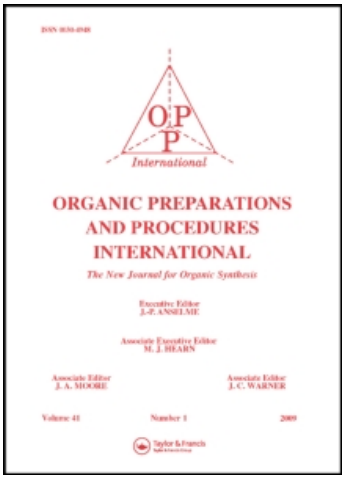

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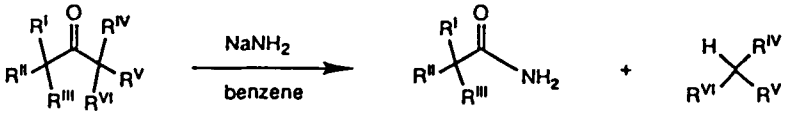
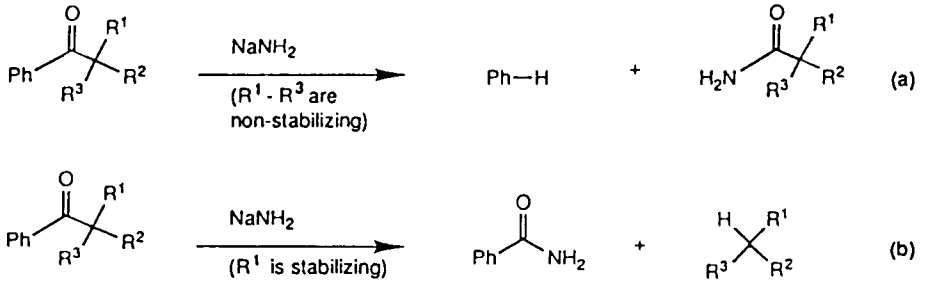
INTRODUCTION

The Haller-Bauer reaction encompasses those base-promoted cleavages of non-enolizable ketones that generate a carboxylic acid derivative and a second product in which the carbonyl group is cleanly replaced by a hydrogen atom. Traditionally, the reaction has been carried out under refluxing benzene conditions using sodium amide as the base. Thus, the process as first described constituted a useful synthesis of amides from more readily available ketones.



Much of the early development of the Haller-Bauer reaction has been reviewed.[1] Since the publication of these summaries, the Haller-Bauer reaction has been the center of investigations into the properties of short-lived intermediates, with particular emphasis on the stereochemical potential of the process. An especially intriguing question is that surrounding the stereochemical outcome of the bond cleavage in those circumstances where one of the α-carbons in the ketone is a non-racemic chiral center. It has long been realized[2] that the original Haller-Bauer reaction (sodium amide as the base) is but one example of a more

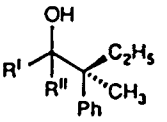
general process capable of being performed with a variety of bases. More relevant to the question of systematic investigation, however, was general acceptance that the process can best be rationalized in terms of anionic intermediates. Thus, for any ketone the direction of the cleavage can be predicted with a high degree of certainty. For example, cleavage of a phenyl α,α-disubstituted alkyl ketone would be expected to deliver benzene and the alkyl acetamide (*reaction a*) rather than benzamide and the corresponding saturated hydrocarbon (*reaction b*). This observation is consistent with preferred formation of the more electron-



ically stabilized phenyl anion rather than breakdown to form a tertiary alkyl carbanion. Significantly, when one of the α-alkyl groups is replaced by a substituent capable of stabilizing negative charge, then base-promoted cleavage proceeds in the alternative direction to provide benzamide and the α-substituted protonated material (*reaction b*). This reversal in regioselectivity has been most often realized by making R^1 a phenyl group[2b,3] or by incorporating the α carbon into a cyclopropane ring.[4] Once the direction of cleavage was considered to be reliably predictable, the stage was set for detailed investigation of the stereochemical outcome of such bond cleavage reactions.

That carbon-carbon bonds could be broken and a carbon substituent *stereospecifically replaced by hydrogen* was ably demonstrated by Cram and co-workers in a series of papers[5] published in the early 1960's and

reviewed some years later.[6] In these publications, detailed attention was given to the reaction of secondary and tertiary alcohols of type 1 with various bases in a variety of solvent systems. The discovery was made that the carbinol center could be replaced with hydrogen either with retention or inversion of configuration, the stereochemical outcome being dependent on the particular base and solvent system employed.



1

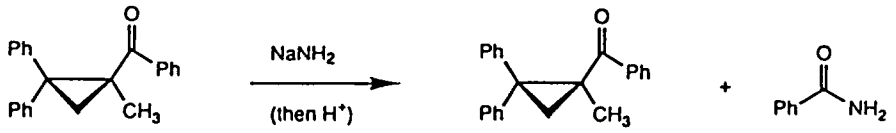
R', R'' = Ph, CH_3, H

I. STEREOCHEMICAL COURSE OF THE HALLER-BAUER REACTION

a. Cleavage of Cyclopropyl Phenyl Ketones

Some years later, the Walborsky group undertook a systematic study of the properties of cyclopropyl carbanions.[4,7] The Haller-Bauer reaction was included among a series of methods used to generate such reactive intermediates. Several 1-substituted-2,2-diphenylcyclopropyl phenyl ketones were prepared in optically active form, and their response to sodium amide subsequently examined.

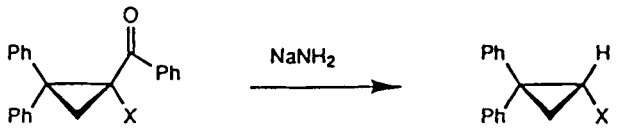
Haller-Bauer cleavage of 2[4a,c] was shown to produce the substituted cyclopropane 3 in optically active form. Furthermore, it was demonstrated that the benzoyl group had been directly replaced by hydrogen, a process which will be referred to in this review as retention of configuration. Comparable cleavage of other substituted cyclopropyl phenyl



2 3

ketones led in all cases to retention of configuration.[4d] However, the

efficiency of the stereochemical transfer has been investigated in only one case, the α-trimethylsilyl ketone 6 studied by Paquette.[8]



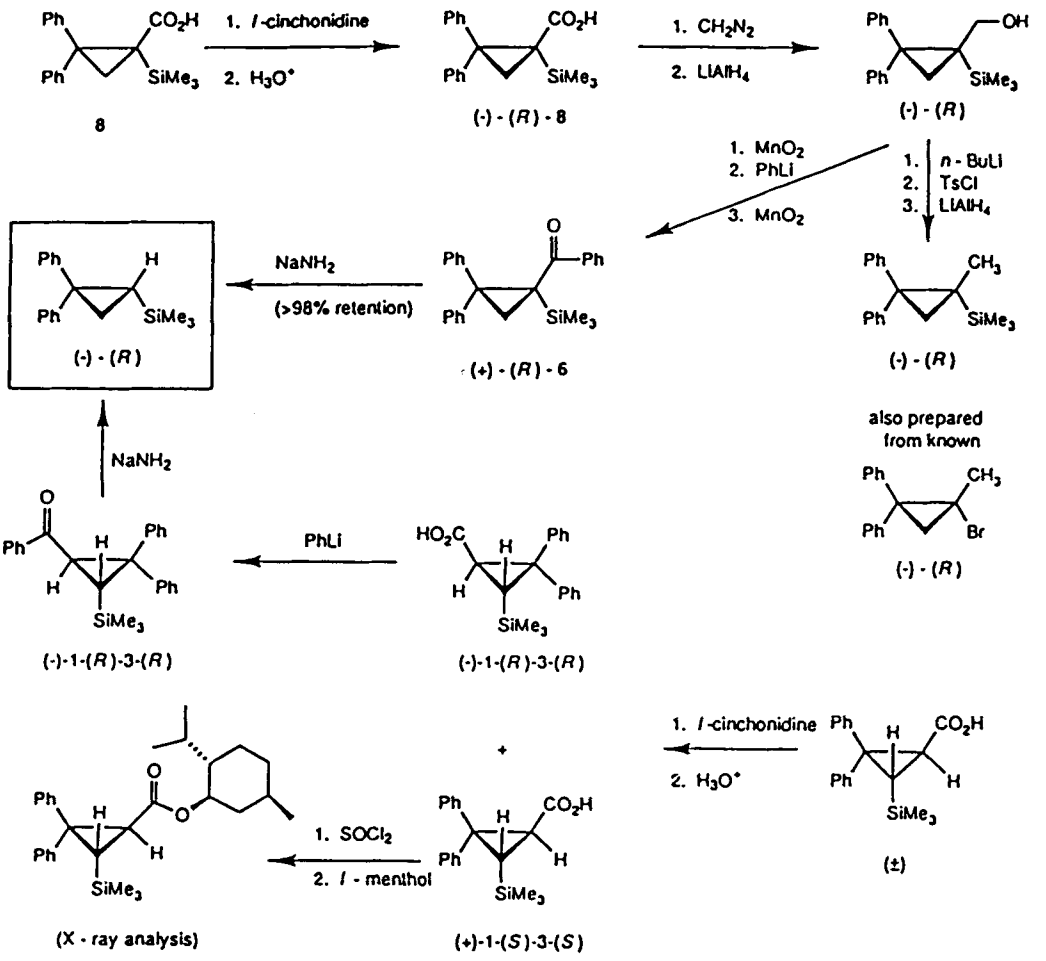
4a, X = Cl (+) - (*S*)
b, X = F (-) - (*S*)
c, X = OCH_3 (-) - (*S*)

