mail: nickon@jhunix.hcf.jhu.edu *Fax*: (410)-516-8420

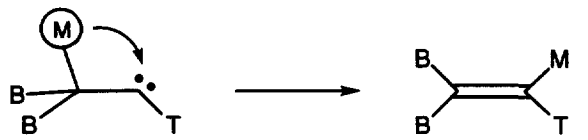
Abstract: The conformationally biased ketones 4-*t*-butyl-*cis*-2-methylcyclohexanone (**1c**) and 4-*t*-butyl-*cis*-2-*trans*-6-dimethylcyclohexanone (**7a**; and its 2,6-dideuterio derivative **7c**) were converted into *p*-toluenesulfonylhydrazone Li salts. Thermolysis or photolysis generated putative singlet carbenes, which underwent competitive axial vs equatorial H shift (or D shift in the case of **7c**) to give alkenes. Product analysis showed that a bystander Me_{eq} substituent promotes a geminal H shift several times more efficiently than does a bystander Me_{ax}. This geometry-dependent activating power parallels behavior noted earlier for OMe and Ph bystander groups; but as Me groups are rotationally symmetric and possess no lone pair or π electrons this phenomenon cannot be attributed solely to rotameric considerations or to effects involving mobile electron clouds. For the *trans*-dimethylcarbenes **10a** and **10c** the primary deuterium isotope effect (k_H/k_D) for axial migration (I_{ax}) was determined to be ca. 1.5 times larger than that for equatorial migration (I_{eq}). This finding invalidates the common assumption that $I_{ax} = I_{eq}$ and suggests that published data on deuterium isotope effects and on H_{ax}/H_{eq} migration selectivities need to be adjusted. © 1997 Elsevier Science Ltd.

Introduction

The regio- and stereochemistry of 1,2-H shifts in singlet carbenes has received considerable research attention.[1] Investigators have long recognized that nonmigrating (i.e. bystander) substituents influence the ease of rearrangement, although how they exert their influence is not understood. Recently, an empirical analysis of published data on 1,2-H migration in acyclic and cyclic carbenes drew attention to three factors that contribute to the ease of migration: inherent migratory aptitude of the moving group (termed M); assistance to migration provided by a bystander group (termed B factor); and efficiency with which two geminal bystanders combine their activating effects (G factor).[2]

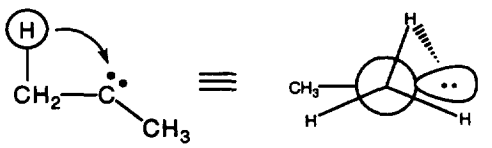
The inherent migratory aptitude of a hydrogen, symbolized M[H], has been defined[2] as the first-order, specific rate constant (k_H) for shift of a single designated H in the parent prototype carbene, dimethylcarbene. In the next higher homolog, ethylmethylcarbene, the rate of Ha shift (i.e. k_{Ha}) is governed by the intrinsic migratory aptitude of H (i.e. M[H]) and also by any activation provided by the bystander Me substituent (termed B[Me]). The amount of activation differs for the anti and the syn transition states (see accompanying

†Present address: Naval Surface Warfare Center, Indian Head, MD 20640-5035



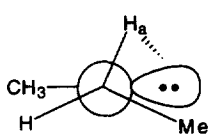
M = Migrating group (can be H, R, Ar, etc.); T = Group at Terminus;

B = Bystander groups other than H (can be same or different)



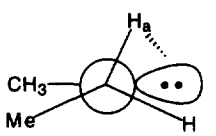
$k_H = M[H]$

drawings), which are experimentally distinguishable because they lead, respectively, to E- and to Z-2-butene. (For two or more H's that are chemically equivalent, statistical corrections must be applied to experimental data, so that rate comparisons are always on a "per H" basis.) Analysis of the alkene products from ethylmethylcarbene generated by thermal Bamford-Stevens reactions revealed[2] that an anti-Me bystander accelerates H shift by a factor of 20.1 (i.e. $B[Me^A] = 20.1$), whereas for a syn-Me bystander, $B[Me^S] = 8.4$.



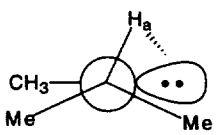
ANTI

$k_{Ha} = M[H] \bullet B[Me^A]$



SYN

$k_{Ha} = M[H] \bullet B[Me^S]$



ANTI and SYN

$k_{Ha} = M[H] \bullet B[Me^A] \bullet B[Me^S] \bullet G[Me^A, Me^S]$

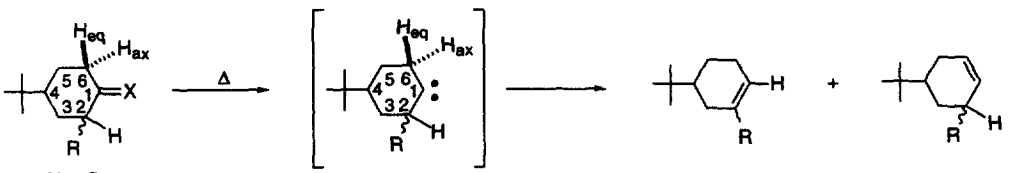
(Found: $B[Me^A] = 20.1$; $B[Me^S] = 8.4$; $G[Me^A, Me^S] = 0.31$)

In the *gem*-disubstituted homolog, isopropylmethylcarbene, which has both an anti and a syn bystander Me, we might expect Ha shift to be accelerated by a net factor of 20.1 x 8.4, namely 169. However, product studies revealed that k_{Ha} increases only 58 fold.[2] Therefore, the rearrangement rate is less than expected by a factor of 58/169, namely 0.31. This diminished activating power when two bystanders act together is termed the *geminal* efficiency factor and is symbolized G. The numerical value of G is the rate

enhancement observed experimentally divided by the rate enhancement that would have been expected based on the individual B values of the two bystander groups. For the case of isopropylmethylcarbene, the G factor can be more fully symbolized as $G[Me^A, Me^S]$, which identifies each bystander substituent as well as its *Anti* or *Syn* relationship to the terminus group in the transition state for Ha shift. Accordingly, the full expression for Ha migration in this carbene is $k_{Ha} = M[H] \times B[Me^A] \times B[Me^S] \times G[Me^A, Me^S]$. Evaluation of G factors can uncover subtle features that influence carbene rearrangements, especially in cycloalkylidenes.

Several experimental studies on constrained cyclohexylidenes—and particularly on the tricyclic carbene homobrexylidene, which is free of twist boat ambiguities—have established that when epimeric *secondary* ring H's compete with each other the shift preferences are small.[2] For example, published experimental H_{ax}/H_{eq} values are 1.73 and 1.17 for carbenes generated respectively by thermal and photic Bamford-Stevens reactions.[4] This low ax/eq preference was accommodated in Kyba's MNDO and MINDO/3 calculations[5] and later in ab initio treatments by Evanseck and Houk.[6a] According to the latter calculations, the H_{ax}/H_{eq} selectivity in cyclohexylidene is low because the geometries of the two transition states strikingly resemble each other: viz., the three nonmigrating entities (namely the two tethered ring carbons and the nonmigrating H) adopt a flat, alkene-like disposition, while the moving H leans toward the carbene's vacant p-orbital. Purportedly, the activation energies needed to achieve this flat-type geometry for H_{ax} and for H_{eq} shift are virtually the same, even though these H's start off with distinctly different spatial orientations.

In contrast, when a *tertiary* H migrates in a substituted cyclohexylidene the H_{ax}/H_{eq} selectivity can be low or high depending on the initial stereochemistry of the *nonmigrating* geminal substituent. For example, the OMe_{eq} and OMe_{ax} epimers **4a** and **4b** (derived by thermal Bamford-Stevens reactions) produce alkenes **5** and **6** by competitive H shifts.[7] (Note that when the 3° H rearranges from C-2, the two bystanders are OMe



1 X = O
2 X = NNHTs
3 X = NNLiTs

a R = eq OMe
b R = ax OMe
c R = eq Me
d R = ax Me

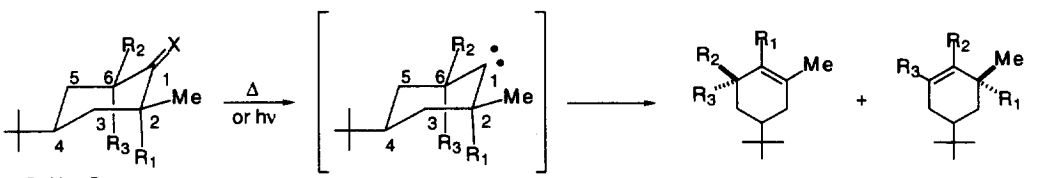
a 95.1 %
b 29.4 %
c 79.7 %
d —

a 4.7 %
b 58.4 %
c 20.3 %
d —

and the C-3 ring residue; and when either H_{ax} or H_{eq} moves from C-6 only one bystander group is present at that carbon, namely ring residue C-5.) Analysis of the alkene ratios in terms of competition among the three available H's revealed that OMe_{eq} promotes geminal H shift more effectively than does OMe_{ax} by a factor of 23.2. This number arises from the ratios of their respectively derived G factors of 1.58 and 0.068.[2] In fact, the latter (very low) G value of 0.068 indicates that an axial OMe on a cyclohexane ring exerts very little effect

on the H shift. (Contrast this situation with that of open chain carbenes, where a bystander OMe is among the most powerful activating groups.[2]) Geometry-dependent activation by a bystander group is not unique to OMe. Similar analysis[2] of product ratios[8] for an epimeric pair in which the bystander is a phenyl substituent disclosed that Ph_{eq} promotes H shift better than does Ph_{ax} by a factor of *ca.* 1.6 (i.e. their respective G factors are 0.76 and 0.47).

The reasons why equatorial OMe or equatorial Ph accelerate H better than when these bystander groups are axial are not obvious on the basis of a transition state geometry akin to the one prescribed by the ab initio calculations.[6a] Possibly, selective activation could be associated with the lone pair electrons on OMe and the π electrons on Ph and/or with rotameric geometry about the C—OMe and C—Ph bonds. For example, rotation around a C—OMe bond leads to a set of diastereomeric conformers, each with possibly different spatial and electronic interactions with the rest of the molecule during the H migration. Since the conformer sets from OMe_{ax} and OMe_{eq} are not identical in a ring that starts off chair-shaped, they could retain some of these differences at the transition state and, consequently, could exert different activating power. In view of these complexities, a study of the relative activating ability of a bystander Me_{ax} vs a bystander Me_{eq} would be particularly informative, as CH_3 has neither lone pair nor π electrons, and the C—CH_3 bond is rotationally symmetric.



