Alkylidenecarbenes, Alkylidenecarbenoids,† and Competing Species: Which Is Responsible for Vinylic Nucleophilic Substitution, [1 + 2] Cycloadditions, 1,5-CH Insertions, and the Fritsch−Buttenberg−Wiechell Rearrangement?

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Received September 4, 2003

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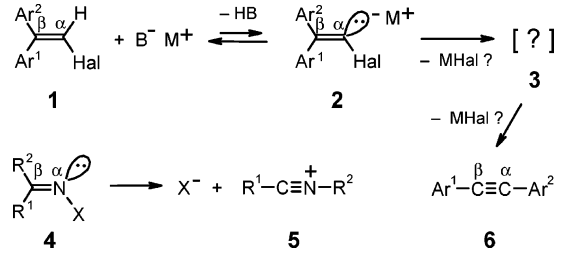
1. Introduction

The Fritsch−Buttenberg−Wiechell (FBW) "rearrangement" was discovered[1] as the formation of diarylacetylenes (**6**) from 2,2-diaryl-1-halogenoalkenes (**1**) under the action of sodium ethoxide (B^-M^+) in ethanol at 180−200 °C. Applying the



stronger base potassium *tert*-butoxide (KO*t*-Bu) in [OD]-*tert*-butyl alcohol (DO*t*-Bu), Pritchard and Bothner-By[2] were the first to demonstrate the reversible formation of a (halogen,metal)-alkylidenecarbenoid† (**2**) by isolation of the completely α-deuterated starting bromide [α-D]-**1** (Hal = Br) with

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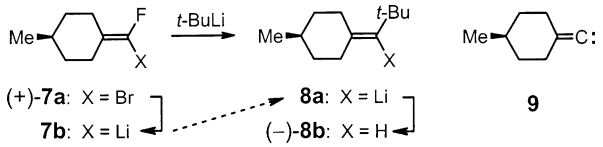
† In this article, carbenoids are understood to bear a metal cation and a nucleofugal group at the same carbon atom, as in **2**, in accord with the short historical report in the first footnote (*) on page 558 of ref 8. Carbene moieties with a double bond to a transition metal do not meet this carbenoid criterion and should be called "carbene complexes". The nomenclature of alkylidenecarbenes is explained in ref 10b.

10.1021/cr030616h CCC: $48.50
Published on Web 09/08/2004

Rudolf Knorr was born (1935) and educated in the German town of Kassel. Having studied chemistry in Marburg and in Munich, he earned his Diploma and Doctoral degrees in Munich under the direction of Prof. Rolf Huisgen, demonstrating the composition of the then somewhat controversial reactive intermediate benzyne (C_6H_4) by selectivity data. After postdoctoral research in Munich on the mechanism of the Dakin–West reaction of *sec*-amino acids, he investigated the inversion processes of fluorinated seven- and eight-membered ring molecules in the group of Prof. John D. Roberts at Caltec. His habilitation in Munich and subsequent work concerned the NMR shift mechanisms of tetrahedral bis(chelate) Co(II) and Ni(II) complexes. Later on, he explored the 2,2-bis(iminomethylation) of 1,1-enediolates, the nitrogen inversion mechanism of Schiff bases, the stereochemistry and reactions of *N*-lithio-enamines, and the structures and stereodynamics of alkenyllithium compounds. Together with his wife (also a chemist) he has brought up two daughters. Today his extra-chemical interests include reading and the practicing of classical music.

retained configuration. Because this preequilibrium is established much faster than the conversion of **1** to **6**, measured at +95 °C in this system, the overwhelming majority of the intermediate carbenoid molecules **2** are obviously captured by the solvent (DO*t*-Bu), which is more acidic than the halogenocarbons **1**. The authors[2] showed that the global reaction rates (for Hal = Br > I ≫ Cl) are proportional to the concentrations of **1** and of the kinetically active portion of the base.

Several aspects of the FBW "rearrangement" formally resemble those of the Beckmann rearrangement[3] of oxime derivatives **4**: The C=N moiety in **4**, with its lone electron pair at the nitrogen atom symbolized by an sp^2 hybrid orbital lobe, is seen to be isoelectronic with the anionic Cβ=Cα part of **2**, as are the products **5** and **6** of the two processes.[4,5] Avoiding the formation of a valence electron sextet at nitrogen in this classic example, the migration of R^2 in **4** is concerted with the escape of the nucleofuge X. The FBW process (**1** → **6**) is a less simple event and hence less easily elucidated in its mechanistic course from carbenoid creation along possible intricacies, as hidden under "[?]" in **3**, down to the final development of the C≡C triple bond in **6**. Because the latter lacks the natural elemental "labeling" of the C≡N triple bond, an assignment of the migrating group (Ar^1 or Ar^2) is no longer immediately evident. As will be explained in section 3.4.2, it is well established that unencumbered ("free") alkylidene*carbenes* $Ar_2C{=}C{:}$ do *not* occur as the *only* essential intermediates **3** in this particular process although they generally furnish the same products. Nevertheless, their chemical behavior will be described here first, to provide a simpler background for later comparisons with and interpretations of related carbenoids such as **2**. In trying to establish the migratory aptitudes of the β-substituents (Ar^1 and Ar^2, and more generally R^1 and R^2), we shall discover indications that the nonmigrating (stationary) β-substituent is not a spectator group but can influence and perhaps even prevent FBW migrations: the normally very fast migration of a phenyl group may become sufficiently retarded in a carbene to fail in competition with an accelerated 1,5-CH insertion reaction (section 2.3.1) or to proceed only slowly in a carbenoid (**379** in section 3.4.2) that appears to be stable almost up to ambient temperature. It will also be demonstrated that FBW processes in alkylidenecarbenoids $R^1R^2C{=}CMX$ are *not* stereospecific and occur with only modest anti/syn stereoselectivity, contrary to the conventional wisdom disseminated by many authors. Furthermore, formation of an alkylidenecarbene $R^1R^2C{=}C{:}$ as the reactive species from $R^1R^2C{=}CMX$ will be shown to depend on the nature of the expelled α-substituents M^+X^-, using evidence for or against the free carbene from studies of some of the other title reactions as presented in the following example.



Vinylic nucleophilic substitutions (S_NV) may occur with remarkable ease at alkylidenecarbenoids such as **7b**. The Br/Li exchange reaction of optically active 4-methyl(bromofluoromethylidene)cyclohexane, (+)-**7a**, with 3 equiv of *tert*-butyllithium (*t*-BuLi) in diethyl ether afforded 40% of the optically pure[6] product (−)-**8b** via substitution of fluorine in **7b** by *t*-BuLi within 5 min at −110 °C. The *achiral* alkylidene*carbene* **9** cannot in this case be responsible for production of (−)-**8b** because it would inevitably produce the racemic mixture (±)-**8b**. On the other hand, the plain occurrence of an S_NV-type reaction does not provide prima facie evidence for a carbenoid, as will be demonstrated in section 2.4.2.

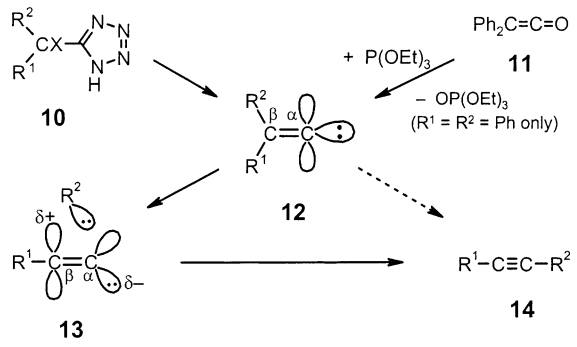
Rather than to merely repeat the contents of former reviews,[5,7−13] the purpose of this article is to relate earlier mechanistic knowledge to recent significant developments (or to indicate the need thereof). The system for conveying information will involve the depiction of the diverse synthetic methods in terms of reaction mechanism, through use of the more instructive examples. Sufficient experimental detail will be presented so as to allow a critical evaluation and to remain close to preparative practices. Chemical selectivity is used here as the "leitmotiv", so even unusual reaction modes will be considered if they may possibly provide mechanistic information.

Section 2 is confined to the presentation of α,β-unsaturated carbenes $R^1R^2C{=}C{:}$ (**12**), of the evidence for their role as reactive species, first in the gas phase and then in solution, of the products to be expected from them, and of side reactions involving their precursors. Section 2 ends with an exposition of the probable intermediacy of isopropylidenecarbene

(Me_2C═C:) in cycloaddition reactions. Section 3 is devoted to the consideration of evidence for alkylidenecarben*oids* R^1R^2C═CMX; it includes the special version of FBW rearrangements leading to cycloalkynes or their equivalents, opening the view of surprising and hitherto apparently almost unnoticed features of the two (anti and syn) FBW mechanistic variants. Section 4 (Synopsis) contains collections (Table 2) of most of the information on selectivity presented earlier, in an abbreviated presentation that can serve as a key for potential users. Kinetic criteria will then be developed for recognizing the free alkylidenecarbenes formed from alkylidenecarbenoids.

2. Migratory Aptitudes and Competing Processes in the Free Alkylidenecarbenes

In an early example[14] of a metal-free source, the tetrazole derivatives **10** were pyrolyzed at ~ +145 °C or dehydrated (X = OH) with carbodiimide to yield alkynes (acetylenes) R^1—C≡C—R^2 (**14**, $R^1 = R^2$ = H or aryl only). In an even earlier thermolysis,[15] deoxy-



genation with triethyl phosphite was restricted to the stable ketene diphenylethenone (Ph_2C═C═O, **11**), furnishing 65% of diphenylacetylene (**14** with $R^1 = R^2$ = phenyl) together with triethyl phosphate. Experiments to prove the intermediacy of carbenes **12** were not performed with **10** and **11**, but at least for **10** it would be difficult to design any kind of carbenoid intermediate in place of **12**, and a zwitterionic "carbenoid" derived from **11** would not contain a metal atom. In view of the observed products, it appears reasonable and convenient to classify tentatively such alkyne formations from possibly generated alkylidenecarbenes as *quasi*-FBW rearrangements, or "FBW" (with the quotation marks) in shorthand notation, with the reservation of later corrections.

The contents of this section will be arranged according to the available synthetic methods. However, their collection under the present heading of Free Alkylidenecarbenes[10,11] must be understood as preliminary and subject to critical assessment.

2.1. "FBW" Rearrangements in the Gas Phase

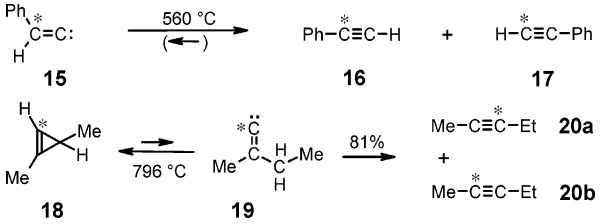
As the prototype of this genuine rearrangement, the isomerization of the singlet ground state[16] (**12**) of methylidenecarbene (alias vinylidene, H_2C═C:) to give acetylene (H—C≡C—H, **14** with $R^1 = R^2$ = H) was computed[17−19] to be strongly exothermic by −45 kcal/mol (experimental[20] −47.4 ± 4.0 kcal/mol), with an activation energy E_a = 1.5 kcal/mol corresponding to a very small lifetime, in the picosecond range (contrasting with F_2C═C:).[16,21,22] However, the computational inclusion of molecular dynamics led to the prediction[23,24] of much "longer" lifetimes for the final conversion[25] to ground-state acetylene, perhaps up to microseconds. This applies to the gas phase, whereas for H_2C═C: in hydrocarbon matrixes this acetylene formation was observed[26] even at −196 °C. A closer analysis[18] of the late transition state[17,19] for vinylidene (**13**, $R^1 = R^2$ = H) suggested sp-hybridization (bond angle ~180°) for C-β and preponderant bonding[21] of the migrating entity R^2 to C-α, which is still holding the lone electron pair in an sp^2-like orbital; therefore, the additional new π-bond of the prospective acetylene remains temporarily underdeveloped, with the consequence of some electron deficiency at C-β and an increased polarity of the transition state. However, the p-orbital drawn at C-β of **13** is not "empty" and hence does not strive as much for stabilization by π-donors as a true carbenium ion; rather, it is engaged[18] in weakened bonding to R^2 = H and to the lone pair at C-α. But because the s-character (and with it the electronegativity) of C-β must increase in going from the ground state (sp^2) to the transition state (sp), it appears defensible in the sequel to judge the (de)stabilizing effect of the stationary (nonmigrating) β-substituent R^1 of **13** in a coarse manner by its inductive substituent constant[27] (σ_I), in lieu of a better choice and with recognition of the possibility that additional factors could be important. Although theoretical results reported[28] for the rearrangement of H_3Si—CH═C: point in the same direction, it is not intended by this choice to propose a strict correlation with σ values of the stationary β-substituents. On the other hand, the computed transition state ($E_a \approx 1$ kcal/mol)[19,29,30] for hydrogen atom migration in (fluoromethylidene)carbene (F—CH═C:) was characterized[30] as being less productlike, with bond angles F—Cβ—Cα = 160° and H—Cβ—Cα = 77° somewhat closer to those of the starting point F—CH═C:, but an attempt to explain this accelerating substituent effect was not made. The result indicates that certain substituents may change the geometry of the transition state, thus complicating the interpretation of kinetic substituent effects. Comparison of the topologies[17,30] suggested that an angle R^1—Cβ—R^2 ≈ 124° will often be conserved during approach to the transition state, in accord with the H_2C-β rocking vibration regarded[17,29,30] as an approximation to the initial reaction coordinate which crosses the shallow well leading to the top of the barrier.

Migration of a methyl group in isopropylidenecarbene (Me_2C═C:) was computed[31,32] to require an activation energy $E_a \approx 11$ kcal/mol. With R^1 = H (in Me—CH═C:)[33a] or R^1 = F (in Me—CF═C:)[33b] as the stationary β-substituent, the barrier to migration of methyl was calculated to be higher, but a numerical comparison is not meaningful in view of the different methods of computation. A calculated $E_a \approx 30$ kcal/mol[16,21,33b] disqualifies a fluorine atom for the 1,2-shift in **12** (R^1—CF═C:) → **13** → **14** (R^1—C≡C—F). While

extrapolation from the computed hydrogen 1,2-shift to the migration of larger groups can be misleading with respect to activation energies, it appears admissible to expect the development of electron deficiency at C-β on the way to the transition state (as modeled by **13**) for such "FBW" rearrangements of carbenes **12** at large. This expectation is based on the electronic drain toward the empty p-orbital at C-α, in combination with the approach to sp-hybridization at C-β but with completion of the acetylenic π-bond lagging behind.

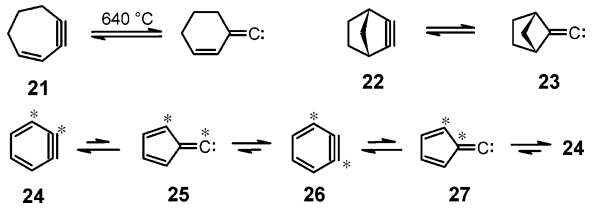
The computational thermodynamic picture agrees with observations[34] on rearrangements of alkynes in the gas phase, typically performed at ~800 °C, which may be viewed as *retro*-1,2-shifts of hydrogen (R^2) in going from the alkynes R^1—C≡C—H (**14**) back to the alkylidenecarbenes R^1—CH=C: (**12**). Despite the drastic thermal conditions, synthetically useful isomerizations were reported.[12,35,36] By coordination to certain transition metal ions[37−39] (M in R^1CH=C=M) the carbene **12** (R^2 = H) can become more stable than the terminal alkyne R^1—C≡CH from which it was created.

Recognition of the migrating group in an alkylidenecarbene R^1R^2C=C: (**12** with $R^1 \neq R^2$) obviously requires isotopic labeling in **12** and its sources. With the advent of ^{13}C NMR spectroscopy, this isotope has been applied quite often to solve such questions. When the labeled (*) benzylidenecarbene (**15**) was generated from benzylidenemeldrum acid via decarbonylation of 3-phenylpropadienone (Ph^{13}CH=C=C=O) at 560 °C/0.1 Torr, hydrogen migrated faster than phenyl, producing[40] the isotopomers **16** and **17** in a 3:1 ratio. This may be attributed to the very



small computed[17,18] migration barrier for hydrogen, perhaps assisted by phenyl as a more accelerating stationary substituent R^1 than hydrogen in the transition state model **13**. However, this experiment may not mirror the intrinsic migratory aptitudes, considering the possibility of repeated return of hydrogen over the barrier[25] in the gas phase. At 700 °C, the labeled phenylacetylene **16** changed to the expected equilibrium mixture (50:50) of **16** and **17**. This isomerization may certainly pass for an analyzed "FBW" example performed by a genuine alkylidenecarbene.

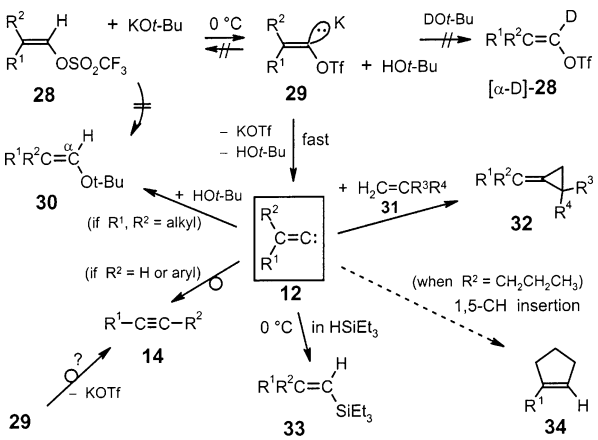
The strained cyclopropene ring in ^{13}C-labeled **18** was opened[41a,42,43] at 796 °C to its isomer 2-butylidenecarbene (**19**) in a reverted (and reversible[44]) 1,3-C−H bond insertion, followed by an "FBW" rearrangement to give the isotopomeric 2-pentynes **20a** and **20b** (3:1). Thus, ethyl traveled easier than methyl, and the authors[41a] concluded that a migrating alkyl group has to carry a positive partial charge in the transition state. This is to be expected if the empty p-orbital at C-α in the skeletal plane of **12** begins to deduct electron density from the R^2−Cβ bond on the way to a transition state such as **13**. However, isopropyl migrated only 1.4-times as fast as methyl under these conditions,[41a,42] and this suggests that additional factors may also be important.[41b] Homologues of **19** with longer alkyl chains would very much prefer to form cyclopentenes by intramolecular 1,5-CH insertion,[35,45] as exemplified further below.



Reversal of these carbon migrations is kinetically disfavored and hence very rare in acyclic alkynes even at 570 °C[46] or above 700 °C.[47] It is confined mainly to cycloalkynes suffering from internal strain, such as 3-cycloheptene-1-yne[48] (**21**) or 3,4-dihydro-1-naphthyne[49] or better still the highly strained norbornyne (**22**), which should be energetically comparable[50] to its isomer bicyclo[2.1.1]hex-5-ylidenecarbene (**23**). However, benzyne (**24** or **26**) was calculated[51] to be 31 kcal/mol more stable than its isomer cyclopentadienylidenecarbene (**25** or **27**). Because neither component can be analyzed directly and their products derive only from the trapping of benzyne, double labeling by ^{13}C was required for the detection[34] of their interconversion (**24**−**27**) under equilibrium conditions.

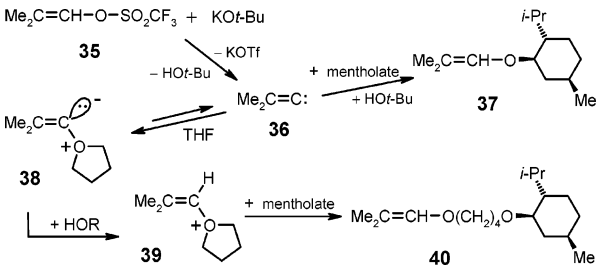
2.2. Alkylidenecarbenes from Primary Alkenyl Triflates

At lower temperatures in solution, a good way to generate alkylidenecarbenes such as **12** consists of the deprotonation of primary alkenyl triflates **28** in a weakly polar solvent at 0 °C. The choice[52] of potassium *tert*-butoxide (KO*t*-Bu) as the most appropriate base entails formation of *tert*-butyl alcohol (HO*t*-Bu) with the possible disadvantage of trapping **12** (R^1 and R^2 = alkyl) as enol ethers **30** by an intermolecular O−H insertion reaction which could also be taken to result from nucleophilic vinylic substitution (S_NV) by KO*t*-Bu at the carbenoid **29** or

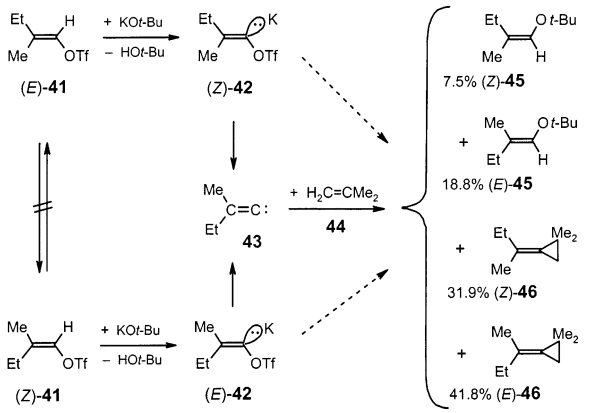


at the source **28**. But the latter two possibilities can be dismissed because of observation of a surprisingly large primary kinetic isotope effect $k_H/k_D \approx 9.9$ estimated[52] from the deuterium content of the enol ether [α-D]-**30** as obtained after the deprotonation of $Me_2C{=}CH{-}OTf$ (**28**) in a stirred mixture of DO*t*-Bu and pentane during 48 h at 0 °C. This points to a rather high propensity of the carbene **12** to discriminate between intermolecular O−H and O−D insertion and is inconsistent with a rate-determining nucleophilic substitution step which would imply a much smaller secondary isotope effect. Remarkably, the residual starting material **28** was recovered without any deuterium incorporated, in contrast to the H/D exchange reaction[2] described for **1** in the Introduction. This requires that the carbenoid **29** is generated but possesses insufficient lifetime to await reprotonation with return to **28**, partially because triflate (TfO^-) is known[52] to be a much better leaving group than the halides, with the consequence of rapid transmutation of **29** into the alkylidenecarbene **12** as the next intermediate. The reaction enthalpy for conversion of the triflate **28** into the high-energy intermediate **12** is believed by the present author to be balanced by the energy equivalent of the very large pK_a difference[53] (>30 p*K* units or >41 kcal/mol at 25 °C) between KO*t*-Bu (a very strong base in aprotic solvents[54]) and potassium triflate (KOTf). Placing a metal such as potassium next to an electron-pair lobe in formula **29** and later examples is meant to allude to the high ionic character of the C−K bond, but the entailing electric charges are omitted for the sake of clarity.

In an olefin $H_2C{=}CR^3R^4$ (**31**) as a nonpolar solvent with a KO*t*-Bu suspension, cycloadducts **32** were produced[52] a little faster than the enol ethers **30** from $R^1R^2C{=}C$: (**12**) when R^1 and R^2 were alkyl groups. Because a similar product ratio of the vinylsilane **33** and the enol ether **30** (85:15 when $R^1 = R^2 =$ methyl) was obtained[52] in triethylsilane as the solvent at 0 °C, the relative rates of intermolecular Si−H insertion and [1 + 2] cycloaddition should also be similar if carbene **12** is the common intermediate. Complete retention of the configuration at silicon was observed[55] in the vinylsilane $Me_2C{=}CH{-}SiMePhNap$ isolated from optically active methyl(1-naphthyl)-phenylsilane (HSiMePhNap) with 1-(2-methylpropenyl)triflate ($Me_2C{=}CH{-}OTf$, **35**) and KO*t*-Bu in 1,2-dimethoxyethane at −40 °C. But in accord with the aforesaid results from gas-phase reactions, the intermediates in question isomerized to alkynes $R^1{-}C{\equiv}C{-}R^2$ (**14**) as the sole products[52] when $R^2 = H$ or aryl. These "FBW" rearrangements thus occur much more easily than the intermolecular trapping reactions with HO*t*-Bu or $HSiEt_3$ or with the olefin solvent, which in turn are much faster than the "FBW" migrations of alkyl groups R^1 or R^2, that were indeed never observed in this[52] experimental procedure. Also, a further mode of isomerization, the *intra*molecular 1,5-CH insertion into the methyl of a propyl group (the least efficient insertion mode) to give **34**, could not compete[52] with alkyne formation by hydrogen migration.



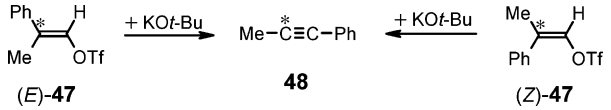
The putative intermediate isopropylidenecarbene ($Me_2C{=}C$:, **36**), generated from the alkenyl triflate **35** with KO*t*-Bu in tetrahydrofuran (THF), has little inclination to rearrange by C−H insertion or by methyl migration. In the presence of potassium mentholate (which had been planned[56] to serve as a hydride transfer reagent but did so with only 5% yield), it added to the solvent to form the oxonium ylide **38** that may be protonated (**39**) and then opened by nucleophilic substitution to afford 17% of the menthyl ether **40**. Formally, the oxonium intermediate **39** could arise also by protonation of $Me_2C{=}C$: (**36**) via the primary (hence unfavorable) vinyl cation $Me_2C{=}CH^+$, but **36** would then be consumed by irreversible quenching to give **39** directly whereas the oxonium ylide **38** can store **36** reversibly, as will be shown later in section 2.4.3, so that **38** constitutes a secondary source for **36** with slow creation of the enol ether **37** (27%).



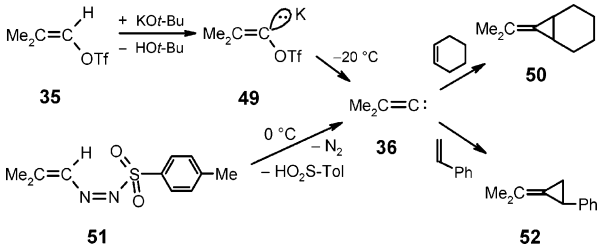
An important indication for an alkylidenecarbene (**12** or **43**) as the product-determining intermediate (rather than a carbenoid **29** or **42**) was found by skillful utilization[52] of the stereochemical properties in the following manner. The isolation of significantly different product mixtures from the configurational isomers (*E*)-**41** and (*Z*)-**41** under the same conditions would rule out a common intermediate such as 2-butylidenecarbene (**43**) as the sole species responsible for the products; it would perhaps be compatible with an earlier trapping of the stereoisomeric 2-butylidene*carbenoids* (*Z*)-**42** and (*E*)-**42** (broken arrows). The experimental realization in 2-methylpropene ($H_2C{=}CMe_2$, **44**) as the solvent at −26 °C led to identical ratios (within the error limits, averaged values denoted) of (*Z*)-**45**, (*E*)-**45**, (*Z*)-**46**, and (*E*)-**46** from both (*E*)-**41** and (*Z*)-**41**, satisfying "a necessary albeit not sufficient condition for"[52] the common 2-butylidenecarbene (**43**) as the responsible actor. The usual two reservations concern first the interconversion of the two precursors of **43**, which was experimentally excluded for the sources (*E*)-**41** and

(*Z*)-**41** but not for the carbenoids (*Z*)-**42** and (*E*)-**42**. (The factual example[52] was the unlabeled pair (*E*)/(*Z*)-**47** illustrated further below.) Second, the two carbenoids **42** might perhaps exhibit identical selectivities purely by chance (broken arrows, a rather unlikely possibility) or for some other reason. In any case, the tentative evidence for carbene **43** at this point applies only to the intermolecular O−H insertion and [1 + 2] cycloaddition reactions; it does not rule out the direct formation of alkynes R^1—C≡C—R^2 by "FBW" rearrangements of alkylidenecarbenoids such as **42** or **29**.

Stronger reservations apply to the analogous comparison of migratory selectivities in the "FBW" rearrangements of ^{14}C-labeled (*) configurational isomers[57] (*E*)-**47** and (*Z*)-**47** in pentane plus 1,2-dimethoxyethane ("glyme") at −20 °C, where interconversion of the starting triflates **47** but not of their carbenoid descendants had been excluded.[52] While isolation of [2-^{14}C]-1-phenylpropyne (**48**) as the *only* isotopomer confirmed that phenyl always migrates much easier than methyl, it is just this very preference which does not allow a decision to be made in this instance as to whether the product was generated from two different intermediates. For example, one could imagine that **48** was derived from (*Z*)-**47** via the free (α-methylbenzylidene)carbene (PhMeC═C:) by the preferred phenyl migration, but from (*E*)-**47** via the K,TfO-carbenoid by a perhaps more highly preferred phenyl migration. Of course, formation of differently labeled samples of **48** from (*E*)- and (*Z*)-**47** (stereodivergence) would have excluded the free carbene PhMeC═C: as the *only* intermediate.



A well-established approach in trying to find out the identity or nonidentity of C_{2v}-symmetric intermediates such as Me_2C═C: (**36**) from different sources consists of measuring their selectivities as mirrored by the product ratios obtained with *competing* pairs of reactants. Although a rather wide span of 94:1 for the relative rates of [1 + 2] cycloadditions of ethyl vinyl ether versus 2,3-dimethyl-2-butene (Me_2C═CMe_2) had been found[58] for the intermediate from triflate Me_2C═CH−OTf (**35**), cyclohexene and styrene were chosen[59] for the standard pair, furnishing cycloadducts **50** and **52** in a rate ratio of 1.74 (±0.14) from **35** with KO*t*-Bu suspended in the olefin mixture at −20 °C. Because practically the same competition constant 1.78 (±0.13) resulted when the KO*t*-Bu had been dissolved by pretreatment with the macrocyclic 18-crown-6 hexaether before initiation, the authors[59] concluded that the potassium cation had no influence because it had been masked in this run. An even better comparison was possible with the source 1-tosylazo-2-methylpropene (**51**), written in the (*Z*) configuration to suggest how it might generate the suspected isopropylidenecarbene (Me_2C═C:, **36**) spontaneously, producing[60] the cycloadducts **50** and **52** in the ratio 1.84 (±0.17) at 0 °C without bases[61] and devoid of any metal cations in the olefins as a solvent. If these equal selectivities arise from a common intermediate, it must be exempt from KOTf as well as from nitrogen and from the sulfinic acid, leaving Me_2C═C: (**36**) as the common species responsible for the products. But because equal selectivities of different intermediates may perhaps turn up owing to a casual similarity (however improbable) of such properties, they are only a necessary albeit not sufficient condition for the intermediacy of carbene **36** and would become more convincing with an extended set of different sources exhibiting always the same competition constant. It is therefore appropriate to examine some further progenitors of the alkylidenecarbenes.

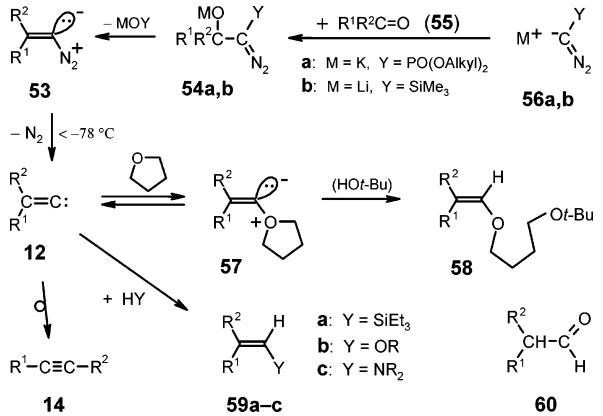


2.3. Alkylidenecarbenes from Diazoalkenes

The smooth decomposition of the tosylazo-alkene **51** described above raises questions about the potential role of a diazoalkene R^1R^2C═CN_2 (**53**, perhaps the successor of **51**) as the precursor of an alkylidenecarbene R^1R^2C═C: (**12**). Quantum chemical calculations[62] of diazoethene (H_2C═CN_2, **53** with $R^1 = R^2$ = H) revealed a strongly bent ground state (angle C−C−N = 118°) with the characteristic features of a diazonium salt, while the alternative linear CCNN arrangement, perhaps naively conceivable but energetically unfavorable with a strongly electron-withdrawing substituent, contains more energy by 21 kcal/mol. This diazonium ylide **53** appears to profit from the energetically favored N≡N triple bond and to behave like a carbene complex of N_2; indeed, the computed barrier against dediazoniation (which seems[62] slightly exothermic) is only 7 kcal/mol, translating[62] into the half-life time $t_{1/2}$ = 0.3 ms at −90 °C. Conversely, F_2C═C: adds to N_2 even at −263 °C to give diazo-difluoroethene (F_2C═CN_2).[21,22]

2.3.1. From Carbonyl Compounds with Deprotonated Diazomethane Derivatives

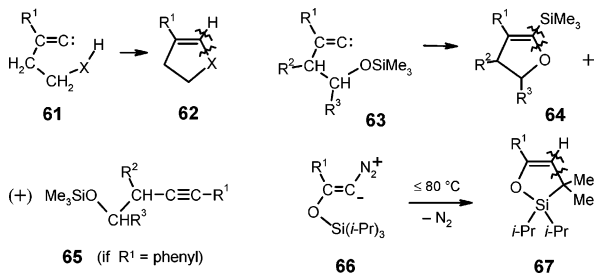
The best routes to the presumed diazoalkenes **53** are the diazoolefinations of aldehydes and most types



of ketones $R^1R^2C{=}O$ (**55**) by the Wittig−Horner method[63a] via **54a** or by a Peterson elimination[63b] from **54b**, starting at low temperatures with deprotonated diazomethylphosphonic esters **56a** or with the lithiated diazomethylsilane **56b**, respectively. Despite the earlier impression[64] of a rather limited scope, the olefinations with **56b** are synthetically useful,[65−71] and those with **56a** occur smoothly even at −78 °C, using the bases KH[72,73] or K_2CO_3[65,74] or LiOH,[74] but most often using a suspension of KO*t*-Bu.