5a, X = Cl (+) - (*S*)
b, X = F (-) - (*S*)
c, X = OCH_3 (+) - (*S*)

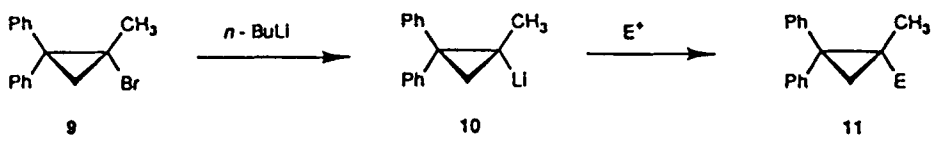
For this purpose, an accurate assessment of the stereochemical purities of 6 and the silane product had to be made. With this information in hand, The Haller-Bauer reaction was shown to proceed with > 98% retention of configuration. The enormous synthetic potential of the process is thereby demonstrated. Carboxylic acid 8 was readily resolved and then transformed into phenyl ketone 6 by conventional chemistry (Scheme I). Haller-Bauer cleavage delivered the optically active 2,2-diphenylcyclopropyl silane, thereby producing a compound that itself cannot be resolved directly.

Unquestionably, the Haller-Bauer reaction of cyclopropyl phenyl ketones is a process that can proceed with high levels of configurational retention at carbon. Thus, the transformation represents an example of *stereospecific electrophilic exchange*. One's excitement at these developments has to be tempered by the realization that other processes which normally induce loss of configuration at tetrahedral carbon proceed equally well with retention of configuration when the seat of reaction resides in a three-membered ring.[7] For example, chiral cyclopropane 9 reacts with *n*-butyllithium to provide the lithium species 10.[7b,f] Following quenching with electrophiles, optically active 11 was obtained. At -72 °C, retention of configuration was nearly complete (> 98%). At higher temperatures, the lithio species likewise retained

Scheme I



its configuration until the onset of decomposition. If the methyl group in 10 was replaced by a substituent capable of resonance stabilization, the strong predilection of configurational integrity was partially (as with isocyanide)[7f] or completely (as with nitrile)[9] lost. Configura-



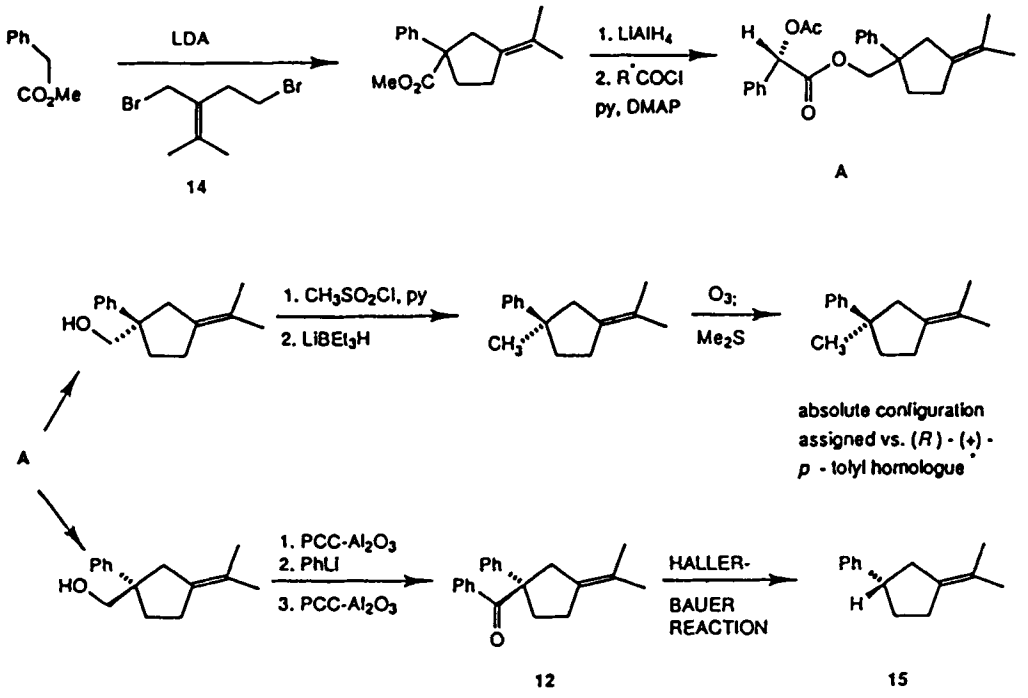
tional stability was also observed when the carbanion was generated from lithium in liquid ammonia[7d] or when Grignard reagent[7b] or alkyl sodium[7c] formation was undertaken. The realization that these cyclopropane examples constitute a special class of carbanion is apparent. Was the stereochemical course of the Haller-Bauer cleavages of 2, 4, 6, and related three-membered ketones biased by the impressive configuration-holding properties inherent to cyclopropyl anions? Since little information was available as to the outcome of Haller-Bauer reactions in larger ring systems and in acyclic molecules, attention was turned to substrates such as these.

b. Cleavage of Cyclopentyl Phenyl Ketones

The carbon atoms in a cyclopentane ring system are essentially unstrained, unlike their cyclopropane counterparts. Study of the Haller-Bauer cleavage of a series of cyclopentyl phenyl ketones has been performed.[10] The simplest, and least sterically congested examples 12[11] and 13,[12] readily available from the enolates of appropriately substituted methyl acetates and dibromide 14, could also be prepared in optically active form by resolution of the intermediate alcohols (Schemes II and III). The cleavage of both optically active ketones provided non-racemic products. A series of structual intercorrelations were then required in order to derive the necessary information for ascertaining the efficiency and direction (retention or inversion) of the cleavage reactions.

Schemes II and III illustrate the elaborate level of chemistry required to establish enantiomeric excesses and absolute configurations within classes of molecules possessing quaternary chiral centers, particularly when one of the substituents is trimethylsilyl.