7 X = O
8 X = NNHTs
9 X = NNLiTs

10 **11** **12**

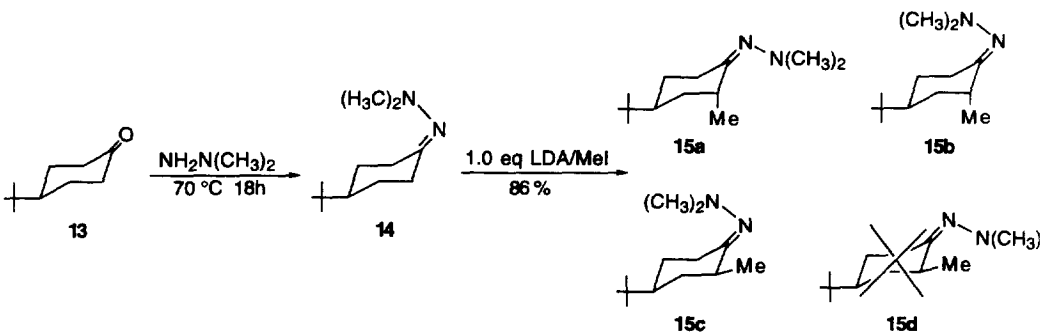
		Δ	hv	Δ	hv
a	$R_1 = R_2 = H$, $R_3 = Me$	87.4 %	86.5 %	12.6 %	13.5 %
b	$R_1 = R_3 = H$, $R_2 = Me$	—	—	—	—
c	$R_1 = R_2 = D$, $R_3 = Me$	82.0 %	81.7 %	18.0 %	18.3 %
d	$R_1 = R_3 = D$, $R_2 = Me$	—	—	—	—

In principle, determination of alkene product ratios from the epimeric methyl substituted carbenes **4c** and **4d** (obtained from the *t*-butyl anchored ketones **1c** and **1d**) would disclose how effectively each type of Me promotes rearrangement of H-2. Accordingly, we prepared and obtained data from the Me_{eq} epimer **4c**; but we were unable to study the Me_{ax} epimer **4d** owing to Me epimerization during attempted conversion of Me_{ax} ketone **1d** to its tosylhydrazone **2d**. However, we achieved our ultimate objective through a study of the dimethyl analog **10a**, which simultaneously possesses one equatorial and one axial Me. The ratio of alkenes **11a** and **12a** produced from carbene **10a** directly revealed the H_{ax}/H_{eq} selectivity and hence the relative efficiencies of activation by bystander Me_{ax} vs bystander Me_{eq}. Furthermore, we also conducted a parallel investigation of the 2,6-d_2-analog **10c**, which provided hitherto unavailable information about

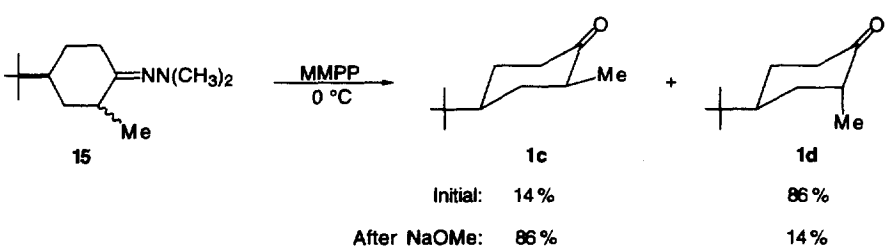
deuterium isotope effects. Our preliminary findings on thermally generated carbenes have been published,[3] and we now report details of that work as well as extensions to carbenes derived photolytically.[9]

Synthesis

Ketones. The key compounds in our study are the monomethyl ketones **1c** and **1d** and the dimethyl ketones **7a** and **7b**. Beckwith and Easton have prepared **7a** and **7b** from 2,6-dimethyl phenol.[10] Although their method is appealing, we developed a route from 4-*t*-butylcyclohexanone (**13**) that not only provided **7a** and **7b** but also allowed access to the dideuterated analogs **7c** and **7d** as well as to the monomethyl ketones **1c** and **1d**.



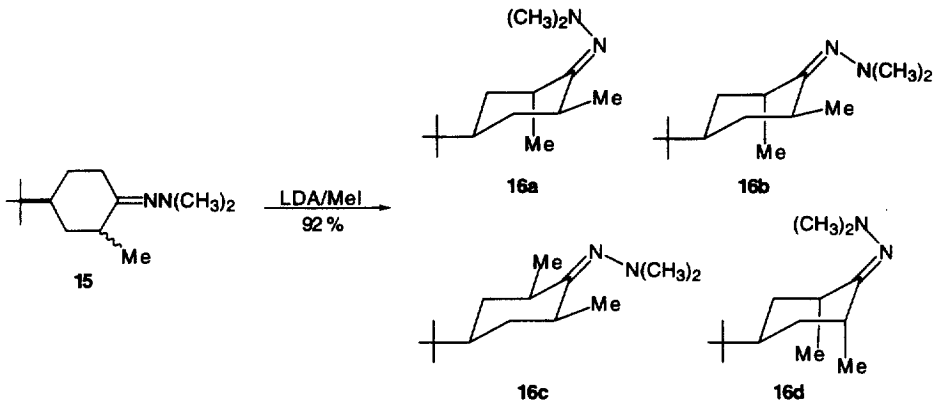
Reaction of 4-t-butylcyclohexanone **13** with 1,1-dimethylhydrazine gave us the known N,N-dimethylhydrazone **14**.[11] We monomethylated[12] **14** (LDA/MeI) as reported and obtained **15** as a mixture of three stereoisomers, **15a**, **15b**, and **15c**, in the ratio 88 : 3.5 : 8.5, which became 30.5 : 55.5 : 14 after distillation. We determined the ratios by NMR integration of each ketone's tertiary α-H, which appeared as a



well defined peak between δ 3.0-3.6. The fourth possible isomer **15d** was not detected, and its formation was probably precluded due to 1,3-allylic strain between the $N(CH_3)_2$ moiety and the Me_{eq}.[13]

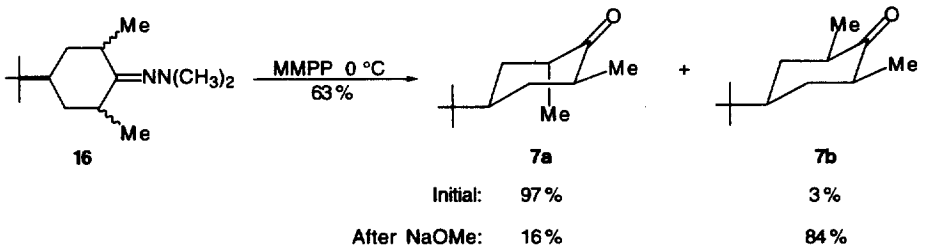
We used magnesium monoperoxyphthalate (MMPP) to convert the mixed hydrazones into a mixture of Me_{eq} ketone **1c** and Me_{ax} ketone **1d** (ratio 14 : 86).[14] These epimers could not be separated by column chromatography, but partial equilibration in MeOH/NaOMe changed their proportion to 86 : 14 (coincidentally

the exact reversal of the original ratio). Therefore, mixtures enriched in either Me_{eq} (**1c**) or Me_{ax} (**1d**) were readily prepared in this manner.



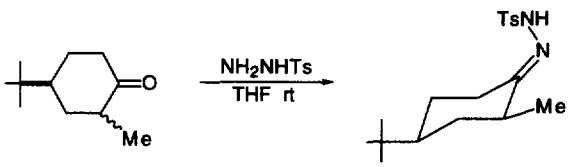
To obtain dimethyl ketone **7a** we remethylated hydrazones **15** to furnish **16** as an isomeric mixture.[11] Gas chromatography showed four components, but quantitative assays were not reproducible owing to isomerizations of the Me and/or the $N(CH_3)_2$ during analysis.[15] The isomer ratio also could not be determined by ^1H NMR for lack of suitable and identifiable signals. On steric grounds, **16a** (one axial Me one equatorial Me) is expected to be the most stable isomer, as it is the only one free of allylic 1,3-strain and free of serious diaxial interactions.

Cleavage of hydrazone mixture **16** with MMPP liberated the dimethyl ketones **7a** and **7b** as a 97 : 3 mixture, which was readily assayed by NMR[23] and which confirmed that **16a** was the major component of the starting hydrazones. No diaxial dimethyl ketone (in principle derivable from precursor **16d**) was detected. Refluxing the 97 : 3 ketone mixture in MeOH/NaOMe converted it to a new mixture now enriched in the diequatorial epimer, viz. **7a** : **7b** = 16 : 84.



Tosylhydrazones. We applied a modified Bertz procedure for hindered ketones[16] on a mixture of **1c** and **1d** (86 : 14) and ultimately obtained pure tosylhydrazone **2c** after several recrystallizations. When placed in $CDCl_3$ for routine NMR analysis tosylhydrazone **2c** decomposed quickly to ketone, tosylhydrazide, and unidentified products. This type of sensitivity has also been reported in other cases by Garner[17] and by

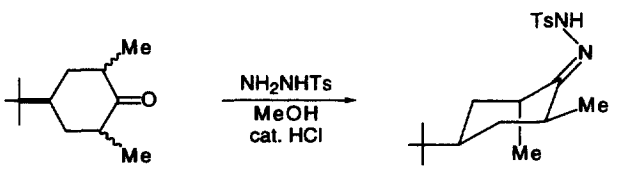
Paquette.[18] Decomposition was slowed (but not prevented) when the $CDCl_3$ had been stored over molecular sieves before use. Interestingly, all the tosylhydrazones we synthesized were more stable in CCl_4 (also distilled and stored over molecular sieves), so many of our routine ^1H NMR spectra were run in CCl_4.[19] Signals were assigned based on published data on similar tosylhydrazones. We removed the NNHTS moiety by treatment with N-bromosuccinimide (NBS) under non-enolizing conditions[20] and obtained only the Me_{eq} ketone **1c** (ca. 99% pure), whose NMR spectrum is reported.[10]



1c + 1d (86 : 14) **2c**

Our attempts to prepare pure Me_{ax} tosylhydrazone **2d** were unsuccessful. Concerned with epimerization of the Me_{ax} during tosylhydrazone formation, we sought conditions to minimize enolization. For example, an 8 : 92 mixture of **1c** and **1d** when treated mildly with tosylhydrazide gave only the Me_{eq} tosylhydrazone **2c**. Obviously, epimerization had occurred, and we made numerous attempts to preclude it through use of shorter reaction times, lower temperatures, extra pure reagents, and freshly distilled solvents—all without success. Garner and co-workers have reported that tosylhydrazones can α–epimerize faster than the parent ketones[21]; and they found that use of acid-free CH_2Cl_2 can suppress epimerization.[17] Even under their specialized conditions, however, we were unable to obtain **2d** pure enough for our purposes.

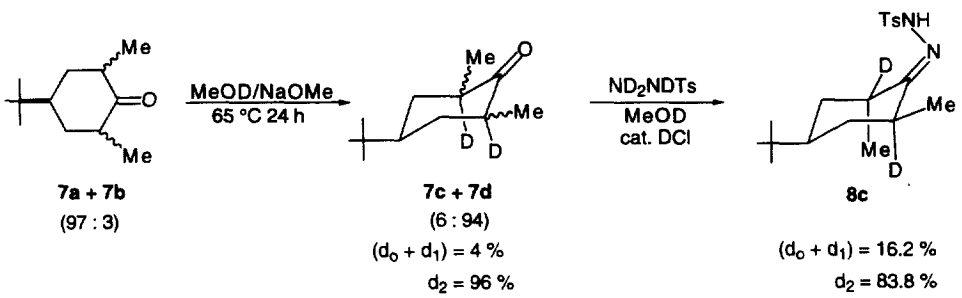
We prepared pure *trans*-dimethyl tosylhydrazone **8a** by treating a 97 : 3 mixture of **7a** and **7b** with $TsNHNH_2$ in MeOH/ cat. HCl followed by several recrystallizations of the crude product. Fuchs and Bunnell have found that ^{13}C NMR can be used to assign syn/anti stereochemistry in sulfonylhydrazones based on chemical shift differences of the two α ring carbons.[22] Our analysis of **8a** by ^{13}C NMR indicated the –NHTs unit is syn to the Me_{ax}. The mono-axial, mono-equatorial stereochemistry of the Me groups in tosylhydrazone **8a** was confirmed by oxidative regeneration of the parent ketone with N-bromosuccinimide under non-enolizing conditions. ^1H NMR revealed that this reaction produced the Me_{eq}, Me_{ax} ketone **7a** containing only 2 % of the diequatorial isomer **7b.** None of the 2,6-diaxial-dimethylcylcohexanone was detected.[23] In a separate control experiment, we established that **7a** and **7b** do not epimerize during the NBS reaction.