In accord with the migratory aptitudes reported above for alkylidenecarbenes $R^1R^2C{=}C$: (**12**), aldehydes[75,76] as well as aryl ketones[64,70,75] (that is, R^2 = H or aryl in **55** → **54** → → **14**) in THF at −78 °C produced only the alkynes **14** because hydrogen and aryl normally migrate the fastest. But the migration of R^2 = 4-nitrophenyl (when R^1 = methyl in ketone **55** → → **14** plus **59b**) was sufficiently retarded at room temperature to allow competition from intermolecular O−H insertion into the solvent methanol, as shown[76] by the parallel production of 1-(4-nitrophenyl)propyne (**14**) and the enol ether **59b** (with Y = OCH_3). Because the isopropylidenecarbene ($Me_2C{=}C$:, **36**), generated from acetone (**55**) with **56a**, has little propensity toward rearrangement, it added a molecule of the solvent THF to form the oxonium ylide **57** (already established as **38** when engendered from the alkenyl triflate **35**), which was then opened by a *tert*-butoxy reagent to give[75,77] the diether **58** (related to **40**). A corresponding addition of THF was not reported[70] for **53** → **12** (R^1 = Me, R^2 = Ph−CH=CH, from **54b**), which presumably preferred the "FBW" migration of the R^2 group cinnamyl, producing[70] the alkyne Me−C≡C−CH=CH−Ph (**14**, 34% yield). Formation of the oxonium ylide **57** was likewise suppressed[78] by triethylsilane, whose Si−H (or Si−D) bond was cleaved at or above −78 °C by the putative isopropylidenecarbene ($Me_2C{=}C$:, **36**), providing the vinylsilane $Me_2C{=}CH{-}SiEt_3$ (**59a**) or its deuterated twin. This result excludes carbenium intermediates (and also their chain reactions) that would have abstracted[79] a hydride anion from triethylsilane, furnishing a different product. The reported[78] kinetic isotope effect k_H/k_D = 1.44 (±0.02), determined at −78 °C and at +21 °C in the presence of only 4 equiv of [H or D]-triethylsilane, may be too small because the simple competition formula used is valid then for the first 10% of conversion only (which was not detailed). For comparison, the primary isotope effect k_H/k_D = 2.06 (±0.05) was measured[80] at −70 °C for the hydride transfer from diphenylsilane to a diarylcarbenium ion in methylene chloride. The addition to THF was also suppressed in the presence of alcohols[74] to give enol ethers $R^1R^2C{=}CH{-}OR$ (**59b**), or of 15 equiv of secondary amine,[74,81] furnishing enamines $R^1R^2C{=}CH{-}NR_2$ (**59c**), the latter to the exclusion[81] of *intra*molecular CH insertions into sufficiently long alkyl chains of the presumed intermediates $R^1R^2C{=}C$: (**12**). After hydrolysis, aldehydes $R^1R^2CH{-}CH{=}O$ (**60**, R^1 and R^2 = alkyl) were obtained as the sole[81] products from the ketones $R^1R^2C{=}O$ (**55**) via enamines **59c**.

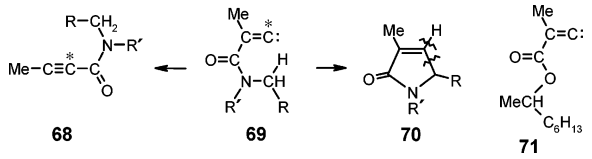
Kinetic isotope effects up to k_H/k_D = 3.5 were found[82] for the 1,5-CH insertion reactions leading to cyclopentene derivatives **62** via carbenes **61** (R^1 = CH_3 and X = **CHD**Me or **CHD**Ph). The 1,5-CH insertion into XH = **CH**RR′ of **61** (from **54a**) in competition with a second alkyl chain R^1 to give two cyclopentene derivatives **62** revealed[83] increasing reactivities in the series primary < secondary < benzylic secondary < tertiary CH = 1:30:76:240 (on a per hydrogen basis) at temperatures between −78 °C and ambient, while the solvent THF no longer produced the diether **58**. At the stereogenic *tert*-CH in optically active 5-phenyl-2-hexanone ($CH_3{-}CO{-}CH_2CH_2{-}$**CH**Me−Ph), the 1,5-CH insertion within carbene **61** (R^1 = Me, X = CMePh, via **54a**) was found[82] in the product 1-methyl-3-phenylcyclopentene[84] (**62**) to have proceeded with >99% retention of the configuration. This stereoretentive course extends to **61** → **62** with X = $C(OR)CH_2OR'$ in natural product syntheses.[65,67,69,85] Alkylidenecarbenes **61** with XH = **HC**$(OCH_2)_2$, thought to be generated with reagent **56b**, furnished cyclopentenones[86] (X = CO in **62**) by 1,5-CH insertion into the *tert*-CH bond of the acetal function; they can form pyrrolines[87] (X = NR in **62**) by 1,5-NH insertion when XH = NHR in **61** and even by attack on *tert*-amino functions. It is also remarkable that (putative) alkylidenecarbenes **61** (R^1 = *t*-Bu) with XH = **CH**=CR_2, generated in THF from the corresponding ketones with reagents **56a**[88] or **56b**,[89] chose to produce transitory intramolecular (highly strained) [1 + 2] cycloadducts, thus disdaining all of the alternative reaction modes of 1,4-CH insertion, 1,5-insertion into the sp^2−**CH** bond, addition to THF, or "FBW" rearrangement.



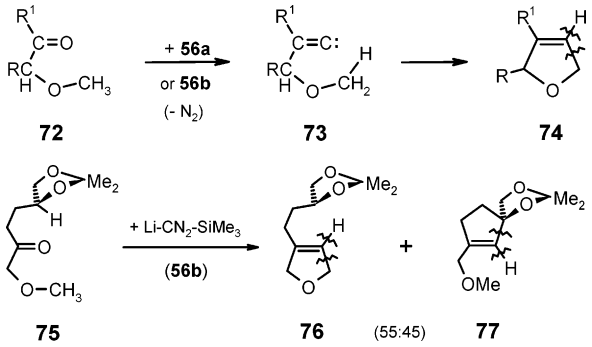
A considerably easier rearrangement was detected[90] in the formal 1,5-O−Si insertion reaction of the putative intermediates **63**, generated with reagent **56b** and leading to the 5-trimethylsilyl-2,3-dihydrofurans[84] **64**. For R^1 = phenyl, **64** was isolated together with a comparable amount of the "FBW" product **65**, indicating comparable rates for this phenyl migration and attack at the O−Si bond. In accord with the easier migration expexted for hydrogen, the alkyne **65** was the only product isolated[90] when R^1 = H.

In the dediazoniation of **66** as the presumed intermediate, created by a 1,3-silyl shift from carbon to oxygen in acyl(silyl)diazomethanes ($R^1{-}CO{-}CN_2{-}SiR_3$)[91,92] at or above room temperature, the 1,5-CH insertion into the *tert*-CH function next to silicon furnished heterocycles[84] **67**, to the exclusion of both alkyl migrations and formation of cyclopentenes that would have been expected when R^1 = alkyl in **66**.

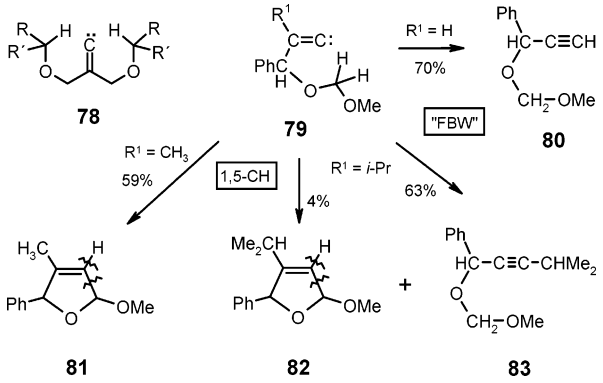
This obviously rather facile insertion was completely suppressed by the aryl migration[92] of R^1 in **66** to give solely the alkynes $(i\text{-Pr})_3Si{-}O{-}C{\equiv}C{-}Aryl$ without any [1 + 2] cycloaddition to added cyclohexene.



Intermolecular O−H insertion reaction into the solvent methanol could not compete[93] with the "FBW" migration of *tert*-amide moieties in **69** (generated from pyruvamides $Me{-}CO{-}CO{-}NR'CH_2R$ with reagent **56a**) at 0 °C, detected[94] by the ^{13}C-labeling (*) in **68** (R = methyl, R′ = ethyl) and believed[94] to imply a transitory positive charge on the amide group during migration. It was certainly also helpful here that a transition state such as **13** (if applicable in this case) can be stabilized better by the methyl group as a stationary substituent than by the electron-withdrawing amide moiety ($\sigma_I = 0.28$).[27] The competing[93] 1,5-CH insertion reactions exhibited partially reversed selectivities here, promoting $N\mathbf{CH}_3$ (R = H in **69**) to the champion in formation of unsaturated γ-lactams[84] **70**, as meticulously explained[94] by conformational analysis. However, α-keto-*N*-*aryl*-carbonamides ($X{-}CO{-}CO{-}NMe{-}Ar$) were later[95] reacted with reagent **56b** to generate the analogues of **69** (with R = H and R′ = aryl) in which addition to the aryl ring (!) competed successfully with insertion into NCH_3. The predominant (*Z*) conformation expected for the O=C−O−C moiety in the corresponding intermediate **71** is topologically unfavorable for 1,5-CH insertion; this may be one of the reasons why the putative carbene **71** (generated from the ester 2-octyl pyruvate in THF at −78 °C via **54a**) performed neither the 1,5-CH insertion nor "FBW" rearrangements but afforded[96] 2% of the diether **58** (with $R^1 = CH_3$, $R^2 = CO_2{-}CHMe{-}C_6H_{13}$).



The 2,5-dihydrofurans[84] **74** can arise by 1,5-CH insertion of an alkylidencarbene **73** into its side chain $CHR{-}O{-}\mathbf{CH}_3$. Once more the usual handicap of primary C−H bonds appears to be abrogated here because 75% of the 2,5-dihydrofuran derivative **74** (R^1 = phenyl, R = OMe) had been isolated[97] from the α-ketoacetal $Ph{-}CO{-}CH(O\mathbf{CH}_3)_2$ (**72**) via **54a** in THF at −40 °C and also from the corresponding 1,1-dibromoolefin $Ph{-}C(=CBr_2){-}CH(O\mathbf{CH}_3)_2$ with methyllithium (procedure given in section 3.2), whereas the alkyne that should have resulted from the expected phenyl migration was not mentioned by the authors. In view of the inductive substituent constant[27] $\sigma_I = 0.22$ for $HC(OH)_2$, it appears possible to conclude that $CH(OMe)_2$ as the stationary group in **73** may be sufficiently electron-withdrawing to decelerate the "FBW" migrations of R^1 (including phenyl) so that a (perhaps accelerated) 1,5-CH insertion reaction would become predominant. Indeed, CH_3 in the simpler side chain $-CH_2{-}O{-}\mathbf{CH}_3$ could compete with even a *tert*-CH function in $-CH_2CH_2\mathbf{CH}R(OR')$ for 1,5-CH insertion, as shown[67] by formation of **76** and **77** (55:45) from ketone **75** with reagent **56b**, while the authors apparently did not detect any "FBW" rearrangement to the alkyne. Thus, the $O\mathbf{CH}_3$ insertion reaction within both **73** and **75** seems to be favored by an undetermined effect. It is difficult to assess the significance of the possibly adverse statement[98] that insertion into $-CH_2O{-}\mathbf{CH}RR'$ of the putative carbene **78** was accompanied by "only very low quantities of the alkynes". This would indicate these 1,5-CH insertion reactions to be almost as slow as the "FBW" rearrangement of **78**.



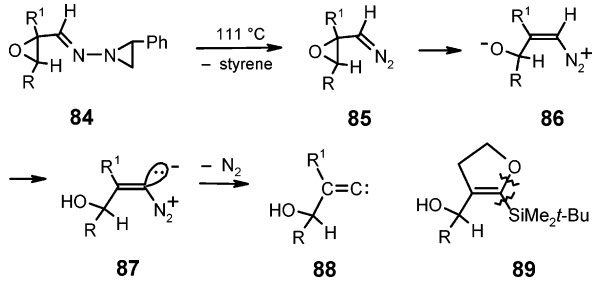
Selectivities were more clearly disclosed by studies[98] of the putative alkylidenecarbene **79** (generated with reagent **56b**), where only hydrogen migration providing **80** was reported for R^1 = H, while only 1,5-CH insertion into $-CHPh{-}O{-}\mathbf{CH}_2{-}OMe$ to give **81** occurred when R^1 = methyl. With R^1 = isopropyl, the "FBW" product **83** seems to have been formed roughly 16 times (63:4)[98] as fast as the side product **82** of insertion into the acetal C−H bond. Hence, either the system reported that isopropyl ≫ methyl for the migratory aptitudes as referenced against the 1,5-CH insertion reactions into $-CHPh{-}O{-}\mathbf{CH}_2{-}OMe$ furnishing **82** and **81**, respectively, or the (unproven) "FBW" migration of $-CHPh{-}O{-}CH_2{-}OMe$ had been accelerated by the stationary β-substituent isopropyl. In either case, 1,5-CH insertion into the acetal CH_2 group of **79** appears to have occurred with a significantly *diminished* rate as compared to H_3C insertion within the acetal **73** (where $R = H_3C{-}O$), which is normally faster than alkyl migration. Final clarification of the factors controlling selectivity in the system **79**−**83** requires identification of the migrating group when R^1 = alkyl (higher than methyl).

In another demonstration of the selectivity of the intermediate in question, 1,5-CH insertions into aryl groups are regularly avoided (but an exception will be mentioned in the arenesulfinate part of section

2.4.3). Even when phenyl seems to be optimally disposed, as in Me−C(=C:)−CHMe−Ph (generated via **54a**), for 1,5-CH insertion into one of its *ortho* positions, this pathway is apparently unattractive because no 1,2-dimethylindene was isolated,[83] but 5% of 4-phenyl-2-pentyne (Me−C≡C−CHMe−Ph) was obtained presumably from "FBW" migration of the *sec*-benzylic moiety at reduced temperature.[83]

2.3.2. From Fragmentation of N-(1-Aziridinyl)aldimines

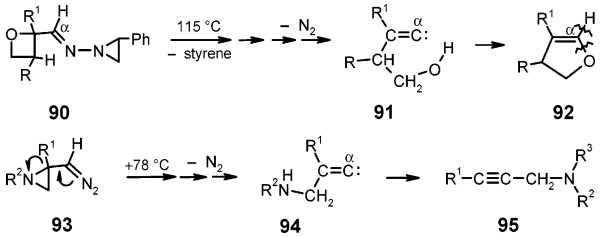
Thermal decomposition of the oxiranealdehyde *N*-(2-phenyl-1-aziridinyl)imines (**84**) in boiling toluene was thought[99] to generate monosubstituted diazomethanes **85** as the primary products. Their ring-opened isomers **86**, in a deviation[99] from the usual Eschenmoser fragmentation, were assumed to give rise to diazoalkenes **87** and thence to the alkylidenecarbenes **88**. With substituents R and R^1 suitable for



84 85 86 87 88 89

1,5-CH insertions it was possible[100] to prepare a wide variety of cyclopentenes, including annellated and bicyclic types. Several examples of the faster 1,5-insertion into the O−Si bond (as previously in **64**) of R^1 = *t*-BuMe_2**SiO**−CH_2CH_2− and affording 2,3-dihydrofurans[84] **89** (where R = ethyl or R = CH_2CH_2Ph had remained inactive) were discovered[101] by this method; examples of the slower 1,6-OSi and 1,7-OSi insertions were also observed. When a less attractive 1,5-O-alkyl or 1,5-O-benzyl cleavage was offered instead, the intermediate made evasive use of hydrogen transfer[101] from the neighboring *sec*-alcohol function in **88**. However, the "FBW" migration of R^1 = H to give ≥90% of terminal alkynes[100,101] was again the fastest of all of these rearrangements, and in no instance was "FBW" migration of the HO−CHR moiety of **88** observed. Hence, the sequence of decreasing reactivity in the rearrangements presented here may be seen as 1,2-H ("FBW") > 1,5-O−Si > 1,5-C−H ≥ 1,6-O−Si and 1,7-O−Si.

If the related opening of the oxetane ring in **90** under the same conditions[102] generated the alkylidenecarbenes **91** (which was not established), the ensuing intramolecular 1,5-OH insertion must have been very efficient because it remained successful even when R^1 = H (55% yield of **92** with R = phenyl);



90 91 92 93 94 95

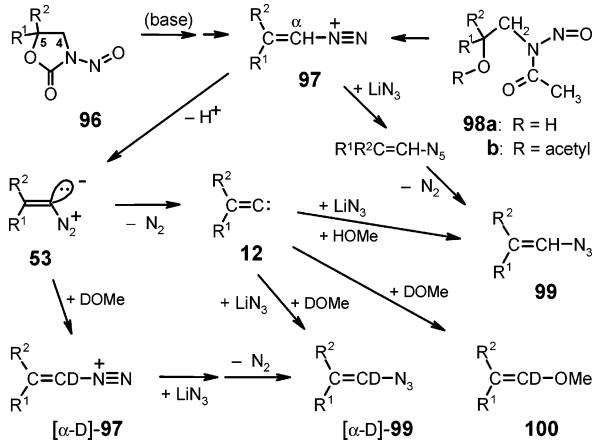
that is, the possible 1,2-shift of hydrogen was not observed. However, an alternative mechanism was considered[102] making use of a continuous preservation of the Cα−H bond during the conversion of **90** to **92**. In all of the preceding variants with diazoalkenes as the key precursors, cycloadditions[12] were studied rarely and then mainly for the purpose of selectivity comparisons, the discussion of which is deferred until section 2.6.

A similar azahomoallyl opening may have occurred during the nitrosation of 2-(aminomethyl)aziridines[103] at +78 °C whereof to expect the monosubstituted diazomethane derivatives **93**. If alkylidenecarbenes **94** are subsequent intermediates, they undergo mainly the anticipated 1,5-CH insertions into R^2 = benzyl or into sufficiently long alkyl chains R^1, in competition with the "FBW" route, which yielded ∼4% of the alkynes **95** (with R^3 = NO arising from an excess of the nitrosation reagents). In the absence of ^{13}C-labeling it cannot be decided whether the R^2HN-CH_2 moieties migrated faster than either simple alkyl groups R^1 in **94** or the seemingly immobile HO−CHR groups in **88**. Consistently, terminal alkynes **95** became the sole products[103] when R^1 = H in **93**−**95**.

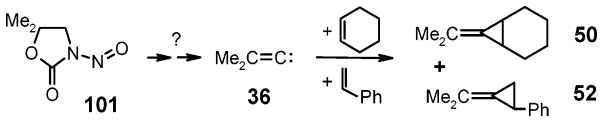
2.3.3. From N-Nitrosocarbonamides

The *N*-nitrosooxazolidines **96** are notorious[104,105] for their rather complicated chemical behavior when subjected at or above room temperature to base-induced decomposition, which only partially takes the route to the desired alkenediazonium intermediates **97**. Without substituents in the 4-position of **96** and hence at C-α of **97**, these intermediates are relatively long-lived (namely, hesitating to generate unstabilized primary alkenyl cations $R^1R^2C{=}CH^+$) and they may equilibrate with diazoalkenes **53**, a feature that complicates mechanistic analyses of the reaction course. Isolation[106] of a completely α-deuterated enol methyl ether **100** (65% yield from **96**) with R^1-R^2 = $(CH_2)_5$ produced in alkaline [OD]-methanol/1,2-dimethoxyethane at 0 °C is clearly incompatible with a *direct* conversion **96** → **97** → **100** because residual starting material **96** was recovered without any deuterium incorporation; but it provides strong evidence for the occurrence of a diazoalkene **53** somewhere in the process. Of course, this intermediacy of the highly labile **53** implies an open route to alkylidenecarbenes **12**. Accordingly, the base-induced "FBW" migration of the cyclopropyl group (R^2 in **96** and perhaps in **12**) at room temperature to give cyclopropyl alkynes could compete[107] with the [1 + 2] cycloaddition to cyclohexene and with intermolecular OH insertion into the solvent methanol (producing $R^1R^2C{=}CH-OMe$ with R^2 = cyclopropyl). On the other hand, alkenyl cations $R^1R^2C{=}CH^+$ (rather than **12**) were believed[108,109] to arise from **96** in alkaline 2-methoxyethanol[108] or in the mixed solvent pentane/aqueous sodium hydroxide/phase transfer catalyst[109] via the dediazoniation of **97** with subsequent addition of halide[108] and other nucleophiles.[109] However, the increased production[108] of cycloheptanone from **96** via **97** with R^1-R^2 = $(CH_2)_5$ in more polar solvents would nowadays be considered in terms of a concerted carbocationic ring expansion

during the *attempted* (yet avoided) generation of $R^1R^2C{=}CH^+$, as will be discussed for **106** in section 2.4.1. Furthermore, in benzene with triethylsilane as a cosolvent, the generation of carbenium ions on treatment of **96** with lithium ethoxide can be excluded because these would quickly extract a hydride anion from triethylsilane, whereas alkenylsilanes $R^1R^2C{=}CH{-}SiEt_3$ (**59a** = **33)** were isolated[108,110] in over 60% yield, testifying to the intermediacy of alkylidenecarbenes $R^1R^2C{=}C$: (**12**). Unfortunately, this test was apparently not repeated in the usually employed protic solvents, thus not allowing a comparison and conclusions. The acyclic *N*-nitrosoacetamides **98a** (with base)[109,111,112] and **98b** (in boiling THF)[113] were regarded to be more suitable starting materials than the *N*-nitrosooxazolidones **96**.



The somewhat cloudy mechanistic picture became much clearer when the primary alkene-diazonium cations **97** could for the first time be demonstrated[114,115] to be leading intermediates. In an elegantly conceived strategy using lithium azide (for instance, 1-molar) as a sufficiently basic nucleophile in methanol at +25 °C, it was shown with [^{15}N-3]-**96** that the main product[114] alkenyl azide (**99**) could conserve high portions of the label and hence was formed mainly via an alkenyl pentazene ($R^1R^2C{=}CH{-}N_5$) or an isomeric pentazole[115] rather than via the dediazoniation of a fairly long-lived alkenediazonium cation **97**. In [OD]-methanol as the solvent, **97** could be deprotonated to give a diazoalkene **53** which will be α-deuterated very rapidly to produce [α-D]-**97**, nota bene without deuteration of the source **96**, as mentioned above. By careful comparisons of the deuterium and ^{15}N contents of the alkenyl azides **99** and [α-D]-**99** under varying conditions, the authors[114,115] concluded that the alkylidenecarbenes **12** ($R^1{-}R^2 = (CH_2)_5$ or dimethyl) in the presence of the stronger base LiOMe could become the main progenitors of the alkenyl azides. Furthermore, **12** was always on the main route to the enol ethers **100**, and only a very small fraction of the products was derived from primary alkenyl cations $R^1R^2C{=}CH(\text{or D})^+$ unless their formation was increased by salt effects. Therefore, the demarcation line between the realms of $R^1R^2C{=}C$: and $R^1R^2C{=}CH^+$ as possible intermediates deriving from the *N*-nitrosoamides **96** and **98** is still not completely settled, and a final determination may require further carefully planned experiments under even more strictly controlled conditions.



If isopropylidenecarbene ($Me_2C{=}C$:, **36**) is one of the intermediates from 5,5-dimethyl-3-nitrosooxazolidone (**101**), its [1 + 2] cycloaddition selectivity for cyclohexene versus styrene, providing **50** and **52**, must be at least comparable to, if not equal to, the competition constants 1.76 or 1.84 for the same species generated from the alkenyl triflate **35** or from the tosylazo-2-methylpropene **51**, respectively, as discussed earlier. However, this selectivity was actually found[104] to be 0.16 (favoring attack on styrene!) for the species from **101** and lithium 2-ethoxyethoxide in the olefin mixture at +40 °C. This could argue against the intermediacy of **36** from **101**, because such a large discrepancy certainly cannot be ascribed to analytical imprecision. It must, however, be considered that the source **101** was added in one batch[104] to the already heated olefin mixture containing 5 g of the volatile cyclohexene, releasing 3.5 mmol of N_2 within 5 min at +40 °C (or above?). On the other hand, the relative [1 + 2] cycloaddition rates[104] for cyclohexene, cyclooctene, 1-octene, and 2,3-dimethyl-2-butene were quite similar to those reported[58,59] for attack of **36** as formed from $Me_2C{=}CH{-}OTf$ (**35**) and KO*t*-Bu at −20 °C, suggesting that the contradictory result for styrene[104] should be reexamined. Indeed, one could hardly imagine that the cycloadducts **50** and **52** might have been formed from **101** via a species other[76] than **36**, and thus, this issue has for now to remain unresolved. (It will be returned to in section 2.6.)

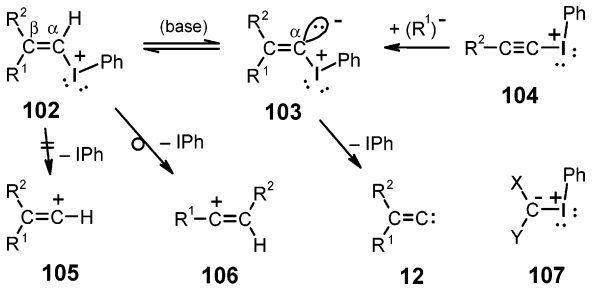
2.4. Alkylidenecarbenes from Iodine(III) Derivatives

The chemistry of organic iodine compounds has been a fascinating field over the last three decades for reasons to be mentioned further below. Alkynyl iodonium (**104**) and alkenyl iodonium[116] salts such as **102** are topologically characterized in the solid state by an almost orthogonal bond angle[116a,117] at iodine (∼94°). If the somewhat elongated ionic bonds to the anion are included, the bonding situation is better described as T-shaped,[116a] as shown further below in **112** and **113**, or sometimes as tetracoordinated-planar,[117] such as **114**, owing to dimeric arrangements which can also be generated[118] by the interaction of **102** with bromide anions in chloroform solution.

2.4.1. Iodonium Ylides, but No Primary Alkenyl Cations

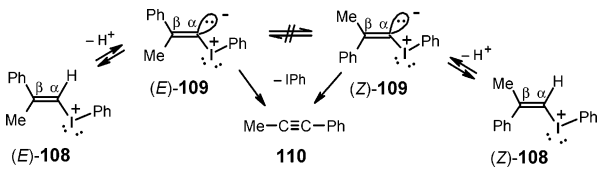
Primary (α-unsubstituted) alkenyl(phenyl)iodonium salts **102** are stable at room temperature when $R^2 \neq H$ because the straightforward escape of iodobenzene is thermally not possible, albeit photochemically feasible,[119] for energetic reasons: Being high-energy intermediates, the primary alkenyl cations **105** are thermally inaccessible from **102** even though

the kinetic nucleofugality of iodobenzene is 10^6-fold higher than that of the triflate group or 10^{12}-fold higher than that of a tosylate, as measured[120] by the generation of the strained secondary alkenyl cation **106** with $R^1-R^2 = CH_2CH_2-CH(t\text{-Bu})-CH_2$ from 4-*tert*-butyl-1-cyclohexenyl(phenyl)iodonium. During thermolyses of **102** at +60 °C in protic solvents[119−121] or in chloroform,[122] formation of a primary carbenium ion **105** is circumvented by obligatory neighboring group participation, leading directly to rearranged alkenyl cations[119] **106**, which should be more stable than **105** by 17.8 kcal/mol.[123] This high energy content of **105** suggests that alkylidenecarbenes should be quite weak bases. The general conviction that **105** will not be formed from **102** has been reinforced[123] by a most elegant proof that consists of the complete[121] transfer of enantiomeric excess from optically active **102** via **106**, both with $R^1-R^2 = CH_2CH_2-CHMe-CH_2CH_2$, to the optically active 4-methylcycloheptanone that was produced by ring expansion[122] in aqueous methanol at +60 °C. A carbenium intermediate **105** with these substituents would be achiral and hence produce racemic 4-methylcycloheptanone. Therefore, consideration of **105** can be neglected in this system, which implies a welcome simplification of the search for carbene reactions in the iodine(III) system.



Alkenyl triflates ($R^1R^2C{=}CH-OTf$, **28**) can be prepared[123,124] from the thermodynamically less stable alkenyl(aryl)iodonium salts **102**. Because of the considerable CH acidity of the salts **102** with an estimated[125] $pK_a \approx 2-5$, these are deprotonated already by the solvent methanol,[121a] albeit less so[126] by water or ethanol; but the bases routinely employed are KO*t*-Bu or triethylamine. It is not known whether the computational disclosure[127] of a thermodynamically weak I^+-C^- bond in a saturated iodonium ylide (**107**) applies also to the iodonium ylide **103** generated in this way. The sp^2-carbanion part of **103** is well stabilized by the extremely high inductive electron-withdrawing power ($\sigma_I = +1.24$)[128] of the phenyliodonium substituent. Despite the enormous nucleofugality[120] of iodobenzene, the iodonium ylides **103** possess a finite lifetime sufficiently long for their α-deuteration[117a,b] in situ, similar to the case of the diazonium ylides **53** (section 2.3.3), perhaps owing to better accessibility of the lone electron pair at C-α, which is not blocked by a cation in these cases. Alkyl(aryl)iodonium ylides of the saturated type **107** are well-known[116b,129] and rather stable at ambient temperature if supplied with charge-stabilizing substituents X and Y, but there is no experimental evidence[130] for a C=I double bond character, while quantum chemical calculations[127] of **107** with X = Y = H suggested a high energy content albeit moderate kinetic stability (and also "some double bond character"). Although unstabilized *alkenyl* iodonium ylides **103** cannot be isolated much less analyzed, they are again sufficiently long-lived to be captured[116a,131−136] by protonation (unless fractured into iodobenzene and the carbene $R^1R^2C{=}C{:}$) after their creation by the addition of nucleophiles to the "Michael system" of alkynyl(aryl)iodonium compounds **104**.

Because an intermediate **103** carrying (or perhaps loosing) the steric reminiscence of its source **102** is encountered here for the first time, questions about its configurational stability will emerge during attempts to establish its differentiation from a stereochemically unbiased alkylidenecarbene $R^1R^2C{=}C{:}$ (**12**). Of the very rare investigations that might bear on this problem, two are stereochemically[117a,b] inconclusive because the H/D exchange reactions were done without presenting evidence of an unchanged stereoisomer ratio, an objection which applies also to many cases of the Michael additions at **104** leading to **103**. A third occasion[137] at which this stereo problem was addressed by reisolation of unchanged residual starting material **102** after treatment with KO*t*-Bu in THF would be conclusive only with the assumption that deprotonation under these conditions was readily reversible, which is probably correct but was not established (for example, by isotopic exchange under these conditions). The issue is not trivial because soon we will meet a reacting system (**118**) in which exchange of deuterium with the solvent methanol was not the prevailing process. Indirect evidence for configurational stability may be seen in the recent measurements[119] of the absolute rate constants of (*E*)- and (*Z*)-2-phenyl-1-propenyl-(phenyl)iodonium tetrafluoroborates **108** with sodium acetate as the base in methanol at room temperature, where it has been shown that the final product 1-phenylpropyne (**110**) was formed from (*Z*)-**108** 3.7 times faster than from (*E*)-**108**, presumably without any evidence in the GC analyses for conformational leakage between (*E*)- and (*Z*)-isomers. Provided again



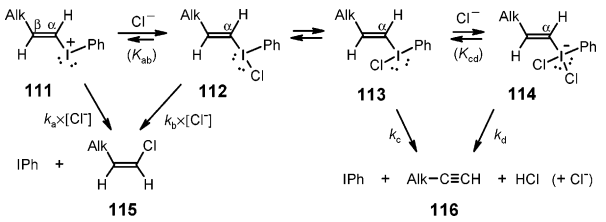
that the cleavage of iodobenzene from **109** is the rate-determining step, and hence **109** is in mobile equilibrium with **108**, this rate difference permits the conclusion that the iodonium ylides (*E*)-**109** and (*Z*)-**109** do not interconvert quickly. This would agree with general knowledge[138−140] about configurational inversions that are strongly decelerated by inductively electron-withdrawing α-substituents (see $\sigma_I = +1.24$ above[128]). Of course, the irreversible formation of α-methylbenzylidenecarbene (PhMeC=C:) as a common further intermediate from (*E*)-**109** and (*Z*)-**109** on the way to **110** is neither supported nor excluded by these kinetic results: as already noted for production of **48** (= ^{13}C-labeled **110**) from the

alkenyl triflates[52] (*E*)- and (*Z*)-**47**, even Cα- or C*β*-labeling could serve merely to *exclude* the carbene by showing that (*E*)- and (*Z*)-**108** led to *differently* labeled samples of the final product **110** due to differences in phenyl versus methyl migration.

It may perhaps come as a surprise that the chemical behavior of iodine(III) compounds is more intricate than the structures **102** or **108** would lead one to expect. Therefore, it appears expedient to interpose a preparatory section presenting a closer look at some unexpected reaction modes of **102** prior to the consideration of the alkylidenecarbenes $R^1R^2C{=}C{:}$ descending from **102** (reviewed in section 2.4.3).

2.4.2. Some Unexpected Abilities To Compete with α-Elimination of the Iodine(III) Compounds

The past decade has seen the discovery of several quite unexpected reaction modes for the escape of iodobenzene from alkenyl(phenyl)iodine(III) compounds such as **111**−**114**, giving rise to substitution (**115**) and elimination products (**116**). As these might be mistaken for arising from the alkylidenecarbenes Alk−CH=C:, it is appropriate to explain some of the events[116e,g] by means of a very thoroughly investigated example[141] that also illustrates the structural ambiguities which could hamper interpretations in this system. The ionic structure **111** of such iodanes will be more favored in a polar solvent such as acetonitrile than in chloroform.[142] Nevertheless, **111** in acetonitrile retains an appreciable affinity for chloride anions, with the two equilibrium constants[142] $K_{ab}(+25\ °C) \approx 7000$ L mol^{-1} to form the rapidly interconverting pair **112** and **113** of T-shaped pseudorotation isomers (called also[143] 10-I-3)[144,145] and $K_{cd}(+25\ °C) \approx 15$ L mol^{-1} for the weaker chloride affinity of this pair to give the tetracoordinated (12-I-4)[143] iodate(III) anion **114** where Alk = 1-octyl. Similar mobile equilibria have been conjectured with other nucleophiles in place of chloride, even with methanol[146] or trifluoroacetate.