Scheme II

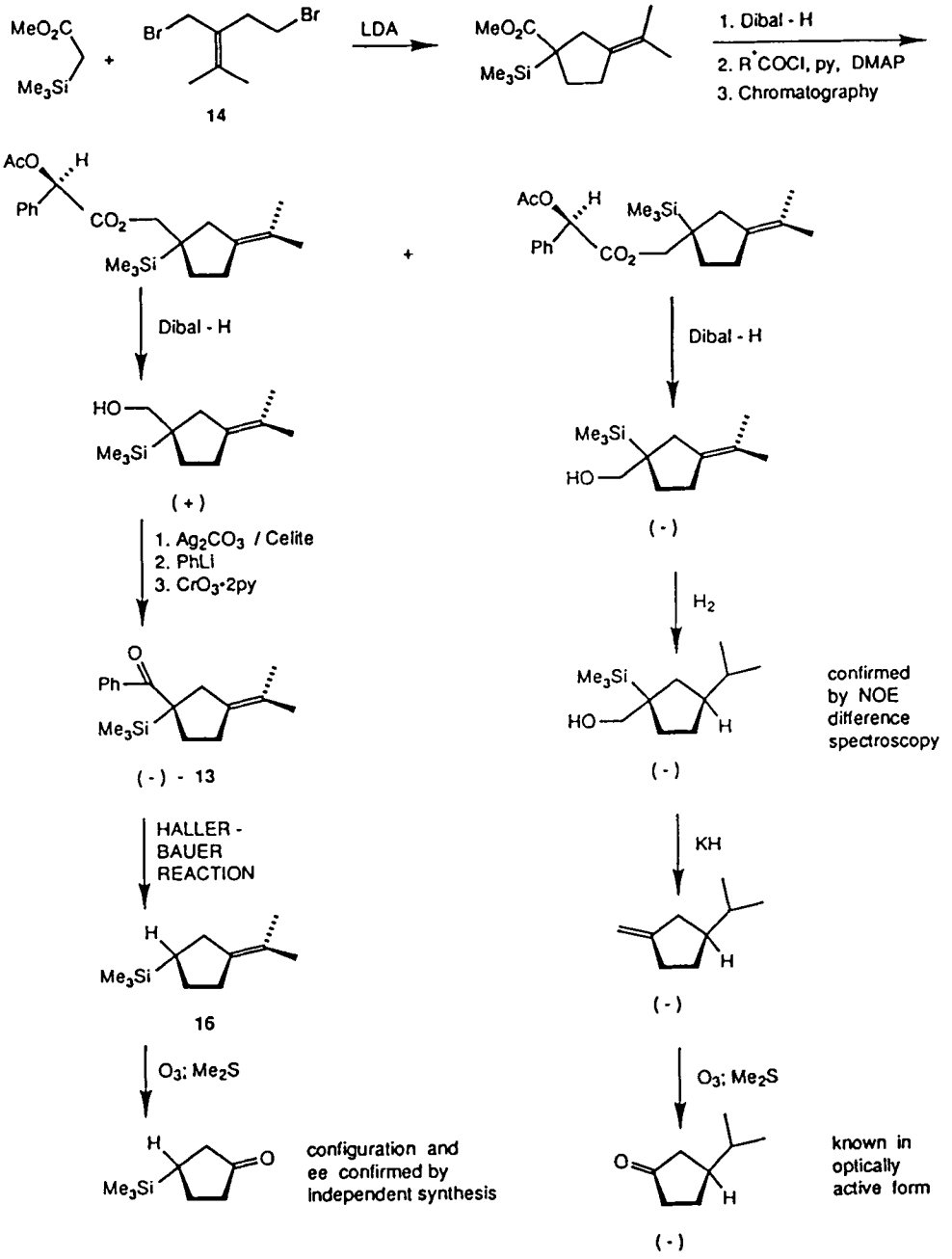


The Haller-Bauer transformation, when carried out on ketones 12 and 13 generally produced products with configurational retention. While the cleavage of 12 could be performed with a variety of bases, the α-trimethylsilyl analogue was prone to desilylation with bases other than sodium and potassium amide. The optical course of each of these reactions can be found in Table 1. High levels of retention are observed throughout.

c. Cleavage of Acyclic Phenyl Alkyl Ketones

In a more stringent test of the stereochemical course of these reactions, series of acyclic ketones structurally related to 12 and 13 were examined. As in the cyclopentyl examples, phenyl[10a,13] and trime-

Scheme III



thylsilyl[10b,14] groups were incorporated as the anion-stabilizing functionalities. For the purpose of establishing absolute configuration and

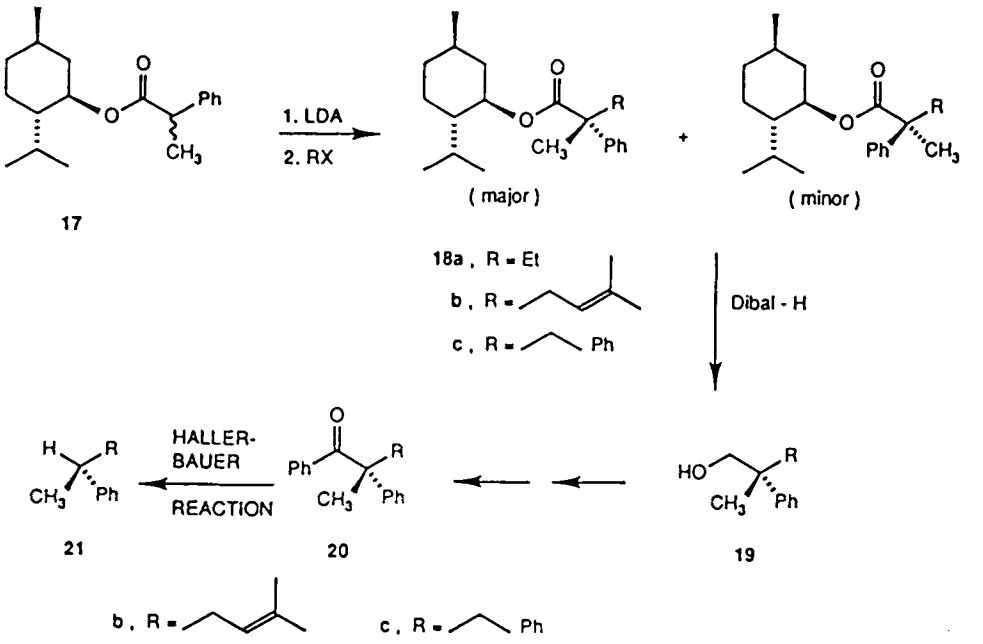
Table 1. Haller-Bauer Results for 12 and 13

Substrate (% ee)	Base	Solvent	Product	ee, %	Net Optical Course
12 (36%)	$NaNH_2$	C_6H_6	15	16	44% ret
	KNH_2	C_6H_6		20	88% ret
	$LiHN_2$	C_6H_6		21	60% ret
	KO*t*-Bu	*t*-BuOH		29	80% ret
13 (40%)	$NaNH_2$	C_6H_6	16	38	96% ret
	KNH_2	C_6H_6		36	92% ret

enantiomeric excesses, ketones 20 and 24 were prepared from menthyl ester precursors. Where the α-phenyl ketones are concerned, the enolate of ester 17 was alkylated with ethyl iodide, prenyl bromide, and benzyl bromide (Scheme IV). One diastereomer always predominated. Since the products all stem from a common precursor, the assumption was made that the major constituents (18) had the same absolute configuration. When reduced, 18a provided the known alcohol 19a having the (*R*) configuration. Thus, the absolute configurations of 18b and 18c were considered secured, and their enantiomeric excesses were readily determined by capillary gas chromatography of the menthyl esters 18.

Following conversion of 19 to the desired ketone 20, its cleavage under various conditions provided optically active products. Again, the retention pathway predominated, except when the cleavage was performed with potassium ethyleneglycolate in ethylene glycol as shown in Table 2. In the latter strongly dissociating solvent, the solvent-separated product pair is redirected away from frontside protonation by the sol-

Scheme IV



vating power of a strategically positioned hydroxyl group.

Similar correlation within the α-trimethylsilyl series was possible after the crystal structure of menthyl ester 22 was determined by X-ray methods. Two routes to the required esters were devised, such that either enantiomeric form at the new chiral center could be made to predominate (Scheme V).

After conventional conversion of esters 22 to their phenyl ketones 24, the Haller-Bauer reaction was performed in the presence of sodium and potassium amides. Again, optically active silanes were obtained, the reaction occurring with high levels of retention (Table 3). Because the cleavages of 24c and 24d produced known silanes, the optical course of these reactions could be calculated directly from the $[\alpha]_D$ values of the products. In addition, the actual course of events was now deemed reliable enough to permit assignment of $[\alpha]_D$ values to optically pure

Table 2. Haller-Bauer Results for 20b and 20c.

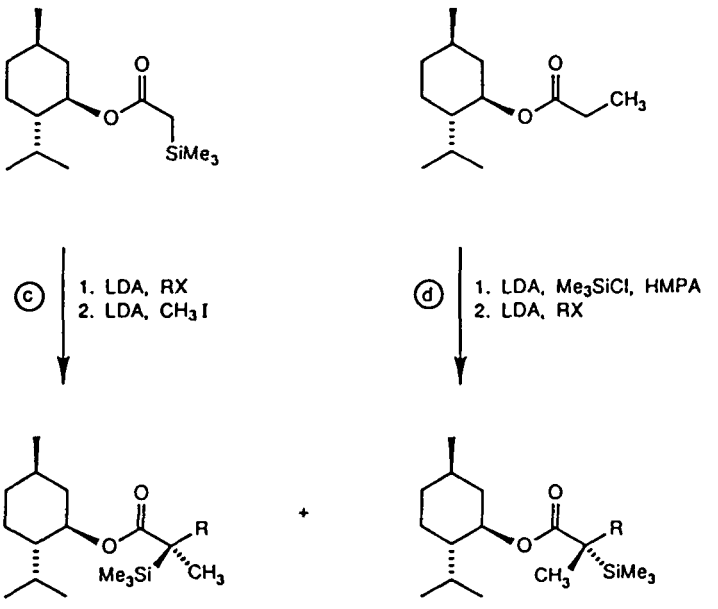
Substrate (% ee)	Base	Solvent	Product ee, %	Net Optical Course
(38)	KO*t*-Bu	*t*-BuOH	32	84% ret
(40)	NaO*t*-Bu	*t*-BuOH	35	88% ret
(40)	LiO*t*-Bu	*t*-BuOH	no cleavage after 80 h	
(40)	KO*t*-Bu	C_6H_6	21b 34	86% ret
20b (40)	KNH_2	C_6H_6	18	44% ret
(38)	$NaNH_2$	C_6H_6	17	46% ret
(38)	$LiNH_2$	C_6H_6	21	56% ret
(40)	$KOCH_2CH_2OH$	$HOCH_2CH_2OH$	16[a]	40% ret
	$NaNH_2$	C_6H_6	22	44% ret
20c (50)	KO*t*-Bu	*t*-BuOH	41	82% ret
	KO*t*-Bu	C_6H_6	21c 30	60% ret
	$KOCH_2CH_2OH$	$HOCH_2CH_2OH$	11[a]	22% ret

[a]Product of opposite $[\alpha]_D$.

samples of the new silanes 25a and 25b (Scheme VI).