7a + 7b (97 : 3) **8a**

Deuterium Labeling. Refluxing a 97 : 3 mixture of ketones **7a** and **7b** in MeOD/NaOMe gave us a d-labeled product that was then re-subjected to fresh MeOD/NaOMe. After the second exchange the **7c** : **7d** ratio was approximately 6 : 94; and integration of the combined residual α-H_{ax} and α-H_{eq} signals between δ 2.3–2.6 (versus the *t*-butyl singlet at δ 0.89 as internal standard) indicated a total α-H content of ca. 4 % ($d_0 + d_1$ species), which implied a d_2 content of 96 %.

To obtain the labeled tosyl hydrazone **8c**, we used deuterated solvents and reagents[24] to minimize D loss during tosylhydrazone formation. Thus the 6 : 94 mixture of **7c** and **7d** was treated with D_2NNDTs/MeOD and catalytic DCl/D_2O to afford **8c** after recrystallizations. (Note that even though the starting d_2-ketone was largely Me_{eq}, Me_{eq}, the d_2-tosylhydrazone is Me_{eq}, Me_{ax}, a consequence of $A_{1,3}$-type destabilization of an equatorial substituent by a syn-oriented group on the imine nitrogen.) A small amount of deuterium was lost after each recrystallization as was evident from a progressive increase in the residual α-H_{eq} and α-H_{ax} signals. For example: 8.7 % H_{eq} and 2.8 % H_{ax} were observed after the first recrystallization; 9.7 % H_{eq} and 6.5 % H_{ax} after the third. Interestingly, D_{ax} was lost faster than D_{eq}.



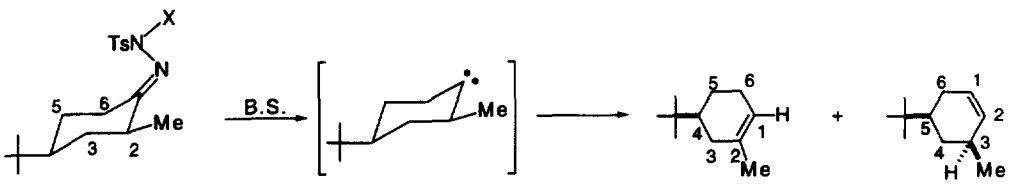
7a + 7b
(97 : 3)

7c + 7d
(6 : 94)
$(d_0 + d_1)$ = 4 %
d_2 = 96 %

8c
$(d_0 + d_1)$ = 16.2 %
d_2 = 83.8 %

Results and Discussion

Bamford-Stevens Reactions. Thermal and photic Bamford-Stevens (B.S.) reactions are established ways to generate singlet carbenes from aryl sulfonylhydrazone salts.[25] All our tosylhydrazones were converted with *n*-BuLi to their Li salts, which were thoroughly dried and then pyrolyzed (or photolyzed). The major products from the thermolytic B.S. reaction of **3c** were alkenes **5c** and **6c** (from competitive shifts of H from C-2 and C-6) in the proportions shown in Table 1. No cyclopropyl product from 1,3 insertion was detected by ^{1}H NMR. Alkenes **5c** and **6c** are known and are easily distinguished by NMR[23]; and to facilitate our assays we separately synthesized **6c** by a Shapiro reaction on **2c**.[4c,26] Control experiments assured us that **5c** and **6c** are individually stable to simulated B.S. conditions (i.e. thermolysis in the presence of an equimolar amount of anhydrous lithium *p*-toluenesulfinate).



2c X = H
3c X = Li

4c **5c** **6c**

Table 1. Thermolysis of *p*-Tosylhydrazone Li Salt 3c

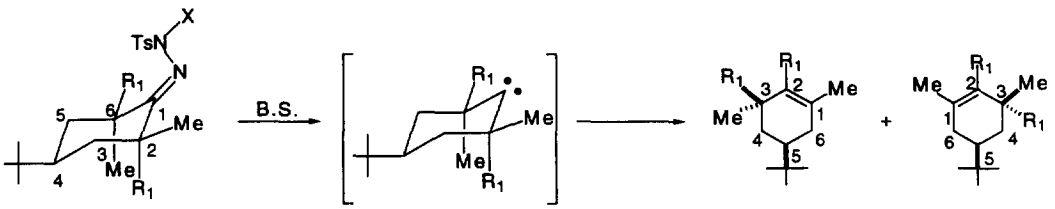
Conditions (160 ± 3°)	Alkenes Rel (%)		G_{Hax}[a]
	5c	**6c**	
Neat (760 mm)	20.3	79.7	0.31
Diglyme	20.5	79.5	0.30

[a]Full symbolism is $G[Me^A, R^S]_{Hax}$. The A and S indicate that Me and ring residue R are respectively Anti and Syn to the group at the migration terminus during migration of H_{ax}.

Alkene **5c** arises by shift of H_{ax} from C-2, and the rate of this shift (designated as k_2) depends on three factors: the inherent migratory aptitude for H (i.e. M[Hax]; the assistance (i.e. B value) potentially available from the bystander Me as well as from the bystander ring alkyl unit C-3 (symbolized as R_3); and the efficiency (i.e. G value) with which these two bystanders combine their assistance.[2] These factors are expressed in the numerator of Equation 1. On the other hand, alkene **6c** arises from movement of H_{ax} or H_{eq} from C-6, and each H is assisted by only one bystander group, namely ring alkyl unit C-5 (symbolized as R_5). Therefore, the total rate of shift from C-6 (designated as k_6) is the sum of two contributions: M[Hax] assisted by R_5, and M[Heq] assisted by R_5. These relationships appear in the denominator of Equation 1. As R_3 and R_5 are virtually identical alkyl groups, we assume their B values in this equation will cancel out. The experimental **5c** : **6c** ratios in Table 1, together with the known[2] value of 20.1 for $B[Me^A]$ and the known[4b] relationship $M_{Hax} = 0.58\ M_{Heq}$, lead to a G_{Hax} value of 0.31 (last column, Table 1). Therefore, in the Me_{eq} carbene **4c** the H_{ax} migration from C-2 is accelerated to an extent that is 31% of the amount that would have been expected based on the potential activating capacities of its geminal bystander alkyl groups. Interestingly, in the comparable open chain analog isopropylmethylcarbene where, ostensibly, groups can adopt optimum spatial arrangements, the G value for the two Me bystanders is also 0.31.[2] This exact agreement is, of course, fortuitous, but the close parallelism does suggest that an equatorial methyl is optimally situated to facilitate H shift. We did not conduct any photic B.S. reactions on substrate **3c**.

$$\frac{k_2}{k_6} = \frac{M[H_{ax}] \bullet B[Me^A] \bullet B[R_3{}^S] \bullet G[Me^A,R_3{}^S]_{Hax}}{M[H_{ax}] \bullet B[R_5{}^S] + M[H_{eq}] \bullet B[R_5{}^S]} = \frac{\mathbf{5c}}{\mathbf{6c}} \qquad \text{(Eq. 1)}$$

In the dimethyl cases, thermal and photolytic B.S. reactions of the Li salt **9a** gave predominantly alkenes **11a** and **12a**; and the deuterated counterpart **9c** gave the deuterated alkenes **11c** and **12c**. Table 2 summarizes the relative proportions. Alkenes **11a** and **12a** are both known, and for reference we separately prepared a 91: 9 mixture of these two isomers by a Shapiro reaction[26] and demonstrated that they were stable to the B.S. reaction conditions. No cyclopropyl products derived from 1,3-insertions into Me groups were detected by ^{1}H NMR.



8a X = H, R_1 = H
8c X = H, R_1 = D
9a X = Li, R_1 = H
9c X = Li, R_1 = D

10

11a R_1 = H
11c R_1 = D

12a R_1 = H
12c R_1 = D

Table 2. Thermolysis and Photolysis of *p*-Tosylhydrazone Li Salts 9a and 9c

Conditions	Alkenes Rel (%)				Migration Ratio		$\frac{G_{Hax}}{G_{Heq}}$ [b]	G_{Heq}	$\frac{I_{ax}}{I_{eq}}$
	from **9a**		from **9c**		**11a/12a**	**11c/12c**			
	11a	**12a**	**11c**[a]	**12c**[a]	H_{ax}/H_{eq}	D_{ax}/D_{eq}			
Neat (760 mm,160 °C)	87.4	12.6	82.0	18.0	6.94	4.54	4.02[c]	0.077	1.53
Tetraglyme 160 °C	89.7	10.3	84.8	15.2	8.71	5.59	5.10[c]	0.061	1.56
hv, pentane 35 °C	86.5	13.5	81.7	18.3	6.41	4.45	3.72[c]	—	1.44

[a]These relative percentages have been corrected for d_0 and d_1 species and represent d_2 species only (see experimental section in ref. 9). [b]Full terminology $G[Me^A,R^S]_{Hax}/G[Me^A,R^S]_{Heq}$ (see ref. 2). [c]Computed from the experimental **11a/12a** ratio and the inherent M[Hax]/M[Heq] = 1.73 (ref. 4).

Thermal Results. The alkene ratios obtained from shifts of the tertiary hydrogens in **9a** represent H_{ax}/H_{eq} selectivities of 6.94-8.71 (average 7.83), which are distinctly higher than that (1.73) reported for

secondary hydrogens.[4] Clearly, Me_{eq} promotes geminal H shift more effectively than does Me_{ax} by a factor of about 4.5 (i.e. 7.83 / 1.73).[3]

Hydrogen shift from C-2 (to give **11a**) is assisted by two different bystanders, namely Me and ring alkyl unit C-3 (designated as R_3); whereas H shift from C-6 (to give **12a**) is assisted by Me and the ring alkyl unit C-5 (designated as R_5). Consequently, geminal efficiency (G) and individual B factors are relevant in each case and can be related to the observed alkene proportions as shown in Equation 2. As before, R_3 and R_5 are taken to be equivalent; and after cancellations and appropriate substitutions this equation provides the G_{Hax}/G_{Heq} ratios displayed in Table 2. These numbers are then used in conjunction with the G_{Hax} value of 0.31 (obtained previously from the monomethyl carbene **4c**, Table 1) to provide G_{Heq} values of 0.077 (neat) and 0.061 (tetraglyme), also shown in Table 2. Thus, on a cyclohexane ring, an axial Me acting on a migrating H_{eq}, only exerts ca. 6.1-7.7 % of its potential activating power.

$$\frac{k_2}{k_6} = \frac{M[H_{ax}] \bullet B[Me^A] \bullet B[R_3{}^S] \bullet G[Me^A,R_3{}^S]_{Hax}}{M[H_{eq}] \bullet B[Me^A] \bullet B[R_5{}^S] \bullet G[Me^A,R_5{}^S]_{Heq}} = \frac{\mathbf{11a}}{\mathbf{12a}} \qquad \text{(Eq. 2)}$$

Photochemical Results. Irradiation of Li salt **9a** (and its d_2 analog **9c**) suspended in pentane gave alkene proportions similar to those from the thermal B.S. reactions and ultimately provided a G_{Hax}/G_{Heq} ratio of 3.72 (see Table 2). However, as no irradiations were conducted with the monomethyl substrate **3c**, we have no photolytic G_{Hax} value to permit calculation of an accurate photolytic G_{Heq} from this ratio. Because migration selectivities in photic and in thermal B.S. reactions can sometimes differ appreciably,[27] all previous discussions of M, B, and G factors[2-4] have been confined to data from thermally generated carbenes. Accordingly we have excluded photolyses data from any numerical averages that are used in this paper.