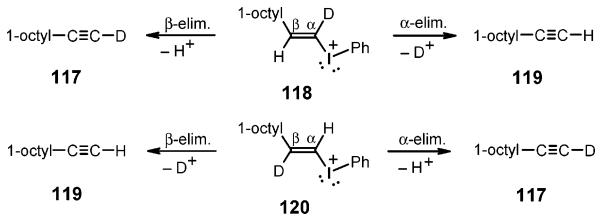


Treatment[142] of an acetonitrile solution of **111** (Alk = methyl, 1-octyl, or isopropyl) with tetramethylammonium chloride afforded the products **115** of substitution and **116** of *β*-elimination. In the absence of bases, a deuterium label[147] at C-α remained preserved in both products, so that **116** may have been formed in an intramolecular syn deprotonation by the chloride anions coordinated at **113** and **114**, while **115** arose from **111** and **112** by vinylic substitution with complete inversion of the configuration, with no more than traces of the stereoisomer (*E*)-**115** being detectable. One of these mechanisms appears as surprising as the other, but both received support from quantum chemical calculations[148] and by further experimental examples in ethereal solvents,[147] with fluoride transfer[149] from the gegenion tetrafluoroborate in chloroform, with the solvents acetic acid[150] or *N*,*N*-dialkylformamide[151] as nucleophiles at +50 °C, and with a *β*-phenyl group[152] in lieu of the *β*-alkyl in **111**. The formerly ill-reputed in-plane vinylic S_N2 substitution mechanism ($S_NV\sigma$)[116f] with inversion at an sp^2 center[148,153−156] is doubtlessly facilitated by the very high nucleofugality of iodobenzene mentioned before; it can hardly be feigned by an addition−elimination mechanism that would lead in **115** to predominant retention[157] of the configuration.

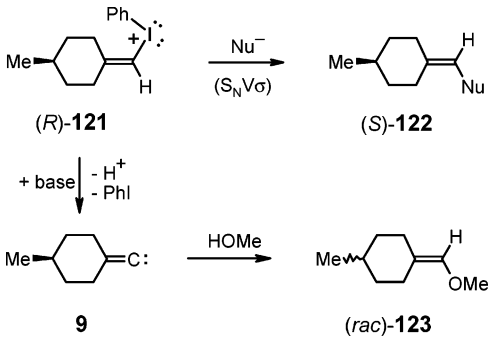
It is instructive to inspect the four rate constants k_{a-d} that have resulted from careful analyses[142] of the coupled ensemble **111**−**114** (Alk = 1-octyl) in an internally consistent kinetic scheme together with the equilibrium constants K_{ab} and K_{cd} detailed above. The configurationally uniform (*Z*)-1-chlorodecene (**115**) arose in acetonitrile at +25 °C from the iodonium (8-I-2)[143] species **111** with the second-order rate constant $k_a = 0.3$ L mol^{-1} s^{-1}, eleven times faster than from the uncharged 10-I-3[143] compound **112** with $k_b = 0.028$ L mol^{-1} s^{-1}. However, a large part of the reaction was proceeding via the 10-I-3[143] components **112** and **113** because of the large association constant K_{ab} (see above), while the smaller first-order (that is, indepedent of chloride-ion concentration) decomposition rate constants $k_c = 2.8 \times 10^{-4}$ s^{-1} of **113** and $k_d = 2.8 \times 10^{-5}$ s^{-1} of **114** gained predominance when the amount of excess tetramethylammonium chloride was reduced. Thus, the mere formation of a substitution product (**115**) or of a terminal alkyne **116** cannot be taken as prima facie evidence for a carbene mechanism.

The same system **111**−**114** but with ethanol as both the solvent and the base (chloride ion omitted) at +25 °C exhibited kinetic behavior[146] similar to that in acetonitrile, although the reaction rates were distinctly lower and 1-decyne (**116**) became the sole product. Increasing concentrations of the bases sodium acetate or other carboxylates first raised the rates as expected, but still higher concentrations caused inhibition[146] because of formation of an unreactive 12-I-4[143] species of type **114** (with carboxylate replacing chloride). The curtain was lifted somewhat higher by investigation[146] of the deuterated iodine(III) compounds **118** and **120** in methanol at +50 °C. Loss of deuterium from **118** to give **119** is only a necessary but not a sufficient condition for carbene intermediates because this first step of α-elimination might be reverted by methanol, with ensuing conversions of the unlabeled source **118** not involving carbenes. In contrast, the retention of roughly one-third of the label in [1-D]-1-decyne (**117**) with trifluoroacetate ($pK_a = 0.23$) or with methanol as the only bases revealed that at least this fraction of **118** must have undergone a syn-*β*-elimination, presumably via a 10-I-3[143] intermediate analogous to **113** but with MeO at iodine in lieu of Cl. It also showed that the base-catalyzed H/D *exchange* reaction of **118** was *not very* efficient, because otherwise the resulting unlabeled source **118** should have delivered more than the observed two-thirds of unlabeled product **119**. A more precise answer could have been obtained by reisolation of unreacted start-

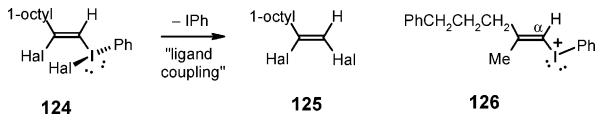
ing material **118** and determination of its deuterium content.



Positive evidence for the α-elimination came (perhaps paradoxically) from *β*-deuterated **120**, which produced[146] [1-D]-1-decyne (**117**), either as the main component by an "FBW" shift of deuterium with methanol or trifluoroacetate as a base, or as the only product via deprotonation by the more basic sodium acetate (complete reaction within 6 min at +50 °C). The low proportions (<14%) of *syn*-*β*-elimination product (**119** from **120**) were caused partially by an adverse kinetic isotope effect,[146] $k_H/k_D \approx 2$, for this mode. These results indicate that either 1-octyl-C(H,D)═C: or an equivalent intermediate had performed the main conversion and could be generated by very weak bases. The nonnucleophilic halide tetrabutylammonium fluoride (like other bases of pK_a > 3) afforded[147] exclusively [1-D]-1-decyne (**117**) from **120** by α-elimination, abstaining like acetate from any *β*-elimination or substitution. To be sure, a primary alkenyl cation **105** from **118** or **120** need no longer be considered (section 2.4.1), and the concerted formation of the *secondary* carbenium ion octyl-C$^+$═CHD as the only intermediate by migration of hydrogen or deuterium can also be excluded because it would generate this same cation from both **118** and **120** and hence furnish the same product mixture, which was not the case.



The in-plane $S_NV\sigma$ substitution is still possible at C-α of a *β*,*β*-disubstituted alkenyl(phenyl)iodine(III) compound, as shown in the conversion of the optically active (*R*)-**121** by the nucleophiles tetrabutylammonium bromide[158] or methanesulfonate[122] in chloroform at +60 °C to give the optically active products (*S*)-**122** with >92% inversion[159] of the configuration. The role of neutral aqueous methanol as a base[126,146] received support here by isolation of the almost racemic[121a] enol ether **123** as a side product from (*R*)-**121**: the alkylidenecarbene **9** remains as the conceivable achiral intermediate in this side reaction because the corresponding achiral primary alkenyl cations R^{1}R^{2}C═C$^+$—H had been ruled out in section 2.4.1. If **9** is indeed generated in this side reaction, its six-membered ring does not expand ("FBW") in methanol solution because racemic 4-methylcycloheptanone (or a derivative thereof) was not observed.[121] Consistently, a base (triethylamine in this case) was required[122] for preparation of the cycloadduct (in 76% yield) expected via **9** from **121** with cyclohexene.

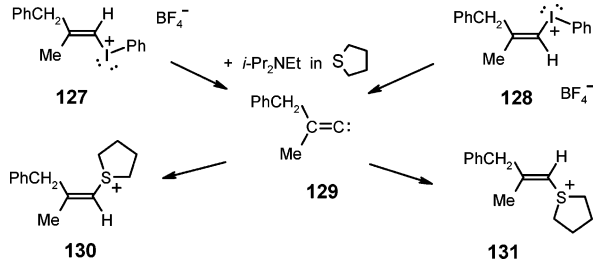


A (2-halogeno-1-decen-1-yl)phenyliodonium cation was found to combine immediately[142,160] with a tetrabutylammonium halide (Hal = Cl or Br) in acetonitrile at +60 °C to afford the iodine(III) compound **124**, which decomposed slowly with first-order kinetics,[160] giving the dihalides **125** with completely *retained* (*Z*) configuration. This "ligand coupling" mechanism[148,155,161] ("LC") was also characterized by quantum chemical calculations[148] as an *out-of-plane* vinylic S_N2 reaction (equivalent[161] to a reductive elimination); it can emerge here not only because syn-*β* elimination as a first choice of a 10-I-3[143] intermediate (as in **113**) is obviously impossible for **124** but perhaps also due to some steric shielding against the in-plane $S_NV\sigma$ mode. Higher concentrations of the halide anions may retard[160] this LC process by formation of an unreactive 12-I-4[143] species such as **114**. Similar steric retardation of substitution at C-α of the *β*,*β*-disubstituted system **126** by halide anions allowed inversion (through S_NV) to be accompanied by retention (through "LC") of the configuration[162] with rates that were considerably lower at +50 °C than those for the *β*-monosubstituted system **111**−**114**. Although α-elimination induced by sodium acetate or triethylamine occurred rapidly[163] with **126**, leading to 1,5-CH insertion and "FBW" rearrangement, it can be accompanied by the solvent-dependent heterolysis of **126** with concerted (hence accelerated) rearrangement (as in **102** → **106**) as a second pathway producing 6-phenyl-2-hexyne, so that unambiguous interpretation becomes difficult.

In short, it appears advisable to be cautious when appraising the potential role of alkylidenecarbenes in reactions of 1-alkenyl(phenyl)iodine(III), as is further considered in the following section.

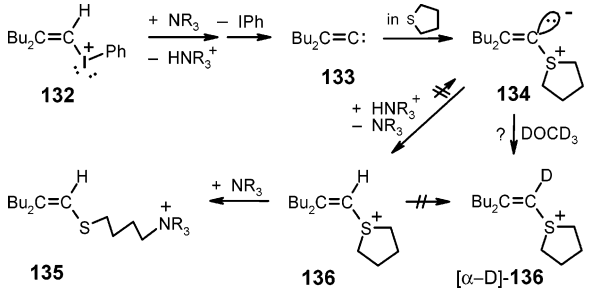
2.4.3. Evidence for and Properties of Alkylidenecarbenes from Iodine(III)

A formal "proof" for (phenylisopropylidene)carbene (**129**) as the common intermediate from two different sources in their reaction with the nucleophilic solvent tetrahydrothiophene (THT) was obtained by the



observation[164] of stereoconvergence as follows. The (*E*)-isomer **127** was induced by ethyldiisopropylamine to replace iodobenzene by THT, affording the sulfonium salts **130** and **131** in a 38:62 ratio at ambient temperature. The same product ratio (36:64) within the error limits was obtained from the (*Z*)-isomer **128**. This stereoconvergence is in accord with a common intermediate such as **129** and rules out S_NV processes (described in the previous section) that take place directly at **127** or **128**. The usual reservation of a necessary but not sufficient condition is weakened here by the supplementary observation[164] that diphenylsulfide in place of THT furnished the (*E*) and (*Z*) products corresponding to **130** and **131** in a 31:69 ratio from the (*E*)-isomer **127** (in CH_2Cl_2 within 30 min at ambient temperature) and in a 29:71 ratio from the (*Z*)-isomer **128**. Such a twofold issue of distinctly selective stereoconvergence means diminution of the probability for casual equality of the product ratios. However, these ratios appear to come suspiciously close to the presumptive (*Z*)/(*E*) equilibrium ratios expected for thermodynamic termination, which would invalidate mechanistic conclusions. The kinetic termination (required for the exploration of selectivity) could have been ascertained by subjecting a mixture of **130** and **131**, more enriched in one of the isomers, to the reaction conditions in order to rule out equilibration. Instead, evidence for an irreversible generation of sulfonium product from the carbene was reported[164] for at least **133** → **134** → **136**. Thus, it appears justified to confer on **129** the status of the probable common intermediate, remembering that a primary alkenyl cation cannot (section 2.4.1) play this role.

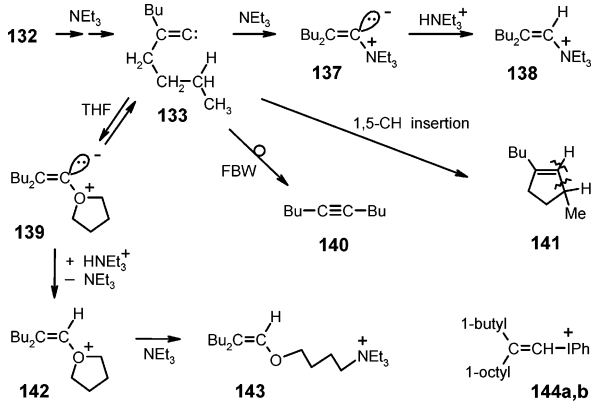
Extending this conviction to the dibutyl derivative **132** and its alkylidenecarbene $Bu_2C{=}C{:}$ (**133**), it may be concluded that the addition of **133** to THT affording **134** was fast and irreversible because the ability of **133** to perform rearrangements by the "FBW" method or by 1,5-CH insertion (see below) did not materialize here. With triethylamine as the base, the main product **136** (87% after 10 h at room temperature) was indeed formed irreversibly[164] and was partially converted to **135** as the only side product (7% yield). The isolation[164] of 88% of [α-D]-**136**



containing 0.6 D at C-α from a run in THT diluted with [D_4]-methanol after 30 min at room temperature could have provided evidence for trapping of the sulfonium ylide **134** and against the direct substitution mechanism ($S_NV\sigma$) on **132** if an expected (section 2.4.1) antecedent H/D exchange reaction had been excluded by reisolation of the undeuterated starting material **132**. At least, **136** was shown[164] not to be transformed into [α-D]-**136** under the same conditions. Cycloadditions cannot be compared with these THT additions because they were apparently not attempted in this solvent.

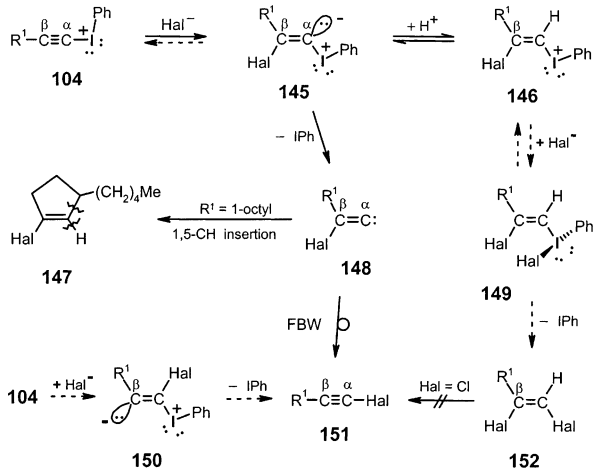
In contrast to THT, the less nucleophilic solvent THF allowed the "FBW" and 1,5-CH insertion reactions of the alkylidenecarbene **133** to give 5-decyne (**140**) and 1-butyl-3-methylcyclopentene (**141**), respectively. This means that the addition of THF to produce an oxonium ylide **139** (previously encountered in **38** and **57** but never directly observed) is either slow or rapidly reversible; the latter explanation is supported by semiempirical calculations[164] as well as by the temperature dependence of the product pattern, as is described in the sequel.

Deprotonation of **132** by 1.2 equiv of triethylamine between −60 °C (very slow) and +60 °C afforded[164] product ratios of **138**:**140**:**141**:**143** that varied from 4:2:41:45 below 0 °C to 1:8:75:15 at +20 °C, showing that the "FBW" product 5-decyne (**140**) can be formed in this competition even below 0 °C. It further demonstrated that the putative carbene descendants **140** and **141** increase at the expense of the ammonio derivative **143** of the oxonium ylide **139**. In qualitative accord, MNDO calculations[164] with Me_2 in lieu of Bu_2 indicated that **139** is only 4 kcal/mol below the carbene **133**, whereas the ammonium ylide **137** is 31 and the sulfonium ylide **134** is 48 kcal/mol beneath it. The corresponding experimental investigations[164] with isopropylidenecarbene ($Me_2C{=}C{:}$, **36**) generated from $Me_2C{=}CH{-}I^+{-}Ph$ in THF furnished similar results, except that the 1,5-CH insertion was no longer possible. The migration of *β*-hydrogen in the monosubstituted (1-octylidene)carbene[165] (1-heptyl-CH=C:) in THF was much faster than nucleophilic attack by triethylamine. Only the 1,5-CH insertion reactions induced by deprotonation of the (*E*)- and (*Z*)-isomers **144a** and **b** with several bases were studied[165] at different temperatures. The mixture of isomeric cyclopentenes obtained in a 50:50 (±1) ratio from either starting material under any conditions can certainly be expected for the common intermediate 1-butylnonylidenecarbene but is hardly a proof because such a nonselectivity may also be explained in other ways. For a more interesting and conclusive example, 1,5-CH insertions into a *tert*-C−H bond versus CH_2 in intramolecular competition should have been tried.



Migratory aptitudes in the iodine(III) system were studied chiefly via "Michael addition" to alkynyl-

(aryl)iodonium compounds **104**. In this very convenient additional method of generating iodonium ylides **145**, the anti addition of hydrogen chloride to give **146** (Hal = Cl) was observed for R^1 = phenyl in a very early paper,[166] showing that the iodonium ylide **145** was sufficiently long-lived to pick up a proton. In much later studies[133] with R^1 = alkyl in *acidified* methanol, chloride and bromide anions were added to afford the pure (*Z*)-isomers **146** whereas fluoride did not react and iodide generated a short-lived ylide **145** that escaped protonation by its immediate transformation into the unstable alkyne **151** (Hal = I).

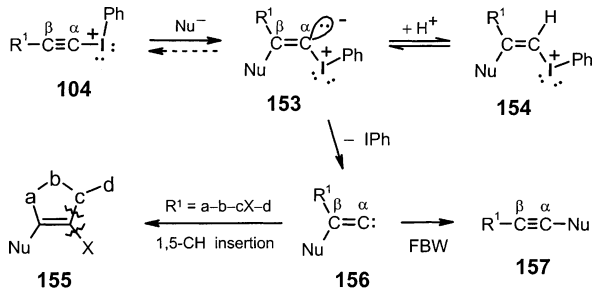


Attack of the lithium halides on the [^{13}C-β]-labeled cation Ph−C≡C−I^+−Ph in CH_2Cl_2/methanol at −78 °C furnished the α-halogenoalkynes [^{13}C-β]-**151** as a single isotopomer[135] in each case (R^1 = phenyl; Hal = Cl, Br, and I). These results alone would be compatible with the following three reasonable reaction mechanisms. First, if Michael addition of the halides at C-β of **104** (which seems[135] to be reversible) generated the iodonium ylide **145** and then the β-halogenocarbene **148**, the ensuing "FBW" rearrangement observed to give [^{13}C-β]-**151** would indicate that phenyl migrated slower than the halogen atoms. Second, addition of a halide anion at C-α of **104** to give **150**, followed by expulsion of iodobenzene, would also furnish the observed alkyne product [^{13}C-β]-**151**. However, neither **151** nor a derivative of **150** were detected under otherwise similar conditions by protonation, which allowed trapping[133] of the ylide **145** to afford the β-halogenoalkenyliodonium cation **146**; therefore, alkyne **151** was probably formed not via **150** but by halide addition at C-β via **145**. Third, the protonation product **146** in equilibrium with **145** can add a further halide anion to provide the 10-I-3 intermediate[143] **149**, which might form the dihalide **152** by reductive elimination in the "ligand-coupling" mechanism (explained above for **124** → **125**). This pathway can be excluded at least for Hal = chlorine, because (*Z*)-α,β-dichlorostyrene (Hal = Cl; R^1 = phenyl in **152**) would not[167] be converted to alkyne **151** under the reaction conditions. This leaves the first mechanism, "FBW" rearrangement, with the migratory aptitudes of Hal (Cl, Br, I) ≫ phenyl. However, deprotonation of **146** (Hal = Cl, R^1 = *1-octyl*) at 0 °C furnished[135] 1-chloro-1-decyne (1-octyl−C≡C−Cl, **151**) and 1-chloro-3-pentylcyclopentene (**147** with Hal = Cl) in a 59:41 ratio that was independent of the applied bases (sodium hydrogencarbonate in CH_2Cl_2/aqueous methanol, or tetrabutylammonium fluoride). Hence, the migration of chlorine now occurred with a rate approximately equal to the rate of 1,5-CH_2 insertion into the octyl chain of **148**. (In contrast, the corresponding insertion was outrun[135] by migrating bromine in **148** → **151**.) Combined with the observation reported above that chlorine migrated faster than phenyl, this would imply the startling rate sequence 1,5-CH_2 insertion ≈ Cl migration ≫ phenyl migration. Although the authors[135] cited the earlier evidence that 1,5-CH insertions cannot compete with the easier $\beta \rightarrow \alpha$ phenyl ("FBW") migration, they did not explain the apparent contradiction. One way out of this dilemma would be to assume that the usually fast phenyl migration becomes decelerated when the transition state model **13** (displayed at the beginning of section 2) finds a halogen substituent at its electron-deficient C-β atom, perhaps because of the destabilization of **13** by the inductive electron-withdrawing character ($\sigma_I = 0.47$)[27,168] of chlorine and bromine. In addition to or instead of such a deceleration, the 1,5-CH insertion reaction may become accelerated by chlorine as the β-substituent.

Arenesulfinate anions ($ArSO_2^-$) as the nucleophiles add quite rapidly[134,169,170] at C-β of the Michael system of several alkynyl(aryl)iodonium salts **104**, leading at or below room temperature to the alkynyl sulfones R^1−C≡C−SO_2−Ar (**157**, Nu = SO_2Ar). With suitable substituents R^1 = a−b−cX−d in **156**, the 1,5-CH insertions yielding cyclopentene derivatives **155** were somewhat[134] faster than the "FBW" migration (proven[134] by ^{13}C-labeling) of the phenylsulfonyl moiety. Migration of R^1 = cyclopentylmethyl was not detected (≤1%)[134] in the ^{13}C-labeling experiment, so that the rate sequence 1,5-CH_2 insertion > ≈ migration of $PhSO_2$ ≫ cyclopentylmethyl migration might be postulated, in seeming contradiction to the butyl shift (**140**) occurring not much more slowly[164] than the 1,5-CH_2 insertion (**141**) within carbene Bu_2C=C: (**133**). This new dilemma (not discussed by the authors[134]) might be treated as above by considering deceleration of alkyl migration and/or acceleration of 1,5-CH insertion, caused by the strong electron-withdrawing property of arylsulfonyl (σ_I = 0.56 for tosyl).[27,168]

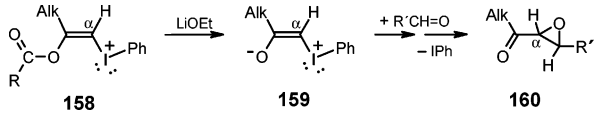
Alkenyl(phenyl)iodonium salts **154** (Nu = $ArSO_2$, R^1 = alkyl) were obtained[134] as the only products from **104** and arenesulfinic acids ($ArSO_2H$) via **153** at 0 °C in methanol alone but not in water. With the benzenesulfinate anion as the nucleophile (Nu^-) in Michael addition to generate **153**, variation of the counterion from lithium to tetrabutylammonium was found[134] to have almost no influence in water solution on the insertion/"FBW" (**155**/**157**) ratios of 76:24 which might be characteristic of the free alkylidenecarbene Alk−C(=C:)−SO_2−Ph (**156**). This tentative conclusion[134] gained support from observation of the same 1,5-CH_2 insertion/"FBW" ratios with triethylamine deprotonating **154** (Nu = $ArSO_2$; R^1 = alkyl) in either benzene or water. However, in THF solution at 0 °C the ratio **155**/**157** was found[134] to

depend on the cation, changing from 89:11 (±1) for benzenesulfinate with an alkali metal cation to 97:3 (±1) with tetrabutylammonium. This may perhaps be taken as evidence for a different intermediate not yet established; but seen from a pragmatic point of view, it suggests the insertion/"FBW" selectivity to be not very sensitive to medium effects. With the 1-butylsulfonyl group, introduced in **153** (R^1 = methyl) with the butanesulfinate anion,[134] the alkyne Me−C≡C−SO_2−Bu (**157**) was isolated[134] along with a 2-sulfolene derivative **155** where a−b−cH−d = SO_2−CH_2CH_2Et and X = H. Surprisingly, even 1,5-CH insertion into an aromatic *ortho* position of a diaryl-hydroxymethyl substituent R^1− = $Ar_2C(OH)$− was found[171] to occur in parallel with the "FBW" rearrangement leading to $Ar_2C(OH)$−C≡C−SO_2−Ar′. It is also remarkable that a phenylsulfonyl group as an activating *β*-substituent (Nu = $PhSO_2$ in **154**) seemed to promote the replacement of iodobenzene by nucleophiles in THF with total retention of the (*Z*) configuration, as reported for the enolate of 2-phenyl-1,3-indanedione[172] and for the formation of (*Z*)-1,2-bis(phenylsulfonyl)-1-decene with excess benzenesulfinate,[173] perhaps via addition−elimination or via the "ligand-coupling" depicted in **124** → **125**.



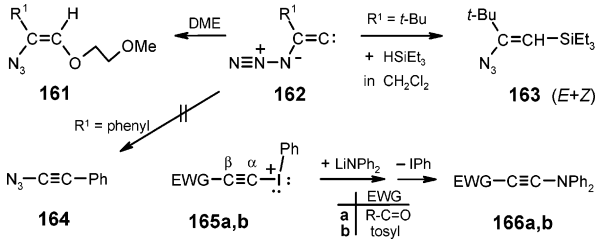
Displacements of non-hydrogen groups X in R^1 = CH_2CH_2O−X of **104** occurred[174] after the addition of sodium 4-toluenesulfinate in boiling THF, leading via iodonium ylides **153** to 2,3-dihydrofurans (**155** with "cd" = oxygen and X = trialkylsilyl or 2-oxacycloalkyl). These O−X insertion processes were again faster than sulfonyl migration, as was the 1,5-OH insertion into R^1 = CH_2CH_2**O**−**H** occurring on treatment[134] of **154** (Nu = $PhSO_2$) with triethylamine and producing 4-phenylsulfonyl-2,3-dihydrofuran alone (**155** with "cd" = oxygen and X = H). Although the alkynone moiety in *β*-acylalkynyl(phenyl)iodonium salts **104** (R^1 = R−C=O) offered an alternative Michael system, sodium *p*-toluenesulfinate in CH_2Cl_2 continued to attack at C-*β*, affording the 1,5-CH insertion products (C=O for "a" in **155**) within 15 min at +20 °C to the exclusion[175] of alkynes **157**, whereas at least the sulfonyl group could have migrated as it did[134] when R^1 = alkyl. This suppression of "FBW" rearrangements may be attributable either to the tosyl (σ_I = 0.56)[27,168] and the *β*-acyl groups (σ_I = 0.30)[27,168] as the stationary *β*-substituents, if these are detrimental to the transition state model **13** with its electron-deficient C-*β* atom, or else to an acceleration of the intramolecular insertion caused by those stationary *β*-substituents or by a favorable conformational situation. Phenylthio (PhS−) and benzenesulfinyl (Ph−SO−) groups migrated[165] faster than phenylsulfonyl, perhaps[134,176] via thiirenium ylides resembling the well-known[177,178] thiirenium cations.

Alkynyl carboxylates,[179,180] sulfonates,[180] and phosphates[181] (Nu = O_2C−R, OSO_2−R, or O−PO(OR′)$_2$ in **157**) were believed[179,181] to arise in a similar way by slow nucleophilic additions to C-*β* of alkynyl(phenyl)-iodonium salts **104** via ylides **153** (R^1 = alkyl), followed by quick but unspecified ("FBW"?) rearrangements at room temperature. It is conceivable that these rearrangements proceeded by nucleophilic addition of an oxygen center to C-α within the carbene **156** via the five-membered ring of a 1,3-dioxolenium 4-ylide rather than via the usual "FBW" 1,2-shift. Nevertheless, the iodonium ylides **153** could again be trapped by protonation: the examples **158** were prepared[136] from **104** with a carboxylic acid in large excess and with sodium carboxylate as a catalyst. Trans-esterification of **158** with lithium ethoxide in THF at −78 °C occurred faster than α-deprotonation, as proven by retention of the hydrogen isotope at C-α in **158**−**160**; the resulting iodonium enolates **159** (or their lithium salts)[136] decomposed at −20 °C, but at −30 °C they could add in situ diverse kinds of aldehydes (but not ketones) and then eliminate iodobenzene to yield cis/trans mixtures of the epoxyketones **160**.



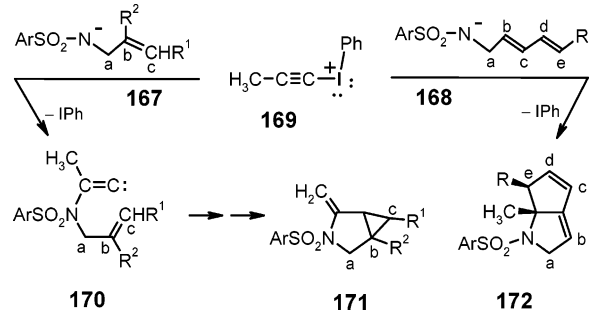
Anionic nitrogen nucleophiles (or their equivalents) such as sodium azide in methanol[131] (or trimethylsilyl azide in CH_2Cl_2 together with water)[132] added to alkynyl(aryl)iodine(III) (**104**) in the usual anti mode to give **154** (Nu = N_3) without any proclivity to "FBW" rearrangements even of R^1 = phenyl,[131] while 1,5-CH insertions into suitably substituted chains in R^1 could be observed.[131] The similarly startling formation of the unrearranged diethers **161** in basic 1,2-dimethoxyethane (DME) solution with R^1 = phenyl (or *tert*-butyl) at −10 °C was at first[131] qualified as evidence against an alkylidenecarbene **162** but later[116a] ascribed to just this carbene. If true, these observations would raise the question as to why the migration of R^1 = phenyl was not observed (with or without the base KO*t*-Bu) when azido was the stationary substituent in **162**. A possible reason may be seen in the strong inductive electron-withdrawing power (σ_I = 0.43)[27,168] of the "pseudohalogen" azide that would cause strong destabilization in the transition state model **13**. Moreover, the expected product *β*-azidophenylacetylene (**164**) would be an unstable substance whose transitory existence must be considered as dubious on account of contradictory reports in the literature; anyway, its purported derivatives[182] have never been detected in the iodine(III) system. The occurrence under such conditions of an intermediate such as **162** capable of intermolecular insertion into **H**−**Si**Et_3 is indicated by isolation[131] of the vinylsilanes **163** as side products (accompanying **161** with R^1 = *tert*-butyl) in DME or as the main products

in CH_2Cl_2 solution. Regrettably, the (*E*)/(*Z*) ratio of **163** as a selectivity index was not reported.



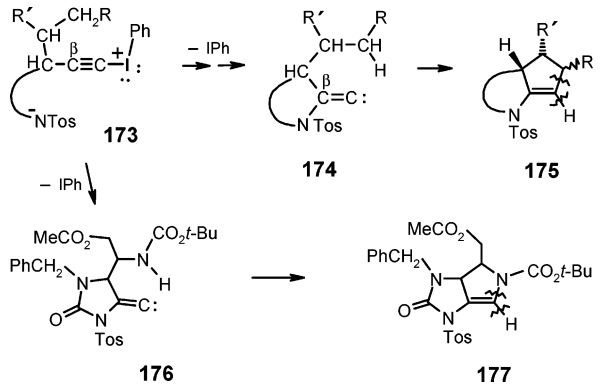
161 162 163 (*E*+*Z*) 164 165a,b 166a,b

Diphenylaminoalkynes (**166**) carrying the electron-withdrawing groups (EWG) acyl or tosyl at C-β were the only products isolated[183] from reaction of β-acyl- (**165a**) or β-(4-toluenesulfonyl)ethynyl(phenyl)iodonium salts (**165b**), respectively, with lithium diphenylamide in diethyl ether at room temperature. The mechanism is unknown but may circumvent the suspected substituent problems ($\sigma_I = 0.30$ for acyl groups and 0.56 for tosyl)[27,168] of "FBW" rearrangement by the alternative Michael addition of the nucleophile at C-α (instead of C-β) of **165** and thence expulsion of iodobenzene (addition−elimination mechanism) from the anionic intermediate (not displayed), in contrast to the earlier mentioned examples[175] where 1,5-CH insertion products into the acyl chain had signaled a nucleophilic attack of 4-toluenesulfinate at C-β of **165**.



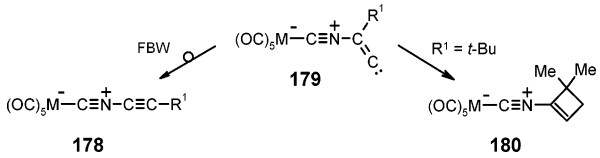
167 169 168 170 171 172

The very high and reliable selectivity of alkylidenecarbenes favoring intramolecular 1,5-CH insertions has been exploited in rather sophisticated syntheses of bicyclic aliphatic nitrogen compounds as follows. Deprotonated sulfonylamides **167** and **168** are weak bases and sufficiently selective nucleophiles for attack only at the Michael system of phenyl(1-propynyl)iodonium triflate (**169**) in boiling THF. The alkylidenecarbene **170** expected with **167** had no good route available other than the intramolecular [1 + 2] cycloaddition to its own C=C double bond,[184,185] because CH insertion at the sp^2-hybridized carbon atoms tagged as **b** (if R^2 = H) or **c** is usually inopportune. The resulting methylenecyclopropane (not displayed) was not isolated because it quickly released its internal strain by a formal 1,3-hydrogen shift that produced the bicyclic pyrrolidine **171**. The 2,4-pentadienyl amide anion **168** as a second example[186] is thought to behave in the same manner in the initial steps but then to reduce the strain of its methylenecyclopropane intermediate in a different way that implies cleavage between atoms **b** and **c** of the carbon chain tagged **a** through **e**; only the three central untagged carbon atoms in the final product **172** are descendants of the propynyl moiety of **169**, and an elaboration of the necessary steps is left to the interested reader's passion for inventing mechanistic pathways.