An inherent feature of the Haller-Bauer reaction is its ability to replace the departing benzoyl group stereospecifically by a proton. In the above examples, the course of debenzoylation has been monitored by means of optical activity. This is a valuable mechanistic probe of the reaction, since it follows that as enantiomers are produced, each is subject to the same steric congestion. As a consequence, the ratio of enantiomeric products depends entirely on the stereospecificity of the cleavage. The steric course of selected Haller-Bauer reactions has also

Scheme V



22 23

		DIRECTION c		DIRECTION d	
		INITIAL	PURIFIED[a]	INITIAL	PURIFIED[a]
Compound	R	22 : 23	22 : 23	22 : 23	22 : 23
a	CH_2Ph	55 : 45	>99 : 1[b]	31 : 69	20 : 80
b	$CH_2CHC(CH_3)_2$	55 : 45	91 : 9	38 : 62	10 : 90
c	CH_2CH_2Ph	55 : 45	>99 : 1[b]	25 : 75	8 : 92
d	$(CH_2)_4CH_3$	50 : 50	94 : 6	38 : 62	10 : 90

[a]Figures apply to 40 - 50 % mass return of the starting material after one chromatography. [b]Crystallization effected.

been monitored by making recourse to geometrically isomeric cycloalkyl systems as discussed below.

II. STERIC COURSE OF THE HALLER-BAUER REACTION

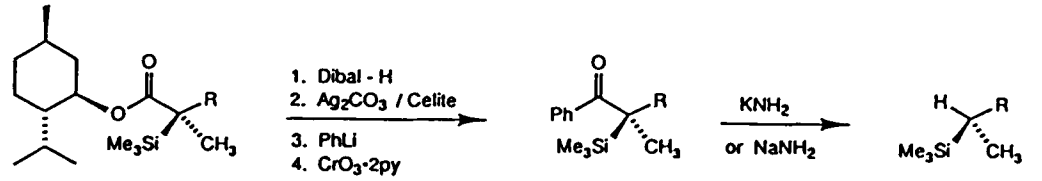
When two or more substituents are present on a cycloalkane ring, interactions between the groups can have a profound effect on conforma-

Table 3. Haller-Bauer Cleavage of Optically Active 24a-c (Refluxing C_6H_6 Solution).

Substrate (% ee)	Base	Product ee, %	Net Optical Course
24c (99)	$NaNH_2$	81	81% ret
	KNH_2	77	77% ret
24d (89)	$NaNH_2$	74	84% ret
	KNH_2	68	76% ret
24a (99)	$NaNH_2$	$[\alpha]_D^{23}$ + 31.6° (CCl_4)[a]	
	KNH_2		
24b (46)	$NaNH_2$	$[\alpha]_{365}^{23}$ + 24.6° (CH_2Cl_2)[a]	
	KNH_2		

[a]Extrapolated values for enantiomerically pure 25a and 25b on the basis of consistent 83% and 76% retention levels for $NaNH_2$ and KNH_2, respectively.

Scheme VI



22a. R = CH_2Ph
b. R = $CH_2CH=C(CH_3)_2$
c. R = CH_2CH_2Ph
d. R = $(CH_2)_4CH_3$

24

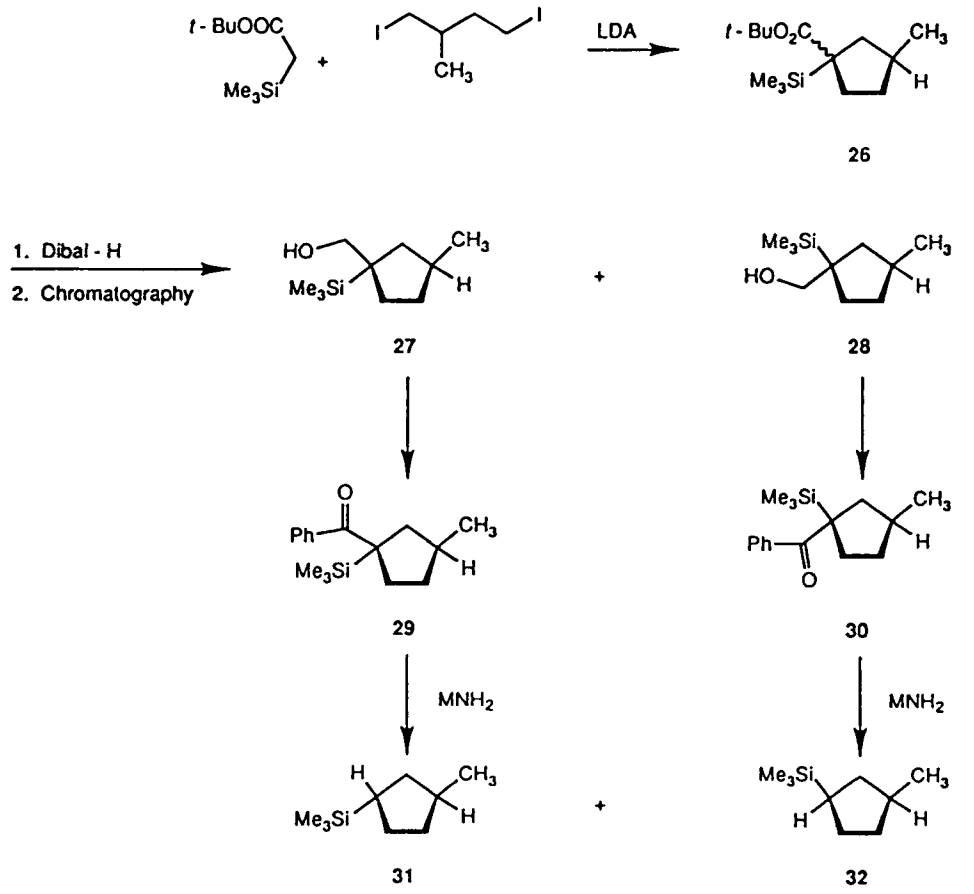
25

tion. The reactivity of a directly-linked functional group can experience modification as a result. In order to evaluate such factors, the Haller-Bauer reactions of two ring types have been investigated.

a. Phenyl α-(Trimethylsily)cyclopentyl Ketones

Phenyl ketones 29 and 30[12] were elaborated by α,α-dialkylation of

Scheme VII



the *tert*-butyl ester of (trimethylsilyl)acetic acid as in Scheme VII. Their degradation to silanes 31 and 32 was monitored by capillary gas chromatography and the results are compiled in Table 4. The presence of a methyl group β to the reaction center is seen to have little effect on the cleavage reaction. In fact, the net retentive ability of the process is virtually identical to that reported for the related ketone (-)-13.

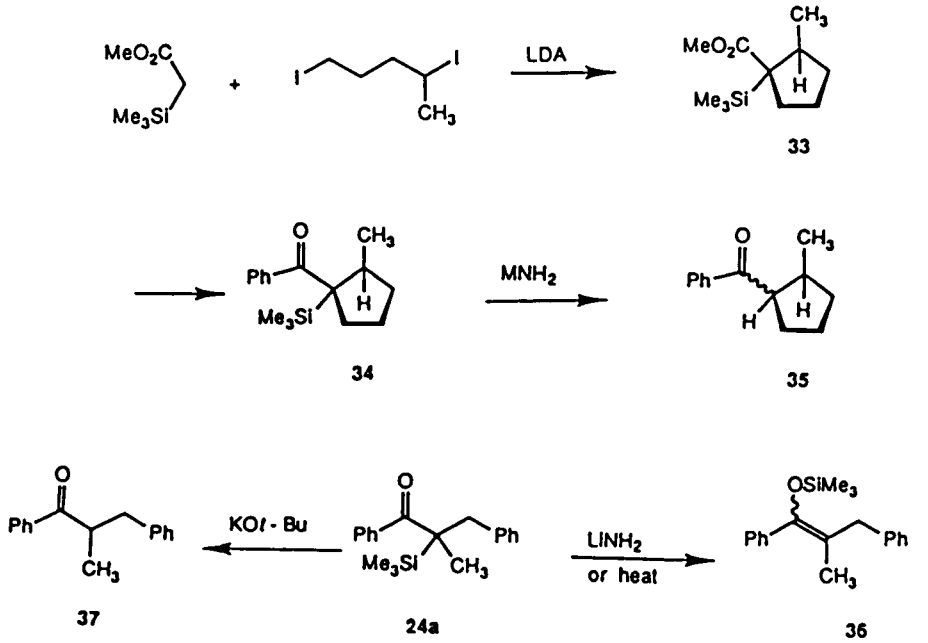
The α-methyl isomer 34[12] was prepared in a similar route (Scheme VIII). Interestingly, the spiroalkylation step employed to construct

Table 4. Haller-Bauer Cleavages of Ketones 29 and 30.

Substrate	Base	Ratio 31:32	Net Steric Course
29	$NaNH_2$	98:2	96% ret
	KNH_2	96:4	92% ret
30	$NaNH_2$	5:95	90% ret
	KNH_2	5:95	90% ret

the cyclopentane ring provided only the isomer shown. In 34, one face of the carbonyl group is effectively shielded by the methyl substituent.