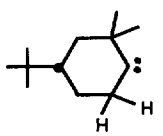
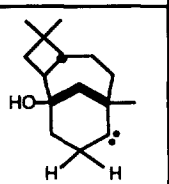
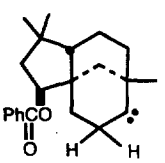
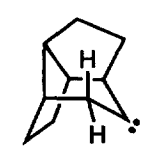
Primary Deuterium Isotope Effects. To date, all published experimental studies on H_{ax}/H_{eq} selectivity in carbene rearrangements have employed selective d-labeling to distinguish the two competing H's.[2,4,28] In such cases, an observed alkene product ratio reflects not only stereochemical selectivity but includes any retardation of the D shift attributable to a primary deuterium isotope effect, I, defined as $I = k_H/k_D$. (Secondary isotope effects are relatively small by comparison and are usually disregarded.[29]) If the mono D_{ax} and mono D_{eq} epimers are separately studied, the two independent sets of data permit evaluation of (and thereby adjustment for) the primary isotope effect if an assumption is made, namely, that k_H/k_D isotope effects are inherently equal for the axial and the equatorial trajectories (i.e. researchers must assume $I_{ax} = I_{eq}$).[2,4,28] (In fact, a similar assumption must be invoked whenever isotopic substitution is used to determine stereoselectivity involving two diastereotopic H's in any intramolecular competition.[30]) To our knowledge, this assumption has not been validated (or tested) experimentally.

By definition, $I_{ax} = k_{Hax}/k_{Dax}$ and $I_{eq} = k_{Heq}/k_{Deq}$. Therefore, the ratio I_{ax}/I_{eq} corresponds to $(k_{Hax}/k_{Heq})\bullet(k_{Deq}/k_{Dax})$, and this ratio should be unity if the two isotope effects are equal. The two "Migration Ratio" columns in Table 2 contain the numbers that provide these I_{ax}/I_{eq} values, which are displayed in the last column of Table 2, and which are clearly not unity for shift of a 3° H. These findings

constitute the first experimental demonstration that the magnitude of k_H/k_D does indeed depend on the *stereochemistry* of the H undergoing rearrangement, contrary to previous assumption.[30]

It is not unreasonable to impute similar differential isotopic behavior to axial/equatorial *secondary* hydrogens, such as those involved in previous studies of carbenic H shifts.[31] On this basis, the published

Table 3. Published H/D Isotope Effects and H_{ax}/H_{eq} Migration Ratios for Cyclohexylidenes Generated by Thermal Bamford-Stevens Reactions. Original Values vs Adjusted Values.

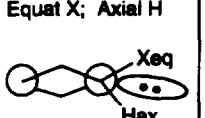
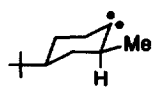
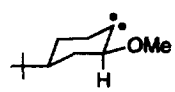
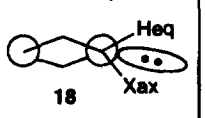
	Temp (°C)	k_H/k_D Isotope Effect (I)			H_{ax}/H_{eq} Migration Ratio	
		I_{orig}	I_{ax}	I_{eq}	Original	Adjusted
	155 °	1.9[a]	2.4	1.5	1.5[a]	1.9
	135 °	1.8[b]	2.2	1.5	ca. 1[b]	ca. 1.2
	170 °	2.1[b]	2.6	1.7	ca. 0.7[b]	ca. 0.9
	120-160 °	2.30[c]	2.85	1.85	1.73[c]	2.15

[a]Reference 27. [b]Unpublished work by postdoctorates H. Yagi (caryolane), K. Matsuo and J. Morgan (clovane). The research was conducted at Johns Hopkins University between 1966-1968, a time when quantitative NMR assays were less reliable than with current instrumentation. Therefore, these data should be regarded as less accurate. [c]Reference 4.

values for isotope effects and for the H_{ax}/H_{eq} migration selectivities based upon them (as well as for derived numbers such as G values) should be amended to improve their quantitative validity. To make these numerical adjustments we adopt the value $I_{ax}/I_{eq} = 1.53$ from our neat thermal experiments. Table 3 lists cyclohexyl substrates previously studied[29a,b] along with their originally reported primary isotope effects (termed I_{orig}) and the H_{ax}/H_{eq} migration selectivities that resulted from them. The same table also lists the newly recognized *individual* I_{ax} and I_{eq} values and their corresponding adjusted H_{ax}/H_{eq} migration ratios.[32]

With adjusted H_{ax}/H_{eq} values in hand we are now in a position to recalculate new G_{Hax} and G_{Heq} values for our monomethyl system as well as for G's published earlier[2] for monomethoxyl and monophenyl cyclohexylidines. Table 4 depicts the ax/eq epimers in these three systems along with their original and their adjusted G values. The differences between original and adjusted values are small and in some cases could very well be negated by cumulative experimental errors in the data underlying G values.

Table 4. G Values for Substituted Cyclohexylidenes Generated Thermally by Bamford-Stevens Reactions

		 17			
G_{Hax}	Original	0.31	1.58[a]	0.76[a]
	Adjusted	0.29	1.46	0.71
		 18			
G_{Heq}	Original	0.077[b]	0.068[a]	0.47[a]
	Adjusted	0.089	0.077	0.53
$\frac{G_{Hax}}{G_{Heq}}$	Original	4.02	23.2[a]	1.62[a]
	Adjusted	3.26	19.0	1.34

[a]Reference 2. [b]Calculated from the neat thermolysis data on carbenes **4c** and **10a**.

Conclusions

The G value for a *ring* substituent reveals what fraction of expected activating power was made available to promote the H migration . As can be seen from the adjusted G ratios in Table 4, a Me_{eq} bystander (G = 0.29) assists geminal H-shift 3.26 times more effectively than does Me_{ax} (G = 0.089). This greater activation provided by an equatorial bystander group parallels the behavior recognized earlier[2] for the OMe and Ph systems, also shown in Table 4. Thus, for OMe the respective adjusted G's are 1.46 and 0.077; so OMe_{eq} is 19 times a better activator than OMe_{ax}. (Note: A value of G greater than unity indicates the activation efficiency exceeds 100%.) In the case of Ph, the equatorial epimer (0.71) is also better than the axial (0.53), although only by a small factor (1.34).[33] This dependence of activating power on the spatial disposition of the bystander group cannot be ascribed *entirely* to rotameric differences or to interactions associated with lone pair or π electrons because, unlike OMe and Ph, a methyl group is rotationally symmetric, and its molecular orbitals involve only sigma-type bonding electrons.

The disposition of the atoms in transition state **17**, where H_{ax} migrates and X = Me, OMe, Ph (see Table 4), must differ appreciably from that in transition state **18**, where H_{eq} migrates. Houk et al.[6a] have attributed the low H_{ax}/H_{eq} stereoselectivity in *unsubstituted* cyclohexylidenes to a strongly-product-like transition state (for the nonmigrating groups), in which the erstwhile geometric difference between an axial and an equatorial hydrogen is virtually absent. Clearly, this situation must not apply to the nonmigrating groups in our *dimethylsubstituted* cyclohexylidenes, since the alkene ratio obtained from carbene **10a** would be close to 1 : 1 if the initial geometric distinction between Me_{ax} and Me_{eq} were lost at the transition state.

Based on experiments with d-labeled compounds, previous conclusions about stereoselectivity in carbene rearrangements required an assumption that the primary isotope effect (k_H/k_D) for cleavage of C— H is independent of the stereochemistry of the H. Our present finding that the isotope effect for shift of an axial hydrogen (I_{ax}) is ca. 1.5 times larger than for shift of an equatorial hydrogen (I_{eq}) invalidates that assumption, at least for the 3° H's under investigation (and perhaps for any two diastereotopic[34] hydrogens). Factors related to zero point energy and/or quantum mechanical tunneling could contribute to k_H/k_D differences for diastereotopic hydrogens.[34-36]

Finally, we wish to point out, as we have previously,[2] that photolysis (and perhaps also thermolysis) of certain nitrogen-containing precursors can sometimes give products of "carbene" reactions directly from excited species in which the departing nitrogen plays some role.[35a-c,37] In such cases, alkenes could arise from more than one product-forming species. For internal consistency, our analyses of M, B, and G factors pertain to rearrangements induced by thermolysis of dry tosylhydrazone salts (Bamford-Stevens reactions), and we have attributed the outcomes to conventional carbenes (derived by loss of N_2 from intervening diazo compounds). Experiments reported in 1967 by Robson and Shechter suggested that N_2 loss precedes H rearrangements in such thermolyses.[38] However, if further research establishes that other intermediates can play a role in these thermal processes, then the mechanistic details may need to be suitably reinterpreted.

Experimental Section

General. All reactions were run under argon unless otherwise noted. THF was freshly distilled from Na°/benzophenone; CH_2Cl_2 was distilled from CaH_2 and CCl_4 was distilled from P_2O_5, and both were stored over molecular sieves; Et_2O and diisopropylamine were distilled from CaH_2. ^1H NMR and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz, respectively, and chemical shifts were referenced to the residual H (δ 7.26) in $CDCl_3$. Spectra taken in CCl_4 used $CDCl_3$ as an internal reference. Low-resolution GC/MS were run at 9–70 eV on mass spectrometers equipped with an SE-54 or Carbowax capillary column. Isotopic analyses were based on several scans and on averaged peak ion intensities. Analytical GC (He carrier gas) was performed on capillary columns SE-54 (30 m x 0.32 mm i.d.) at 150° C, 11 psi, or with Carbowax (30 m x 0.32 mm i.d.) at 60° C, 5 psi. TLC was conducted on analytical plates coated with silica GF (250μm). Column chromatography was carried out on silica gel, 70-230 mesh. Solvents were removed on a rotary evaporator. Melting and boiling points are uncorrected. Elemental analyses were performed by Desert Analytics Laboratories, Tucson, Arizona. All reagents or compounds not explicitly referenced were obtained from the Aldrich Chemical Co. MMPP = magnesium monoperoxyphthalate; EIMS = Electron Ionization Mass Spectrometry.