173 174 175 176 177

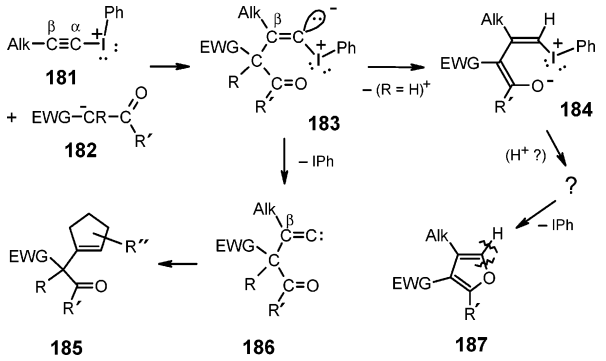
Sulfonylamide anions have also provided the first examples[187] of *intra*molecular Michael addition in the alkynyl(phenyl)iodine(III) compounds **173**. These precursors were, however, rather unstable and hence difficult to handle. The nucleophilic addition at C-β could be chosen to furnish five-, six-, or seven-membered rings in the purported alkylidenecarbene **174**, whose subsequent 1,5-CH insertion led to the diastereomeric product[84] mixture **175**. Likewise, the anion of a sulfonylurea unit in **173** is still sufficiently nucleophilic to add at C-β and to create presumably the alkylidenecarbene **176**. The bicyclic product **177** isolated in low yield by an experimentally demanding procedure[188] indicates that the final 1,5-NH insertion reaction into the carbaminate function of **176** can be easier than a 1,5-CH insertion into the adjacent $MeCO_2\mathbf{CH}_2$ group. When positioned on a more rigid scaffold[189] generated by sulfonamide addition, the carbene may be compelled to attack an aryl substituent with formation of a tropone derivative (not displayed).



178 179 180

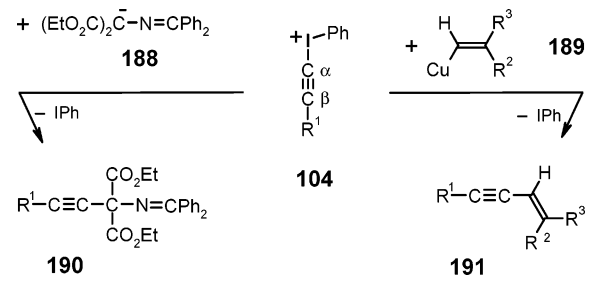
The nitrile group in the anionic cyano complexes $[(OC)_5M{-}CN]^-$ of M = Cr or W is sufficiently activated for a nucleophilic attack at alkynyl(phenyl)-iodonium cations **104**. Postulating the usual Michael addition to **104** and expulsion of iodobenzene from the resultant iodonium ylides of type **153** to liberate the alkylidenecarbenes **179**, the authors[190] could propose straightforward rationalizations of the observed rearrangements. The "FBW" products **178** were formed by migrations of R^1 = hydrogen, phenyl, or trimethylsilyl rather than of the coordinated cyano moiety. This follows from the failure of any "FBW" migration with alkyl substituents R^1 in **179**, which preferred either the usual 1,5-CH insertion mode or, as a singular event, the unprecedented 1,4-CH insertion into R^1 = *tert*-butyl generating the cyclobutene ring in **180**. The nitrogen atoms in this system are

sp-hybridized with angles C−N−C ≈ 177°, as disclosed by crystal structures[190] of **178** (R^1 = phenyl) and **180**.



While simple enolate anions apparently did not add[116a] to the Michael system of alkynyl(phenyl)-iodine(III) (**181**) for unknown reasons, the "softer" anions[191] of additionally stabilized enolates **182** (electron-withdrawing groups EWG = carbonyl, ester, cyano, or phenylsulfonyl) entered probably at C-β of **181** to afford the iodonium ylides **183**. Within 10 min at room temperature in THF or dioxane or HO*t*-Bu, only the expected products of 1,5-CH insertion into the β-alkyl groups (**185**) or else (comparably fast) into an alkyl chain R (introduced with **182**) but not into the acyl substituent R′ were observed; thus, the fragment **182** within **186** was not eager to perform an "FBW" rearrangement. Surprisingly, the isomeric furan derivatives **187** emerged as the sole or main products[191] when R = H in **183**. Because these furans can hardly have been formed via enolization of the short-lived alkylidenecarbene **186**, they should derive from the precursor **183** or from its protonated form having a lifetime sufficient for enolization. Transformation of the purported iodonium enolate (or enol) **184** into **187** might have occurred by α-elimination via the carbene or perhaps by a temporary O−I bond formation and a subsequent stereo-retentive[148,161] "ligand-coupling" reaction of the 10-I-3[143] cyclic intermediate (section 2.4.2). As expected, the cyclopentenes **185** arising by 1,5-CH insertion were no longer formed when a phenyl[166,191] or a trimethylsilyl[192] group or hydrogen[192] in place of alkyl performed its easier "FBW" migrations.

Despite its good stabilization by four charge-delocalizing substituents, the anion **188** of the disguised aminomalonate was found[193] with alkynyl(phenyl)iodonium **104** to produce **190** in THF below 0 °C. The substituent pattern of R^1 ($SiMe_3$, Ph, *n*-Bu, *t*-Bu) in **104** included butyl groups which would destabilize an adjacent negative charge at C-β, and this disqualifies an addition−elimination mechanism

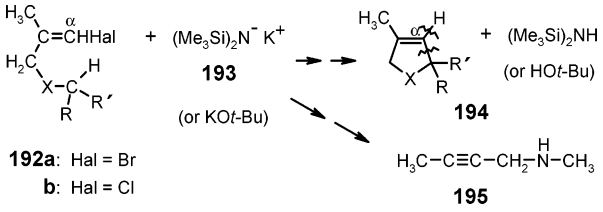


with attack at C-α of **104**. Should the unknown course involve an alkylidenecarbene formed by attack at C-β, then the migratory aptitude of the fragment **188** in the intermediate with R^1 = Bu would have to be unusually high for an alkyl moiety (more like that of an allyl group).

Configurationally pure alkenylcopper reagents (**189**) in diethyl ether displaced iodobenzene from **104** to afford 1-ene-3-ynes **191** with retention of their configuration.[194] As the mechanism is not established, the process cannot be used to assess the migratory aptitude of an alkenyl moiety.

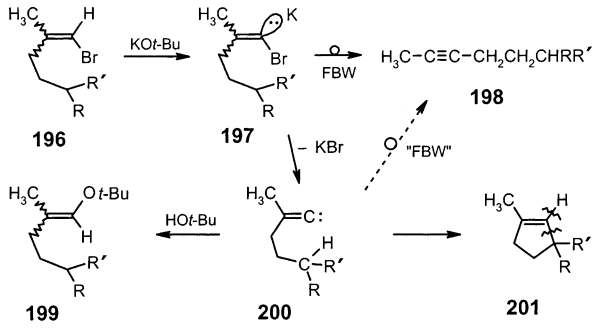
2.5. Alkylidenecarbenes from Terminal 1-Halogenoalkenes: Approaching the Borderline to Carbenoids

The α-deprotonation of a β,β-disubstituted alkenyl bromide such as **192a** should not be tried with a butyllithium base which might prefer the Br/Li exchange reaction.[195,196] Good choices[69,197] are the sodium or potassium salts (KHMDS, **193**) of the sterically shielded base hexamethyldisilylamine (but not *i*-Pr_2NLi or NaH)[69] that deprotonated **192a** or **b** in diethyl ether slowly at room temperature, indicating pK_a < 30 for **192a,b** as CH acids. Since the production of cyclopentene derivatives[84] **194** (X = CH_2 or CMe_2) by 1,5-CH insertion was apparently not plagued by side reactions caused by the weak nucleophiles **193** or HMDS, this procedure (together with the syntheses of **192a**,**b**) is sometimes[69,197] preferred to the shorter route of carbene formation directly from the corresponding ketone with the diazo reagent **56b** (section 2.3.1).

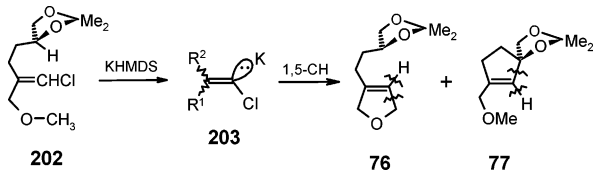


The more drastic conditions[198] required with KO*t*-Bu as the base (16 h in boiling THF) gave rise to side products (such as allyl compounds) when α-elimination of HHal from **192a** was slow. A (*Z*)-isomer of **192b** (X = oxygen) reacted only twice as fast as the (*E*)-isomer, and recovered starting material was not isomerized. The 2,5-dihydrofurans **194** (X = O) but no alkynes were detected, in accord with the supposedly accelerated 1,5-CH insertion reactions into side chains of the type $-CH_2-O-CHRR'$ to be expected from experience with **73** and **75** (section 2.3.1). Both stereoisomers of amines **192a** (X = NH; R = R′ = H) with KO*t*-Bu afforded[198] 3-methyl-2,5-dihydropyrrol (**194**) and 1-methylamino-2-butyne (**195**) in a roughly 7:4 ratio. This result resembles that observed[103] for the purported carbenes $R^2NH-CH_2-C(R^1)=C:$ (**94**, section 2.3.2), with the same uncertainty concerning the FBW migratory aptitudes of $CH_3-NH-CH_2$ versus CH_3 because ^{13}C-labeling was not applied. Exchange of α-H for deuterium in the starting

material with KO*t*-Bu in DO*t*-Bu proved the α-deprotonation to be reversible.

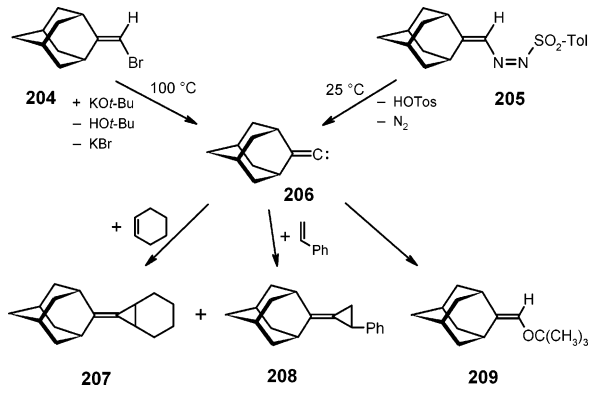


Unactivated 2-(bromomethylene)alkanes (**196**) treated with KO*t*-Bu are mechanistically more informative because they displayed selectivity by the familiar product pattern (**198**, **199**, **201**) that was found equal for (*E*)- or (*Z*)-**196** and did not change very much[199] between +50 °C and +240 °C. The FBW alkyl migrations (**198**) occurred roughly as fast[199,200] as the 1,5-CH insertion reactions (**201**), whereas the carbene $Bu_2C{=}C{:}$ (**133**, from the iodonium salt **132**) had shown the corresponding "FBW"/insertion product ratio 2:41 (**140**/**141**)[164] for these two rearrangements at or below 0 °C (section 2.4.3). This could mean that the alkynes **198** are descendants not only of alkylidenecarbenes **200** but also of Br,K-alkylidenecarbenoids **197**, the latter in accord with the presentation of **1** → **6** made in the Introduction: Held against the small fraction of "FBW" product from $Bu_2C{=}C{:}$ (**133**), the larger fraction resulting from **196** may be suspected to arise by FBW migration in the carbenoids **197** themselves rather than after a previous α-elimination of KBr via the carbene **200**. On the other hand, the selectivity of *insertion* reactions into primary < secondary < tertiary CH = 1:54:240 (on a per hydrogen basis) as measured[200] with reference to **198** after 1 min at +240 °C agreed closely with the ratio 1:30:240 determined[83] at below +25 °C (section 2.3.1) by intramolecular competition in the carbenes $R^1{-}C(=C{:}){-}CH_2CH_2\mathbf{C}\mathbf{H}RR'$ (**61**, from **54a**); hence, it appears justified to tentatively proclaim an alkylidene*carbene* **200** alone as the intermediate responsible for *insertion*. If true, the carbenoid FBW alkyl migration **197** → **198** would have to compete with simple α-elimination of KBr (**197** → **200**) rather than with the 1,5-CH insertion. It is also worth noting that alkylidenecarbenes **200** are very selective in insertion reactions when compared to the more frequently studied saturated carbenes,[201] perhaps owing to hyperconjugative stabilization of the empty p-orbital in **12** by the $R^{1,2}{-}C\beta$ bonds.



A parallel set of experiments with a 2-(*chloro*methylene)alkane corresponding to **196** has not been reported, probably because 1-chloroalkenes react much more slowly[198] than 1-bromoalkenes. But competition of the two arms in the 1-chloroalkene **202** after α-deprotonation with KHMDS (**193**) at room temperature[67] yielded 93% of **76** and **77** as a 91:9 mixture, demonstrating that the responsible intermediate favored 1,5-CH insertion into the arm $-CH_2O\mathbf{C}\mathbf{H}_3$ rather than into the $-CH_2CH_2\mathbf{C}\mathbf{H}(OR)-CH_2OR'$ chain. The heuristically important result consists of the difference from the product ratio 55:45 reported[67] for the same pair of products **76**/**77** as obtained from ketone **75** with reagent **56b** via the alkylidenecarbene corresponding to carbenoid **203**. Clearly then, **202** must have reacted, at least to some extent, via an intermediate of different selectivity (91:9), probably the **Cl**,K-alkylidenecarbenoid(s) **203**.

Evidence for the probable role of 2-adamantylidenecarbene (**206**) in [1 + 2] cycloadditions was obtained[202] by the following pair of experiments. Treatment of 2-(bromomethylene)adamantane (**204**) in toluene solution with cyclohexene/styrene mixtures, KO*t*-Bu, and a catalytic amount of the macrocyclic 18-crown-6 hexaether for 40 h at +100 °C provided the adduct **207** to cyclohexene 2.50 times faster than the adduct **208** to styrene, together with the enol ether **209** that became the main product (90% yield) in the absence[203] of the two olefins. Formation of the strained "FBW" product 4-homoadamantyne from **206** was not detected, certainly because this would recontract to **206**, as known from observations[204] on the corresponding triflates (**204** with OTf in place of Br). Fragmentation of the 2-(tosylazomethylene)-



adamantane (**205**) at +25 °C produced[202] **207** 2.08 times faster than **208**. These two competition constants from **204** and **205** appear sufficiently similar to support the authors' interpretation that 2-adamantylidenecarbene (**206**) should be the common intermediate (rather than a carbenoid), of course with the usual reservation of a necessary albeit not sufficient criterion. This interpretation gains further probability from the similar grading in the reactivity scale of diverse olefins[203] toward **206**, compared with that for isopropylidenecarbene[60] ($Me_2C{=}C{:}$, **36**). Regrettably, the experiments were not extended to the treatment of **204** with a suitable organolithium (or amide) base that would perhaps react via the Br,Li-2-adamantylidenecarbenoid and exhibit presumably a different **207**/**208** selectivity. An equivalent demonstration of the borderline to alkylidenecarbenoids in [1 + 2] cycloaddition reactions on a broader basis is reported in the immediately following section.

To summarize the conclusions to be drawn from this section, the borderline *for 1,5-CH insertion* reactions seems to show up between Cl,K-alkylidenecarbenoids $R^1R^2C{=}CKCl$ (**203**), that may be directly involved, and Br,K-alkylidenecarbenoids $R^1R^2C{=}CKBr$, which prefer to transform into their alkylidenecarbenes before involvement in either insertions (**200** → **201**) or [1 + 2] cycloadditions (**206**). However, the carbenoids $R^1R^2C{=}CKBr$ may participate directly in FBW rearrangements (**197** → **198**).

2.6. Cycloadditions to Styrenes Are Performed by Isopropylidenecarbene (36) from Most (but Not All) Sources

Cycloadditions to mixtures of cyclohexene and styrene were reported in section 2.2 to reveal equal selectivities (ca. 1.8:1) for the reactive intermediate from the two different sources $Me_2C{=}CH{-}OTf$ (**35** in Scheme 1) and 1-tosylazo-2-methylpropene (**51**). The preliminary conclusion that isopropylidenecarbene ($Me_2C{=}C$:, **36**) may be the common intermediate is subject to the previously mentioned reservations and will gain a higher degree of probability by concordant evidence from independent investigations. It is indeed supported in this section by the relative rates $k(y_2)/k(y_1)$ of [1 + 2] cycloadditions for competing pairs of *p*-substituted styrenes to produce pairs of the isopropylidenecyclopropanes **211a**,**b**. Although the total span of such competition constants did not exceed a factor 2.5, these measurements[59] on a series of related olefins (with Y = OMe, Me, H, and Cl) can provide strong support based on internal consistency because the rate ratios obey the Hammett relation $\log[k(y_2)/k(y_1)] = \rho[\sigma(y_2) - \sigma(y_1)]$, where $\sigma(y)$ are the Hammett substituent constants. The Hammett factor ρ as a logarithmic measure of the sensitivity to electron demand will be negative for the attack of an electrophilic reagent. Under the conditions collected in entries 1 and 2 of Table 1, $\rho = -0.75(4)$ was determined[59] for the triflate **35** with and without the macrocyclic 18-crown-6 hexaether, and comparison with $\rho = -0.71(2)$ as measured[60] for the azo derivative **51** leaves little doubt that **36** is responsible for these [1 + 2] cycloadditions. Indeed, the diazonium ylide **53** generated from acetone (**55**, entries 3 and 4 in Table 1) displayed slightly solvent-dependent ρ values centering about ~ -0.6 which were interpreted[205] as evidence for the *free* carbene $Me_2C{=}C$: (**36**) and against solvent-complexed **36** (such as **57** or **139**) as the relevant intermediate. Because these [1 + 2] cycloadditions occurred already[76] at −78 °C, the alternative possibility that **211a**,**b** derive from [2 + 3] cycloadditions of the styrenes to **53** can be dismissed, since the resulting pyrazolines would not decompose to alkylidenecyclopropanes (**211**) at this low temperature.[59]

Phenylisopropylidenecarbene, $PhCH_2{-}C(Me){=}C$: (**129**), is very probably the reactive intermediate that had been trapped by thioether solvents (section 2.4.3) after its formation from alkenyl(phenyl)iodonium tetrafluoroborate. Similarly, the iodine(III) compound $Me_2C{=}CH{-}I^+{-}Ph$ (**102**, $R^1 = R^2$ = methyl in Scheme 1) as the source of the iodonium ylide **214** was found[206] to generate $Me_2C{=}C$: (**36**) as the liable intermediate in [1 + 2] cycloadditions to the styrenes on account of its Hammett factor $\rho = -0.55$ (entries 5 and 6). Thus, the concordance of four different sources for **36** as their common intermediate appears to set the stage for reliable comparisons with other systems that may be more prone to carbenoid intermediacy.

Fluorodesilylations of the α-trimethylsilyl derivatives **212a** and **212b** should lead to the tetraalkylammonium salts **210** and **213**, respectively. The salt R_4N^+ TfO^- had probably left **210** before the styrenes were attacked, as suggested by the Hammett factor $\rho = -0.44(7)$ shown in entry 7 of Table 1. While this might be hardly surprising in view of the similar behavior of the short-lived carbenoid **49** (Scheme 1) that eliminates KOTf immediately (section 2.2), the same conduct follows also for **213**, as indicated by the determination[207] of $\rho = -0.41$ (entry 8): $Me_2C{=}C$: (**36**) is again the reactive intermediate although its precursor **213** could have been its competitor in the cycloaddition reactions; namely, the carbanion in **213** should remain available in a mobile equilibrium with **36**, as suggested by the regeneration of similar carbenoids through the addition of halide anions[108] to cyclohexylidenecarbene, $(CH_2)_5C{=}C$:, or through the addition of lithium

Scheme 1. Competing Cycloadditions of 4-Substituted Styrenes to Isopropylidenecarbene (36) from Six Different Sources

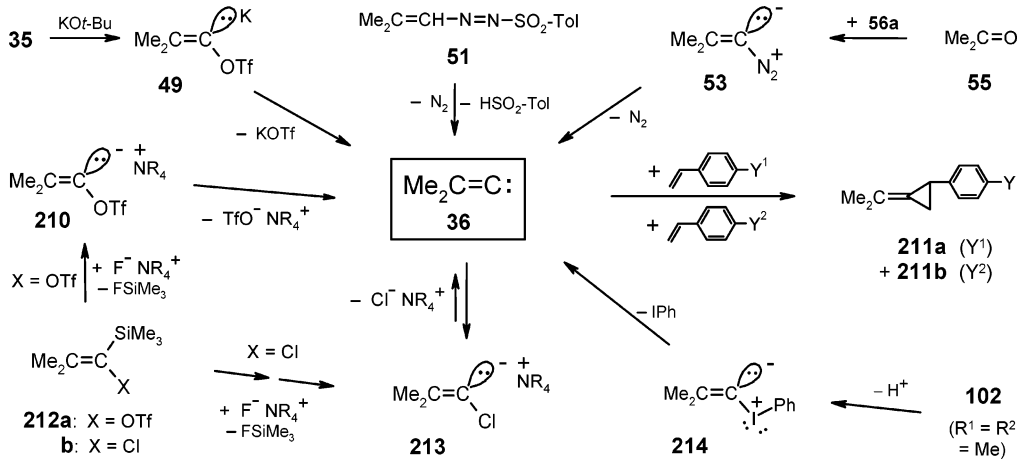
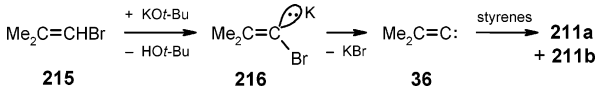


Table 1. Selectivity of Isopropylidenecarbene (Me_2C=C:, 36, from Various Sources) in [1 + 2] Cycloadditions to *para*-Substituted Styrenes As Quantified by the Hammett ρ Values

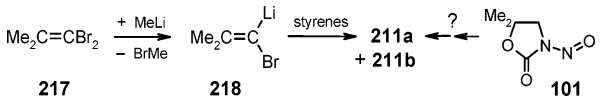
entry	source	base	temp. °C	time	solvent	ρ value	ref no.
1	Me_2C=CH−OTf (**35**)	KO*t*-Bu	−20	22 h	styrenes[a]	−0.75(4)[b]	59
2	Me_2C=CH−N_2−SO_2−Tol (**51**)	none	0	24 h	styrenes	−0.71(2)[b]	60
3	Me_2C=O + **56a**	KO*t*-Bu	−20	?	benzene[a]	−0.43[b]	205
4	Me_2C=O + **56a**	KO*t*-Bu	−20	?	CH_3CN	−0.83[b]	205
5	Me_2C=CH−I−Ph$^+$ (**102**)	KO*t*-Bu	+3	4 h	CH_2Cl_2	−0.55[b]	206
6	Me_2C=CH−I−Ph$^+$ (**102**)	NEt_3	+3	15 min	CH_2Cl_2	−0.56[b]	206
7	Me_2C=CH(OTf)−$SiMe_3$ (**212a**)	$Me_3NBn^+F^-$	0	24 h	$(MeOCH_2)_2$	−0.44(7)[b]	60
8	Me_2C=CHCl−$SiMe_3$ (**212b**)	$Me_4N^+F^-$	+25	?	$(MeOC_2H_4)_2O$	−0.41[b]	207
9	Me_2C=CH−Br (**215**)	KO*t*-Bu	−10	?	styrenes	*c*, *d*	209
10	Me_2C=CBr_2 (**217**)	MeLi	−40	?	Et_2O	−4.3[c]	209
11	*N*-nitrosamide **101**	$LiOC_2H_4OEt$	+40	?	styrenes	−3.4[c]	104

[a] With or without 1.1 equiv of 18-crown-6 hexaether. [b] Using the Hammett substituent parameters $\sigma(p)$. [c] Using the Hammett substituent parameters $\sigma^+(p)$. [d] See text.

chloride (section 3.4.1)[208] to the related (4-methylcyclohexenylidene)carbene, $MeCH(CH_2CH_2)_2C$=C: (**9**).



In view of the [1 + 2] cycloadditions to 2-adamantylidenecarbene (**206**), as generated from 2-(bromomethylene)adamantane (**204**) with KO*t*-Bu (section 2.5), the large ρ value −4.3 reported[209] for the related 1-bromo-2-methylpropene (Me_2C=CH−Br, **215**) with KO*t*-Bu may appear strange because it is incompatible with carbene Me_2C=C: (**9**); but sources such as **215** are known[198] for their unpredictable behavior. Indeed, a redetermination[210a] under the original conditions (entry 9 of Table 1) led to revision of ρ to a value similar to that in entry 1, permitting the repatriation of **215** → **216** into the family of sources for [1 + 2] cycloaddition via the free carbene **36**. However, such evidence for free carbenes does not extend to the FBW rearrangements **1** → **6** sketched in the Introduction, and in section 3.4.2 more reactions will be presented that are clearly performed by Br,K-alkylidenecarbenoids rather than by the corresponding carbenes.



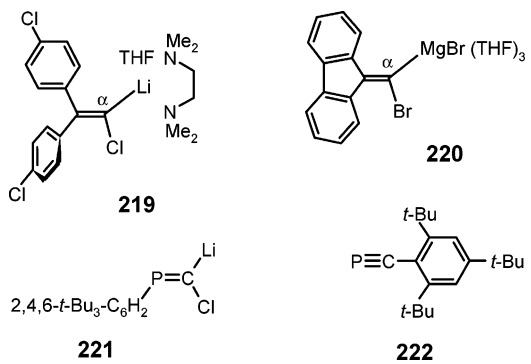
The Br/Li exchange reaction of the α,α-dibromide Me_2C=CBr_2 (**217**) with methyllithium under the conditions of entry 10 in Table 1 must lead to the Br,Li-alkylidenecarbenoid **218**. Using **217**, the competitive [1 + 2] cycloadditions to give **211a** and **211b** were also characterized[209] by the Hammett factor ρ = −4.3, which excludes **36** and suggests **218** as the liable intermediate; but the rather large magnitude of this ρ has been challenged[59] as being "extremely unusual" because it would announce an unexpectedly high electrophilic nature of the intermediate. Similar reasoning could apply to ρ = −3.4 (entry 11) reported[104] for the intermediate from the *N*-nitrosocarbaminate **101** at +40 °C and considered[210b] to represent "a mystery"; it may be recalled from section 2.3.3 that **101** had already presented an unsolved discrepancy for the relative rate of [1 + 2] cycloaddition to styrene. In view of the Cl,K-alkylidenecarbenoids R^1R^2C=CKCl (**203**) being convicted of insertion (rather than carbene formation) in section 2.5, it is regrettable that a ρ value was not determined for 1-chloro-2-methylpropene (Me_2C=CH−Cl) although its α-deprotonation by KO*t*-Bu was known[211] to render [1 + 2] cycloadditions possible.

To summarize, it appears rather safe to consider the [1 + 2] cycloadditions to olefins as proceeding via alkylidenecarbenes such as **36** when generated from the source types depicted in Scheme 1 (and in entries 1−9 of Table 1), even if a TfO,K-carbenoid (**49** in Scheme 1) or related species (**210**, **213**) or an ylide (**53** and **214** in Scheme 1) has to be passed through as a preceding intermediate. In retrospect, this should lend increased credibility also to the role of 2-butylidenecarbene (**43**, from (*E*)- and (*Z*)-**41**) and 2-adamantylidenecarbene (**206**) as the intermediates responsible for the [1 + 2] cycloadditions. For intramolecular insertion reactions, a borderline may be operative within β,β-dialkyl-α-halogenovinylpotassium compounds: a **Cl**,K-alkylidenecarbenoid R^1R^2C=CKCl (**203**) preferred direct 1,5-CH insertions, whereas **Br**,K-alkylidenecarbenoids R^1R^2C=CKBr (**197**) appeared to eliminate KBr, reserving the 1,5-CH insertions for their carbenes.

3. Alkylidenecarbenoids

3.1. Structures and Calculations

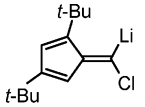
The existence of Cl,Li-alkylidenecarbenoids as metastable compounds in solution with finite lifetimes at very low temperatures was proven by Köbrich[5] through chemical trapping and later by Seebach[212] through ^{13}C NMR spectroscopy. Subsequently, Boche and collaborators[213] provided a "di-



rect" view on a crystallized β,β-diaryl-α-chlorovinyllithium (**219**) whose bond angles at C-α deviate impressively from the sp^2 value 120°: C−C−Cl = 112.6°, C−C−Li = 137.1°, and Cl−C−Li = 108.7°. Crystals of the more stable (up to −30 °C)[214] Br,Mg-fluorenylidenecarbenoid **220** exhibited comparable distortions (CCBr = 116°; CCMg = 147°) that were believed to anticipate bond changes on the way to carbene products.

The phospha analogue **221** did not show these distortions in the crystal[215] and was (perhaps therefore) stable as a monomeric (*Z*)-isomer in THF solution[215−217] up to −50 °C, whereas its (*E*)-isomer under these conditions had very quickly been transformed to the FBW product **222**. This proves that a (*Z*)- to (*E*)-isomerization of **221** did not take place below −50 °C.

According to their ^{13}C NMR spectra, the Cl,Li-cyclopentadienylidenecarbenoid[218] **223** was stable at −70 °C and the F,Li-(9-fluorenylidene)carbenoid[219,220] **224** (R−R = 2,2′-biphenyldiyl) at −40 °C, whereas **224** with R = alkyl was reported[219] to be too unstable for measurement even at −120 °C. The criterion of ^{13}C,Li NMR coupling constants, developed[212] by means of the Br,Li-cyclohexylidenecarbenoid (**225**), was considered as indicating that **221** and **223**−**225** are all monomeric in THF solution.



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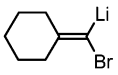

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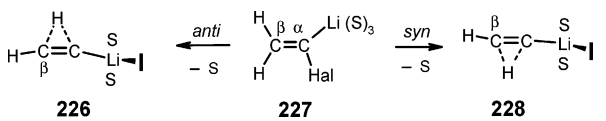
Quantum chemical calculations on α-fluoro-,[13,221] α-chloro-,[13,222,223] and α-iodovinyllithium[224] (**227**) reproduced the geometrical features of **219** when solvation (S) and electron-correlation were included,[222] and they revealed a tendency for shifting the halogen from C-α toward bonding at lithium. According to higher-level calculations[224] on solvated monomeric α-iodovinyllithium (**227**, Hal = I), the separation of solvated LiI from the free methylidenecarbene (H_2C=C:) requires only 12.5 kcal/mol (via an energy barrier of 16.0 kcal/mol), and an additional 2.3 kcal/mol is sufficient to leap through the transition state for "FBW" rearrangement to acetylene. The considerably larger separation energy for LiF and the conclusion that "H_2C=CLiF cannot decompose into the free carbene under mild conditions" need not be the last word in view of the low-level method of calculation[221] and because it refers to the gas phase. In calculations[224] of solvated transition state models with concerted FBW migration of a β-hydrogen atom, the barrier for anti migration (**226**) was found to be only 0.7 kcal/mol smaller than that for syn migration (**228** with 14.0 kcal/mol), corresponding to a 3:1 rate ratio at room temperature. Judging from the tabulated[224] parameters, the C-β atoms in **226** and **228** have become nearly sp-hybridized, but it is not completely clear in which ways the electronic structures of these carbenoid transition states differ from that of the late transition state model **13** for R^1R^2C=C: and how LiI interacts with the C_2H_2 part in **226** and **228**.

With all of these possibilities in mind, we shall now try to discover which properties of the intermediates in question are different from those of the alkylidenecarbenes described in section 2. With a proper attitude exempt from all prejudices, we should acknowledge, taught by the above example[224] of β-hydrogen migration in the carbenoid H_2C=CLiI, first that an FBW rearrangement via a free carbene such as H_2C=C: (transition state +14.8 kcal/mol above the ground state of H_2C=CLiI) may be hardly more expensive than one via the direct anti migration within a carbenoid, and second that the syn migration may be almost as easy as the celebrated anti mode.

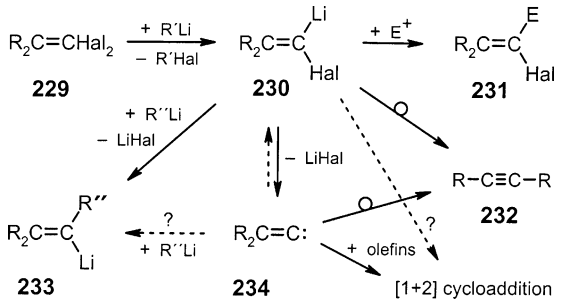


226 **227** **228**

3.2. Alkylidenecarbenoids from 1,1-Dihalogenoalkenes

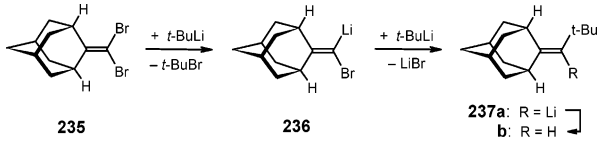
The halogen/lithium exchange reaction, normally confined to Br and I, proceeds so fast with geminal dihalides such as R_2C=$CHal_2$ (**229**) that even 1,1-dichloroalkenes react easily[56,225,226] at low temperatures, perhaps because the favorable thermodynamic qualities of the resulting carbenoids R_2C=CLiHal (**230**) imply some kinetic advantage. As an organolithium compound, **230** could be captured by electrophiles E^+ (H^+, CO_2,[227−229] $ClSiMe_3$,[207,230−232] benzylhalides,[230,233] iminium chlorides,[234] alkyl iodides,[233] and others) at low temperatures where its lifetime sufficed to produce R_2C=CHal−E (**231**); even hydrogen migration in H_2C=CLiCl was sufficiently slow[229] in ethereal solvents at −110 °C. THF solutions of Br,Li-isopropylidenecarbenoid (Me_2C=CLiBr, **218**), prepared from the dibromide Me_2C=CBr_2 (**217**) below −100 °C, reacted stereoselectively[235] with chiral aldehydes, and their carboxylation[227] furnished α-bromo-β,β-dimethylacrylic acid (Me_2C=CBr−CO_2H) in 94% yield after 3 h at −110 °C or 46% after 2 h at −90 °C, while tetramethylbutatriene (Me_2C=C=C=CMe_2, see **245a**) was isolated[236] after the reaction mixture was allowed to warm to −60 °C. A second factor of paramount importance for the stability of R_2C=CLiHal (**230**) is the donor quality of the solvent: only 6% of the above acid was obtained[227] from Me_2C=CLiBr (**218**) in diethyl ether by carboxylation after 3 h at −110 °C. In THF solution, decomposition with FBW migration of aryl groups R producing alkynes **232** could be avoided at −110 °C for R = 4-methoxyphenyl[227] (Hal = Br in **230**) and at −77 °C for R = phenyl[228,237] (Hal = Cl in **230**). Diethyl ether as a solvent was again detrimental for this purpose because it accelerated the FBW rearrangement of **230** with R = phenyl.[228,237] Vice versa, this solvent dependence may be helpful when an FBW rearrangement is intended but slower than decomposition by proton transfer in ethereal media. Nonpolar solvents can be used instead because the initiating Br/Li exchange reaction to give a carbenoid is sufficiently fast in such media; but this technique was rarely applied. For example, when (R'−C≡C)$_2$C=CBr_2 was reacted with *n*-butyllithium in hexane solution (instead of Et_2O or dioxane or THF), alkynyl migration

took place in $(R'-C\equiv C)_2C=CLiBr$ and afforded triynes[238] (**232**, R = R′—C≡C−) at below −10 °C, and it was also successful with less symmetrical[239] substrates. In the latter cases it is conceivable (though not established) that R′—C≡C ($\sigma_I = 0.30$)[27,168] migrated whereas aryl ($\sigma_I \approx 0.15$)[168] preferred to act as the stationary β-substituent.