Scheme VIII

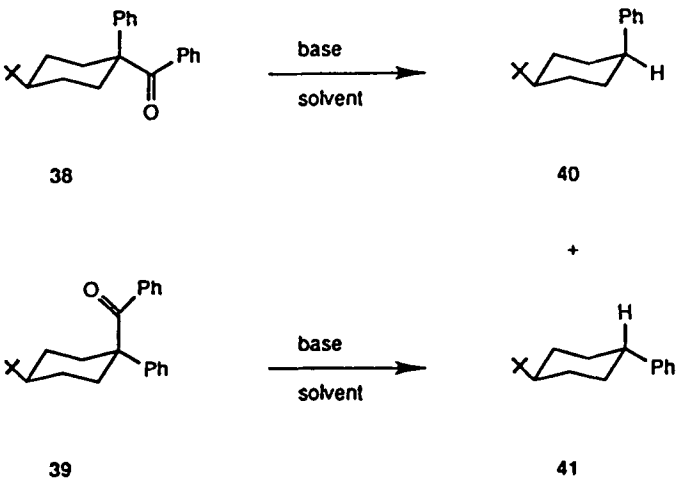


As a consequence, its treatment with amide bases under standard conditions gave rise only to 35, the product of simple desilylation. The steric congestion around the carbonyl center in 34 is presumably sufficient to preclude normal operation of the Haller-Bauer cleavage. In a related reaction, attempted cleavage of ketone 24a with oxygen-centered nucleophiles also resulted in efficient desilylation. When heated in benzene alone or with lithium amide, 24a was observed to rearrange instead to 36, the isomeric compound also isolated when 24a was subjected to preparative gas chromatography. The conclusion has been reached that desilylation is achieved by nucleophilic attack at the silicon atom. When base is not present, thermal migration of the silicon substituent to provide enol ethers becomes the favored reaction. The Haller-Bauer reaction can therefore tolerate the presence of groups in the reacting substrate as long as the reaction center itself is not sterically congested.

b. Benzoylcyclohexanes

The cyclohexane ring system differs from the cyclopentane and cyclopropane frameworks in that substituents may occupy positions that are either axial or equatorial. When bulky groups are present, cyclohexanes may be locked into one chair form with the largest groups occupying an equatorial position. In order to investigate the effect of spatial orientation on the stereochemical outcome of the Haller-Bauer reaction, two pairs of benzoylcyclohexanes (38,39 and 42,43) were prepared.[11] Each cyclohexene has a *tert*-butyl group in the 4-position to act as an anchor and fix the cyclohexane ring into the illustrated chair conformation.

The α-phenyl ketones 38 and 39 were cleaved with a series of bases



under a range of solvent conditions. The results of the cleavage reactions are compiled in Table 5. Quite apparent is the influence generated by the environment of the ketone, since the steric course and reaction times differ substantially between 38 and 39. The most significant results, those involving the amide bases, are shown in diagramatic form in Figure 1.

Cleavage by potassium *tert*-butoxide is seemingly not affected by the change in environment. High (84-86%) levels of retention were found in both examples, these results exactly paralleling those observed for the optically active ketones. The amide-catalyzed cleavages reveal trends that are strikingly opposite for the stereoisomeric ketones.

The differences have been accounted for by according due consideration to ion pair intermediates. When optically active substrates are involved, the intermediate carbanions are generated in a form having nominally planar geometry, wherein coordination to the metal counterion ensures stereoselective protonation. Thus, Cram's extensive investigation of base-catalyzed cleavages of alcohols revealed that solvents of low dielectric constant promote cleavage with the highest levels of

Table 5. Haller-Bauer Cleavages of 38 and 39.

Reactant	Base[a] (no. of equiv.)	Reflux Time,h	Yield,[b] (%)	Ratio of 41:40	Net Stereochemical Course
39	$LiNH_2$ (100)	120	7.3[c]	45:55	10% inv
	$NaNH_2$ (18)	91	73	70:30	40% ret
	KNH_2 (12)	16.5	87	89:11	78% ret
	KO*t*-Bu (20)	64	79	92:8	84% ret
	KO*t*-Bu (20)[d]	86	36[c]	90:10	80% ret
	$KOCH_2CH_2OH$ (24)[e]	105	2.3[c]	28:72	44% inv
38	$LiNH_2$ (100)	120	24[c]	15:85	70% ret
	$NaNH_2$ (18)	16	64	29:71	42% ret
	KNH_2 (12)	16.5	79	40:60	20% ret
	KO*t*-Bu (20)	2	86	7:93	86% ret
	KO*t*-Bu (20)[d]	86	90	15:85	70% ret
	$KOCH_2CH_2OH$ (24)	105	3.2[c]	84:16	68% inv

[a]Solvent is benzene unless otherwise noted. [b]All yields were calculated by capillary GC analysis using *n*-$C_{15}H_{32}$ as internal standard. [c]Considerable amounts of the starting material remained at the end of these experiments. [d]Solvent: *t*-BuOH. [e]Solvent: ethyleneglycol.

stereochemical retention. The concentration of proton donors was found to be of little importance.

The first step of the Haller-Bauer process involves nucleophilic attack at the carbonyl group by the incoming base to provide tetrahedral intermediate (A). Breakdown of the initially formed oxyanion then provides a carbanion that remains strongly coordinated to the metal counterion and the leaving group as in (B). A tightly-bound ion pair

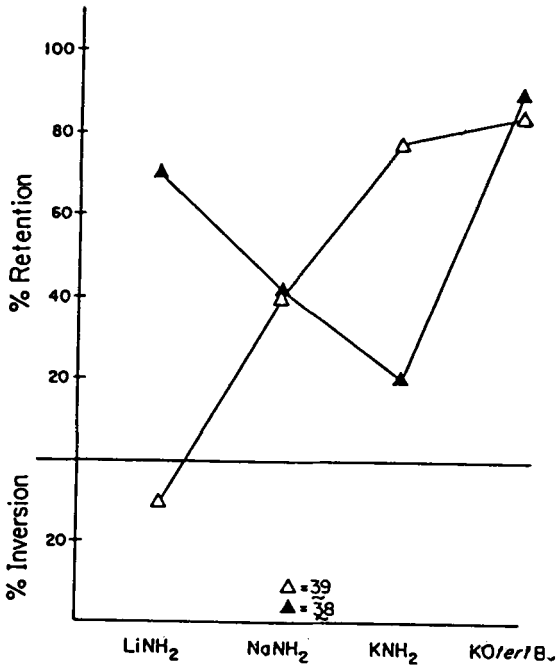


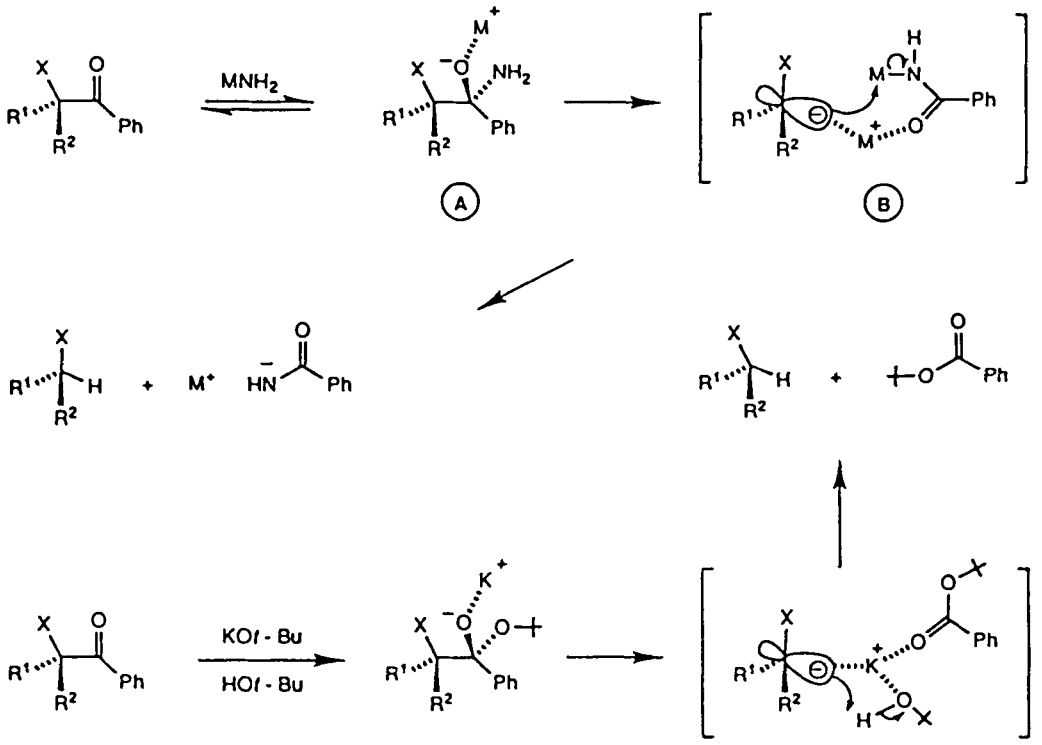
Fig. 1. Stereochemical course of the Haller-Bauer cleavage of α-phenyl ketones 38 and 39 in refluxing benzene as a function of base.

would be anticipated within solvents such as benzene and *tert*-butyl alcohol because of their low dielectric constants. Subsequent proton transfer from the leaving benzamide occurs from the same face as the departing metal ion, thereby giving rise to the high retention that is invariably seen. This mechanism was essentially proposed by Walborsky.[4c,d] When *tert*-butyl alcohol is used as the solvent, deuterium labeling has shown that deuterium is incorporated within the hydrocarbon with the same levels of stereochemical retention. Formation of the new C-H or C-D bond is not the rate-determing step since no deuterium isotope effect operates. Cleavage in benzene with amide base or in *tert*-butyl alcohol with *tert*-butoxide ion occurs within an environment containing an obvious proton source. In the latter base-solvent system, the stereochemical outcome is very much more substrate dependent.