4-*t*-Butylcyclohexanone-N,N-dimethylhydrazone (14).[11] 4-*t*-Butylcyclohexanone (**13**, 10.6 g, 67.9 mmol) was added to 1,1-dimethylhydrazine (5.7 g, 95.0 mmol) at 0 °C. **[Caution! Aldrich Chemical Co. warns that 1,1-dimethylhydrazine is highly toxic and a cancer suspect agent.]** The mixture was gently swirled and then refluxed 18 h at 70 °C. The cooled aqueous layer was separated from the organic phase and extracted with Et_2O. The extracts were combined with the organic phase, dried ($MgSO_4$), concentrated, and distilled under vacuum to give a light yellow oil (12.3 g, 92 %): bp 75–78 °C (1.1 mm) [lit.[11] bp 53 °C (0.04 mm)]. GC (SE-54) purity = 99 %. ^1H NMR ($CDCl_3$) δ 3.20-3.30 (m, 1 H), 2.35-2.45 (m, 1 H), 2.42 (s, 6 H), 1.60-2.25 (m, 4 H), 1.00-1.40 (m, 3 H), 0.86 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 169.3, 47.49, 47.38, 35.51, 32.26, 28.03, 27.90, 27.41, 27.11; IR (neat) 2950, 2862, 2814, 2769 (NMe_2), 1638 (C=N) cm^{-1}.

4-*t*-Butyl-2-methylcyclohexanone-N,N-dimethylhydrazone (15).[12] A solution of *n*-BuLi (33.6 mL, 80.6 mmol, 2.5 M) was added dropwise by syringe to a stirred solution of dry diisopropylamine (11.3 mL, 79.7 mmol) in THF (172 mL) at 0 °C. Stirring was continued 15 min, then **14** (12.3 g, 62.0 mmol, purity = 99.0 %) was added dropwise. The mixture was stirred 3 h at 0 °C, and the resulting yellow solution was cooled to -78 °C. By syringe, MeI (5.0 mL, 11.4 g, 80.5 mmol) was added in one portion, and the mixture was stirred 17 h at -78 °C, after which it was allowed to warm to room temperature. The volatiles were evaporated and the yellow residue was taken up in Et_2O (500 mL), which was washed successively with $Na_2S_2O_3$ and brine, dried ($MgSO_4$), concentrated, and then distilled to give a light yellow oil (11.24 g, 86 %); bp 65–66 °C (0.30 mm) [lit.[11] bp 75 °C (0.04 mm)]. GC (SE-54) showed three components in the following proportions: **15a** (t_R 4.33 min, 30.5 %), **15b** (t_R 4.40 min 55.7 %), **15c** (t_R 4.27 min, 13.8 %); purity of mixture = 99.3 %. ^1H NMR ($CDCl_3$): δ 0.86 (s, *t*-Bu), 1.13 (d, J = 7.2 Hz, ax CH_3, **15a**), 1.12 (d, J = 7.3 Hz, ax CH_3, **15b**), 1.07 (d, J = 6.5 Hz, eq CH_3, **15c**), 1.2–2.7 (m, ring H), 2.41 (s, $N(CH_3)_2$, **15a**), 2.42 (s, $N(CH_3)_2$, **15b**), 2.40 (s, $N(CH_3)_2$, **15c**), 3.54–3.61 (m, tertiary α-ring H, **15a**) 3.09-3.17 (m, tertiary α-ring H, **15b**), 3.27–3.34 (m, tertiary α-ring H, **15c**); IR (neat) 2770 (NMe_2), 1633 (C=N) cm^{-1}

4-*t*-Butyl-2,6-dimethylcyclohexanone-N,N-dimethylhydrazone (16). A solution of *n*-BuLi (28.6 mL, 68.59 mmol) was added dropwise by syringe to a stirred solution of dry diisopropylamine

(9.53 mL, 6.81 g, 67.3 mmol) in anhydrous THF (150 mL) at 0 °C. After 10 min, the mixture of **15a**:**15b**:**15c** (11.19 g, 52.8 mmol, purity = 99.3 %) obtained above was added dropwise by canula. The light golden solution was stirred 20 h at 0 °C, was cooled 2 h at -78 °C, and MeI (4.31 mL, 9.73 g, 68.5 mmol) was added in one portion by syringe. The mixture was stirred 10 h (-78 °C), and then allowed to warm to room temperature. The clear yellow solution was concentrated and the residue was taken up in Et_2O, which was then washed with $Na_2S_2O_3$ and brine, dried ($MgSO_4$), and concentrated to give crude product (14.2 g). GC (SE-54) showed four major components (excluding solvent peaks) in the following relative proportions: t_R 4.09 min, 24.6 %, t_R, 4.43 min, 16.2 %, t_R 4.53 min, 9.1 % and t_R 4.72 min, 50.1 %. After vacuum distillation (bp 73–76 °C, 0.60 mm) the light yellow oil (10.9 g, purity 96.7 %) now showed a ratio 14.4 : 69.1 : 9.4 : 7.2. TLC one spot (no R_f; severe streaking). Assignment of individual GC peaks to specific stereoisomers of **16** was not feasible owing to the ax/eq possibilities for the Me groups and the syn/anti possibilities at C=N. ^1H NMR ($CDCl_3$) δ 0.84 (s, 9 H), 1.05 (d, J=6.4 Hz, 3 H, eq CH_3), 1.10 (d, J=7.3 Hz, 3 H, ax CH_3), 1.00-2.00 (m, 5 H), 2.40 (s, 6 H), 2.35-2.50 (m, 1 H), 3.40–3.80, (m, 1 H); IR ($CDCl_3$) 2965, 2868, 2820, 2775 (NMe_2), 1624 (C=N), 1468, 1450 cm^{-1}.

General Procedure for Oxidative Cleavage of N,N-dimethylhydrazones 15 and 16 to Ketones.[14] A 0.95 M solution of **15** or **16** in MeOH was added dropwise to a stirred suspension of MMPP (1.30 equiv) in a solution of MeOH (74 mL) and pH 7 phosphate buffer (74 mL) at 0 °C. The mixture was stirred at 0 °C until reaction was judged complete by TLC (ca. 30 min) and then was poured into a 2 : 1 Et_2O : H_2O mixture. The aqueous phase was re-extracted with Et_2O, and the combined organic layers were washed with saturated $NaHCO_3$, H_2O, and brine, then dried ($MgSO_4$) and concentrated to give the crude product.

(a) Mixture of *cis*-2-Methyl-4-*t*-butylcyclohexanone (1c) and *trans*-2-Methyl-4-*t*-butylcyclohexanone (1d) from 15.[10] Crude yellow oil (3.1 g); TLC (2 spots), **1c** R_f 0.48, **1d** R_f 0.41 (7 : 93, ethyl acetate : pentane); GC (SE-54), **1c** (t_R 3.10 min, 12.04 %), **1d** (t_R 3.16 min, 78.5 %). Column chromatography (silica gel, ethyl acetate : pentane = 7:93) gave a mixture of **1c** and **1d** (2.89 g, 93 %) as a slightly yellow oil: GC purity = 96 %; ^1H NMR showed the ratio of **1c** : **1d** to be 14 : 86.[39] A second column chromatography raised the GC purity to 98 %. For **1c**: ^1H NMR (CCl_4) δ 1.13 (s, 9 H), 1.17 (d, J = 6.5 Hz, 3 H, eq CH_3), 1.40–2.90 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 14.7 (eq CH_3), 27.6 (*t*-Bu CH_3), 28.7, 32.4, 37.3, 41.4, 44.5, 47.1, 203.2 (C=O); IR ($CDCl_3$) 1706 (C=O) cm^{-1}. Data for **1d**: ^1H NMR (CCl_4) δ 1.12 (s, 9 H), 1.32 (d, J = 7.2 Hz, 3 H, ax CH_3), 1.40–2.90 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 16.86 (ax CH_3), 26.20, 27.37, 27.63, 32.98, 38.02, 41.27, 42.97, C=O not discernible. IR (neat) 1713 (C=O) cm^{-1}. (Our ^{1}NMR assignments for **1c** were available from a pure sample prepared below; those for **1d** were assigned from the mixture NMR by subtraction.

(b) Mixture of r-4-*t*-Butyl-*cis*-2-*trans*-6-dimethylcyclohexanone (7a) and r-4-*t*-Butyl-*cis*-2-*cis*-6-dimethylcyclohexanone (7b) from 16.[10] Vacuum distillation of the crude product gave a clear oil (5.40 g, 63 %): bp 65–68 °C (0.55 mm) [lit.[10] bp 104-105 °C (10 mm)]; TLC (2 spots), **7a** R_f 0.63, **7b** R_f 0.56 (7 : 93, ethyl acetate : hexane); GC (SE-54) indicated 95.9 % purity, but the ratio of **7a** : **7b** was not determinable due to epimerization during GC. However, ^1H NMR integration of the α-methyl signals[23] in **7a** and in **7b** gave their relative proportions as 96.8 : 3.2. Repeated silica column chromatography gave pure **7a**: ^1H NMR (CCl_4) δ 1.11 (s, 9 H), 1.16 (d, J = 6.6 Hz, 3 H, eq CH_3), 1.35 (d, J = 7.3 Hz, 3 H, ax CH_3), 1.3–1.4 (m, 1 H), 1.75–2.0 (m, 3 H), 2.1–2.2 (m, 1 H), 2.5–2.75 (m, 2 H); ^{13}C NMR (CCl_4) δ 212.94, 42.55, 41.31, 40.10, 36.02, 33.68, 32.19, 27.47, 17.27 (ax CH_3), 15.19 (eq CH_3); IR (neat) 2964, 2870, 1713 (C=O) cm^{-1}.

General Procedure for Partial Equilibration of Ketones. A mixture of ketones **1c** + **1d** or **7a** + **7b** (1.0 equiv) was added to a 0.10 M solution of NaOMe (1.58 equiv) in MeOH. The mixture was

refluxed 24 h, was diluted with brine, and was extracted with pentane, which was dried ($MgSO_4$) and passed through a course fritted filter, and concentrated to afford crude product.

(a) Mixture Enriched in 1c. From **1c+1d** (initially rich in **1d**) we obtained 2.75 g (93 %) of light yellow oil, 97 % pure by GC (SE-54); **1c** (t_R 3.10 min, 89.5 %), **1d** (t_R 3.16 min, 10.5 %), but the GC peaks were not baseline resolved. However, ^{1}H NMR ($CDCl_3$) of the methyl signals indicated **1c** (86 %, δ 1.00, d, J = 6.5 Hz) and **1d** (14 %, δ 1.14, d, J = 7.1 Hz). After chromatography on silica gel, a sample of **1c** showed:^{1}NMR ($CDCl_3$) δ 0.91 (s, 9 H, *t*-Bu), 1.01 (d, J = 6.5 Hz, 3 H, eq CH_3), 1.10-1.23 (m, 1 H, ring H), 1.34-1.51 (m, 1 H, ring H), 1.53-1.66 (m, 1H, ring H), 2.00-2.15 (m, 2 H, ring H), 2.23-2.47 (m, 3 H, ring H).

(b) Mixture Enriched in 7b. From **7a+7b** (initially rich in **7a**) we obtained 379 mg (76 %) of a light yellow oil. GC assay was not possible due to epimerization on the column. Integration of the α-Me signals gave the **7a** : **7b** ratio as 16 : 84. Repeated silica column chromatography gave a fraction with 91 % enrichment of **7b**: ^{1}H NMR (CCl_4) δ 1.11 (s, 9 H), 1.14 (d, J = 6.5 Hz, 6 H), 1.2–1.45 (m, 1 H), 1.80–2.0 (m, 2 H), 2.2–2.3 (m, 2 H), 2.4–2.6 (m, 2 H); ^{13}C NMR (CCl_4) δ 210.41, 47.03, 43.90, 37.75, 32.24, 27.68, 14.81; IR (CCl_4) 2968, 2869, 1716 (C=O) cm^{-1}.