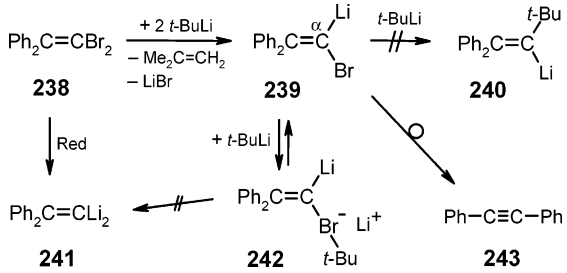


[1 + 2] cycloadditions are carried out conveniently when **230** is generated in the presence of excess olefins or enol ethers. A cheap and simple method was found[240] in the reduction of (dibromomethylene)-cyclohexane and -cyclopentane with metallic lithium or magnesium, but equally simple competition experiments were not reported which might perhaps have provided some hint as to whether the carbenoid **230** or else the ensuing carbene **234** was the species responsible for the cycloadditions. The same question had been left open in section 2.6 for [1 + 2] cycloadditions of the carbenoid $Me_2C=CLiBr$ (**218**) as prepared[209] from $Me_2C=CBr_2$ (**217**).

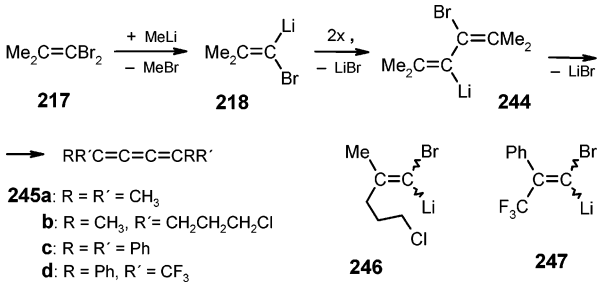
After treatment[209,241] of **217** in olefinic solvents with methyllithium in diethyl ether, 2-bromo-3-methyl-2-butene ($Me_2C=CBr-Me$) was frequently isolated[241] as a side product, which was explained in terms of electrophilic methylation of $Me_2C=CLiBr$ (**218**) by R′Hal = CH_3Br, which is the byproduct formed in the initial Br/Li exchange reaction. Later observations[237,242] of butylated side products were apparently interpreted along similar lines, but such alkylations would not always be possible within the short lifetime of carbenoids **230** under the reaction conditions. With knowledge[13] presently available, which will be detailed in section 3.4.3, these side products can also be understood to arise from the *nucleophilic* substitution at **230** by R″Li (≡ R′Li in these cases) to give **233** and its further derivatives (the configurational problems will be treated later in section 3.4.3). This sequence of an initiating Hal/Li exchange reaction (**229** → **230**) followed by Hal/R″ substitution (observed when R = alkyl in **230** → **233**) was proven[243] by the sequential application of first R′Li = *t*-BuLi and then R″Li = ethyllithium and also by earlier examples to be mentioned later in section 3.4.3. It should likewise apply to the preparation of 2-(neopentylidene)adamantane[244] (60% of **237b**) from 2-(dibromomethylene)adamantane (**235**) in pentane with excess R′Li = R″Li = *t*-BuLi via carbenoid **236** rather than via the postulated[244] reverse sequence of substitution and Br/Li exchange. Such substitutions must be rather fast because the time scale is limited by the lifetime of **230** and also by the racemization possible in optically active Hal,Li-(4-methylcyclohexylidene)carbenoids, $MeCH(CH_2CH_2)_2C=C$-LiHal; but they are normally slower than the initiating Hal/Li exchange reaction, as demonstrated by the many examples of successful preparations of **230** from **229** with the equivalent amount of R′Li.



The Hal,Li-alkylidenecarbenoid substitution reaction may be sensitive to steric shielding in the C=C double-bond plane: α-Bromo-β,β-diphenylvinyllithium (**239**) is available by the usual treatment of the dibromide **238** with 2 equiv of *tert*-butyllithium in THF at −70 °C, but it is not substituted (to give **240**) by 2 further equiv of *t*-BuLi (that had been added in search[245] of the dilithio derivative **241**). Instead, **239** was believed[245] to become arrested at the usual (but here inactive) "ate complex" **242** of the Br/Li exchange mechanism. Return to **239** with ensuing FBW rearrangement at −70 °C would explain the observed production of diphenylacetylene (**243**). Substitution at the carbenoid **239** was discovered[245] with the more reactive dilithio compound **241**, which had been independently prepared by reduction of **238**.

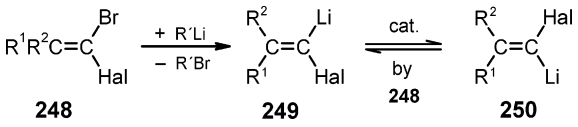


The presumed steric shielding by two β-aryl substituents became profitable when *n*-butyllithium in excess was applied to macrocyclic β,β-diaryl-α,α-dihalogenoethenes: The macrocyclic alkylidenecarbenoids $Ar_2C=CLiHal$ corresponding to **239** were generated but were not substituted by the excess of *n*-BuLi; they rather performed the desired[246−248] ring expansions by FBW rearrangement, if topologically possible, to produce macrocyclic diaryl alkynes.



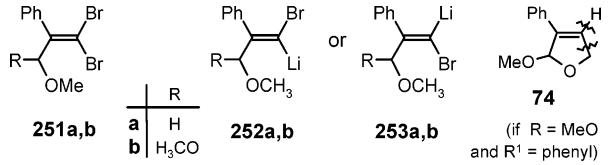
The finite lifetime of $R_2C=CLiHal$ (**230**) allows a "dimerization" reaction that is normally not available to the transient alkylidenecarbenes $R_2C=C:$ (**234**): when present in sufficiently high concentrations, $R_2C=CLiHal$ (**230**) may play the part of R″Li in the formation of $R_2C=CLi-R''$ (**233**). (The additionally conceivable reaction $R_2C=C:$ (**234**) → $R_2C=CLi-R''$

(**233**) with a nonracemic carbenoid $R_2C{=}CLiHal$ (**230**) as R″Li will be discussed in section 3.4.3.) A good example already mentioned above is provided by α-bromo-*β*,*β*-dimethylvinyllithium ($Me_2C{=}CLiBr$, **218**), which is not endangered by rearrangements (FBW or insertion) but decomposed[236] at −60 °C in THF to afford 50% of 2,5-dimethyl-2,3,4-hexatriene ($Me_2C{=}C{=}C{=}CMe_2$, **245a**). The related carbenoid **246**, prepared[232] from the parent α,α-dibromoalkene in THF with 1 equiv of *n*-BuLi and TMEDA[249] at −110 °C, decomposed exothermically already above −90 °C to afford the butatrienes **245b** (∼60% of an (*E*,*Z*) mixture). Possibly caused by TMEDA, neither 1,5-CH insertion nor intramolecular S_N2 alkylation could compete here with the "dimerization" to **245b**, for cyclopentenes were not detected. A corresponding butatriene derivative was prepared[250] from 2-(dibromomethylene)adamantane (**235**) with 1 equiv of *n*-butyllithium in THF; but only a tiny amount of butatriene **245c** was isolated[228] after decomposition at −77 °C of the carbenoid $Ph_2C{=}CClLi$ (from $Ph_2C{=}CClBr$ with *n*-butyllithium) in diethyl ether because of its much faster FBW rearrangement. The latter was avoided for $Ph_2C{=}CBrLi$ (**239**) in THF at −90 °C by use of certain Cu(I) catalysts[251] or other reagents[252,253] furnishing aryl-substituted butatrienes. In striking contrast, the carbenoid α-bromo-*β*-phenyl-*β*-trifluoromethylvinyllithium (**247**) did not exhibit any proclivity to FBW rearrangement in diethyl ether but afforded only[254] the butatriene **245d**. Thus, trifluoromethyl as an electron-withdrawing stationary *β*-substituent ($\sigma_I = 0.40$)[27,168] obviously prevented the expected phenyl migration, supposedly[255] due to the electronic destabilization of the transition state. The steps leading to a butatriene are so slow in the case of the Cl,Cu(I)-alkylidenecarbenoid corresponding to **247** that some intermediates were observable[255] by NMR spectroscopy, especially one comparable to **244** which eventually converted to **245d**.



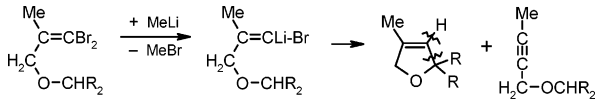
248 **249** **250**

Two differing *β*-substituents R^1 and R^2 in **248** evoke the synthetically important feature of (*E*,*Z*)-stereoisomerism in the alkylidenecarbenoids **249**/**250**. Residual starting material **248** (if Hal = Br) can accelerate the approach to equilibrium by means of its very fast Br/Li exchange reaction with **249** or **250**. This "catalysis" was exploited for highly stereoselective syntheses with **248** (Hal = Br, R^1 = alkoxymethyl) by changing from kinetic ((*E*)/(*Z*) roughly 1:1) to thermodynamic control of the **249**/**250** ratio without FBW migrations of R^2 = phenyl in THF[256] at −94 °C or of R^2 = H in diethyl ether[257,258] below −104 °C. Other examples exhibited similarly poor kinetic (*E*)/(*Z*) stereoselectivity in THF,[259] but the migration of R^2 = H at −105 °C could not always be avoided. If the pure (*E*) or (*Z*) stereoisomers of **248** (Hal = Cl) are available, one can rely on retention[260] of the configuration in **249** (Hal = Cl) when generated by Br/Li exchange.



251a,b **252a,b** **253a,b** **74** (if R = MeO and R^1 = phenyl)

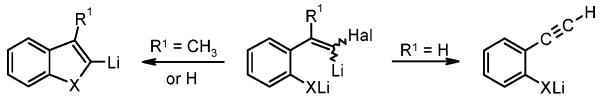
In the absence of residual starting material **251a**, the (*E*)- (**252a**) and (*Z*)-carbenoids (**253a**) in THF at −94 °C are configurationally stable[256] in a 73:27 ratio, far from their equilibrium composition (*E*)/(*Z*) = 10:90. Although such analyses of the (*E*)/(*Z*) ratios of an alkylidenecarbenoid before and during its reactions can be very simple, for example, by quenching with methanol, this valuable piece of evidence has been rarely collected. Thus, the carbenoid (**252b** or **253b**) generated from acetal **251b** had been mentioned in section 2.3.1 for its refusal to admit the expected FBW migration of phenyl, as was shown by isolation[97] of the 2,5-dihydrofuran **74** (if R = MeO and R^1 = phenyl) as the sole product. An observation of a predominant (*Z*) configuration **253b** under reaction conditions would have excluded the possibility that phenyl migration could be blocked by LiO chelation that might in the (*E*)-isomer **252b** increase the electron-withdrawing (hence decelerating) power of the acetal moiety. It may be recalled that the corresponding alkylidene*carbene* **73** (R = OMe; R^1 = phenyl) had exhibited the same trait[97] of suppressed phenyl migration and had led to the assumption of an undetermined effect favoring 1,5-CH insertion into the CHR−O**CH**$_3$ moiety. This property should be preserved in the following examples.



254 **255** **256** **257**

The Br,Li-alkylidenecarbenoid **255** generated from reaction of **254** with 2 equiv of methyllithium in diethyl ether at room temperature for 1−3 min was reported[261] to furnish the products of 1,5-CH insertion (**256**) and FBW rearrangement (**257**) in the ratio 1:1.8 for R = H but 5.4:1.8 for R = methyl. The facile (putative) migration of $-CH_2O-CHR_2$ in this alkylidene*carbenoid* (**255**) is surprising in view of only traces of alkynes obtained[98] from the corresponding (but diazo-derived) alkylidene*carbene* ($R'RCH-O-CH_2)_2C{=}C$: (**78**) and also by comparison with the almost immovable *β*-substituent −CHR−OH (**88** in section 2.3.2). Carbenoid substitution by the applied excess of methyllithium (=R″Li in **230** → **233**) was not observed,[261] which might indicate that both **256** and **257** were produced in accelerated processes. The related substrate $ArCH_2O-CHR-CH{=}CBr_2$ with *n*-BuLi (2 equiv) in THF[262] produced predominantly the alkyne $ArCH_2O-CHR-C{\equiv}CH$, but this conversion may have involved the 1,2-elimination of HBr rather than a *β*-hydrogen migration. This increased trend toward the FBW reaction channel, tentatively ascribed to the alkylidenecarbenoid **255**, parallels that observed for a Br,K-carbenoid Alk−C(Me)=CKBr (**197** in section 2.5) and hence may support carbenoid rather than carbene involvement. With the

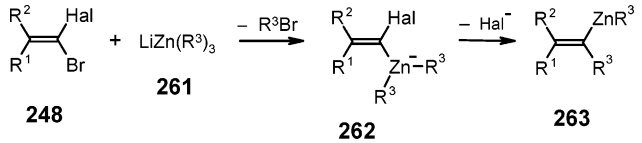
reasonable assumption that the competing FBW process (**255** → **257**) may be used for reference because it should be equally fast for R = H or CH_3 in the stationary β-substituent $-CH_2O-\mathbf{CH}R_2$, the rate ratio 5.4:1 (derived from the numbers reported[261] above) for insertion into tertiary versus primary C—H bonds may be considered to characterize the Br,**Li**-carbenoid **255**. This rate quotient is far off (albeit not directly comparable with) the ratio 240:1 noted earlier for insertion within the alkylidene*carbenes* $R'R\mathbf{CH}-CH_2CH_2-C(R^1)=C:$ (**61** in section 2.3.1 and **200** in section 2.5). Summing up, the increased formation of FBW product (**257**) and perhaps the diminished selectivity provide evidence not directly for carbenoid **255** but definitely against its alkylidenecarbene as the *only* responsible intermediate.



258 **259** **260**

A direct demonstration of an in-plane vinylic nucleophilic sustitution at a carbenoid center was provided[263] by the intramolecular example **259** (X = O; Hal = Br or Cl) that afforded only **258** when R^1 = methyl. Hence, this nucleophilic attack was sufficiently fast in THF at −100 °C (for 5 h) to prevent any FBW migration of aryl. With R^1 = H in **259** (X = O or NH), the products of cyclization (**258**) and (perhaps) hydrogen migration (**260**) were isolated in nearly equal amounts; but reliable interpretations are not possible because the (*E*) and (*Z*) proportions of **259** and their time dependence are not known and because R^1 = D was not studied.

Among the few other organometallic compounds that are able to carry out the Br/metal exchange, the lithio zinc-ates **261** are particularly useful and remarkable for their easy reaction with **248** (Hal = Cl or Br) in THF at −85 °C. The resulting Hal,ZnR_2-alkylidenecarbenoids **262** are configurationally stable[256,264] and are not inclined to FBW rearrangements, even with R^2 = H, in contrast to some Cl,*ZnBr*-alkylidenecarbenoids (**392**) described further below at the end of section 3.4.2. Mixtures of (*E*)- and (*Z*)-**262** were obtained when Hal = Br in **248**, usually with a preference[260,264] for exchange of the sterically more oppressed bromine atom. This kinetic preference for the (*E*)-isomers could be increased by use of the magnesio analogues $ClMgZn(R^3)_3$ of **261**, which, however, tended (like lithium cuprates) to admit the (putative) FBW migration of hydrogen[264] at −85 °C.



248 **261** **262** **263**

Alkenylzinc compounds **263** were formed upon warming **262** to 0 °C with normally clean inversion of the configuration in a type of intramolecular vinylic substitution that resembles many analogous processes[265] with other metal(oid)s, such as boron, aluminum, zirconium,[266] and so forth, in place of zinc. However, with one or more R^3 = *tert*-butyl groups in the zinc-ate **261**, the Br/Zn exchange reaction at **248** may be accompanied by the migration (or β-elimination?) of R^2 = H, and the substitution process (**262** → **263**) may become non-stereospecific. The final demetalation of **263** by protons or by CC coupling reactions (with Pd catalysis if necessary[264]) completes an obviously useful olefin synthesis.

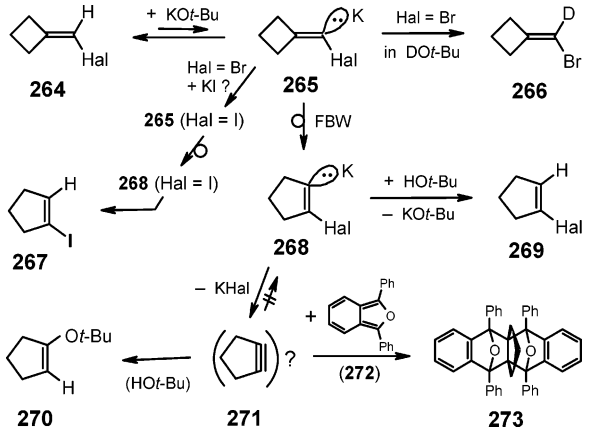
The corresponding metalation of 1,1-dibromo- or 1,1-dichloroalkenes by samarium(II) iodide was believed to proceed via a radical mechanism, generating Hal,SmI_2-alkylidenecarbenoids that decayed at room temperature by rapid FBW migrations[267] of β-hydrogen or β-aryl groups but otherwise chose[268] the usual 1,5-CH insertion, along with reductive dehalogenation.

3.3. Cycloalkynes by FBW Rearrangements

Ring expansion is the necessary consequence when a cycloalkylidenecarbenoid (or -carbene) undergoes the FBW rearrangement. Cyclononyne and its isomers were obtained[269] by treatment of (bromomethylene)cyclooctane with KO*t*-Bu at +240 °C, while cyclobutylidenecarbenoids such as **265** seem to generate unexpected intermediates whose detailed investigation will be an important aspect of this section.

3.3.1. Ring Expansion of Cyclobutylidenecarbenoids: Caught in the Act of FBW Rearrangement?

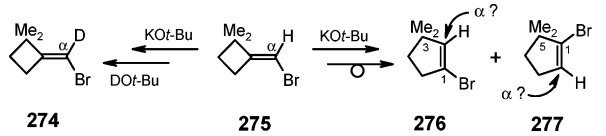
(Halogenomethylene)cyclobutanes **264** (Hal = Cl, Br, I) could be isomerized to give 1-halogenocyclopentenes (**269**) by treatment[270] with KO*t*-Bu in boiling toluene. The authors[270] indicated that the bases *n*-butyllithium and sodium amide could also be used successfully, but details or mechanistically informative tests were not published for these reagents. The cyclobutylidenecarbenoid **265** (Hal = Br) was easily identified[270] as the first intermediate in boiling DO*t*-Bu by the slow deuteration (**266**) of the starting material, as similarly observed for **1** in the Introduction. The angular strain in **265** is released by the FBW ring expansion to give the more basic 2-halogenoalkenylpotassium derivative **268**, that is quickly protonated by the small quantity of HO*t*-Bu (formed in the first step) to give the main product **269**. When the deprotonation was carried out[271] in the presence of potassium iodide in *N*,*N*-dimethylformamide at +80 °C, up to 55% of 1-iodocyclopentene (**267**) was



264 **265** **266** **267** **268** **269** **270** **271** **273**

produced, perhaps via I/Br exchange at the Br,K-carbenoid **265** followed by ring expansion to **268** (Hal = I) and hence to **267**. The reaction rate was moderately solvent-dependent,[272] increasing in the sequence HO*t*-Bu (80 °C) < DMSO (100 °C) < THF (65 °C) ≪ toluene (5 min at 100 °C), and in toluene the reaction could be carried out at +25 °C.

The mechanistic formulation **264** → **265** → **268** → **271** postulates that 2-halogenocyclopentenylpotassium (**268**) be the precursor of cyclopentyne (**271**), which is the alkyne expected as the FBW product. This proposition might be supported by finding increased yields of the products derived from **271** in the absence of HO*t*-Bu, the trapping agent for **268**. As of this writing, suitable organopotassium compounds (such as $KCPh_3$ in THF instead of KO*t*-Bu)[273] have not been applied in this system to perform the test; hence, it is only possible to recognize in the following way that **268** is not a successor of the conjectured cyclopentyne (**271**). Because of the transient nature of cyclopentyne, its detection has to rely on selective trapping by agents that react faster than the otherwise observed processes. As an example of the latter, the enol ether **270** observed as the minor product should derive from an intermediate having the symmetry of **271**, as shown by the equal degree of ^{13}C-labeling of the two olefinic carbon atoms in two isotopomeric 1-butoxycyclopentenes[274,275] related to **270** (depicted later in **290a**,**b**). The trapping quinodimethane reagent 1,3-diphenylisobenzofuran (**272**) reacted more readily with the *same* intermediate by [2 + 4] cycloaddition, as shown by formation of 12% of the bis(adduct)[270,276] **273** at the expense of the enol ether **270**, whose yield dropped to zero. However, the formation of 1-bromocyclopentene (**269**) was not impaired[270] by this trapping, proving that its predecessor **268** was not generated from the intermediate in question (**271**) and did not react quickly with **272**. Although the cyclopentyne story will be shown in the next section to contain more intricate problems, it appears justified to proclaim 2-halogenocyclopentenylpotassium (**268**) as the *FBW primary intermediate* that can either generate cyclopentyne (**271**) or become captured by proton transfer. The irreversible[275] 1,2-syn elimination of KBr from **268** was obviously a little slower than protonation, but it may reasonably be expected to occur faster in related *unstrained* (open-chain or macrocyclic) species.



274 **275** **276** **277**

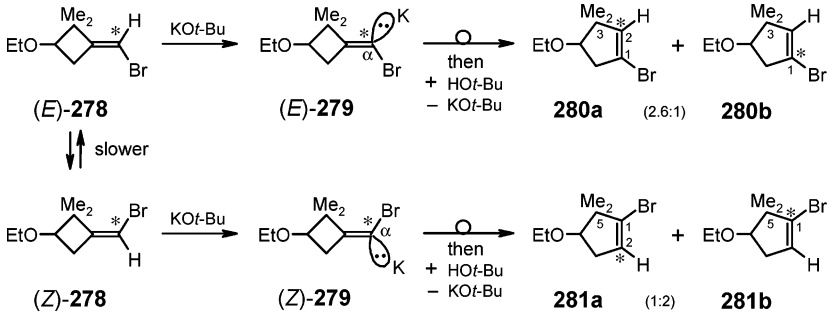
Complementary studies of (bromomethylene)-2,2-dimethylcyclobutanes such as **275** revealed surprising features. The configuration of **275** was reported[277] to be conserved (as expected) during the fast α-deuteration to give **274** by KO*t*-Bu in DO*t*-Bu at ambient temperature. But FBW rearrangement of the pure (*E*)-isomer **275** induced by dry KO*t*-Bu (5 min at +100 °C, no solvent) furnished 1-bromo-3,3-dimethylcyclopentene (**276**) together with only a trace of the 5,5-dimethyl isomer **277** that was ascribed[277] to the accompanying slow (*E*) → (*Z*) mutation of the starting material. If so, the ring expansion would be surprisingly stereoselective and — assuming that the bromine atom has to undergo a 1,2-shift, as is known for the Beckmann rearrangement[3] — it would occur (viewed superficially) as a pure anti migration of the Me_2C group. Starting with **275** labeled at C-α, **276** should then be labeled at C-2 ("α"). However, this simple and familiar scheme ignores concealed traits of the FBW process that were disclosed in the following way.

The usual treatment of the ^{13}C-labeled (*) alkenyl bromide (*E*)-**278** (Scheme 2) with KO*t*-Bu in pentane (3 h at +36 °C)[275] furnished 1-bromo-4-ethoxy-3,3-dimethylcyclopentene (**280**), as expected by analogy with **275** → **276** above, again along with some 5,5-dimethyl isomer **281**, owing to the (verified and controlled)[275] slow (*E*)- to (*Z*)-isomerization of the source **278**. The label distribution 2.6:1 in **280a**/**b** proved the predominant [1,2]-migration of the Me_2C group (anti to Br), accompanied by a formal 1,2-shift of the bromide along the double bond, leading to **280a**. This formally "dyotropic" process[278] was dubbed the "Beckmann mechanism" by the authors[275] and later[279] called "double migration", but its detailed course is uncertain. It appears to resemble the corresponding carbene rearrangement depicted in the transition state model **13** inasmuch as development of a certain degree of contact-ion-pair character[278] by partial C—Br heterolysis in (*E*)-**279** would provide for an emptying atom orbital at C-α (*) into which the bond electron pair of the migrating carbon atom can be delivered. But the minor isotopomer **280b** must derive from the unforeseen migration of the CH_2 group (syn to Br) *without a net breaking* of the Br—Cα bond; this view relies on the evidence described above that a cyclopentyne intermediate such as **271** should not be the precursor of 1-halogenocyclopentene derivatives (**268** → **269**) and hence of the products **280a**,**b**. The authors[275] suggested a "rehybridization mechanism", but the role of the metal cation was left open. Because the potassium cation has to travel from C-α in (*E*)-**279** to C-2 of the cyclopentene precursor of **280b** (with K in place of 2-H), this CH_2 syn shift might have been facilitated by participation of empty p-orbitals[278,280,281] at the metal cation. However, this variant may be energetically too expensive[138—140] when it involves the in-plane inversion of an α-bromovinyl anion. Thus, the detailed mechanisms of both syn and anti migrations are open problems.

The same two processes appear to take place in the carbenoid (*Z*)-**279** that preferred syn migration of the Me_2C group, with apparent conservation of the C—Br bond (affording **281b**), over anti migration of CH_2 (**281a**) by a factor 2. Although some of these factors changed with increasing temperature (10 min for reaction at +100 °C)[275] in a not easily understandable manner, it is evident that these FBW rearrangements can occur with comparable rates, contrary to the commonly held prejudice claiming a generally preferred anti migration.

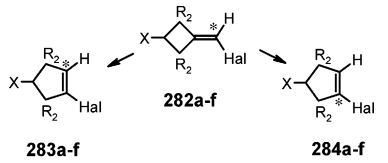
As a unique chance of studying the final phase (and perhaps the primary products) of the FBW process,

Scheme 2. Carbenoids (*E*)-279 and (*Z*)-279 Were Caught after Their Ring Expansions in the Act of Anti (a) and Syn (b) FBW Rearrangements



this rewarding research object deserves further attention and elaboration in order to render the interpretations still more convincing. Its instructive quality depends on the fact that 2-bromocyclopentenylpotassium (**268**) and derivatives thereof can be trapped by the byproduct HO*t*-Bu, thus avoiding the loss of information connected with bonding to KBr. A weak point can be seen in the stereochemical lability of the starting material that thwarted a more precise proof of complete stereodivergence. This proof would be essential because finding some proportion of equal product mixtures obtained from either stereoisomer (such as (*E*)- or (*Z*)-**278**) would delimit that portion of the process that involves the free alkylidenecarbene (obviously much less than 100% here), provided that (*E*)/(*Z*) interconversion of the sources can be ruled out. The stronger C−F bond in Cα-labeled analogues of **275** or **278** (F in lieu of Br) might perhaps[279] drive the mechanistic balance to a greater proportion of the syn mode (see the ratio of **283c**/**284c**) with conservation of the C−Hal bond. It is also conceivable that a Hal,**Li**-cyclobutylidenecarbenoid may behave differently after having passed through transition states such as **226** or **228**: Namely, $(CH_2)_3C{=}CLiBr$ (**301**) will be reported in the following section 3.3.2 to convert at best partly to the expected cyclopentene **299**. To investigate the cation dependence of the results displayed in Scheme 2, $LiN(SiMe_3)_2$ might be used as a base instead of KO*t*-Bu, whereupon the primary FBW products formed from the Li analogues of (*E*)- and (*Z*)-**279** will possibly be captured with HMDS in place of HO*t*-Bu.

Given that the primary FBW products were generated as formulated above for (*E*)- and (*Z*)-**278** without scrambling, the [^{13}C-2]-labeled compounds (**280a** or **281a**) indicate anti migration whereas the peculiar syn migration with apparent conservation of the C−Hal bond leads to the [^{13}C-1] isotopomers (**280b** or **281b**). If this holds true also for the achiral (X = H) or the racemic (X ≠ H) examples **282**, then the anti and syn CH_2 groups in **282a** migrated almost equally fast (**283a**/**284a** = 1.2/1) under the conditions[275] described before (+36 °C or +100 °C), while the anti versus syn rate ratio 3.5/1 was found[275] for the Me_2C groups in **282b**. The anti/syn selectivity of **282d**−**f** upon deprotonation by KO*t*-Bu in a hydrocarbon milieu was reported[279] to increase with the temperature, amounting at +180 °C to 1.52 (for **283c**/**284c**), 2.80 (for **283d**/**284d**), 2.84 (for **283e**/**284e**), and 3.88 (for **283f**/**284f**).

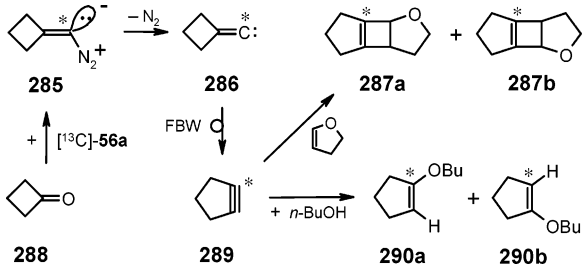


	Hal	R	X
a	Br	H	H
b	Br	Me	H
c	F	H	1-hexyl
d	Cl	H	1-hexyl
e	Br	H	1-Hexyl
f	I	H	1-hexyl

In conclusion, the seemingly straightforward FBW rearrangement has been shown to exhibit a partial but puzzling disobedience to the popular rule of anti migration. Further examples of this trait will be presented in section 3.4 for acyclic substrates where the formally dyotropic course of the two FBW mechanisms can no longer be recognized directly.

3.3.2. Small-Ring Cycloalkynes as Intermediates: Yes or No?

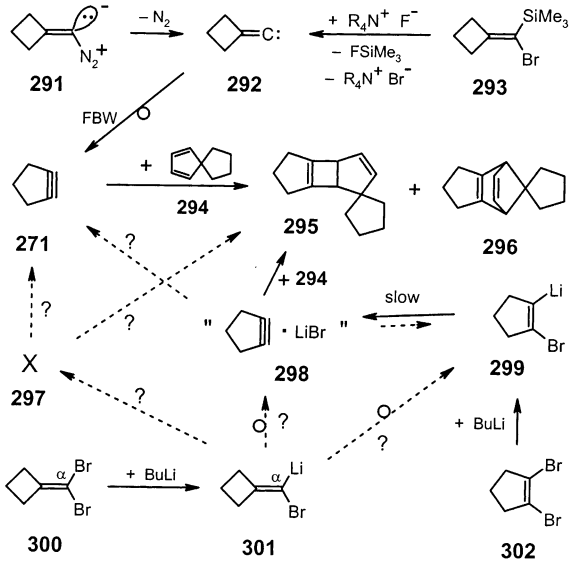
According to quantum chemical calculations,[282] the unencumbered cyclobutylidenecarbene (**286**) is only 8 kcal/mol less stable than its FBW product cyclopentyne (**289**), whose exocyclic (in-plane) π-bond is so highly bent that it may be taken as almost[282] completely broken. Presumably as a consequence, cyclopentyne (or a symmetry-equivalent intermediate) is able to produce cyclobutenes such as **287a**,**b** by stereospecific [2 + 2] cycloadditions to olefins[283,284] or enol ethers[72,283] with configurational retention (thermally forbidden as a concerted process) because it probably reacts first as though it were a 1,2-dicarbene,[50] followed immediately by a 1,2-carbon shift. With regard to its possible relevance for the analysis of FBW rearrangements, this intermediate and its congeners merit a more detailed inspection in this section.



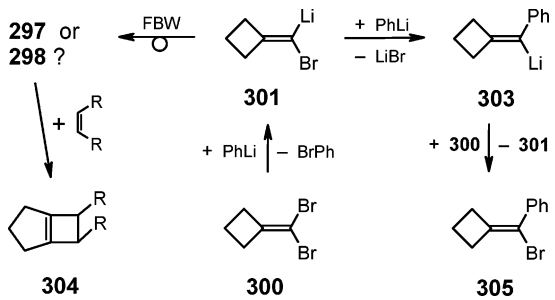
The labeled (*) bona fide cyclobutylidenecarbene **286** was generated[274] via the diazonium ylide **285** from reagent [^{13}C]-**56a** and cyclobutanone (**288**) with KO*t*-Bu at 0 °C. Its "FBW" rearrangement should produce the labeled intermediate in question (**289**), whose symmetry became evident by isolation of 1:1 mixtures of either the formal [2 + 2] cycloadducts **287a**,**b** in the solvent 2,3-dihydrofuran or else the

isotopomeric enol ethers **290a** and **b** in the solvent 1-butanol. Remarkably, the FBW ring expansion was much faster than the conceivable [1 + 2] cycloadditions of **286** to olefins. 3-Azacyclobutylidenecarbenes $RN(CH_2)_2C{=}C$: provided counterexamples: because they could be trapped[285] by [1 + 2] cycloaddition to cyclohexene, the expected FBW migration of an aminomethyl group was obviously impeded (perhaps endothermic[285]).