Indeed, attempts to identify the proton source by a series of deuterium labeling experiments have demonstrated that the course of the cleavage is changed by the presence of deuterium atoms. Several different proton sources were concluded to be available such that the incorporation of deuterium causes some sites to be less available, thereby altering the normal course.

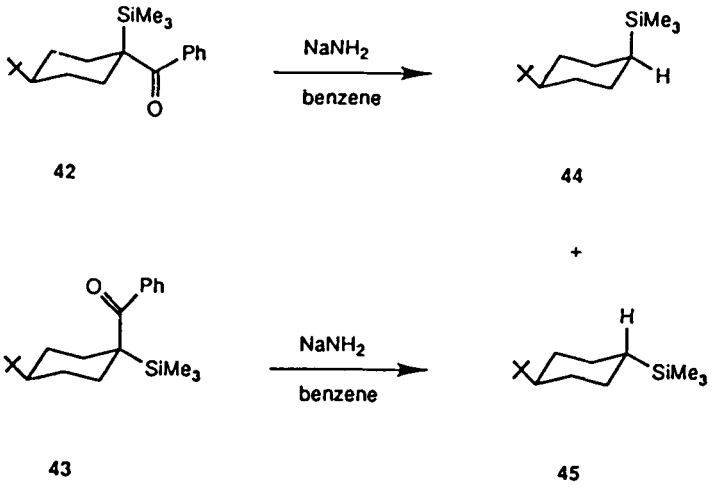
During the cleavage of ketones with metal amide bases, the tightness of ion pair (B) should vary with the nature of the metal ion (Scheme IX). Additionally, when lithium ion is utilized, the carbon-metal-oxygen coordinative bonds should be stronger and less prone to reorganization than during activation with potassium ion. Potassium

Scheme IX



counterions do give rise to faster reaction, presumably by more rapid attack at the carbonyl and faster breakdown of intermediate (A). Further evidence for these mechanistic features was garnered from cleavage of the cyclohexanes outlined above. When the benzoyl group is in the equatorial position as it is in 38, breakdown of the initially formed intermediate provides a species whose prevailing 1,3-diaxial interactions would force the phenyl group into the equatorial position. When the metal ion is lithium, the small ionic radius and tight coordination does not allow for increased leakage away from the normal retentive pathway. With sodium and potassium counterions, loosening of the coordination increases the ability of the phenyl group to move to the equatorial position. Under these circumstances, net retention drops appreciably to 20%. Conversely, when the carbonyl group is axial, the steric requirements of the tightly bound lithium ion pair cannot be easily accommodated. As a result, protonation from the rearside becomes competitive and indeed is the major process. Net 10% inversion is seen. When lithium is replaced by sodium and potassium, increased retention is manifested. Such a change materializes because the ion pairs once again are looser and less sterically compressed. Also, carbanion reactivity increases, quenching occurs faster, and a strong preference for axial protonation is seen to preclude the phenyl group from becoming involved in 1,3-diaxial interactions.

The analogous ketones 42 and 43 were prepared and subjected to cleavage with potassium and sodium amides.[12] With sodium amide as base, the levels of retention are greater than 95%. Reaction with potassium amide produced lesser quantities of 45 from 43, giving rise instead to moderate yields of 4-*tert*-butylcyclohexanone. This product presumably derives from oxidation of the initially formed potassium enolate that is



42 44

+

43 45

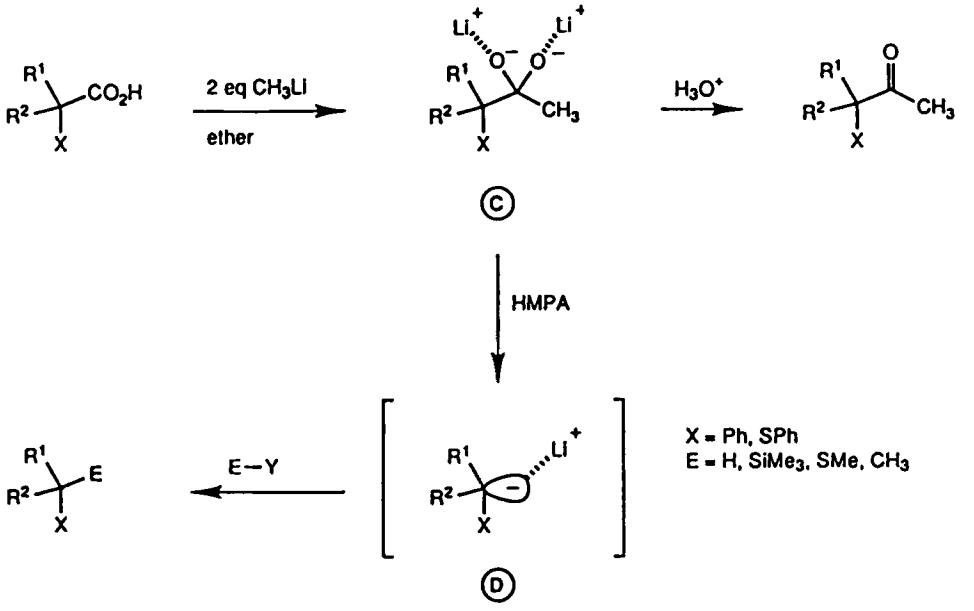
generated via desilylation. Unfortunately, the important trends exhibited by the α-phenyl compounds are not reflected in the behavior of α-trimethylsilyl ketones 42 and 43. As with the optically active substrates, higher levels of retention are encountered when the intermediate carbanion is stabilized by silicon rather than by phenyl.

III. MECHANISTIC INVESTIGATIONS

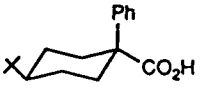
The strong preference exhibited by the Haller-Bauer reaction for carbon-carbon bond cleavage with retention of configuration has been convincingly rationalized. More recently, additional studies have been completed that reinforce and expand upon the mechanistic notions originally advanced.

In the first instance, a related cleavage reaction, the alkyl lithium-induced decarboxylation of non-enolizable carboxylic acids,[15] was developed to provide additional evidence that coordinated carbanion species are indeed involved in the Haller-Bauer reaction. Thus, treatment of a non-enolizable carboxylic acid with methyllithium in ether

Scheme X



gives rise to intermediate (C) (Scheme X). Dilution of this solution with HMPA promotes the dissociation of (C) to (D), an anion which has a significant lifetime in this solvent system and may be quenched with a proton source or electrophilic reagent. Of course, the stereochemical integrity of the carbanionic center is not now preserved and racemic products result. However, this efficient transformation is related to the Haller-Bauer reaction in that structure (C) is directly analogous to the first tetrahedral intermediate traversed in the latter process. The distinction is that (C) is doubly charged and therefore capable of fragmentation at room temperature. More significantly, when acids 46 and 47 were cleaved and protonated in different media, the observation



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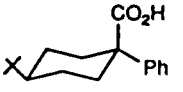


47

was made that solvents of higher coordinating ability gave proportionally more 41 than 42. This finding is fully consistent with the arguments advanced above, viz. the less associated the ion pair, the greater the extent to which axial protonation is favored (see Figure 2).