***Cis*-2-Methyl-4-*t*-butylcyclohexanone *p*-Toluenesulfonylhydrazone (2c).** Modifying a published procedure[16] we added an 84 : 16 mixture of **1c** and **1d** (2.75 g, 13.9 mmol, 85 % pure + 6 % Et_2O) to a stirred solution of *p*-toluenesulfonylhydrazide (2.70 g, 14.1 mmol) in THF (29.0 mL) under Ar. The reaction was monitored by TLC and, after 8 h at room temperature, evaporation left a viscous yellow-orange oil. Dry hexane (50 mL) was added to the oil, and a cream colored solid precipitated. The hexane was evaporated and the solid was dried 24 h under vacuum (0.10 mm). Several recrystallizations from Et_2O provided 1.43 g, (30.5 %) of pure tosylhydrazone **2c** as white crystals, mp 129-131.5 °C (dec.); TLC (1 spot), R_f 0.55, (5 : 1, benzene : Et_2O); ^{1}H NMR (CCl_4) δ 1.05 (s, 9 H), 1.20 (d, J = 6.3 Hz, 3 H, eq CH_3), 1.10–1.50 (m, 3 H), 1.80–1.90 (td, J = 13.9, 4.5 Hz, 1 H), 2.00–2.15 (m, 2 H), 2.25–2.40 (m, 1 H, *tert.* α-H_{ax}), 2.64 (s, 3 H), 3.06 (broad d, J = 14.3 Hz, 1 H, α-H_{eq}), 7.47 (d, J = 8.2 Hz, 2 H), 8.01 (d, J = 8.2 Hz, 2 H), 8.17 (s, 1 H); ^{13}C NMR (CCl_4) δ 17.14, 21.83, 26.88, 27.35, 27.96, 32.68, 37.49, 39.43, 47.68, 128.74, 129.08, 136.59, 142.57, 162.67; ^{13}C NMR (CD_2Cl_2) δ 16.84, 21.69, 26.91, 27.53, 27.60, 32.55, 37.62, 39.63, 47.47, 128.59, 129.67, 135.74, 144.48, 165.14; IR (KBr) 3190, 2959, 2864, 1648 (C=N), 1598, 1325 (SO_2), 1306, 1165 (SO_2) cm^{-1}. Analysis. Calc'd for $C_{18}H_{28}N_2O_2S$: C, 64.25; H, 8.39. Found: C, 64.43; H, 8.45.

Attempted Preparation of Tosylhydrazone 2d. A ketone mixture comprised of **1c** : **1d** in the ratio 8 : 92 was treated as described above but the reaction time was limited to 70 min. ^{1} NMR showed the crude product to be tosylhydrazone **2c**, and recrystallization gave material identical in all respects to authentic **2c**. Various experimental modifications designed to minimize epimerization were unsuccessful; and even the use of specially purified CH_2Cl_2 as recommended by Garner et al.[17] helped only partially. In this latter case ^{1}NMR indicated that our crude tosylhydrazone may have contained ca. 60 % of the desired **2d**, but attempted recrystallizations served only to isomerize it all to **2c**.

Preparation of *r*-4-*t*-Butyl-*cis*-2-*trans*-6-dimethylcylohexanone *p*-Toluenesulfonylhydrazone (8a). A 97 : 3 mixture of **7a** : **7b** (593 mg, 3.03 mmol, purity = 93 %) and a small amount of concentrated HCl (0.04 mL, 18.2 mg, 0.50 mmol) was added to MeOH (4.0 mL). Recrystallized *p*-toluenesulfonylhydrazide (633 mg, 3.47 mmol) was added in one portion to the stirred ketone solution. The reaction was monitored by TLC and allowed to proceed 0.5 h at room temperature. After ~2 min a white precipitate crashed out of solution, which became too thick to stir after 5 min. The thick paste was concentrated and was dried 20 h under vacuum (0.10 mm) to give 1.13 g (106 %) of a white solid. Several recrystallizations from Et_2O provided 709 mg (67 %) of **8a**, mp 134-136 °C (dec.). TLC (1 spot) R_f 0.36 (7 : 93, ethyl acetate : pentane); ^{1}H NMR (CCl_4) δ 1.03 (s, 9 H), 0.9–1.3 (m, 1H), 1.18 (d, J = 6.3 Hz, 3 H,

eq CH_3), 1.25 (d, J = 7.2 Hz, 3 H, ax CH_3), 1.45–1.75 (m, 2 H), 1.83 (broad d, J = 12.4 Hz, 1 H), 2.00 (broad d, J = 12.3 Hz, 1 H), 2.44-2.55 (m, 1 H), 2.63 (s, 3 H), 2.90–3.30 (m, 1 H), 7.46 (d, J = 8.3 Hz, 2 H), 8.00 (d, J = 8.2 Hz, 2 H), 8.20 (s, 1 H); ^{13}C NMR (CCl_4) δ 16.96, 17.04, 21.45, 27.50, 28.64, 31.97, 33.26, 34.73, 36.99, 41.12, 128.31, 128.74, 136.27, 142.19, 165.13; IR (KBr) 3218, 2962, 2937, 2868 , 2829, 1633 (C=N), 1598, 1169 cm^{-1}. Analysis. Calc'd for $C_{19}H_{30}N_2O_2S$: C, 65.11; H, 8.63; N, 7.99. Found: C, 65.35; H, 8.64; N, 7.83.

2,6-Dideuterio-*r*-4-*t*-butyl-*cis*-2-6-dimethylcylohexanone (7d) and 2,6-Dideuterio-*r*-4-*t*-butyl-*cis*-2-*trans*-6-dimethylcylohexanone (7c). Sodium hydride (147 mg, 3.68 mmol, 60 % dispersion in mineral oil) was rinsed with dry pentane (3 x 3 mL) in a flame dried flask equipped with a stir bar and reflux condenser. The pentane was removed by syringe and MeOD (21 mL, 99.5 atom % D) was added via syringe at room temperature. A 97 : 3 mixture of ketones **7a** and **7b** (629 mg, 3.45 mmol, purity = 93 %) in MeOD (21 mL) was slowly added by syringe. The mixture was refluxed 24 h at 69 °C, was cooled, and D_2O (100 mL, 99.8 atom % D) was added, followed by extraction with Et_2O. The aqueous phase was poured onto solid NaCl (~ 18 g) and extracted with more Et_2O. The combined Et_2O extracts were dried (Na_2SO_4), and concentrated. The cloudy residue was taken up in pentane, dried (Na_2SO_4), and concentrated to an oil, which was then cycled through a second identical exchange reaction. The final light yellow oil (630 mg, 100 %) was 93.2 % pure by GC. By ^1H NMR the ratio of **7c** : **7d** was 6 : 94, determined by integration of multiplets at δ 1.9–2.0 and δ 2.0–2.1, associated with **7c** and **7d** respectively. Integration (^1H NMR, $CDCl_3$) of the residual α-H signals at δ 2.3–2.6 indicated approximately 4 % of d_0 and d_1 ketone remained. (The *t*-Bu singlet at δ 0.89 was used as an internal standard.) ^1H NMR ($CDCl_3$) δ 0.89 (s, 9 H), 0.99 (s, 6 H), 1.1–1.35 (m, 2 H), 1.6–1.8 (m, 1 H), 1.9–2.2 (m, 2 H). EIMS (m/z 182) d_0 = 0.0 %, d_1 = 1.0 %, and d_2 = 99.0 %.

***p*-Toluenesulfonylhydrazide-d_3.** This reagent was prepared as reported[24] and had mp 108–110.5 °C (dec.). Integration of the residual NH and NH_2 hydrogen signals indicated 5–8 % of undeuterated species; ^1H NMR ($CDCl_3$) δ 2.45 (s, 3 H), 3.56 (s, residual NH), 5.59 (s, residual NH_2), 7.36 (d, J = 8.0 Hz, 2 H), 7.80 (d, J = 8.2 Hz, 2 H); IR (KBr) 3256, 3029, 2923, 2532, 2428, 1598, 1323, 1156 cm^{-1}.

2,6-Dideuterio-*r*-4-*t*-butyl-*cis*-2-*trans*-6-dimethylcyclohexanone *p*-Toluenesulfonylhydrazone (8c). Concentrated DCl (83.1 mg, 0.44 mmol, 99.5 atom % D, 20 weight % solution in D_2O) was added via syringe to a stirred solution of mixed ketones **7c** and **7d** (ratio 6 : 94; 630 mg, 3.18 mmol, 93.2 % pure) in MeOD (5.1 mL, 99.5 atom % D). Freshly prepared d_3-tosylhydrazide (615 mg, 3.25 mmol) was added, and the mixture was monitored by TLC. After 8 h the solution was concentrated and dried 20 h under vacuum (0.10 mm) to leave a beige solid. Several recrystallizations from Et_2O provided **8c** (406 mg, 39 %) as white crystals; mp 135–137 °C (dec.). TLC (1 spot) R_f 0.21 (7 : 93, ethyl acetate : pentane); ^1H NMR (CCl_4) δ 1.03 (s, 9 H), 0.9–1.3 (m, 1 H), 1.17 (s, 3 H), 1.24 (s, 3 H), 1.45–1.75 (m, 2 H), 1.82 (d, J =1 2.5 Hz, 1 H), 2.00 (d, J = 12.6 Hz, 1 H), 2.44–2.55 (m, residual H_{ax}), 2.64 (s, 3 H), 2.90–3.30 (m, residual H_{eq}) 7.47 (d, J = 8.1 Hz, 2 H), 8.00 (d, J = 8.2 Hz, 2 H), 8.33 (s, 1 H, residual NH); IR (KBr) 3218, 2962, 2868, 2398, 1627, 1597, 1345, 1169 cm^{-1} ^1H NMR (CCl_4) showed a small amount of residual α-H_{eq} (δ 2.90–3.30) and α-H_{ax} (δ 2.44–2.55) signals. After each recrystallization each of these residual signals was integrated relative to the *t*-Bu, the axial and equatorial CH_3, the aromatic CH_3, and the two aromatic H signals; the ratios were averaged. After the first recrystallization: α-H_{eq} = 8.7 % ± 0.8; α-H_{ax} = 2.8 % ± 0.3, corresponding to 11.5 % of species with d_0 or d_1; but after the third recrystallization the numbers were α-H_{eq} = 9.7 %; α-H_{ax} = 6.5 %), corresponding to 16.2 % d_0 and d_1 species. This increase revealed that some deuterium was lost upon recrystallization of the tosylhydrazone from Et_2O, and that D_{ax} departs easier than D_{eq}. Attempts to prevent any d-loss during formation and purification of the tosylhydrazone were unsuccessful. Isotope analysis of **8c** by mass spectroscopy was not tried as previous work in our laboratories[4c] had shown that tosylhydrazones do not readily give molecular ions; and assays based on fragment ions are fraught with errors.

Conversion of Tosylhydrazones 2c and 8a to Ketones.[20] Tosylhydrazone **2c** (52 mg, 0.15 mmol) was dissolved in acetone (21 mL) and H_2O (6 mL). The solution was cooled to 0 °C and N-bromosuccinimide (111 mg, 0.626 mmol) was added in one portion. The solution turned yellow immediately, and vigorous evolution of N_2 was apparent after 5 sec. The mixture was stirred 2 min, was quenched with 2 mL of saturated $NaHSO_3$, and was extracted with Et_2O. The combined extracts were washed successively with H_2O, 10 % Na_2CO_3, and H_2O , dried ($MgSO_4$), and concentrated. The GC ratio of **1c** : **1d** in the crude ketone was 98.7 : 1.3.