The same method but with potassium hydride[286] as the base in CH_2Cl_2 was used to generate unlabeled cyclobutylidenecarbene (**292**) via **291** between −40 °C and +25 °C. The spiro[4.4]nona-1,3-diene **294** present in the solution captured solely the ensuing cyclopentyne (**271**) as the [2 + 2] and [4 + 2] cycloadducts **295** and **296** in the ratio 1:1.5, which was independent of the temperature. The same selectivity (1:1.6) was observed[286] for the intermediate generated by desilylation of **293** via carbene **292** in THF/CH_2Cl_2 at −40 °C or +25 °C. These results suggest that both [2 + 2] cycloadditions and formation of enol ethers will proceed via cyclopentyne as the probable reactive intermediate when generated from the sources **291** and **293**.



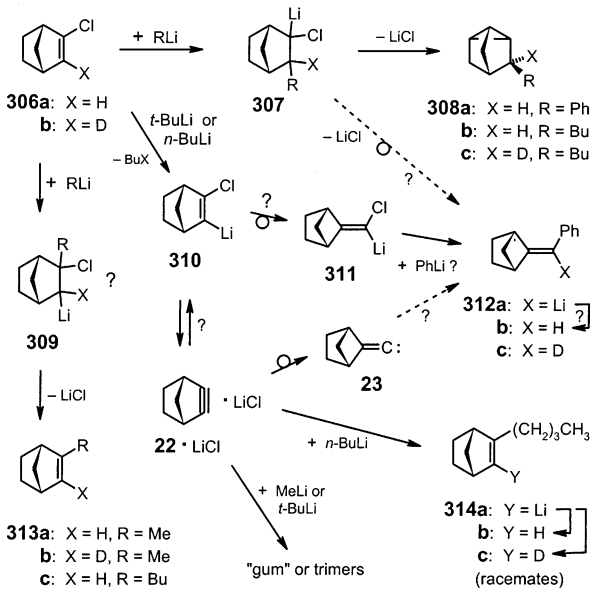
However, the organometallic routes starting with Br/Li exchange reactions of *n*-BuLi at either (dibromomethylene)cyclobutane[283,284] (**300**) or 1,2-dibromocyclopentene[283,286] (**302**) must produce reactive intermediates that differ from **271**: Prepared from **302** in hexane solution, 2-bromocyclopentenyllithium (**299**) was found[73] to decay above 0 °C in slow first-order reactions that were not significantly accelerated in the presence of trapping agents, in total accord with early observations[287−289] on **299** in diethyl ether or in THF. Therefore, **299** does not react directly with a trap such as the spirodiene **294** but must first generate a reactive species (perhaps **298**) that performs the cycloadditions. This species cannot be the poorly selective (1:1.5)[286] free cyclopentyne (**271**) but is believed to be some kind of a LiBr complex (**298**) because it afforded **295** and **296** in product ratios[286] that varied from 36:1 at 0 °C to 21:1 at +60 °C in hexane. A much more enigmatic case was encountered in the Br,Li-cyclobutylidenecarbenoid (**301**) that was stable[286] in THF at −107 °C and decayed in hexane[286] containing spirodiene **294** to give also **295** and **296** but again in temperature-dependent ratios (54:1 at −78 °C, 27:1 at −40 °C, and 12:1 at 0 °C). Although this selectivity looks like a blend of those observed for **298** and **271**, the different degrees of temperature-dependence, if beyond experimental error, in the same solvent (hexane) could be taken as evidence against a simple relationship. It may be necessary to take an unknown intermediate X (**297**) into consideration, and the several broken arrows with question marks in the reaction scheme are intended to express the conviction that at present no interpretation can be given that would be more than pure speculation. It is irrefutably clear only that not all of **301** can have rearranged to **299** (the expected primary FBW product) because the latter would not be reactive at the lower temperatures used for the cycloadditions with **301**. The fate of the major portion of **301** has remained obscure because the yields of cycloadducts (**295** and **296**) did not exceed 14% and the material balance was not reported. Part of the missing material might have comprised unreacted **299**, which upon workup by carboxylation with CO_2 would probably have furnished the easily separable 2-bromocyclopentene-1-carboxylic acid. In view of the intriguing observation in Scheme 2 of both a migrating and a nonmigrating α-Br in **280** and **281**, respectively, it would be interesting to employ the labeled dibromide [^{13}C-α]-**300** for generation of **301** with subsequent (eventual) FBW rearrangement providing **299**, whose ^{13}C distribution over the C=C double bond should be analyzed after carboxylation. To discover whether the unproven nature of the cyclopentyne−LiBr complex **298** and the indistinct behavior of the carbenoid **301** depend on the metal or on the halogen, the impressively sensitive differentiating method of intramolecular competition in the spirodiene **294** should be applied to further sources resembling **300** and **302** with gradual variations of the cations and/or the nucleofuges. Because this selectivity criterion for the intermediacy of cyclopentyne involves the [2 + 2] and [2 + 4] cycloadditions to spirodiene **294** taking place presumably after the rate-determining steps (such as **299** → **298**), it will be irrelevant whether the sources react more or less rapidly, as long as they remain in principle able to eliminate metal halides (in contrast to the kindred but stable five-membered-ring systems[290−293] which also carry the *cis*-2-halogeno-1-lithioethene moiety, not to be discussed here).



Some relative rates can be estimated from the isolation[283] of (α-bromobenzylidene)cyclobutane (10%

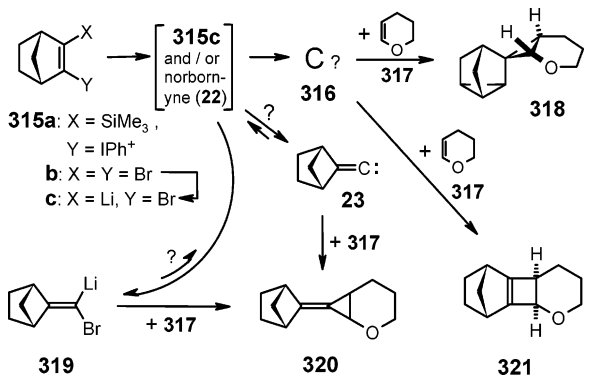
of **305**) along with one of the stereochemically pure[284] [2 + 2] cycloadducts **304** (~30%) after the initiating Br/Li exchange reaction of (dibromomethylene)-cyclobutane[283,284] (**300**) with phenyllithium in olefin/diethyl ether mixtures below 0 °C. Because only 1 equiv[283] of phenyllithium was applied and should have been used up for **300** → **301**, the high rate of this starting exchange must be comparable to that of the carbenoid substitution **301** → **303** (→ **305**) by residual phenyllithium. The potential [1 + 2] cycloaddition of carbenoid **301** to olefins was probably much slower than these two reactions and than the FBW rearrangement of **301**, followed by a cycloaddition to give **304**, as similarly observed[274] for the carbene $(CH_2)_3C{=}C{:}$ (**286**). When **301** was generated in *hexane* solution from **300** with the more reactive *n*-BuLi (2 equiv), only the FBW route **301** → **304** was chosen[286] for unknown reasons.

Some of the properties described above for 2-bromocyclopentenyllithium (**299**) should remain valid for the chiral bicyclic analogue **310**, leading one to suspect a mobile equilibrium with an achiral 2-norbornyne complex **22**·LiCl or a symmetry-equivalent species. It remained unexplained why 2-bromo-3-lithionorbornene (**310** but Br in lieu of Cl) polymerized[294] between −78 °C and room temperature, whereas **310** proper was stable[294] in THF at +25 °C (like **299** and 2-chloro-3-lithionorbornadiene[291]) and up to +45 °C when prepared by deprotonation of **306a** with *t*-BuLi at −45 °C. One should also expect two further features owing to the angular strain inherent in the unsaturated part of this skeleton. The first is known from the gas-phase FBW equilibrium between 2-norbornyne (see **22**·LiCl) and bicyclo[2.1.1]-hex-5-ylidenecarbene (**23**) mentioned already in section 2.1 as an indication of the increased tension in this bicyclic cyclopentyne derivative (**22**): it might give rise to ring contraction of **310** to afford the (yet unknown) intermediate Cl,Li-bicyclo[2.1.1]hex-5-ylidenecarben*oid* (**311**). The second trait consists of the well-known propensity to alleviate strain by additions to the double bond, which renders unusual organometallic additions possible, as follows. Methyllithium in diethyl ether did not dedeuterate 2-chloro-3-deuterionorbornene (**306b**) within 8 days at +25 °C but afforded[295] **313b**, whose retained deuterium content seems to enforce an interpretation in terms of an addition−elimination mechanism via **309** (however questionable) or an equivalent kind of substitution. Under the same conditions, undeuterated **306a** furnished undeuterated **313a** after deuteriolysis. The obvious exclusion of 2-norbornyne (**22**) as an achiral intermediate was reinforced[295] by the same conversion of optically active **306a** to give **313a** with complete retention of the configuration. In the second mode of addition, a more convincing carbenoid intermediate **307** can explain formation[296] of the tricyclic product **308a** (7%) from **306a** with phenyllithium (24 h in a boiling diethyl ether/benzene mixture). The authors[296] suggested that the main product **312b** (87%) was also formed from carbenoid **307**, but unfortunately they abstained from studying the reaction of phenyllithium with **306b**, which should have proceeded to give **312c** or **312b** either with an almost unchanged rate via **307** or via **310** with the significant deceleration caused by a primary H/D kinetic isotope effect (as will be reported below for the case of *n*-butyllithium). In the latter pathway, **312b**,**c** might derive from the alkenyllithium compound **312a** as generated by nucleophilic attack of phenyllithium at the Cl,Li-bicyclo[2.1.1]hex-5-ylidenecarben*oid* (**311**) or else at the corresponding free carbene **23**; but at present the intermediacy of carbenoid **311** is not yet established.

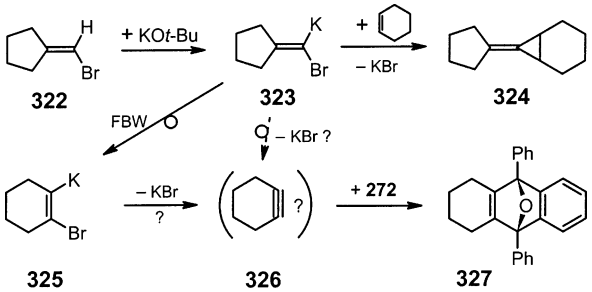


Whereas the *tert*-butyl group of *tert*-butyllithium did not show up in any isolated substance derived from **306a**, incorporation of *n*-butyllithium demonstrated[297] that all three reaction modes postulated with **306a** and **b** occurred in THF at +25 °C (2 h). First, optically active **306a** was predominantly deprotonated to generate **310** in putative equilibrium with **22**·LiCl. The very active nucleophile *n*-BuLi did not wait for eventual ring contractions (to give carbene **23** or carbenoid **311**) but presumably added quickly to the achiral **22**·LiCl (or a rapidly racemized equivalent) to furnish the alkenyllithium compound **314a**, isolated as racemates[297] of **314b** or (after deuteriolysis) of **314c**. Second, a small portion (**313c**) of the same substance **314b** appears to have been formed via **309** with retention of the configuration and with conservation of the hydrogen label X inherited from **306a**. Third, about 38% of the isolated material consisted of the optically active tricyclus **308b** (undeuterated after deuteriolysis) with inverted configuration. Starting with **306b**, tricyclus **308c** became the main product (94%), owing to a large kinetic isotope effect that decelerated the competing formation of **310**, in accord with the proposed mechanism. Some further support for a mobile equilibrium between **310** and **22**·LiCl may be seen in the accelerated[294] decay of independently prepared **310** caused by addition of either *n*-BuLi (that formed **314a**) or the weaker nucleophile *t*-BuLi or methyllithium that did not form 1:1 addition products but initiated

formal norbornyne trimerization and polymerization ("gum"[294]).

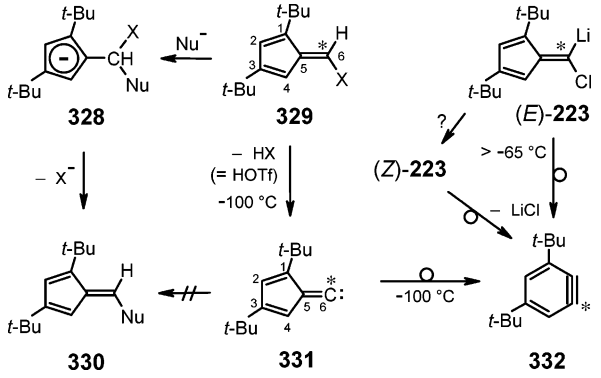


The question as to whether bicyclo[2.1.1]hex-5-ylidenecarbene (**23**) or its Cl,Li-carbenoid **311** can be generated by *retro*-FBW rearrangements in solution received renewed stimulation by preliminary investigations[50,298] of the sources **315a** and **b**. Desilylation of **315a** appears to be a credible route to 2-norbornyne (**22**) in view of the similar generation[299] of the related but even more strained norborn-5-ene-2-yne from phenyl-2-(3-trimethylsilyl-2,5-norbornadienyl)iodonium triflate made possible with tetrabutylammonium fluoride in THF. In the presence of dihydro-4*H*-pyran (**317**), **315a** furnished the cycloadducts **318**, **320** (two diastereomers), and **321** in CH_2Cl_2 solution at −80 °C in a 29:20:21 ratio that was "believed to represent the intrinsic reactivity of norbornyne" (**22**).[298] Although such a conjecture would become more convincing were the same product ratio found via the usual method[287] of (cyclo)-alkyne formation by oxidation of the corresponding 1-amino-1,2,3-triazole or 1,2-bis(hydrazone) derivatives, the observation of the main product **318** is certainly inspiring because it may be visualized as deriving from 2-norbornyne (**22**, or an equivalent intermediate) behaving as though it were a 1,2-dicarbene[298] (or a carbenecarbenoid?). The [2 + 2] cycloadduct **321** was postulated[50,298] as deriving from the same primary intermediate **316** (a saturated carbene dubbed "**C**" here), defining a novel mechanistic pathway with circumnavigation of the thermally forbidden concerted [2 + 2] cycloaddition; if so, the 29:21 ratio of **318** and **321** should be independent of the sources **315a** or **b**. An experimental test was carried out by generating **315c** from 2,3-dibromonorbornene (**315b**) with elemental lithium in THF at +60 °C, and obtained were **318**/**320**/**321** in the ratio 36:4:18. Although the applied temperatures and solvents were too dissimilar to draw final conclusions



from comparisons of the results for **315a** and **b**, it appears possible that the minor product pair **320**, indicating a *retro*-FBW rearrangement, could have been formed at least partially via the carbenoid **319**, in contrast to the route via carbene **23** in the published[50,298] schemes. At present, this question must still be left open.

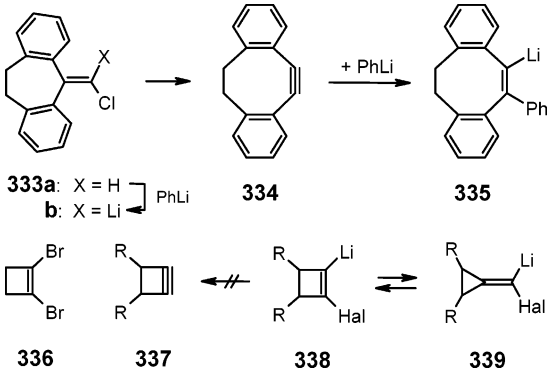
The FBW alkyl migration in Br,K-cyclopentylidenecarbenoid **323**, generated[269] from **322** with KO*t*-Bu in boiling *p*-cymene, is so weakly accelerated by strain release[300] that it admits the [1 + 2] cycloaddition of unrearranged **323** to cyclohexene[269] affording **324** (11%). On the other hand, **323** did not react with the quinodimethane **272**, so that its FBW rearrangement, perhaps via **325**, furnished[269] the adduct **327** (35%) of cyclohexyne (**326**). The Br,K-carbenoid generated in the same way from *ω*-bromocamphene (not depicted) could perform the FBW ring expansion sufficiently fast to give only the *tert*-butyl ethers[301] formed by its bicyclic cyclohexyne derivative that could also be trapped[269] with **272** in 95% yield. A corresponding *retro*-FBW ring contraction of a cage-annulated cyclohexyne was observed[302] to be favored in a strained hydrocarbon cage compound.



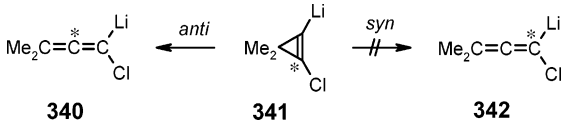
Pentafulvene derivatives such as **329** are prone to addition−elimination[218,303] reactions via **328**, affording substitution products **330** that at a glance may deceivingly simulate the trapping of the carbene 1,3-di-*tert*-butylpentafulvenylidene (**331**). However, **331** has apparently never[218,303] been captured, owing to its faster FBW ring expansion to give **332** in analogy with **25** → **24** in the gas phase. Thus, deprotonation of the labeled (*) triflate [^{13}C-6]-**329** (X = OTf) at −100 °C furnished solely the single isotopomer **332** of 3,5-di-*tert*-butylbenzyne, according to the analyses of a derivative obtained by capturing **332**. This demonstrates the exclusive FBW migration of the C-4 atom in **331**, and because α-deprotonation of alkenyl triflates is known (section 2.2) to generate unencumbered alkylidenecarbenes, this remarkable experiment[218] demonstrates that the migratory aptitudes of electronically similar groups (sp^2 centers in the case of the free carbene **331**) can be very different. The equivalently labeled Cl,Li-cyclopentadienylidenecarbenoid (*E*)-**223** decayed[218] to the same isotopomer **332** only above −65 °C. It is unknown whether (*E*)-**223** produced **332** directly or indirectly via (*Z*)-**223** or via carbene **331**.

A ring expansion was not observed[304,305] in diethyl ether at −35 °C for the Cl,Li-(9-fluorenylidene)-

carbenoid (having the ring system of **220**), which preferred substitution (perhaps via addition−elimination) and dimerization reactions. Nor was ring expansion found[306] in the purported free (9-fluorenylidene)carbene at +80 °C or in the F,Li-(9-fluorenylidene)carbenoid that was stable[220] up to −20 °C, where $t_{1/2} \approx 0.8$ h in THF. The next higher ring enlargement from six to seven did not materialize in the carbene $MeCH(CH_2CH_2)_2C{=}C$: (**9**)[122] or in various Cl,Li-[304] and Br,K-carbenoids.[270] But whereas Br,K-cycloheptylidenecarbenoid, $(CH_2)_6C{=}CKBr$, provided mainly[269] the unrearranged (*tert*-butoxymethylene)cycloheptane, $(CH_2)_6C{=}CH{-}Ot\text{-}Bu$, the dibenzoannelated Cl,Li-carbenoid **333b** furnished[304] mainly (23%) the addition product **335** as formed by the faster FBW aryl migration via dibenzocyclooctyne **334** (or its LiCl complex?).



Moving in the opposite direction, we encounter an understandable propensity to avoid the formation of more highly distorted cycloalkynes as FBW products. Cyclobutynes (**337**) are so highly strained (more than tetrahedrane[282]) that even the question of their theoretical existence is controversial.[282] It was established long ago[307] that the source 1,2-dibromocyclobutene (**336**) is able to add the quinodimethane **272**, deceptively simulating a behavior expected for cyclobutyne (**337**, R = H). A later claim toward the generation and ring contraction[308] of **337** was deemed to need reinterpretation in terms of the equilibrium between **338** and **339** (or some other mechanism).



The 1,2-elimination of LiCl from **341** (generated by Br/Li exchange with methyllithium in diethyl ether at −90 °C) cannot be expected to produce the very highly strained[282] cyclopropyne ring that was calculated[309,310] not to be a local minimum. Indeed, the ^{12}C-labeling (*) of **341** served to prove that solely[311] the isotopomer **340** (not **342**) was trapped by [1 + 2] cycloaddition, thus ruling out cyclopropyne as an intermediate. An equivalent result had been found[312] for the corresponding potassium compound (**341** with K in place of Li) generated by deprotonation with KO*t*-Bu in hot tris(dimethylamino)phosphinoxide (HMPA).

Regarding the title question of this section, it can be said that small-ring cycloalkynes are not always FBW intermediates and not necessarily the primary ones. Cyclobutyne (**337**) and cyclopropyne are energetically out of reach. It is not clear whether the short-lived cyclohexyne (**326**) and its congeners are formed directly as the primary FBW intermediates from a cyclopentylidenecarbenoid such as $(CH_2)_4C{=}CKBr$ (**323**) or indirectly as secondary intermediates after ring expansion to a 2-halogenocyclohexenylmetal (**325**) with subsequent β-elimination of MHal. Similarly, 3,5-di-*tert*-butylbenzyne (**332**) may be a primary or a secondary FBW intermediate when generated from Cl,Li-cyclopentadienylidenecarbenoid **223**; its straightforward formation[218] from the bona fide cyclopentadienylidenecarbene **331** corresponds to the gas-phase interconversion between benzyne (**24**) and pentafulvenylidene (**25**). Similarly, the gas-phase equilibrium of norbornyne (**22**) and bicyclo[2.1.1]hex-5-ylidenecarbene (**23**) extends probably to the liquid state; but the relationship of these two intermediates with the Hal,Li-bicyclo[2.1.1]hex-5-ylidenecarbenoids **311** and **319** is dubious. Cyclopentyne (**271** or **289** or a symmetry-equivalent species) is certainly the primary "FBW" intermediate from the bona fide cyclobutylidenecarbene $(CH_2)_3C{=}C$: (**286** or **292**) as generated from cyclobutylidenediazomethane[274,286] $(CH_2)_3C{=}CN_2$ (**285** or **291**) or by desilylation[286] of $(CH_2)_3C{=}CBr{-}SiMe_3$ (**293**). But cyclopentyne appears to be a secondary intermediate formed quickly from the Hal,K-cyclobutylidenecarbenoids **265** via the primary FBW intermediate 2-halogenocyclopentenylpotassium[270−272] (**268**), and its role is vague in the FBW rearrangement of the Br,**Li**-cyclobutylidenecarbenoid[283,284,286] $(CH_2)_3C{=}C$-LiBr (**301**).

Summing up, so many unanswered questions remain in this field that one may speak of a mechanistically underdeveloped area. As repeatedly explained, possibilities to elucidate some of the dark regions appear to be near at hand.

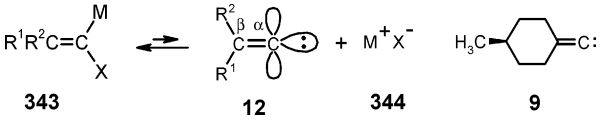
3.4. FBW Migratory Aptitudes and Competing Processes in Alkylidenecarbenoids

The distinction between carbenoids and carbenes as reactive species could be aided by some a priori knowledge about thermodynamic and kinetic aspects of their interconversion.

3.4.1. Interconversion of Carbenoids and Their Carbenes

Carbenes **12** (see below) in their singlet (that is, spin-paired) state may be viewed as the formal union of a carbenium cation (empty p-orbital) and a carbanion (lone electron pair) at the same carbon atom. This ambiphilic nature suggests a "natural urge" of carbenes such as **12** or **9** toward the addition of anions and cations (**344**). Indeed, 16% of 4-methyl(chloromethylene)cyclohexane, $MeCH(CH_2CH_2)_2C{=}CH{-}Cl$, was isolated[208] after the bona fide 4-methylcyclohexylidenecarbene (**9**) had been generated independently[313] in a solution of MX = LiCl (**344**) in THF/TMEDA: it was undoubtedly formed by LiCl addition to the carbene **9**, giving $MeCH(CH_2CH_2)_2C{=}CLiCl$ (the carbenoid **343**), which after 30 min at −70

°C was quenched with methanol. A mechanistically more ambiguous observation[108] of very efficient halide incorporation has been mentioned in section 2.3.3. Quantitative results are available[314] for the very fast MX additions to fluoro(phenyl)carbene (F−C−Ph) with second-order rate constants of about 10^7 M^{-1} s^{-1} in acetonitrile at +25 °C. Preliminary photoacoustic heat measurements[314] indicated the addition of LiBr to be exothermic by −28.6 kcal/mol while *n*-Bu_4N^+ Br^- afforded only −11.4 kcal/mol; one may certainly expect the heat of addition of potassium halides to fall between these numbers. Thermal α-elimination of LiBr from 7-bromo-7-lithionorbornene was reported[315] to occur already at and above +24 °C in vacuo.

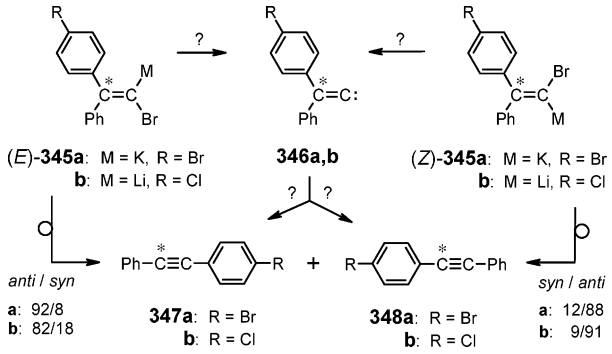


In low-level quantum chemical calculations[316] on simple models of monomeric lithium carbenoids deprived of solvation, FCH_2Li required +55.9 kcal/mol[317] for the α-elimination of LiF while the unsaturated carbenoid $H_2C{=}CLiF$ needed only +36.4 kcal/mol,[221] pointing to an intrinsically lower energy content of alkylidenecarbenes **12** in comparison with saturated carbenes. Attention was called already in section 3.1 to the higher-level computed elimination energy +12.5 kcal/mol[224] for solvated $H_2C{=}CLiI$ (**227** with Hal = I). Energy barriers in this range can easily be surmounted at ordinary temperatures, but a direct experimental identification of the reactive species is difficult because both carbenoids and their ensuing carbenes tend to generate the same products. The backward barrier against addition of lithium iodide to $H_2C{=}C$: was computed[224] as being merely 3.5 kcal/mol.

All of the foregoing arguments foster the reasonable expectation that carbenes can be thermally accessible from the thermodynamically more stable Hal,Li-carbenoids; but faster rival reactions may prevent the attainment of this goal, of course. Although the statement[318] that "only comparatively stable, donor-substituted carbenes CX_2 are formed from carbenoids by α-elimination of MX" was correctly derived from experimental details for examples with donor substituents X stronger than alkyl, it need not be transferable to unsaturated carbenoids: The alkylidenecarbenoids $Alk_2C{=}CK{-}Br$ (but not necessarily the related $Alk_2C{=}CK{-}Cl$) were very probably converted to their alkylidenecarbenes $Alk_2C{=}C$: (sections 2.5 and 2.6), which then performed 1,5-CH insertions or [1 + 2] cycloadditions. These simple α-eliminations of KBr were obviously faster than other potential reaction modes of these carbenoids. On the other hand, it will be demonstrated in the next section that FBW aryl migrations can be faster than simple KBr elimination.

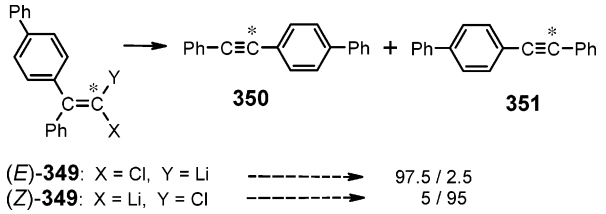
3.4.2. FBW Rearrangements of Carbenoids in Solution

A pioneering publication[4] reported that the isotopomeric alkynes **347a** and **348a** were formed quantitatively in differing ratios from the stereoisomers of ^{14}C-labeled (*) β-bromo-α-(4-bromophenyl)styrene with KO*t*-Bu in HO*t*-Bu (3 days at reflux). As later work (described in previous sections and below) gave no hints toward a stereomutation of open-chain **Br**,**K**-alkylidenecarbenoids such as **345** even at +190 °C in HMPA,[319] the observed product ratios **347a**/**348a** may be considered to describe rate ratios, namely, 92:8 from (*E*)-**345a** but 12:88 from (*Z*)-**345a**. This stereodivergence provides definite proof that the alkylidenecarbene **346a** (or any other symmetry-equivalent species) is *not the only* intermediate because "FBW" rearrangement of the latter must lead to stereoconvergence. Inventing an exaggerated situation, one could imagine that the observed stereodivergence would be compatible with (*Z*)-**345a** forming the carbene **346a** that would furnish its characteristic product mixture (which is unknown), whereas (*E*)-**345a** would perhaps react without converting to carbene **346a**. Of course, such a heretical idea[319]

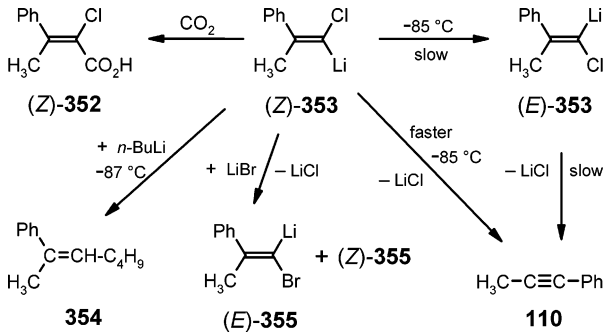


might easily be refuted (or confirmed) by creation of the labeled bona fide carbene **346a** via one of the approved methods presented in sections 2.2−2.4, followed by analyses of the product ratio **347a**/**348a**. In the absence of reliable knowledge, an orthodox attitude dictates belief that FBW aryl migrations are always faster than the simple α-eliminations of MX, so that both isotopomers **347a** and **348a** arise from **345a** directly, leading to anti/syn preferences of 92:8 for (*E*)-**345a** and 88:12 for (*Z*)-**345a**.

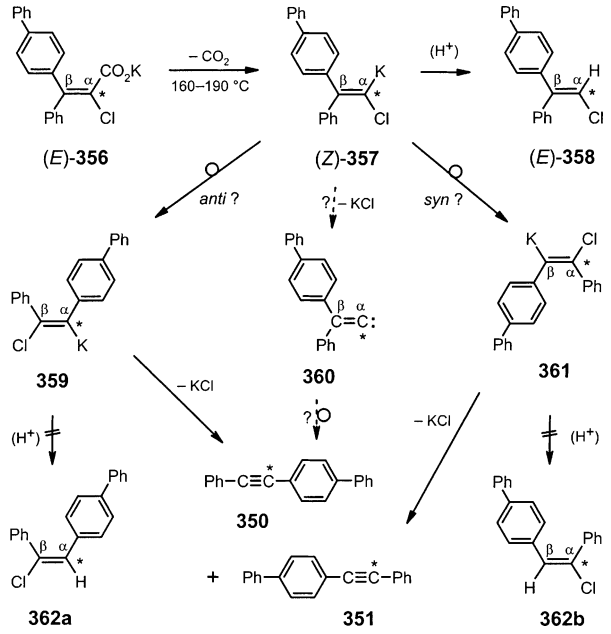
Despite the imminent Br/Li exchange reaction, the related ^{14}C-labeled (*) β-bromo-α-(4-chlorophenyl)-styrenes could be deprotonated[320] by *n*-BuLi in diethyl ether at −35 °C to give the stereoisomeric **Br**,**Li**-carbenoids (*E*)- and (*Z*)-**345b**. Their FBW aryl migrations seem to take place with anti/syn preferences of 82:18 for (*E*)-**345b** and 91:9 for (*Z*)-**345b**. Although not all of the details[320] are completely clear concerning the ^{14}C-distribution and the purity of (*E*)-**345b**, the selectivities appear to be equal to those of the two Br,K-carbenoids (*E*)- and (*Z*)-**345a** within the experimental errors. The salient point emerging from these studies with different cations above and below room temperature is that each pair of stereoisomers furnished stereodivergent product mixtures.



Improved methodology was applied[321] to study the behavior of the stereoisomeric **Cl**,**Li**-carbenoids **349** as a third variant resulting from the low-temperature deprotonation of β-chloro-α,*p*-diphenylstyrenes with *n*-BuLi in ethereal solvents. (A fourth variant with X,Y = Cl,K will be presented in **356**.) This technique is distinguished by successful applications of the possibility to halt the process at the carbenoid stage (**349**) well below −70 °C and then to carry out careful stereochemical assignments[322] ((*E*) or (*Z*)) at reaction time by derivatizations. After warming, the isotopomers **350** and **351** were found[323] in the anti/syn ratios 97.5:2.5 from (*E*)-**349** and 95:5 from (*Z*)-**349**, that is, with slightly higher anti preferences than those from **345a** and **b** (again ignoring the possibility of a free carbene). Because phenyl is a less electron-withdrawing *p*-substituent than R = Cl or Br in **345**, this trend may raise the impression of a weak acceleration of anti migration in (*E*)-**349** and also in (*Z*)-**349** (where 4-biphenylyl is the stationary group). Altogether, these ratios of anti versus syn FBW migrations ranging from 39:1 to 5:1 cannot be dubbed stereospecific but at best stereoselective, corresponding to the isomeric excess between 95% and 64%, or at most 2.2 kcal/mol at +25 °C for the difference between the activation energies on the route to the isotopomers. Of course, this is not surprising in light of present knowledge concerning comparable rates of anti and syn FBW migrations, as discussed on several occasions in previous sections. The following example serves to reinforce this point by demonstrating that *syn*-phenyl migration can be *faster* than *anti*-phenyl migration.