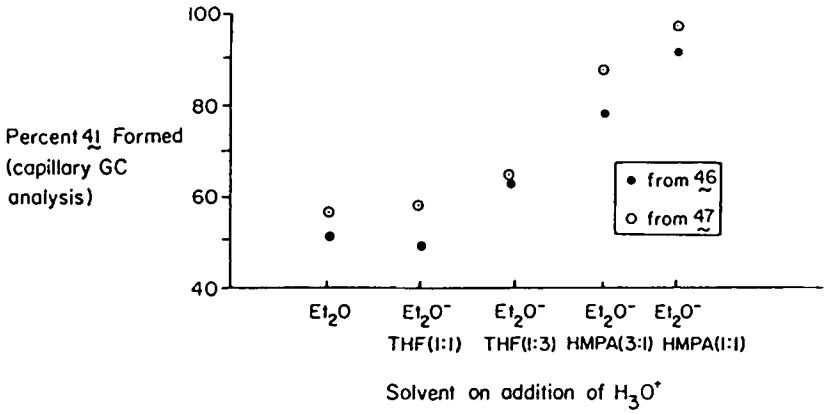
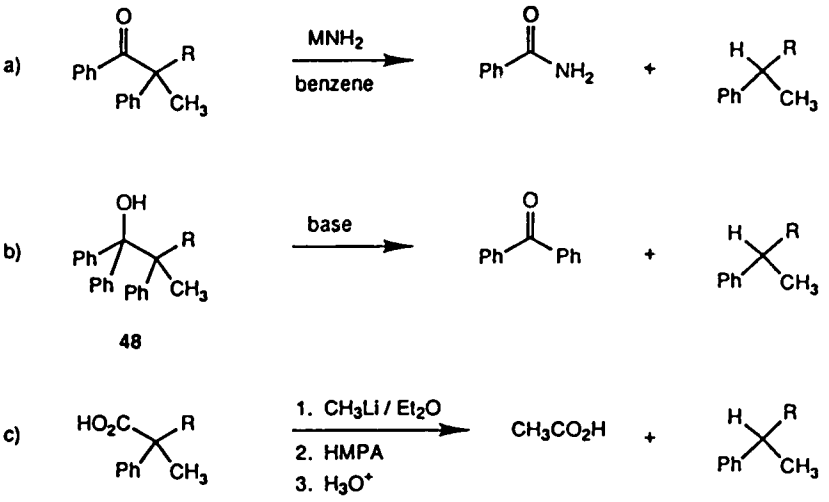


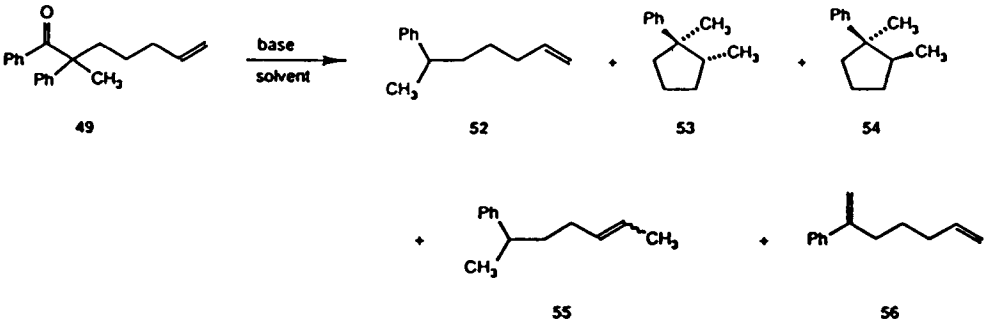
Fig. 2. Product distribution from methyllithium-induced decarboxylation of 46 and 47 as a function of solvent coordinating ability.

The product distributions derived from either carboxylic acid are essentially the same and depend only on the nature of solvent at the time of quenching.

Extensive direct comparison has also been made of three related carbon-carbon bond fragmentation processes: (a) the Haller-Bauer reaction; (b) the cleavage of tertiary carbinols such as 48, believed to cleave predominantly by means of bond homolysis; and (c) the decarboxylation of carboxylic acids as promoted by alkyllithiums in appropriate solvents.[16] In particular, two intramolecular reaction cascades were considered to be capable of defining the reactivity properties of those intermediates involved in each reaction type. The first involved covalent capture of a tethered center of unsaturation present in the mole-



cule via both five- and six-membered transition states. Cyclization of the 5-pentenyl radical is a well-documented process; evidence that 5-pentenyl carbanions can do likewise has more recently surfaced. When compounds such as 49, 50, and 51 were subjected to base-promoted cleavage, very different results were obtained. The Haller-Bauer response of 48 under various conditions is summarized in Table 6.



Informatively, the *tert*-butoxide bases induced a normal Haller-Bauer response. This is because the distal double bond is shielded from the reaction center by the same controlling elements that provide for the highest recorded level of stereochemical retention.

Table 6. Haller-Bauer Results Involving 49.

Base	Solvent	Relative Yield (%) by GC Analysis[a] 52	53	54	55	56	Combined Yield, %
KO*t*-Bu	*t*-BuOH, Δ	> 99.5					94[b]
KO*t*-Bu	C_6H_6, Δ	> 99.5					82[b]
NaO*t*-Bu	*t*-BuOH, Δ	> 99.5					89[b]
KNH_2	C_6H_6, Δ	59	4	0.5	36.5		89[b]
$NaNH_2$	C_6H_6, Δ	62	15	18		5[a]	47[c]
$LiNH_2$	C_6H_6, Δ	99	(1% combined)				51[c]
$NaNH_2$	THF, Δ	41	10	1	48		91[b]

[a]Based on use of *n*-undecane as internal standard. [b]As determined by GC analysis. [c]As isolated by preparative GC.

Cyclization of 53 to 54 is not a major pathway except under the traditional sodium amide/benzene conditions. Notably, when optically active ketone 49 was utilized, cyclopentanes 53 and 54 were produced in racemic condition, while hydrocarbon 52 showed higher than expected optical activity. Thus, only those intermediate molecules that escape the coordination sphere and strong cation association are able to cyclize, but lose complete configurational memory in the process. The difference between the net retention observed for 52 (71%) and the anticipated level (44%) based on earlier investigations can be traced in the form of an accountability tree (Figure 3). Cleavage of the higher homologue 57 under a variety of conditions proceeded with little evidence for cyclization, the product mixture consisting largely of hydrocarbon 58, the *E*- and *Z*-isomers of 59, and diene 60. Cyclization to the

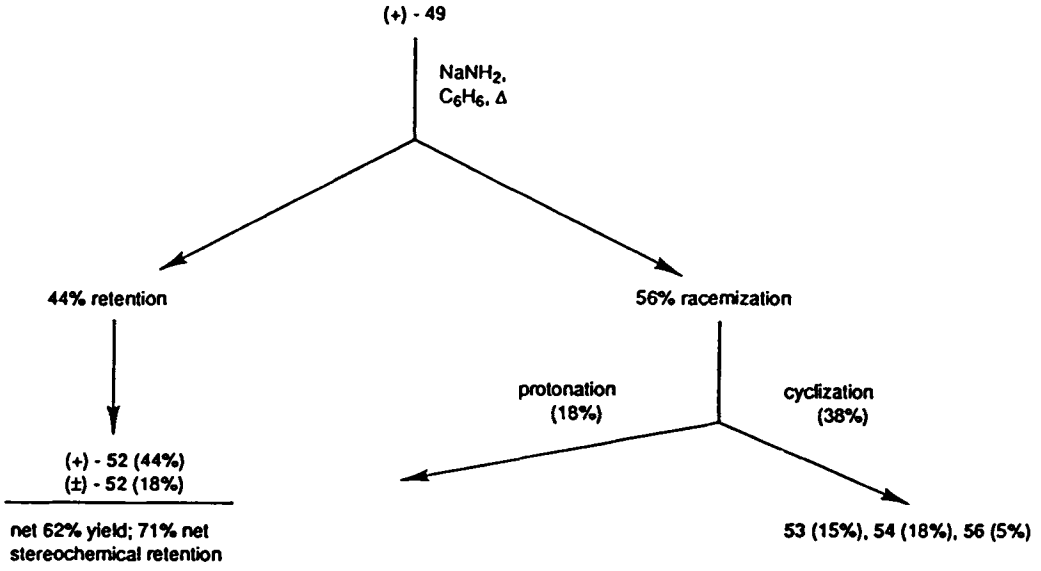
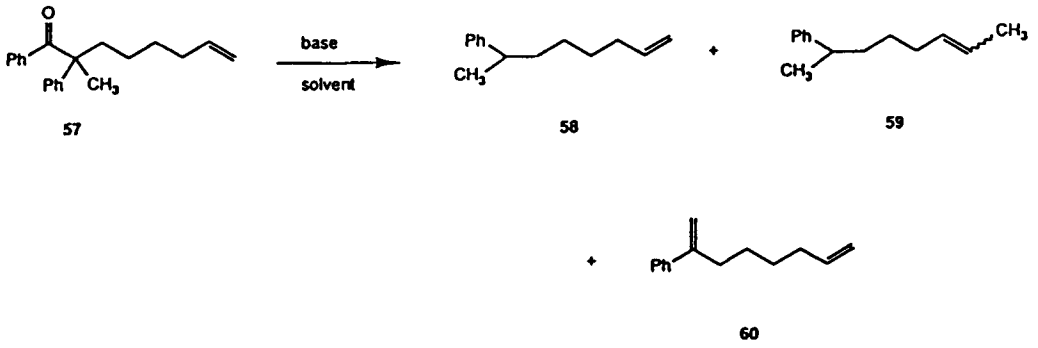


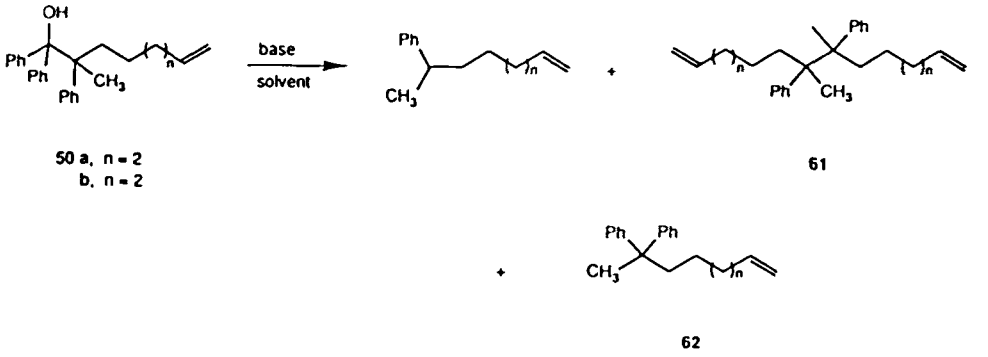
Fig. 3. Accountability tree for the Haller-Bauer cleavage of (+)-49.

six-membered ring is clearly kinetically retarded.