A similar procedure applied to **8a** gave **7a** as the major component, containing not more than 3-4 % of **7b** (via ^1H NMR of the α-CH_3 signals). Accurate GC assay was not possible owing to epimerization during analysis.

Control Reaction. A known mixture of **7a** and **7b** (97 : 3) was treated with NBS and worked up as described above. Analysis of the crude product by ^{1} NMR established that the ratio remained virtually unchanged (96 : 4).

Synthesis of Alkenes by Shapiro Reactions.[26] A stirred 0.25–0.40 M tosylhydrazone solution of **2c** or **8a** (1.0 equiv) in dry THF was cooled to -78 °C, and freshly titrated *n*-BuLi (3.0 equiv) was added dropwise via syringe over 10 min. The deep orange red solution was stirred 2 h at -78 °C and allowed to warm to room temperature. The color gradually faded to pale yellow, N_2 evolution was observed, and H_2O was **cautiously** added to give a clear, two phase system. The mixture was extracted with Et_2O, and the etheral extracts were washed twice with H_2O, once with brine, dried (Na_2SO_4), and concentrated to afford the crude alkenes.

(a) *cis*-3-Methyl-*r*-5-*t*-butylcyclohexene (6c) from 2c.[10] We obtained 33 mg (68 %) of the crude alkene; GC (SE-54, 110 °C, 7 psi) showed three unknowns (37 %) along with alkenes **6c** and **5c** (63 %) in the ratio 99 : 1. Column chromatography (pentane : Et_2O, 6 : 4) provided a pure sample of **6c** . ^1H NMR ($CDCl_3$) δ 0.86 (s, 9 H), 0.97 (d, J = 7.0 Hz, 3 H), 1.10–2.50 (m, 6 H), 5.48 (broad d, J = 9.8 Hz, 1 H), 5.60–5.70 (m, 1 H); IR ($CDCl_3$) 3015 (w), 2960 (s), 2870 (m), 1651 (w, C=C), 1468 (w), 1456 (w), 1394 (w), 1365 (w), 1242 (w), 1216 (w), 1166 (w), 1028 (w) cm^{-1}. The spectroscopic data for **6c** agreed with those reported.[10,23]

(b) *trans*-5-*t*-Butyl-1-3-dimethylcyclohexene (11a) and *cis*-5-*t*-Butyl-1-3-dimethylcyclohexene (12a).[10] From **8a** we obtained 30 mg (46 %) of crude product containing 91.4 %. of **11a** and**12a** in the ratio 91 : 9 by GC (Carbowax, 60 °C). These two alkenes were isolated together (96 % pure) by silica gel chromatography (pentane). ^1H NMR ($CDCl_3$): **11a**, δ 0.87 (s, 9 H), 0.95 (d, J = 7.1 Hz, 3 H), 0.8–2.5 (m, 6 H), 1.65 (s, 3 H), 5.30–5.40 (m, 1 H); **12a**, δ 0.87 (s, 9 H), 0.94 (d, J = 7.0 Hz, 3 H), 0.8–2.5 (m, 6 H), 0.8–2.5 (m, 6 H), 1.65 (s, 3 H), 5.20 (s, 1 H). IR (neat) 2958, 2869, 2832, 1674 (C=C), 1468, 1458, 1365 cm^{-1}. The spectroscopic data for **11a** and **12a** agreed with those reported.[10]

Preparation of Tosylhydrazone Li Salts 3c, 9a, and 9c. The following procedure (100 mg scale) is typical for preparation of Li salts from tosylhydrazones **2c**, **8a**, and **8c**. A 0.32 M solution of the recrystallized tosylhydrazone (1.0 equiv) in anhydrous THF was stirred at 0 °C. Freshly titrated *n*-BuLi in hexanes (1.0 equiv) was added dropwise via syringe. [*Note*: The solution of monoanion is colorless but the dianion (from subsequent abstraction of an enolic α-hydrogen) is pale yellow. This self-indicating feature allows conversion of tosylhydrazones cleanly to their mono-lithium salts.] After 15 min, the THF was carefully removed *in vacuo* at room temperature, and the glassy white residue was dried 24 h under vacuum (0.20 mm). The salt was stored under vacuum, protected from light, and used as common stock for a series of Bamford-Stevens reactions.

Neat Thermolyses at Atmospheric Pressure. Dry Li salt (1.0 equiv, 10–20 mg scale) in a flask equipped with a liquid N_2 cold trap was heated 15 min at 157–161 °C. After 3 min, a colorless liquid condensed in the trap. The apparatus was allowed to come to room temperature and the condensate was taken up in $CDCl_3$ and filtered through glass wool. The clear filtrate was immediately assayed by ^1H NMR (each spectrum was recorded two to four times and integrated three to five times) or by GC (SE-54 for **3c**, Carbowax for **9a** and **9c**; average of four injections per sample). The results reported below are averages from the number of runs indicated. In separate control thermolyses, known ratios of **6c/5c** (or **11a/12a**) in the presence of 1.0 equiv of LiTs were shown not to change after 15 min at 160 °C.

(**a**) **From Li Salt 3c**. Thermolyses were conducted in triplicate; typical yield ca. 60 %. The volatiles consisted of **5c** and **6c** (93–95 %) in the ratio 79.7 : 20.3 by GC (Table 1). Five unidentified minor constituents totalled ca. 6.0 %.

(**b**) **From Li Salt 9a**. Eleven samples were thermolyzed. The volatiles contained ca. 91 % of **11a** and **12a** in the ratio 86.7 : 13.3 by GC and 87.4 : 12.6 by ^1H NMR. Table 2 uses the NMR data. Eleven unidentified constituents, each present in small amounts, totalled ca. 9 %.

(**c**) **From Li Salt 9c.** Thermolysis was carried out on four samples. The product contained **11c** and **12c** (86.8 %) in the ratio 82.9 : 17.1 by GC. Nine minor unidentified constituents, amounted to ca. 13.2 %. The known vinyl ^1H NMR signals in the natural abundance alkenes allowed us to assay the residual H at the vinyl sites in each alkene (arising from H shift in the d_0 and H or D shift in the d_1 species). GC/MS did not resolve **11c** and **12c** but provided the d_0, d_1, and d_2 compositions of both of these isomers combined (15 scans averaged). The NMR data in conjunction with the GC/MS values allowed us to subtract out the contributions from d_0 and d_1 molecules and provided the **11c : 12c** ratios (and hence the D_{ax}/D_{eq} values) shown in Table 2.[9]

Thermolysis of Li Salt 3c in Diglyme. A base washed, oven dried flask equipped with a reflux condenser, stir bar, and glass stopper was flame dried and cooled under Ar. Dry diglyme (259 equiv) was added to the flask and the solution was heated to 159–162 °C . The glass stopper was removed and a small glass boat containing the dry Li salt (1.0 equiv, 10–20 mg scale) was added to the hot diglyme solution, after which the stopper was quickly replaced. [*Note*: Just before addition of the Li salt the Ar flow was stopped to avoid loss of any rapidly formed volatile products.] The Li salt dissolved immediately, and after 5 sec a precipitate appeared. The mixture was heated 30 sec and allowed to stand 10 min at room temperature, after which the colorless mixture was passed through a tightly packed glass wool plug. The filtrate was immediately analyzed repeatedly by GC (SE-54, average of eight injections per sample). The product contained **6c** and **5c** (82.8 ± 5 %) in the ratio 79.5 : 20.5 (average of nine individual experiments). In a separate control, a known ratio of **5c** and **6c** was heated 30 sec at 160 °C in the presence of 1.0 equiv of LiTs, and the ratio did not change.

Thermolyses of Li Salts 9a and 9c in Tetraglyme. Tetraglyme (76 equiv) was used because diglyme interfered with GC analysis of **11a** and **12a**. After thermolysis at 160 °C the mixture was cooled to room temperature, and the volatile products were vacuum distilled away from the tetraglyme into a trap cooled by liquid N_2. The distillate was taken up in $CDCl_3$ and immediately analyzed repeatedly by GC (Carbowax) and by ^1H NMR integration of the vinyl H signals of **11a** (δ 5.35) and **12a** (δ 5.20). Table 2 uses only the averaged NMR data, but the GC and NMR analyses agreed closely. A separate control thermolysis (30 sec, 160 °C) of a known mixture of **11a** + **12a** in the presence of 1.0 equiv of LiTs did not alter the alkene ratio.

(**a**) **From Li Salt 9a.** Thermolysis was done in quadriplicate and gave **11a** and **12a** (purity 66.5 ± 10 %) in the ratio 89.7 : 10.3 by NMR and 89.1 : 10.1 by GC. There were twelve unidentified minor components.

(**b**) **From Li Salt 9c.** Thermolysis (in quadruplicate) gave **11c** and **12c** (86.8 %) in the ratio by GC of 84.8 : 15.2. Nine unidentified minor components totalled ca. 13 %. The known NMR signals in the natural abundance alkenes allowed us to assay the residual vinyl H in each arising from H shift in the d_0

species and from H or D shift in the d_1 species. And GC/MS (15 scans averaged) provided the d_0, d_1, and d_2 compositions of **11c** and **12c** combined. The NMR data in conjunction with the GC/MS values gave the ratios of **11c** : **12c** shown in Table 2.[9]

Photolytic Bamford-Stevens Reactions. The dry Li salt (1.0 equiv) was added to an oven dried, quartz NMR tube (10 mm x 175 mm) equipped with a spin bar. The tube was sealed with a septum, was purged with Ar, and then dry pentane (4.0 mL) was added via syringe. The stirred suspension was positioned 1.0–1.5 cm from the outer wall of the photochemical assembly and irradiated (2 h, 34–36 °C) with a Pyrex-filtered, water cooled, medium pressure Hg lamp. The NMR tube was given a quarter turn every 20 min to help average out any imperfections in the glass. The contents were filtered through glass wool, and the faintly pink filtrate was repeatedly analyzed by GC (Carbowax) immediately as well as 24 h later, after which time the pink color had disappeared. (We thought the color may have been due to some surviving diazo compound). The results reported below are averages from the number of runs indicated. In a separate control irradiation (2h, 34–35 °C), a known ratio of **11a** and **12a** in the presence of 1.0 equiv of LiTs was shown not to change.

(a) From Li Salt 9a. Photolysis was run in quadruplicate, and via GC the product contained **11a** and **12a** (86.8 ± 5 %) in the ratio 85.2 : 14.8 (initially) and 87.8 : 12.2 (after 24 h). Table 2 lists the average of these ratios. Five unidentified constituents were present (total 13.2 %), each in minor amount.

(b) From Li Salt 9c. Quadruplicate runs gave a product containing 85.6 % of **11c** and **12c** in the ratio 78.7 : 21.3 (initially) and 81.6 : 18.4 (after 24 h). We averaged these ratios. Six minor components comprised ca. 15 %. Residual vinyl ^{1}H NMR signals allowed us to assess the amount of H shift from d_0 species and H or D shift from d_1 species; and this information along with GC/MS analysis of the d_0, d_1, and d_2 content of combined **11c** +**12c** led to the D_{ax}/D_{eq} ratios in Table 2.[9]

Acknowledgement. This research was supported by the National Science Foundation (Grant CHE-9005952) and, in part, by the National Institutes of Health (GO1E502300) and by a Vernon K. Krieble Research Fellowship. Departmental NMR instrument grants were provided by NSF (PCM 83-03176) and NIH (1 S1O RR01934). We thank Angela Jones and Rosalie Elder for help in typing initial drafts of this manuscript.