The **Cl**,**Li**-(α-methylbenzylidene)carbenoid (*E*)-**353** was observed[242] to be almost stable at −85 °C, decaying quite slowly to 1-phenylpropyne (**110**); the same product was obtained more conveniently at somewhat higher temperatures. Generated in the same way at −110 °C in ethereal solvent mixtures with *n*-BuLi (1.1 equiv) but from (*Z*)-β-chloro-α-methylstyrene, Ph−C(Me)=CHCl, the carbenoid (*Z*)-**353** had only partially survived after 4 h at −85 °C, with a mere 43% yield of the acid (*Z*)-**352** after carboxylation at this time; the remainder had been converted to the alkyne **110**. After 18 h at −87 °C, **110** was found[242] to be accompanied by small amounts of the carbenoid (*E*)-**353** and a single diastereomer of the substitution product 2-phenyl-2-heptene (**354**). With LiBr present in a solution of (*Z*)-**353**, the **Br**,**Li**-carbenoid (*E*)-**355** (that is, with inverted configuration) and a trace of (*Z*)-**355** were formed by substitution. Thus, although the slow isomerization of (*Z*)-**353** to (*E*)-**353** was observed,[242] it is this stereoleakage accumulating (*E*)-**353** that definitely ensures the *slower anti-phenyl migration* in (*E*)-**353**. This interpretation presupposed that phenyl will migrate much faster than alkyl also in Hal,Li-alkylidenecarbenoids, as proven later[324] by ^{13}C-labeling, and that (*Z*)-**353** at −87 °C would not react via the free carbene. A similar (*E*)- to (*Z*)-isomerization at −60 °C may have initiated the bimolecular β-elimination[325] at (*E*)-Cl,Li-benzylidenecarbenoid (Ph−CH=CLiCl, related to (*E*)-**353** but with H in place of H_3C) in THF/Et_2O to give lithium phenylacetylide (Ph−C≡CLi) and (*E*)-β-chlorostyrene (Ph−CH=CH−Cl) in a 1:1 ratio. It is noteworthy here that both phenyl and hydrogen (unimolecular) FBW migrations were not observed up to this temperature.

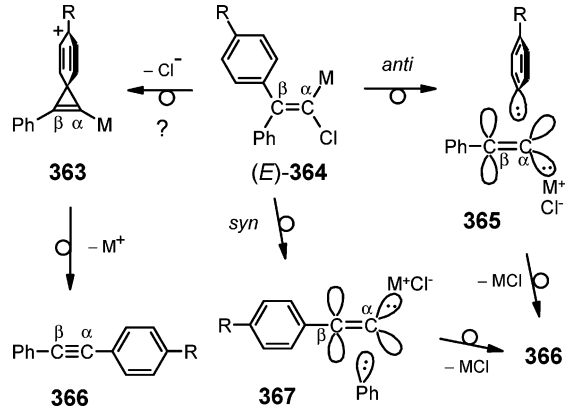


Inspired by the reports in section 3.3.1 that 2-halogenocyclopentenylpotassium (**268**) and its relatives were observed as the primary intermediates after FBW ring expansion, one may wonder whether an open-chain carbenoid such as (*Z*)-**357** might also form the corresponding (*Z*)-2-halogenoalkenylpotassium species **359** and **361** by anti and syn migration, respectively, and whether these primary intermediates could perhaps be captured as **362a**,**b** prior to their elimination of KCl giving the isotopomeric alkynes **350** and **351**. The following experimental setup bears on this question. Decarboxylation of the carboxylate anion of unlabeled (*E*)-**356** in HMPA at up to +190 °C furnished[319] the alkyne **350**/**351** together with a small amount of stereochemically pure (*E*)-**358**. The latter product demonstrates that **Cl**,**K**-carbenoid (*Z*)-**357**, as the presumed carbenoid intermediate, did not invert its configuration before being captured by adventitious protons, because otherwise (*Z*)-**358** would have been generated as well. In the same (base-free) solution, the protonation product **362a**,**b** was not detected although there had been comparable chances of trapping the organopotassium compounds **359**/**361** and (*Z*)-**357**. There-

fore, **359** and **361** either were not formed or decayed too rapidly by elimination of KCl. The latter possibility would be in accord with the fast β-elimination of other unsaturated acyclic intermediates,[326,327] including β-halogenoalkenyl anions which require[140] some rehybridization for halide expulsion.

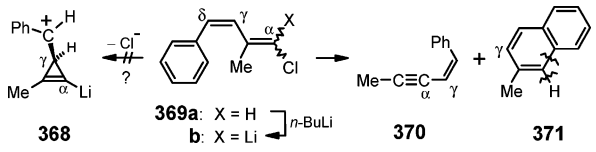
The decarboxylation of ^{13}C-labeled (*) **356** produced mixtures[319] of the isotopomers **350** and **351** in the ratio 81:19 from (*E*)-**356** via (*Z*)-**357** but in a 23:77 ratio from (*Z*)-**356** (not shown) via (*E*)-**357**. On account of this stereodivergence, formation of the free carbene **360**, which demands stereoconvergence, from **357** by simple α-elimination of KCl at +190 °C in the polar solvent HMPA cannot be substantially faster (but may be much slower) than the anti and syn FBW rearrangements of carbenoids **357**.

What is known about the transition states of these FBW rearrangements? The rates were found[321] by semiquantitative measurements to increase slightly with increasing donor qualities of *p*-substituents in the migrating aryl groups at low temperatures in ethereal solvents: The rate sequence Cl < H ≈ phenyl < methyl < methoxy for R in (*E*)- and (*Z*)-**364** (M = Li) was interpreted[321] in terms of an intramolecular electrophilic aromatic substitution by the carbenoid function, leading to the unsaturated phenonium intermediate **363** and thence to the alkyne **366**. But the magnitudes of these substituent effects appear to be much smaller than those observed[328] for aryl migration in alkenyl cations via an unsaturated phenonium intermediate[10a,329] (similar to **363** but with two CH_3 groups in place of Ph and M), expressed by a Hammett factor $\rho = -3.76$ for the (*E*)-isomer.[328] Furthermore, such alkenyl cation rearrangements occurred "very much faster"[10a] from the (*E*)- than from the (*Z*)-isomers of the precursors, owing to concerted phenonium formation from the (*E*)-isomers whereas the (*Z*)-isomers would not enjoy such neighboring group participation. Obviously, comparisons of this type do not directly explain why the carbenoid stereoisomers (*Z*)- and (*E*)-**364** can decay at similar rates, to say nothing of (*Z*)-**353**, Ph−C(Me)=CLiCl, as compared to (*E*)-**353** above. Such comparisons would also not explain whether a similar substituent dependence of the rates could be believed[7,321] to be valid likewise for the *stationary* aryl groups in **364**. Similar objections may be raised against comparisons with the Chapman rearrangement, for which the phenonium mechanism had been suggested[330] in accord with the Hammett factor[3,330a] $\rho = -4.1$ and with the difficulty[331] to extort ring expansion from fluorenone-9-oxime (Ar_2C=N−OH) in the related Beckmann rearrangement[3] (shown as **4** → **5** in the Introduction). Indeed, the phenonium mechanism would enforce a highly strained transition state on the 9-fluorenylidene skeleton (depicted in **220**), and it is true that neither (9-fluorenylidene)-carbenoids[220,304,305] (Ar_2C=CMX) nor a corresponding free carbene[212] (Ar_2C=C:) could be made to expand to phenanthrene derivatives. However, this behavior does not prove a phenonium mechanism; on the other hand, the phenonium pathway of open-chain substrates cannot be disproved by a successful ring expansion such as this one: Thermolysis at +65 °C of the (9-fluorenylidene)methanediazonium ion (Ar_2C=CH−N_2^+) in 1,2-dichloroethane solution yielded[332] 18% of 9-chlorophenanthrene. Thus, it appears more reliable to argue that a fully developed phenonium ion **363** would not be compatible with open-chain carbenoids (*E*)-**364** producing **366** because the magnitudes of substituent effects on the rates were regarded[321] to be much smaller than those of the Chapman rearrangement and because the kinetic anti/syn selectivity is often only moderate.



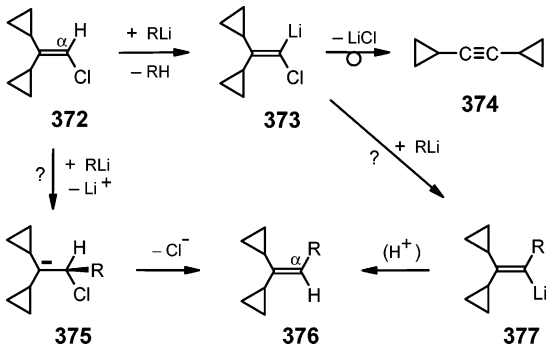
For *anti*-aryl migration as the preponderant mechanism, an easy interpretation is possible, involving a transition state **365** patterned qualitatively after the model **13** of section 2.1 together with **226** of section 3.1. This proposal had been anticipated[6] from the concept of "metal-assisted ionization"[6,7] and implies that the migrating group performs a [1,2]-sigmatropic shift, aiming at the emptying Cl−Cα bond orbital and leaving the duty of stabilizing the electron-deficient C-β atom to the stationary β-aryl moiety (and perhaps to the traveling chloride anion if undergoing dyotropically a 1,2-shift, as had been tentatively predicted[333]). It is conceivable that the aromatic π-system of the migrating group might participate by some kind of interaction (different from that in **363**) which cannot be elaborated at present. The operational differentiation regards **365** to represent a local energetic maximum (transition state with elongated bonds), whereas the phenonium intermediate **363** is thought to describe a local minimum with fully developed C−C bonds.

If the *syn*-aryl migration in (*E*)-**364** starts also with "metal-assisted ionization"[6,7] of the Cl−Cα bond in the spirit of the model **228** (section 3.1), then the syn transition state might have a structure like **367**. This would provide for the possibility that the chloride anion can become reconnected to C-α, as detected for **278** (Scheme 2), on the way to a subsequent primary intermediate such as **361**.



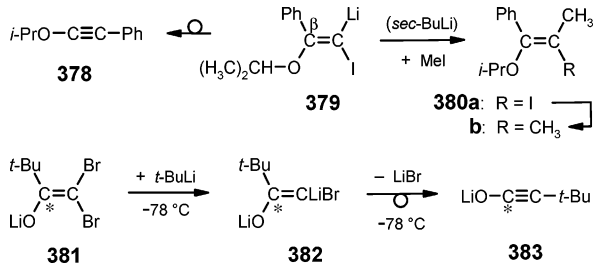
With regard to the rejected phenonium intermediate **363**, an electrophilic π-attack of the carbenoid function at an sp^2 carbon atom appears to also be

incompatible with the stereoretention observed[334] after FBW alkenyl migration in the [*Z*(γ,δ)]-Cl,Li-alkylidenecarbenoid **369b** above −70 °C. Approach of C-γ to C-α would lead to the benzyl cation intermediate[334] **368**, whose broken (γ−δ) π-bond might admit the rapid loss of the (*Z*)-configuration by CC-rotation; but the FBW product **370** was obtained with pure (*Z*)-configuration, again suggesting a [1,2]-sigmatropic shift transition state similar to **365** instead of **368**. The second product 2-methylnaphthalene (**371**) deserves attention for being the result of an extremely rare 1,6-CH insertion[84] reaction, even more so at an sp^2 carbon atom. A distinction from an equally rare aromatic substitution mechanism by attack of C-α at C-*ortho* might perhaps be feasible with [*ortho*-D]-**369b**.



Cyclopropyl had appeared to migrate slower than phenyl but a little faster than methyl[107] in the putative carbenes generated from *N*-nitrosooxazolidones **96** in section 2.3.3, judging from competition with [1 + 2] cycloaddition; but the unknown demarcation line against the incipient alkenyl cation made this conclusion uncertain. A correspondingly modest migration rate of cyclopropyl in the carbenoid α-chloro-β,β-dicyclopropylvinyllithium[335] (**373**) in THF is indicated by the successful competition of bimolecular nucleophilic substitution: The alkyne **374** was produced between −90 °C and −60 °C; but the side products **376** (R = *n*-Bu or *t*-Bu) arose slightly above −90 °C with the deprotonating agents RLi in excess. The proposed[335] addition−elimination mechanism (**372** → **375** → **376**) could have been distinguished from S_NV substitution at the carbenoid (**373** → **377** → **376**) by rate measurements with **372** as compared to [α-D]-**372**, for neither **373** nor **377** could be captured by carboxylation[335] after 72 h at −110 °C.

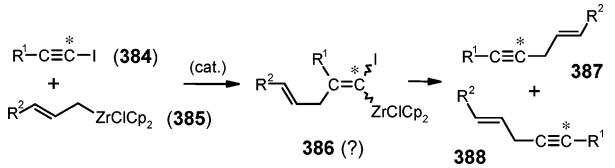
Bis(dialkylamino)acetylenes were believed to arise from Cl,Li-bis(dialkylamino)methylidenecarbenoids, $(Alk_2N)_2C{=}CLiCl$, at room temperature[336,337] by formal FBW rearrangements involving quaternary [1H]azirinium intermediates ("onium rearrangement"[336,338]). An analogous thiirenium intermediate was thought[176,336,339] to occur during migration of the phenylthio group in $PhS{-}C(R^1){=}CLiCl$, displaying a 1,2-shift of similar ease as mentioned in section 2.4.3 for a corresponding carbene[165] $PhS{-}C(R^1){=}C$: (**156**). But a simple oxygen function such as trialkylsiloxy in a diazoalkene $R_3SiO{-}C(R^1){=}CN_2$ (**66**) was described in section 2.3.1 as being unable[91] to perform an "FBW" carbene rearrangement in competition with 1,5-CH insertion. The **I**,**Li**-alkylidenecarbenoid **379** is stable at −20 °C[340,341] and hence seems to disclose the unexpected feature that isopropyloxy impedes both the expected FBW phenyl migration and the 1,5-CH insertion into isopropyl CH_3 groups: After it was allowed to warm to room temperature (!) together with ∼6 equiv of *sec*-BuLi in THF, quenching[341] of **379** with iodomethane afforded only 8% of the FBW product **378** along with 39% of the methylated derivatives **380a** and **380b**, indicating that more than one-third of the carbenoid **379** had survived, perhaps in mobile equilibrium with its "ate complex" (like **242**) as formed with residual *sec*-BuLi. This surely startling stability should not be due to the iodine atom alone in **379** because the heavier halogen induced a lower decomposition temperature in the (*E*)-isomers[342] of carbenoids R−(F)C=CLiHal (Li cis to F), namely, −5 °C for Hal = F but −50 °C for Hal = Cl. Typical for RO− as a β-substituent in place of fluorine, the (*E*)-isomer[343] of EtO−CH=CLiBr (Br cis to H) in diethyl ether outlasted even 6 h at −50 °C without FBW hydrogen rearrangement, despite its presumably better nucleofuge α-bromine and despite the destabilizing solvent Et_2O. Although this lack of reactivity may sometimes[344] be at least in part due to insolubility, the *stationary* β-isopropyloxy substituent in **379** despite its π-donor quality seems to inductively ($\sigma_I = 0.27$)[27] destabilize the C-β center that would become sp-hybridized in the transition state, and ethoxy ($\sigma_I = 0.28$)[27,168] should be no less effective. Taken together, all of these observations indicate that the alkylidenecarbenoid **379** might become even more stable with Br or Cl in place of iodine. Quantum chemical calculations[345] suggested that the isopropyloxy substituent does not take part in coordination at the solvated lithium cation of **379**. Although it appears acceptable that isopropyloxy may be an inefficient nucleofuge and hence unsuitable for the β-elimination of *i*-PrOLi, it remains unexplained why this rather long-lived carbenoid did not dimerize to furnish a butatriene.



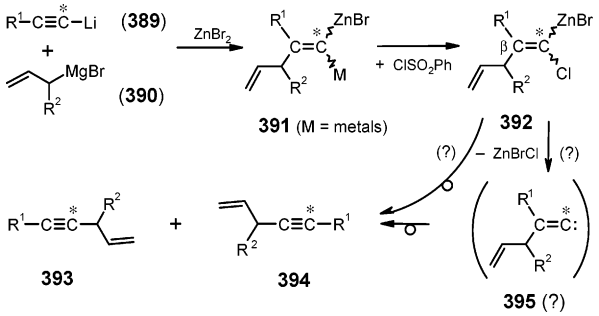
In contrast, the −OLi function ($\sigma_I = -0.12$ for $-O^-$)[346] seems to be a very helpful stationary β-substituent so that it rendered the FBW *tert*-butyl migration possible in the carbenoid **382** within a few minutes at −78 °C (!)[347,348] in THF, producing the alkynolate **383** as the only isotopomer[348] from the ^{13}C-labeled (*) dibromoenolate **381**. It may be noticed that migration of the olate function (which did not take place) might have passed through an electronically unfavorable oxirene structure. The ability of the related iodonium enolate **159** in section 2.4.3 to serve as the potential source of a carbene akin to **382** was not investigated. Because the starting material **381** was prepared from an ester and **383** is an ester in

disguise (which may be visualized by alcoholysis), the rearrangement amounts to a one-pot substitute for the Arndt−Eistert synthesis with diverse kinds of migrating groups. Due to a mechanistic bifurcation,[349] it was necessary to develop a somewhat sophisticated protocol[347,350] in order to suppress side reactions and to accomplish final convergence of the material into **383** and its successors. Without such assistance by an efficacious stationary substituent or by the release of angular strain (section 3.3), FBW migrations of saturated alkyl groups in Br(Cl),Li-alkylidenecarbenoids are not very common, presumably owing to evasive carbenoid reactions such as the dimerization affording butatrienes (**245** in section 3.2).

Nucleofuges such as the halides (and even EtO) as the β-substituents in the trans position with respect to lithium [that is, in the (*Z*)-isomers] are usually detrimental for the stability of Hal,Li-alkylidenecarbenoids because unimolecular anti-β elimination may set in at very low temperatures. Therefore, only the much more stable (*E*)-isomers of R−(Hal′)C=CLiHal are amenable to investigation of carbenoid reactivities. However, it is unknown whether the alkyne products R−C≡C−Hal(′) obtained from the (*Z*)-isomers arise by α-elimination of LiHal (FBW) or by syn-β elimination of LiHal′ because ^{13}C-labeling of C-α or C-β was not applied and because the products could not be isolated but were consumed in rapid substitution reactions,[342,351,352] the mechanism of which is not known. Nevertheless, it is clear that FBW rearrangements did not take place up to the temperature at which decomposition (by whatever the mechanism) began. This threshold temperature is −5 °C for the (*E*)-isomers of R−(F)C=CLiF with R = aryl[342,351,352] in diethyl ether or with R = alkyl[353] in THF (as mentioned earlier), the latter affording no cyclopentenes. It appears possible that fluorine (σ_I = +0.54)[168] as the stationary β-substituent can decelerate FBW migrations of R = aryl and alkyl to such an extent that decomposition at −5 °C occurs preferably by β-elimination. In any case, an FBW shift of β-fluorine need not be taken into consideration because it has never been reported, obviously due to high activation barriers.[16,21,33b] When the free carbene F_2C=C: was generated photochemically, it did not rearrange but was capable of *bimolecular* CH-insertions[354] with very low *prim*/*sec*-CH selectivity. As a further structural limitation, β-hydrogen trans to Hal in the (*Z*)-isomers of R−CH=CLiHal is also detrimental, owing to rapid bimolecular anti-β elimination[229,325] even at −100 °C.[355] Hence, the very low decomposition temperatures of H_2C=CLiHal with Hal = F,[356] Cl,[229] and I[224] render it impossible to observe FBW rearrangements.



Two areas of FBW rearrangements via alkylidenecarbenoids carrying heavier metals were recently discovered by carbometalations. The Al-catalyzed addition of the allylzirconium species **385** (Cp = cyclopentadienyl) to ^{13}C-labeled (*) iodoalkynes **384** was believed[357] to generate the I,Zr-carbenoids **386** that furnished the isotopomeric alkynes **387** and **388** at between −78 °C and ambient temperature. As neither the (*E*,*Z*) configurations nor the constitution of **386** could be controlled, it remained unknown whether the free carbene was involved as a further intermediate prior to rearrangement and whether the initial allylation of **384** took place to some extent in the reverse direction (that is, at C*). If **386** is presumed to be correct, the product mixtures suggest the apparent migratory aptitudes 2-naphthyl ≫ allyl > *n*-$C_{15}H_{31}$ ≫ *sec*-alkyl in a sequence that reminds one of the result ethyl ≥ isopropyl observed[41a] for the free carbenes Alk−C(Me)=C: (such as **19**) at 796 °C. On the other hand, the 1,5-CH insertion reactions into the alkyl groups expected for the free carbene were not mentioned.[357]

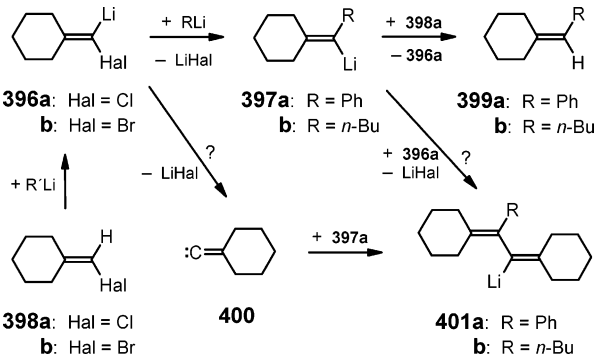


(*E*,*Z*) assignments were feasible in the area of Cl,ZnBr-alkylidenecarbenoids **392**, which were prepared[358,359] by the addition of allylmagnesium derivatives **390** (R^2 = H or CH_3) to ^{13}C-labeled (*) lithium alkylacetylides (**389**) and by subsequent treatment with $ZnBr_2$, followed by chlorination of **391** to give **392**. In the FBW migrations of **392** (in contrast to zinc-ates **262**) starting above −20 °C[360] in diethyl ether, competition between R^1 and the allyl substituents furnished mixtures of the isotopomers **393** and **394** that exhibited the migration sequence[358] 1-octyl ≥ allyl ≈ 1-buten-3-yl > cyclohexyl but showed no correlation with the (*E*)/(*Z*) ratios in the carbenoids **392**, provided that R^1 did not contain heteroatoms. Unfortunately, the conversions were not repeated for varying (*E*)/(*Z*) ratios of the individual carbenoids **392**, to examine the possibility of FBW rearrangements via the free carbenes (**395**) that would lead to stereoconvergent product mixtures. However, the 1-octyl versus *sec*-alkyl migration ratio in **392** of 12:1 is somewhat too large for rearrangement of a free carbene; but the free carbene with R^1 = 1-octyl would have to be dismissed anyway if the expected 1,5-CH insertion were not[358] observed. For unlabeled carbenoids **392** it was established[360] that of a pair of chiral substituents at C-β both retained their configurations during the FBW process. Furthermore, some of the Hal,ZnX-carbenoids such as **392** required Hal = iodine instead of chlorine as the α-nucleofuge[361] even though zinc as the α-metal cation appeared to lead to easier reaction[359−361] than did a lithium cation. Obviously, quite a few mechanistic questions remain open at this time.

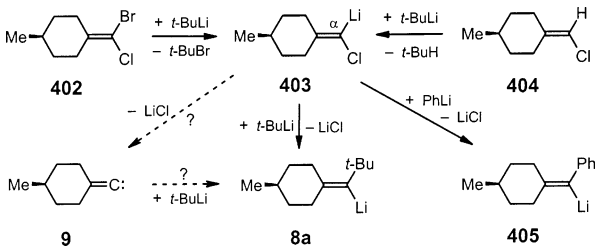
In summary, the notion of comparable rates for anti and syn FBW rearrangements is supported by theoretical investigation and experimental examples. Although direct quantitative comparisons of the migratory aptitudes in alkylidenecarbenoids and the corresponding alkylidenecarbenes could not yet be made, it appears possible that both species rearrange through different transition states but with usually similar energy differences for the competing migrations. As an important restriction, the stationary β-substituent must apparently confer sufficient stabilization to the sp-hybridized C-β atom in the transition state models, **365** (or **367**) and **13**, respectively, of the two species.

3.4.3. Vinylic Substitution S_NV at Alkylidenecarbenoids

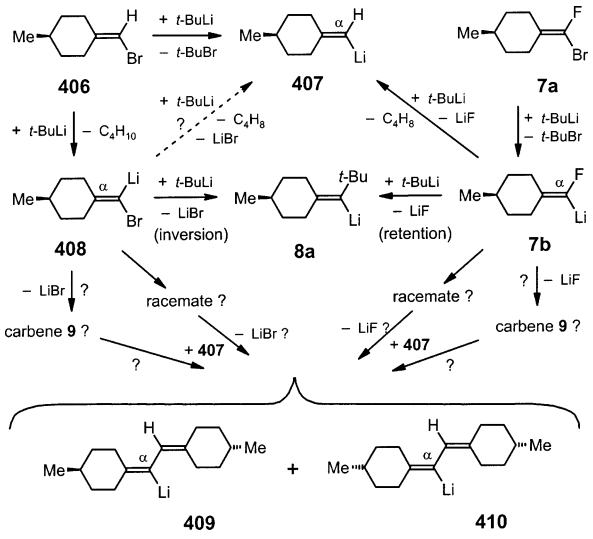
With return to the topic of nucleophilic substitution reactions of $R_2C{=}CLiHal$ (**230**) to give $R_2C{=}CLi{-}R''$ (**233**), as introduced and confirmed[243] in section 3.2, it is intended now to develop deeper insight by inspecting further examples of these S_NV events.



One of the first more detailed investigations used[362] phenyllithium (R′Li = PhLi, 1 equiv) in boiling diethyl ether to deprotonate (chloromethylene)cyclohexane (**398a**), and detected were the alkenyllithium compounds **397a** (12%) and **401a** (5%) by carboxylation but no cycloheptene derivatives which could have been formed by FBW ring expansion. The main product benzylidenecyclohexane (40% of **399a**) was shown to arise by proton transfer from the starting material **398a** to **397a**, the latter competing with R′Li as a base in the formation of carbenoid **396a**. While **397a** was at least partly produced by the S_NV reaction of RLi = phenyllithium with **396a** (instead of carbene **400**), as demonstrated below for **403** → **8a**, it is not known whether **401a** was formed in the same way from **397a** with **396a** or by addition of **397a** to the cyclohexylidenecarbene (**400**) as created by simple LiCl elimination from **396a**. With R′Li = RLi = *n*-BuLi (1 equiv) in place of phenyllithium, the alkenyllithium compounds **397b** and **401b** were generated via **396b** (= **225**) in 2-methyl-THF and then derivatized[363] at −105 °C.



The nucleophilic vinylic substitutions **396** → **397** bear a certain resemblance to the displacement of halide of open-chain carbenoids occurring in the FBW rearrangement mechanisms of section 3.4.2 by backside attack (anti, **365**) or by frontside 1,2-shift (syn, **367**). Correspondingly, both inversion and retention of the configuration[159] at C-α of the optically active Cl,Li-4-methylcyclohexylidenecarbenoid **403** might be anticipated, in contrast to the strict inversion in the $S_NV\sigma$ mechanism of iodonium substitution.[122] Indeed, generation of **403** from optically active (bromochloromethylene)-4-methylcyclohexane (**402**) with 4 equiv of *t*-BuLi in THF at −70 °C (3 h) afforded[6] the optically active protonation product of **8a** with only 38% "net inversion" of configuration. Under the unproven supposition of a stereospecific substitution step **403** → **8a**, the carbenoid **403** must have either racemized to some extent or reacted partly via its achiral carbene **9**, as generated by α-elimination of LiCl from **403**. Unfortunately, residual carbenoid **403** was not quenched and analyzed for racemization, although it had been found[6] that **403**, after its instantaneous generation in the Br/Li exchange reaction in THF at −100 °C, was converted to **8a** with a convenient half-reaction time of roughly 1.5 h. Therefore, it can be concluded only that the achiral carbene **9** cannot have been the sole intermediate because it would have furnished racemic **8a**. If generated by deprotonation[6] of optically active (chloromethylene)-4-methylcyclohexane (**404**) with 2 equiv of *t*-BuLi in either diethyl ether or THF at −75 °C, **403** was again converted to **8a** with 31% or 39% "net inversion", respectively. The intermediacy of **403** was proven[6] by treatment of **404** with only 1 equiv of *t*-BuLi in THF and subsequent substitution at −75 °C (5 h) with phenyllithium (5 equiv) to afford the protonation product of **405** (70%) with 13% "net inversion". (Actually it was the antipodes of **403**, **404**, and **405** that were studied[6] in this last experiment.)

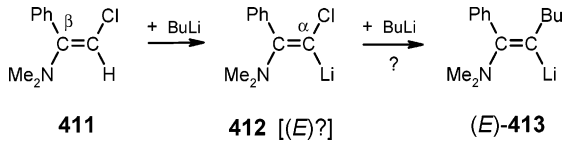


Optically active (bromomethylene)-4-methylcyclohexane (**406**) in diethyl ether or in THF at −90 °C reacted[6] with *t*-BuLi (2 equiv) mainly by Br/Li exchange to give **407** with total conservation of its

configuration, along with the substitution products **8a**, **409**, and **410** derived from the carbenoid **408**. All four alkenyllithium compounds were recognized by deuteriolysis at −90 °C, whereupon the olefin formed from **8a** displayed 50% "net inversion" of configuration. Because optically active **410** and the achiral *meso* compound **409** were found[6] in nearly equal amounts, it might be tempting to conclude that **407** had added the achiral carbene **9** and/or reacted with residual carbenoid **408** after its (partial) racemization. However, **409** and **410** are generated via diastereomeric (albeit closely similar) transition states in either one of the two mechanisms so that their formation in roughly equal amounts could be an accidental result. The mechanistic differentiation by reisolation and optical analysis of unconsumed starting material **406** was not undertaken. On the other hand, when the F,Li-carbenoid **7b** was generated[6] from optically active **7a** and was substituted by *t*-BuLi (3 equiv) in diethyl ether within 5 min at −110 °C, it afforded **8a** (40%) with 100% *retention* of configuration, together with **407**, which was completely converted to the same diastereomers **409** and **410** (1:1, yield 30%) as described above. The stereospecificity of these much faster (as against **403**) substitution reactions of **7b**, as compared with **408**, speaks once more against involvement of the free carbene **9**. The unexpected stereo*retention* may have been caused by the higher affinity of the lithium cation for the "hard" base fluoride, whose expulsion might be facilitated by coordination to two lithium cations (reinforced metal-assisted ionization?[6,7]) so that the associated *tert*-butyl anion is led toward S_NV with retention of the configuration. These substitution processes bear a formal analogy with the *intra*molecular substitution reactions of zinc-ates $R^1R^2C{=}CHal{-}ZnR_2{-}$ (**262**) affording $R^1R^2C{=}CR{-}ZnR$ (**263**) and changing between configurational inversion (preferred) and retention.

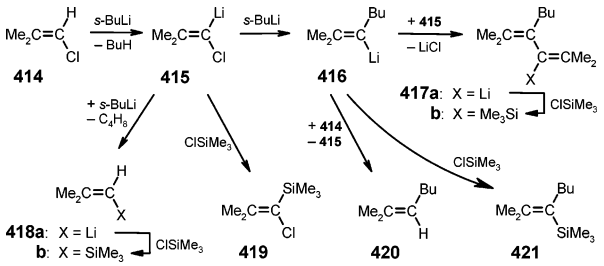
Remarkably, deprotonation of the optical antipode[159] of the α-chloroalkene $MeCH(CH_2CH_2)_2C{=}CHCl$ (**404**) with *t*-BuLi (3 equiv) could not be achieved[208] *in pentane* solution, but in the presence of TMEDA[249] it occurred with a half-reaction time of ∼15 min at −100 °C, giving the totally *racemic* products **8a**, **407**, and **410** (25:21:3, analyzed after deuteriolysis). While it was claimed[208] that racemic **407** had been generated via a (rather improbable) Cl/Li exchange reaction, it was not examined (for example, by [α-D]-labeling) whether **407** arose by hydride transfer[6] from *t*-BuLi to the racemic Cl,Li-carbenoid **403**. A similar objection applies to the racemic carboxylation product of **407** obtained[208] from the antipode of **406** under the same conditions but at −70 °C. In any case, the presence of TMEDA[249] in either pentane or THF solutions[208] of the carbenoids **403** and **408** appears to be responsible for an increased proclivity toward racemization and substitutions, even at −100 °C. It is an open question whether such behavior in pentane/TMEDA solution could be caused by a changed mechanism, involving achiral carbene **9** as the active species. An answer might be obtained from selectivities in cycloaddition reactions if they are determined with a well-chosen pair of competing reactants and checked against the selectivities of bona fide carbene **9** under the same conditions.