57 58 59 60

Cleavage of carbinols 50a and 50b produced hydrocarbons consistent with intervention of radical intermediates. In fact, the main products isolated included dimers such as 61 and compounds 62 in which benzene solvent had been incorporated.

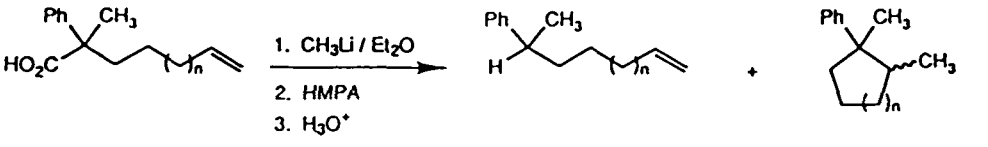


50 a, n = 2
b, n = 2

61

62

The decarboxylative sequence, proceeding as it does via long-lived carbanionic intermediates, results in efficient cyclization within both the five- and six-ring series. A companion series of experiments car-

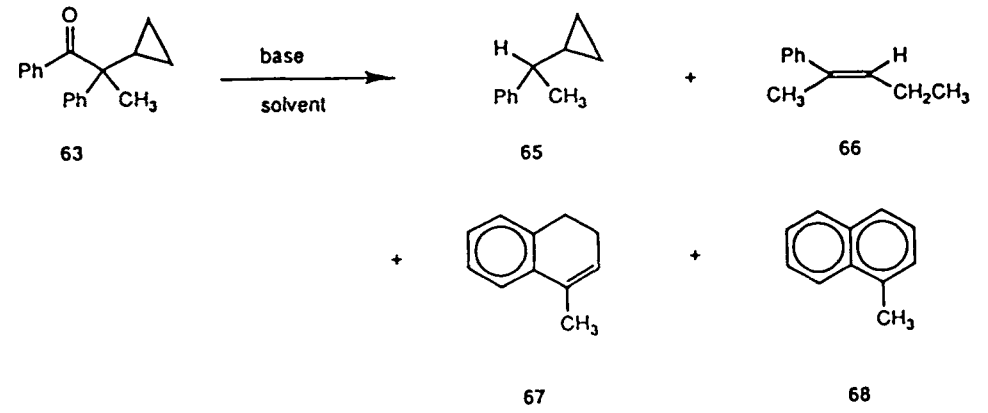


51 a, n = 1
b, n = 2

52
a, n = 1 22%
b, n = 2 13%

53 54
a, n = 1 74% (1:3)
b, n = 2 79% (2.8:1)

ried out on ketones 63 and 64 showed similar trends (Tables 7 and 8).[17] For both 63 and 64, the *tert*-butoxide catalyzed cleavages produced hydrocarbons 65 and 69 in which the benzoyl moiety has been replaced by



63

65

66

67

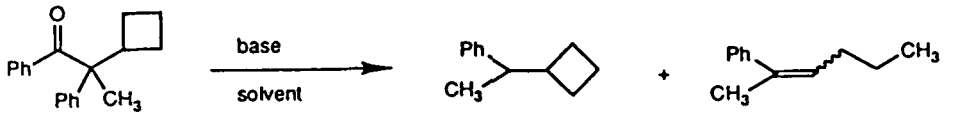
68

Table 7. Haller-Bauer Cleavages of 63.

Base	Solvent	Reflux Time, h	Products, %[a] 65	66	67	68	Yield, %
KO*t*-Bu	C_6H_6	20	> 99	tr	tr		97[b]
KO*t*-Bu	*t*-BuOH	20	> 99	tr			98[b]
KNH_2	C_6H_6	6	90	8		2	41[c]
$NaNH_2$	C_6H_6	12	50	42	7	2	40[c]
$NaNH_2$	THF	3	83	15	1	1	95[b]
$NaNH_2$	heptane	5	63	32	3	2	95[b]
$LiNH_2$	C_6H_6	90	73	19	8	tr	38[c]
$LiNH_2$	THF	1.5	97	3	tr	tr	94[b]
$LiNH_2$	THF-C_6H_6	6	92	6	2		91[b]

[a]Relative percent based on GC analysis. [b]Yields based on capillary gas chromatography integration areas relative to internal standard. [c]Isolated yields following preparative gas chromatography.

hydrogen as usual. When amide bases were employed, products derived from ring opening of the cyclopropane or cyclobutane rings were observed. As would be anticipated, the cyclopropylcarbinyl system was more prone to this particular reaction. Even in the worse case scenario (sodium amide in benzene), however, 50% of the product mixture remained derived from degradative protonolysis without skeletal rearrangement.



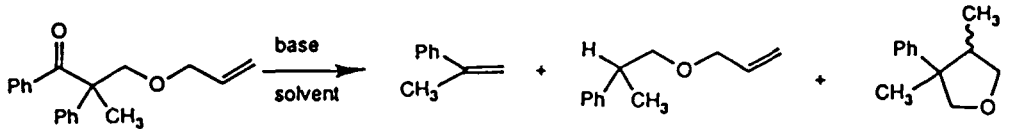
64 69 70

Table 8. Haller-Bauer Cleavages of 64.

Base	Solvent	Time, h	Products, %[a] 69	70	Yield, %
KO*t*-Bu	C_6H_6	20	> 99		98[b]
KO*t*-Bu	*t*-BuOH	20	> 99		92[b]
KNH_2	C_6H_6	8	99	1	37[c]
$NaNH_2$	C_6H_6	14	91	9	46[c]
$LiNH_2$	C_6H_6	114	96	4	35[c]

[a]See footnotes in Table 7.

Finally, the cleavage of ketone 71 under all conditions, except potassium *tert*-butoxide in *tert*-butyl alcohol afforded α-methylstyrene as the major product (> 89%). This olefin arises by elimination of



allyloxide ion via a process consistent only with a transient involvement of carbanionic intermediates. A radical pathway, if operative, would have led instead to dimerization or cyclization of the 5-pentenyl-like radical. Ether 72 was produced in small quantities (< 8%) except under *tert*-butoxide conditions when the yield rose to 37%.

IV. OVERVIEW

Recent developments in the area of Haller-Bauer chemistry have concentrated on two main facets:

(i) the stereochemical outcome of the cleavage of non-enolizable α-substituted phenyl ketones, and

(ii) investigation of the reaction mechanism and the specific reactivity of those intermediates involved.

Evidence now abounds that the Haller-Bauer fragmentation proceeds with retention of configuration under most conditions. Indeed, it is probably easier to consider the problem in terms of why stereochemical integrity is lost, rather than why it is retained. Of the two α-substituents considered in depth, phenyl and trimethylsilyl, the latter provides higher degrees of retention under otherwise similar conditions. This phenomenon may reflect a shorter lifetime/higher reactivity of α-silyl carbanions, or be symptomatic of the greater tetrahedral character of α-silyl carbanions. These two possibilities cannot yet be distinguished.

To the extent that the substrate non-enolizable ketone is not otherwise strained, levels of configurational retention during cleavages run high. With α-phenyl ketones, the process is maximized both in stereochemical and efficiency terms by the utilization of *tert*-butoxide bases in *tert*-butyl alcohol where a net retention of 84-88% can reasonably be expected. When an α-silyl group is present, the net retention levels are highest when sodium amide is used. In this instance, the extent of optical retention levels is usually 82-84% (for acyclic compounds) or 90-98% (for ring systems).

In mechanistic terms, the Haller-Bauer reaction has been shown to be mediated virtually exclusively by carbanionic intermediates. The most critical feature of the reaction is considered to be highly specif-

ic coordination of the metal ion to the carbanion. When this ion pair has a short life and is shielded from solvent effects, protonation is highly stereospecific. Furthermore, little interaction can be effected by external sources, even when functionality (e.g., a remote double bond) is suitably positioned in the same molecule. The only processes sufficiently rapid to compete with protonation are eliminative cleavages of alkoxide ions or of cyclopropane ring bonds. Thus, the lifetime of Haller-Bauer intermediates are short enough to preclude the operation of other transformations except those that require little or no molecular reorganization.

In contrast, the related cleavage of carboxylic acids is a most effective method of generating *long-lived* carbanions, notably serviceable for efficient cyclization to cyclopentanes and cyclohexanes. This protocol constitutes a versatile, though non-stereospecific, complement to the Haller-Bauer process.

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