References and Notes

1. (a) Kirmse, W. *Carbene Chemistry*, 2nd ed.; Academic: New York, 1971. (b) Jones, M., Jr., Moss, R. A., Eds. *Carbenes*; Academic: New York, 1973; Vol. 1. (c) Jones, W. M. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. 2, pp 95-160.
2. Nickon, A. *Acc. Chem. Res.* **1993**, *26*, 84–89.
3. Kenar, J. A.; Nickon, A. *Tetrahedron Lett.* **1994**, *35*, 9657–9660.
4. (a) Stern, A. G.; Ilao, M. C.; Nickon, A. *Tetrahedron*, **1993**, *49*, 8107–8118. (b) Nickon, A.; Stern, A. G.; Ilao, M. C. *Tetrahedron Lett.* **1993**, *34*, 1391–1394. (c) Stern, A. G. Ph.D. Thesis, The Johns Hopkins University, 1986.
5. Kyba, E. P. *J. Am. Chem. Soc.* **1977**, *99*, 8330–8332.

6. (a) Evanseck, J. D.; Houk, K. N. *J. Am. Chem. Soc.* **1990**, *112*, 9148–9156. (b) For recent calculations involving rearrangements of dialkylcarbenes, including ethylmethylcarbene, see Sulzbach, H. M.; Platz, M. S.; Schaefer, H. F.; Hadad, C. M. *J. Am. Chem. Soc.* **1997**, *119*, 5682-5689.

7. Press, L. S.; Shechter, H. *J. Am. Chem. Soc.* **1979**, *101*, 509–510.

8. Segher, L.; Shechter, H. *Tetrahedron Lett.* **1976**, 1943–1946.

9. For full details and calculations see Kenar, J. A. Ph. D. Thesis, Johns Hopkins University, 1994.

10. Beckwith, A.L.J.; Easton, C.J. *Chem. Soc. Perkin Trans. 2* **1983**, *5*, 661–668.

11. Corey, E. J.; Enders, D. *Chem. Ber.* **1978**, *111*, 1337–1361.

12. Fang, J. M.; Sund, S. F.; Rei, M. H. *J. Chem. Soc. Perkin Trans 2* **1989**, *7*, 747–750.

13. For a discussion of 1,3-allylic strain interactions see: (a) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841–1860. (b) Fraser, R. R.; Banville, J.; Dhwawan, K. L. *J. Am. Chem. Soc.* **1978**, *100*, 7999–8001. (c) Broeker, J. L.; Hoffmann, R. W.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5006–5017.

14. Enders, D.; Plant, A. *Synlett* **1990**, *12*, 725–726.

15. For examples of dimethylhydrazone isomerizations see Davenport, K. G.; Eichenauer, H.; Enders, D.; Newcomb, M.; Bergbreiter, D. E. *J. Am. Chem. Soc.* **1979**, *101*, 5654–5659.

16. Bertz, S. H.; Dabbagh, G. *J. Org. Chem.* **1983**, *48*, 116–119.

17. (a) Garner, C. M.; Mossman, B. C.; Prince, M. E. *Tetrahedron Lett.* **1993**, *34*, 4273–4276. (b) Mullica, D. F.; Garner, C. M.; Prince, M. E.; Mossman, B. C.; Sappenfield, E. L. *J. Cryst. Spectro. Res.* **1992**, *22*, 515–522.

18. Paquette, L. A.; Barth, W. *J. Org. Chem.* **1985**, *50*, 2438–2443.

19. In addition to the stability factor, we found that CCl_4 separated the chemical shifts and sharpened the signals for the ax and eq Me groups of the tosylhydrazones.

20. Freeman, P. K.; Balyeat, J. R. *J. Org. Chem.* **1977**, *19*, 3205-3206.

21. For example, menthone tosylhydrazone α–epimerizes 150 times faster than does the parent menthone (ref. 17). For other cases of epimerization in tosylhydrazones see: (a) References 18. (b) Casanova, J.; Zahra, J. P. *Tetrahedron Lett.* **1977**, *21*, 1773–1776. (c) Hutchins, R. O.; Milewski, C. A.; Maryanoff, B. E. *J. Am. Chem. Soc.* **1973**, *95*, 3662–3668. (d) Paquette, L. A.; Ross, R. J.; Shi, Y-J. *J. Org. Chem.* **1990**, *55*, 1589–1598. (e) Nakai, T.; Mimura, T. *Tetrahedron Lett.* **1979**, *6*, 531–534. (f) Satyanarayana, N.; Nayak, U. R. *Indian J. Chem, Sect. B* **1986**, *25B*, 28–31. (g) Tavernier, D.; Hosten, N.; Anteunis, M. *Synthesis* **1979**, *8*, 613–614. (h) Caporusso, A. M.; Giacomelli, G.; Lardicci, L. *J. Chem. Soc. Perkin Trans 1* **1979**, *12*, 3139–3145.

22. Fuchs, P. L.; Bunnell, C. A. *J. Org. Chem.* **1977**, *42*, 2614–2617.

23. (a) Johnson, F.; Duquette, L. G.; Whitehead, A.; Dorman, L. C. *Tetrahedron* **1974**, *30*, 3241–3251. (b) Pasto, D. J.; Johnson, C. R. *"Organic Structure Determination,"* Prentice-Hall, New Jersey, 1969, 174–175.

24. Schwab, F. C.; Brandolini, A. J. *Macromolecules* **1989**, *22*, 2538–2540.

25. Bamford, W. R.; Stevens, T. S. *J. Chem. Soc. C* **1952**, 4735–4740. For reviews of the Bamford-Stevens reaction see: (a) References 1a and 1b. (b) Regitz, M.; Maas, G. *Diazo Compounds*, Academic: New York, 1986, pp 257–295.

26. For the Shapiro reaction see Chamberlin, R. A.; Bloom, S. H. *Org. Reactions* **1990**, *39*, 1–83 and references cited there.

27. (a) Nickon, A.; Huang, F.-C.; Weglein, R.; Matsuo, K.; Yagi, J. *J. Am. Chem. Soc.* **1974**, *96*, 5264–5265. (b) Nickon, A.; Zurer, P. St. J. *J. Org. Chem. 1981, 46*, 4685-4694. (c) For bystander effects on the rates of H shifts in laser flash photolyses of halodiazirines see Liu, M. T. H.; Bonneau, R. *J. Am. Chem. Soc.* **1996**, *118*, 8098-8101, and references cited there.

28. Kyba, E. P.; John. A. M. *J. Am. Chem. Soc.* **1977**, *99*, 8329–8330.

29. For other examples in carbene chemistry see: (a) Ref. 27. (b) Kyba, E. P.; Hudson, C. W. *J. Org. Chem.* **1977**, *42*, 1935–1939. (c) Freeman, P. K.; Hardy, T. A.; Balyeat, J. R.; Westcott, L. D. Jr. *J. Org. Chem.* **1977**, *42*, 3356–3359. For examples in other reactions see: (d) Agosta, W. C.; Wolff, S. *J. Am. Chem. Soc.* **1976**, *98*, 4316–4317. (e) Nickon, A.; Werstiuk, N. H. *J. Am. Chem. Soc.* **1967**, *89*, 3917–3918. (f) Nickon, A.; Werstiuk, N. H. *J. Am. Chem. Soc.* **1972**, *94*, 7081–7086. (g) Corey, E. J.; Sneen, R. A. *J. Am. Chem. Soc.* **1956**, *78*, 6269–6278.

30. Disregarding secondary isotope effects is especially permissible for **9c**, where the non-involved C–D remains sp^3-type throughout the rearrangement.

31. That 3° and 2° H's do not differ markedly in their isotopic behavior is suggested by the recent finding of Moss et al. that the primary kinetic isotope effect for shift of the 3° H(D) in cyclobutylfluorocarbene generated by thermolysis of the corresponding diazirine at 138° C is ca. 2.50 [Moss, R. A.; Xue, S.; Ma, W. *Tetrahedron Lett.* **1996**, *37*, 1929–1932]. Their value is in the range of those found for 2° H(D)'s (Table 3).

32. The square root of the I_{ax}/I_{eq} ratio is the key number that enters into each numerical adjustment. To illustrate: for thermal B.S. $\sqrt{1.53} = 1.24$. Multiplying I_{orig} by 1.24 provides I_{ax}; and dividing I_{orig} by 1.24 gives I_{eq}. Accordingly, the published H_{ax}/H_{eq} migration ratios for thermal cases become increased by a factor of 1.24. Thus, the migration ratio of 1.73 obtained from studies on the homobrexyl system

(last compound in Table 3) now becomes 2.15. (The adjustment factor for photolytic B.S. cases would be the square root of 1.44 , namely 1.20). To avoid confusion as to the sources of all numerical data we have not rounded off any of the original numbers or the adjusted ones. However, in view of the experimental errors involved, readers should regard the data as less quantitative than indicated.

33. Perhaps the large effective size of an axial Ph ["A" value for Ph ~2.8, Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; pp 686–709], pitted against the t-Bu_{eq} anchoring group, distorts the cyclohexane ring to a twist boat, which could allow Ph_{ax} to adopt a more equatorial-like geometry.

34. Fraser, R. R.; Champagne, P. J. *Can. J. Chem.* **1980**, *58*, 72-78.

35. For commentary and references to isotope effects in carbene rearrangements see ref. 31 and reviews by: (a) Platz, M. S.; Modarelli, D. A.; Morgan, S.; White, W. R.;Mullins, M.; Celebi, S.; Toscano, J. P. *Prog. Reac. Kin.* **1994**, *19*, 93–137. (b) Liu, M. T. H. *Acc. Chem. Res.* **1994**, *27*, 287–294. (c) Jackson, J. E.; Platz, M. S. in *Advances in Carbene Chemistry*, Brinker, U. H., Ed.; JAI Press, Greenwich, CT, Vol 1, **1994**, pp 89–160.

36. A large dissimilarity in k_H/k_D isotope effect has been observed for the axial and equatorial trajectories in a photo-induced rearrangement of a cyclohexene to a cyclohexylidene. In that retro-type process, however, it is I_{eq} that exceeds I_{ax} (by a factor of 4.4). Nickon, A.; Ilao, M. C.; Stern, A. G.; Summers, M. F. *J. Am. Chem. Soc.* **1992**, *114*, 9230–9232.

37. (a) Modarelli, D. A.; Morgan, S.; Platz, M.S. *J. Am. Chem. Soc.* **1992**, *114*, 7034-7041 and references cited there. (b) Seburg, R. A.; McMahon, R. J. *J. Am. Chem. Soc.* **1992**, *114*, 7183-7189. (c) Fox, J. M.; Scacheri, J. E. G.; Jones, K. G. L.; Jones, M. Jr. *Tetrahedron Lett.* **1992**, *33*, 5021-5024.

38. Robson, J. H.; Shechter, H. *J. Am. Chem. Soc.* **1967**, *89*, 7112-7114.

39. For data and references to ^1H NMR assignments for **1c** and **1d** see reference 12 and House, H. O.; Tefertiller, B. A.; Olmstead, H. D. *J. Org. Chem.* **1968**, *33*, 935-942.

(*Received in USA* 2 *June* 1997; *revised* 14 *August* 1997; *accepted* 25 *August* 1997)