The intramolecular nucleophilic substitutions[263] illustrated previously in **259** → **258** were cited in section 3.2 as direct evidence for the feasibility of an in-plane ($S_NV\sigma$) mechanism at a carbenoid center. Vice versa, the Br,Li-carbenoid $Ph_2C{=}CLiBr$ (**239**) was unable[245] to produce $Ph_2C{=}CLi{-}tBu$ (**240**) because the in-plane approach of *t*-BuLi was presumably impeded and the out-of-plane π-attack (addition−elimination mechanism, as suspected[304] for the 9-fluorenylidene system) was obviously too slow. With



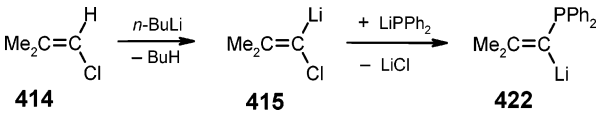
411 **412** [(*E*)?] (*E*)-**413**

this background, it is not clear how *n*-BuLi (2 equiv required) and even *t*-BuLi could succeed in formation of the pure (*E*)-isomers[364] **413** from the Cl,Li-carbenoid **412** [(*E*)-isomer?] in THF at −70 °C by a (perhaps feigned?) approach from the side of the phenyl group: Because the product-forming step was obviously much faster[364] than generation of the carbenoid **412** from **411**, it could not be determined whether (*E*)-**412** mutated to (*Z*)-**412** prior to the attack of BuLi. Remarkably, no product attributable to phenyl migration was observed[364] under these conditions. For comparison, the $S_NV\sigma$ process in an alkenyl-iodonium compound $Alk{-}CH{=}CH{-}I^+{-}Ph$ (**111**) was totally blocked[148] when Alk = *tert*-butyl, whereas Br,Li-(2-adamantylidene)carbenoid (**236**) carrying two *sec*-alkyl groups at C-β was mentioned previously to be easily substituted by *t*-BuLi in pentane.[244]

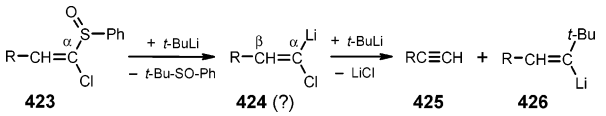


A careful analysis[207] of the products obtained from Cl,Li-isopropylidenecarbenoid (**415**) has established several of the reaction modes that can occur after deprotonation of 1-chloro-2-methylpropene (**414**) with 1.1 equiv of *sec*-butyllithium (*sec*-BuLi, and some of them also with *n*-BuLi) in THF/Et_2O mixtures containing TMEDA[249] at −100 °C (4 h). These comprise hydride transfer (8% of **418a**) and S_NV by *sec*-BuLi to give the alkenyllithium derivative **416** that was slowly protonated (25% of **420**) by the source **414** and partly consumed by the carbenoid **415** (→ 7% of **417a**). Quenching with chlorotrimethylsilane plus HMPA furnished the corresponding silyl derivatives (**418b**, **417b**) and revealed unconsumed **416** (→ 36%

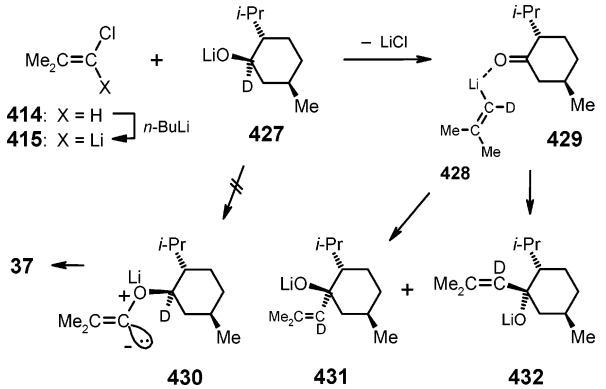
of **421**) as well as the survival of residual carbenoid **415** (→ 5% of **419**).



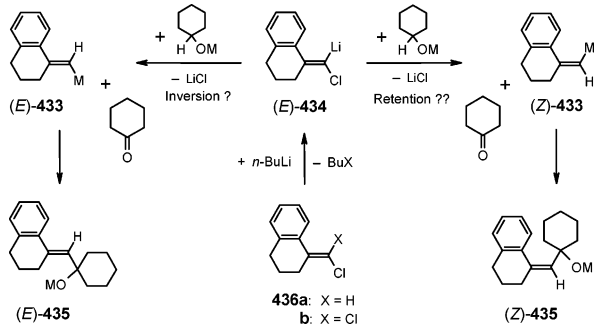
In view of this behavior of **415**, it is hardly surprising that treatment of 1-chloro-2-methylpropene (**414**) with 2 equiv of RLi (R = *n*-Bu, *t*-Bu, methyl, benzyl, or phenyl)[365] in THF/Et_2O mixtures above −80 °C furnished substitution products such as **420** in mediocre yields along with some butatrienes (**245**). Use of better nucleophiles in the product-determining step (for instance, **415** → ≤87% of **422**) provided[365] further confirmation of the two-step S_NV mechanism. It may be recalled that the (*Z*) isomer of Ph−C(Me)=CLiCl (**353**) was substituted by LiBr with predominant inversion of the configuration, affording the (*E*) isomer of Ph−C(Me)=CLiBr (**355**). If the formation of 1-iodocyclopentene (**267**) can be ascribed (section 3.3.1) to the nucleophilic attack of KI on the cyclobutylidenecarbenoid $(CH_2)_3C$=CKBr (**265**), this S_NV reaction must be faster than the competing FBW ring expansion of **265** (Hal = Br).



The fascinating method[366] of carbenoid generation from (1-chloro-1-alkenyl)sulfoxides (**423**) with 3 equiv of *t*-BuLi in THF (10 min at −78 °C) afforded alkynes **425** with R = alkyl or aryl. An S_NV product was detected only in the case of R− = Ph−CH=CH− (cinnamyl (*E*,*Z*) mixture), where **426** (76%) was obviously formed faster than the alkyne **425** (18%). The authors[366] claimed that "this result indicated that the reaction proceeded via the alkylidene carbenoid intermediate", but they did not consider that R− = Ph−CH=CH− might have favored the initial addition of *t*-BuLi at C-α of **423**, affording first Ph−CH=CH−CH=C(*t*-Bu)−SO−Ph and finally **426**. Furthermore, it appears possible that the alkynes R−C≡CH (**425**) were produced from **424** by *β*-elimination of HCl rather than by FBW hydrogen migration.



Hydride transfer from primary or secondary alcoholates such as potassium or lithium mentholate (**427**) to alkylidenecarbenoids in THF was investigated[56] in two phases. First, the Cl,Li-carbenoid **415**, generated from **414** with *n*-BuLi, abstracted deuterium from **427** to form the α-deuterated 1-lithio-2-methylpropene (Me_2C=CD−Li, **428**) located at the *Si* side (that is, below the plane of the paper) of the nascent C=O double bond in **429**. The main *endo* product **431** (5:1) must arise by the immediately following nucleophilic addition of **428** to the carbonyl from the *Si* side because the free alkenyllithium **428**, separately prepared or having escaped from the solvent cage containing **428** and menthone (**429**), afforded solely[56] the *exo* product **432** by exclusive equatorial attack at **429**. (Attack by the unconsumed *n*-BuLi also gave only *exo* product.) Intermolecular C−D insertion of the free carbene Me_2C=C: (**36**) with configurational retention at **427** to furnish **431** might appear conceivable; but **36** and **427** are known to form the ylide **430**, as was shown (section 2.2) by isolation[56] of the enol ether **37** without a trace of (unlabeled) **431** or **432**. This rules out the participation of carbene **36**, and the notion of hydride transfer with in-cage recombination was supported by the temperature-dependent results of crossover experiments (not to be discussed here) in the following system.



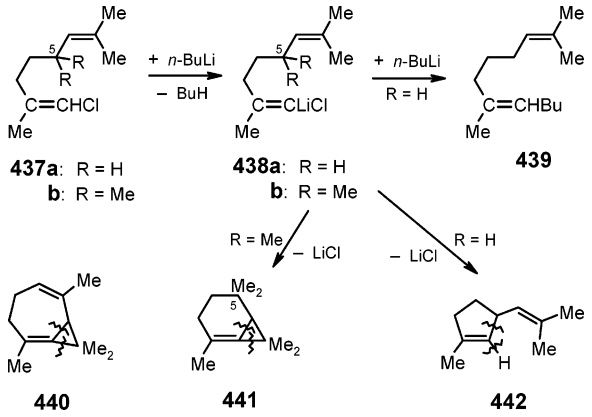
With hydride transfer made reasonably plausible and a free alkylidenecarbene excluded, the second phase was concerned with the stereochemical behavior of the carbenoid performing the hydride abstraction. Predominantly the (*E*)-isomer of Cl,Li-(1,2,3,4-tetrahydronaphth-1-ylidene)carbenoid (**434**, with (*E*)/(*Z*) = 61:1) could be prepared cleanly[56] from either one of the two sources **436a**,**b** in THF at −95 °C, where **434** did not react with subsequently introduced lithium or potassium cyclohexanolate and was thermally stable. At or below 0 °C, the hydride anion was transferred from the olate to (*E*)-**434**, affording the substitution products (*E*)- and (*Z*)-**433**, which recombined with cyclohexanone to furnish the final alcoholates (*E*)- and (*Z*)-**435**, respectively, in the ratio[367a] 2.2:1 from both **436a** and **436b**. Such an independence of the source indicates that the same kinetically active hydride acceptors (presumably **434**) were involved in both cases. The authors stated[367b] "we can reasonably conclude that the hydride abstraction proceeds with inversion of configuration on the carbenoid carbon atom". However, perusal of their report[56] reveals that the low selectivity indicated by the inversion/retention ratio 2.2:1 is similar to further selectivities tabulated[367c] therein, so that the thermodynamically strongly (61:1) preferred[56] (*E*)-**434** must have reacted via both inversion *and*

retention in the case that their (*E*,*Z*) equilibrium was not sufficiently mobile. On the other hand, if their (*E*,*Z*) equilibrium was very mobile, individual selectivities cannot be deduced for the (*E*) and (*Z*) components unless the mechanism of the product-forming steps is already known (Curtin−Hammett principle),[368] which is not the case here. For example, an unknown portion of the material might have reacted via the much less abundant carbenoid (*Z*)-**434** (not depicted) with retention of the configuration. Thus, the issue is still open.

To summarize, nucleophilic vinylic substitution at alkylidenecarbenoids can occur with measurable rates at −100 °C already. Approved solvents are THF or diethyl ether or TMEDA/pentane, but not pentane alone, and TMEDA only when stereochemistry is unimportant. The inversion versus retention stereoselectivity more often than not is quite low, inclusive of the case of hydride transfer from alcoholates. It may be recalled that a similar stereochemical dichotomy was noted for a type of carbene precursors that performed S_NV reactions while disinclined (in the absence of a proton acceptor) to carbene formation; namely, vinylic substitution could occur at iodonium compounds either with strict inversion ($S_NV\sigma$ mechanism, **111** → **115**) or with complete retention of the configuration ("ligand-coupling" mechanism, **124** → **125**).

3.4.4. Insertion and Cycloaddition Reactions of the Alkylidenecarbenoids

The clean 1,5-CH insertion[97] reaction into the H_3CO moeity of the carbenoid $(MeO)_2CH-C(Ph)=CLiBr$ (**252b** or **253b** in section 3.2) was explained in section 2.3.1 by an undetermined accelerating effect in combination with retardation of the competing FBW phenyl migration. But 1,5-CH insertions are normally rare processes in Hal,Li-alkylidenecarbenoids, and in none of the cases reported here[97,261,334,369] was the involvement of the corresponding free carbene excluded.



The Cl,Li-carbenoid **438a**, generated[369] from 1-chloro-2,7-dimethyl-1,6-octadiene (**437a**) in THF at −10 °C, furnished the products of both substitution (13% of **439**) and 1,5-CH insertion[84] (62% of **442**). However, when 1,5-CH insertion was blocked by the presence of 5,5-dimethyl groups[370] in **437b**, the reluctance of carbenoid **438b** as regards 1,4- and 1,6-CH insertions turned out to be sufficiently strong (as is also the case in alkylidenecarbenes) to lead to a preference for the intramolecular [1 + 2] cycloaddition, even though this resulted in formation of a strained olefin[84] (25% of **441**). Refusal of 1,5-CH insertion at sp^2 carbon atoms, as commonly exhibited by alkylidenecarbenes, was also observed[371] for $Me_2C=CH-C(Me)=CH-CH_2CH_2-C(Me)=CLiCl$, generated from 1-chloro-2,6,8-trimethyl-1,5,7-nonatriene with *n*-BuLi in THF at −60 °C: the [1 + 2] cycloadduct[84] **440** (30%) was obtained but the substitution product corresponding to **439** was not mentioned.

Intramolecular competition of two 1,5-CH insertion reactions had revealed the selectivity of a reactive species generated from $H_3C-O-CH_2-C(Alk)=CH-Cl$ (**202**) to be higher than the selectivity of the corresponding alkylidenecarbene in section 2.5. On this basis, the reactive species was thought to be $\mathbf{H_3C}-O-CH_2-C(Alk)=CKCl$. Nothing is known about the course of the formal 1,6-CH insertion at an aromatic *ortho*-position[334] described in section 3.4.2 for $Ph-CH=CH-C(Me)=CLiCl$ (**369b** → **371**).

Intermolecular [1 + 2] cycloadditions may be attributed to the Hal,Li-alkylidenecarbenoids with Hal = Cl[208,237] or Hal = Br[209,240,241] on the basis of competition experiments[209] (section 2.6), which raised the impression that **Br**,**Li**-isopropylidenecarbenoid ($Me_2C=CLiBr$, **218**) did not react via free isopropylidenecarbene ($Me_2C=C:$, **36**). However, the [1 + 2] cycloadditions starting with **Br**,**K**-alkylidenecarbenoids[202,209,269] do quite certainly occur via the corresponding carbenes, as explained for the 2-adamantylidene derivatives **204** → **206** in section 2.5[202] and for **Br**,**K**-isopropylidenecarbenoid ($Me_2C=CKBr$, **216**)[209] in section 2.6. The behavior of **Cl**,**K**-alkylidenecarbenoids[211] has not been analyzed.

4. Synopsis

4.1. General Overview

The contents of the previous sections of this article were classified in terms of the methods used to generate alkylidenecarbenes and alkylidenecarbenoids. In this section, an attempt will now be made to study part of the same material with regard to the competing reaction modes of the two kinds of intermediates involved, a quest that requires us to have available a handy survey of the range of observed selectivities. Such a basis is offered in Table 2, where *qualitative* (apparent) reactivities have been collected for almost all known types of starting materials with respect to their FBW rearrangements, nucleophilic substitutions (including both hydride transfer and the dimerization of carbenoids to give butatrienes **245**), cycloadditions, and intra- (1,5-XY) as well as intermolecular insertion reactions into X−Y bonds. The leading columns containing the β-substituents R^2 and R^1 of $R^2R^1C=C:$ or $R^2R^1C=CMX$ should provide a simple means to spot the required entries, with references to examples, literature citations, and experimental conditions as needed for estimating the chemical behavior of a projected intermediate and its sources, the latter as specified in the penultimate column. The sequences of R^2 and R^1 have been ordered, as far as

possible, by successively decreasing priorities[372,373] of the atoms connecting R^2 and R^1 to the double bond, with the bylaw that priority(R^2) ≥ priority(R^1). For the sake of easier presentation, the relevant chains of the more complicated β-substituents may be symbolized in an abbreviated manner as deemed appropriate. For example, H−C−O−C− in entry 33 may exemplify H_3C−O−CH_2− or Me_2CH−O−CH_2− and so on, while H−C−O−(O=)C− in entry 21 means an ester and −C(=O)−N−C−H in entry 4 an *N*-alkyl amide moiety. Stereochemical information is not included in Table 2 but may be searched in previous sections by means of the formula numbers. It should also be noticed that some reports of synthetically useful work may not have been listed unless containing clear indications of the degree of product selectivity.

The qualitative reactivities in Table 2 must be understood as usually resulting from a highly competitive reaction system in which a rapid reaction ("+ +") may have suppressed alternative modes. Therefore, the symbol "− −" indicates that this mode was not observed under the conditions denoted in the later columns and in the presence of the more successful (that is, the faster) reaction pathway "+ +"; but it does not mean that the suppressed mode cannot be realized by the intermediate in question.

4.1.1. Fritsch–Buttenberg–Wiechell Rearrangements: Do Migratory Aptitudes Depend on the Stationary β-Substituent?

By and large, the rules of the game appear to be similar for the supposed intermediates (alkylidenecarbenoids or alkylidenecarbenes), the sources of which may be distinguished from the nature of the eliminated groups MX (or the method of formation), as presented in the fourth column of Table 2. For hydrogen (entries 29, 35, 58, 83, 96, 112, and 113) or aryl (entries 52−57) as one of the β-substituents, the FBW rearrangement will usually dominate over the other modes of reaction, except for the intramolecular 1,5-OH insertion (entries 85−87) that apparently[102] can swamp out all other routes. Phenyl migration occurs as fast as 1,5-OSi insertion[90] (entry 55), and β-hydrogen migration occurs faster than these two at various temperatures[40,90] (entries 58 and 83). But how can one develop consistent FBW migratory aptitudes from observations such as this: 1,5-CH insertion ≈ Cl migration (entry 3)[135] and Cl ≫ phenyl migration (entry 1)[135] although phenyl migration ≫ 1,5-CH insertion (entry 50)?[70] A possible answer is that chlorine may accelerate 1,5-CH insertion up to a rate over that of phenyl "FBW" migration, so that insertion cannot be used for calibrating the rates of competing FBW processes. At the same time, chlorine as the stationary β-substituent may decelerate phenyl migration (section 2.4.3), and β-phenyl may accelerate the "FBW" shift of chlorine. It may also be disturbing to contemplate on the intramolecular rate sequences 1,5-CH_2 insertion > ≈ migration of $PhSO_2$ ≫ alkyl migration (entry 9)[134] although 1,5-CH_2 insertion was not much faster[134] than alkyl migration, as reported[164] for Bu_2C=C: (**133**) → **141** plus **140** in entry 100. This would be understandable if the "FBW" alkyl shift were decelerated by $PhSO_2$ as the stationary β-substituent (and/or the 1,5-CH_2 insertion accelerated by $PhSO_2$). Vice versa, the relatively slow FBW shift of $PhSO_2$ might become slower if a neighboring alkyl group were exchanged for a more electron-withdrawing β-substituent: Indeed, the small portion of "FBW" product from $PhSO_2$−C(R^1)=C: obtained with R^1 = alkyl (entry 9)[134] dropped to zero with acyl substituents[175] R^1 = AlkC(=O)− (entry 5). There are almost no systematic quantum chemical studies[16,21,31,33] of such substitutent effects, but quite a few experimental data collected in this article seem to support this conjecture: The surprising refusal of phenyl to migrate in the presence of the inductively electron-withdrawing substituents I, Br, or Cl (entry 1),[135] isopropyloxy (entry 15),[340,341] azido (entry 19),[131] dimethylamino[364] (in Me_2N−CPh=CLiCl, **412** in section 3.4.3), trifluoromethyl (entry 20),[254] and so forth does not appear to have been recognized[374] previously. This phenomenon is perhaps at least partly responsible for extending the realm of stability up to room temperature for *i*-PrO(Ph)C=CLiI (**379**, entry 15) in THF. Some uncertainty may remain here because of the absence of butatrienes R^1R^2C=C=C=CR^1R^2 (**245**) that should arise as the products of carbenoid dimerization and that were properly produced from F_3C(Ph)C=CLiBr (**247**, entry 20).[254] Even β-hydrogen migration seems to become retarded with β-ethoxy as the stationary substituent in the (*E*)-isomer[343] of EtO−CH=CLiBr (section 3.4.2). The borderline at which deceleration of FBW phenyl migration will gradually become perceptible may be reached when the inductively electron-withdrawing ability of the stationary β-substituent exceeds $\sigma_I \approx +0.20$, where σ_I is the inductive substituent parameter.[27,168] However, some substituents might act with special effects on either carbenes or carbenoids.

Conversely, there is probably almost no group that cannot migrate if assisted by a sufficiently helpful stationary β-substituent. Simple alkyl groups devoid of heteroatoms migrate rather slowly (roughly as fast as 1,5-CH insertion) at ordinary temperatures, as exposed in entries 27, 38−40, 69, 70, 90, 100, 108, and 111 of Table 2. Notwithstanding assertions to the contrary, these alkyl migrations can occur below 0 °C; for example, see Bu_2C=C: (**133**) → BuC≡CBu (**140**) in entry 100. But the FBW alkyl shift can become fast if driven by the release of ring strain in $(CH_2)_3C$=CXY (entries 101−104) or with LiO− as an electron-releasing β-substituent that can promote *tert*-butyl migration in LiO−C(*t*-Bu)=CLiBr (**382**, entry 16)[347,348] even at −78 °C. This interpretation could be tested by a substrate carrying trialkylsilyl ($\sigma_I = -0.11$)[27,168] as the stationary β-substituent, provided that the FBW shift of Si does not turn out to be too fast[28,375] (to be checked by a ^{13}C-label in the C=C double bond). At present, an experimental estimate of the migratory aptitude cannot be assigned to trimethylsilyl because the examples reported[190,192] at the end of section 2.4.3 (R^1 = $SiMe_3$ in **179**, and **183** with Me_3Si in lieu of Alk) as well as some further investigations[183,193] do not allow a reliable estimation. It may also be recalled that

Table 2. Qualitative Reactivities[a] of Alkylidenecarbenes ($R^2R^1C{=}C{:}$) and X,M-Alkylidenecarbenoids ($R^2R^1C{=}CXM$)

					intramolecular reactions		bimolecular reactions			conditions			
entry no.	β-substituents R^2	R^1	carbenoid[b] MX	formula no.	FBW[c]	1,5-(X−Y) insertion	nucleophiles[d]	insertion into (X−Y)	cyclo-addns	temp, °C	solvent	source no.	ref no.
1	I, Br, or Cl	phenyl	(iod)	**156**	+ > +	--	--	--	0	0?	CH_2Cl_2 + HOMe	**154**	135
2	Br	1-octyl	(iod)	**156**	+ + >	--	--	--	0	0	CH_2Cl_2 + HOMe	**154**	135
3	Cl	1-octyl	(iod)	**156**	+ >	+ (C−H)	--	--	0	0	CH_2Cl_2 + HOMe	**154**	135
4	Ar−SO_2−	−C(=O)−N−*C*−*H*	(iod)	**156**	--	+ (C−H)	0	--	0	+20	CH_2Cl_2	**104**	175
5	Ar−SO_2−	−C(=O)−C−*C*−*H*	(iod)	**156**	--	+ + + (C−H)	0	0	0	+20	CH_2Cl_2	**104**	175
6	Ar−SO_2−	−CH_2CH_2−*O*−*Si*	(iod)	**156**	--	+ + + (O−Si)	0	0	0	+25	CH_2Cl_2	**104**	174
7	Ar−SO_2−	−C−C−*O*−*C*H−O	(iod)	**156**	--	+ + + (O−C)	--	0	0	+65	THF	**104**	174
8	Ar−SO_2−	−CH_2CH_2−*O*−*H*	(iod)	**156**	--	+ + + (O−H)	--	--	0	+25	benzene + NEt_3	**154**	134
9	Ar−SO_2−	alkyl	(iod)	**156**	+ >	+ + (C−H)	--	--	0	+25	benzene + NEt_3	**154**	134
10	Bu−SO_2−	methyl	(iod)	**156**	+ >	+ (C−H)	--	--	0	0	CH_2Cl_2 + NEt_3	**154**	134
11	PhS− or PhS(O)−	−CH_2−CH−CH_2	(iod)	**156**	+ + >	--	--	--	0	−78	THF	**104**	165
12	Me_3Si−	−C−C(=O)−Ar	(iod)	**156**	+ + +	--	--	--	0	+25	HO*t*-Bu	**104**	192
13	H−C−Si−O−	aryl	(diaz)	--	+ + +	--	0	--	--	≤ +80	olefin + benzene	**66**	92
14	*H*−*C*−Si−O−	alkyl	(diaz)	--	--	+ + + (H−C)	0	--	--	≤ +80	olefin + benzene	**66**	91
15	isopropyloxy	phenyl	LiI	**379**	(+)[e]	--	--	0	0	+25	THF	--	340, 341
16	LiO	*tert*-butyl	LiBr	**382**	< + +	0	--	0	0	−78	THF	**381**	347
17	$TolSO_2$−N−	−CH−CH−*NH*Boc	(iod)	**176**	--	+ (N−H)	-- ?	0	0	−20	THF	**173**	188
18	azido	*tert*-butyl	(iod)	**156**	--	--	+ + (DME)	+ (Si−H)	0	+25	$HSiEt_3$ + DME	**104**	131
19	azido	phenyl	(iod)	**156**	--	--	+ + + (DME)	--	0	≤ −10	DME	**104**	131
20	trifluoromethyl	phenyl	LiBr	**247**	--	--	+ + + (dim)	0	0	?	Et_2O	**248**	254
21	H−C−O−(O=)C−	methyl	(diaz)	**58**	--	?	+ (THF)	0	0	≤0	THF	**54a**	96
22	*H*−*C*−N−(O=)C−	methyl	(iod)	**69**	+ >	+ (H−C)	0	--	0	0	HOMe	**54a**	93
23	(Ph*C*H_2O)$_2$HC−	methyl	(diaz)	**(53)**	--	+ + + (H−C)	--	0	0	≤ +20	DME	**54b**	98
24	(*H*$_3$CO)$_2$HC−	phenyl	(diaz)	**61**	--	+ + + (H−CH_2)	--	0	0	−40	THF	**54a**	97
25	(*H*$_3$CO)$_2$HC−	phenyl	LiBr	**252b**	--	+ + + (H−CH_2)	--	0	0	?	?	**251b**	97
26	R_3Si−O−C−	−C−C−*C*−*H*	KBr	--	--	+ + + (C−H)	--	0	0	> −78	KHMDS in Et_2O	**192**	197
27	MeO−*H*$_2$*C*−O−C−	isopropyl	(diaz)	**(53)**	+ +	+ (H−C)	--	0	0	≤ +20	DME	**54b**	98
28	MeO−*H*$_2$*C*−O−C−	methyl	(diaz)	**(53)**	--	+ + + (H−C)	--	0	0	≤+ 20	DME	**54b**	98
29	MeO−H_2C−O−C−	H	(diaz)	**(53)**	+ + +	--	--	0	0	≤ +20	DME	**54b**	98
30	HO−RCH−	−C−C−*O*−*Si*	(diaz)	**88**	--	+ + + (O−Si)	0	0	0	+115	toluene	**84**	101
31	H_3C−O−CH_2−	−C−C−*CH*−OR	(diaz)	**74**	--	+ + + (C−H)	--	0	0	≤ +20	DME ?	**54b**	67
32	H_3C−O−CH_2−	−C−C−*CH*−OR	KCl	**203**	--	+ + + (C−H)	--	0	0	+20	?	**202**	67, 69
33	*H*−*C*−O−C−	methyl	LiBr	**255**	+	+ (H−C)	--	0	0	+25	Et_2O	**254**	261
34	*H*−*C*−O−CH_2−	methyl	KBr	**194**	--	+ + (H−C)	--	+ (O−H ?)	0	+65	THF	**192**	198
35	HO−RCH−	H	(diaz)	**88**	< + +	--	0	0	0	+115	toluene	**84**	100
36	−CH_2−N(R)−CH_2−		(diaz)	--	--	0	--	0	+	0	olefin	**54a**	285
37	*t*-Bu−N−CH_2−	methyl	LiBr	**249**	+ + +	--	--	0	0	+25	Et_2O	**248**	261
38	*H*−*C*−N−CH_2−	methyl	LiBr	**249**	+	+ (H−C)	--	0	0	+25	Et_2O	**248**	261
39	*H*−*C*−N−CH_2−	methyl	KBr	--	+	++ (H−C)	--	0	0	+65	THF	**192**	198
40	R_2N−CH_2−	alkyl	(diaz)	**94**	+	+ + (C−H)	0	0	0	+78	benzene (CCl_4)	**93**	103
41	R_2N−CH_2−	H	(diaz)	**94**	< + +	--	0	0	0	+78	benzene (CCl_4)	**93**	103
42	R−C≡C−	−C≡C−R	LiBr	**230**	+ + +	--	--	0	0 (−)[f]	≤ −10	hexane	**229**	238
43	R−C≡C−	aryl	LiBr	**249**	+ ? +	--	--	0	0	≤ −40	hexane	**248**	239
44	2-naphthyl	allyl	Zr, I	**386**	+ + >	--	--	0	0	> −78	CH_2Cl_2	**385**	357
45	4-BrC_6H_4−	phenyl	KBr	**345a**	+ + +	--	--	--	0	+80	HO*t*-Bu	--	4
46	4-ClC_6H_4−	phenyl	LiBr	**345b**	+ + +	--	--	0	0	−35	Et_2O	--	320
47	4-$O_2NC_6H_4$−	methyl	(diaz)	**(53)**	+ >	--	0	+ (O−H)	0	+25	HOMe	**54a**	76
48	4-PhC_6H_4−	phenyl	LiCl	**349**	+ + +	--	--	0	0	> −70	THF + Et_2O	--	321
49	4-PhC_6H_4−	phenyl	KCl	**357**	+ + +	--	--	0	0	+190	HMPA	**356**	319

Table 2 (Continued)

entry no.	β-substituents R²	β-substituents R¹	carbenoid[b] MX	formula no.	intramolecular reactions: FBW[c]	intramolecular reactions: 1,5-(X−Y) insertion	bimolecular reactions: nucleophiles[d]	bimolecular reactions: insertion into (X−Y)	bimolecular reactions: cycloaddns	conditions: temp, °C	conditions: solvent	source no.	ref no.
50	aryl	alkyl	(diaz)	**(53)**	+ + >	- -	- -	- -	0	- -	THF + HOR	**54b**	70, 74
51	phenyl	phenyl	LiCl	**- -**	+ + +	- -	(+) (dim)	0	0	−77	Et_2O	**248**	228
52	phenyl	cyclopropyl	(diaz)	**(53)**	+ + +	- -	0	- -	0	≥ +25	HOMe	**96**	107
53	phenyl	cyclopropyl	(diaz)	**(53)**	+ + +	- -	- -	- -	- -	≥ +25	olefin	**96**	107
54	phenyl	cyclopropyl	(diaz)	**(53)**	+ + +	- -	- -	- -	- -	+12	olefin	**98a**	107
55	phenyl	−CH−CH−*O*−*Si*	(diaz)	**63**	+ >	+ (O−Si)	- -	- -	0	0	THF	**54b**	90
56	phenyl	methyl	(trif)	**(29)**	+ + >	- -	- -	- -	- -	0	olefin	**28**	52
57	phenyl	methyl	(trif)	**- -**	+ + >	- -	0	- -	0	−20	DME	**47**	57
58	phenyl	H	(heat)	**15**	+ < +	- -	0	0	0	+560	(none)	**- -**	40
59	*tert*-butyl	$-CH_2CH_2-CH{=}C$	(diaz)	**61**	- -	- -	- -	- -	(+)[g]	< +20	THF	**54a,b**	88, 89
60	*tert*-butyl	methyl	(diaz)	**(53)**	- -	- -	- -	+ + + (Si−H)	0	+60	$HSiEt_3$ + benzene	**96**	110
61	*tert*-butyl	methyl	(diaz)	**(53)**	- -	- -	- -	+ (O−H)	+ +	+60	1,2-diene + HOEt	**96**	110
62	Ph−HC=CH−	methyl	(diaz)	**(53)**	+ + +	0	0	- -	0	+65	THF	**54b**	70
63	Ph−HC=CH−	methyl	LiCl	**369b**	+ +	(+)[h]	- -	0	0	> −70	THF + Et_2O	**369a**	334
64	Ph−HC=CH−	H	LiCl	**424**	(+ ?)	- -	+ + (R′Li)	0	0	−78	THF	**423**	366
65	*sec*-alkyl	*sec*-alkyl	LiBr	**230**	- -	0	+ + + (dim)	0	0	≤ +25	THF	**229**	250
66	*sec*-alkyl	*sec*-alkyl	KBr	**206**	- -	0	0	+ (O−H)	+	+100	olefins	**204**	202
67	1-buten-3-yl	cyclohexyl	Zn, Cl	**392**	+ > +	- -	- -	0	0	> −20	Et_2O	**390**	358
68	1-buten-3-yl	1-octyl	Zn, Cl	**392**	+ < +	- -	- -	0	0	> −20	Et_2O	**390**	358
69	*sec*-alkyl	allyl	Zr, I	**386**	< + +	- -	- -	0	0	> −78	CH_2Cl_2	**385**	357
70	cyclohexyl	allyl	Zn, Cl	**392**	+ < +	- -	- -	0	0	> −20	Et_2O	**390**	358
71	cyclopropyl	cyclopropyl	(diaz)	**(53)**	+ +	0	0	+ (O−H)	0	≥ +25	HOMe	**96**	107
72	cyclopropyl	cyclopropyl	(diaz)	**(53)**	+ +	0	- -	- -	+	≥ +25	olefin	**96**	107
73	cyclopropyl	cyclopropyl	(diaz)	**(53)**	- - ?	0	- -	- -	+ + +	+12	olefin	**98a**	107
74	cyclopropyl	cyclopropyl	LiCl	**373**	+ +	- -	+ (R′Li)	0	0	> −90	THF	**372**	335
75	cyclopropyl	methyl	(diaz)	**(53)**	+	0	0	++ (O−H)	0	≥ +25	HOMe	**96**	107
76	cyclopropyl	methyl	(diaz)	**(53)**	+	0	- -	- -	+ +	≥ +25	olefin	**96**	107
77	cyclopropyl	methyl	(diaz)	**(53)**	- -	0	- -	- -	+ + +	+12	olefin	**98a**	107
78	Ph−(Me)HC−	methyl	(diaz)	**61**	+	- -	- -	- -	0	≤ +20	THF	**54a**	83
79	isopropyl	methyl	(heat)	**19**	+ ≥ +	0	0	0	0	+796	none	**18**	41a
80	allyl−S−CH_2CH_2−	methyl	LiBr	**249**	- -	+ + + (H−S!)	- -	0	0	+25	Et_2O	**248**	261
81	*H*−*S*−CH_2CH_2−	methyl	LiBr	**249**	- -	+ + + (H−S)	- -	0	0	+25	Et_2O	**248**	261
82	R−(O=)C−C−	alkyl	(iod)	**186**	- -	+ + + (C−H)	- -	- -	0	+25	THF or *t*-BuOH	**181**	191
83	Si−O−CH−CH−	H	(diaz)	**63**	< + +	- -	- -	- -	0	0	THF	**54b**	90
84	MeO−CH_2−CH_2−	methyl	LiBr	**249**	+ (?)	- -	- -	0	0	+25	Et_2O	**248**	261
85	*H*−*O*−CH_2−CH_2−	$-CH_2CH_2Ph$	(diaz)	**91**	- -	+ + + (H−O ?)	0	0	0	+115	toluene	**90**	102
86	*H*−*O*−CH_2−CH_2−	methyl	LiBr	**249**	- -	+ + + (H−O)	- -	0	0	+25	Et_2O	**248**	261
87	*H*−*O*−CH_2−CH_2−	H	(diaz)	**91**	- -	+ + + (H−O ?)	0	0	0	+115	toluene	**90**	102
88	*H*−*N*−CH_2−CH_2−	alkyl	(diaz)	**61**	- -	+ + + (H−N)	- -	- -	0	≤ +20	THF	**54b**	87
89	*H*−*N*−CH_2−CH_2−	methyl	LiBr	**249**	- -	+ + + (H−N)	- -	0	0	+25	Et_2O	**248**	261
90	allyl	*n*-$C_{15}H_{31}$	Zr, I	**386**	+ > +	- -	- -	0	0	> −78	CH_2Cl_2	**385**	357
91	Cl−$(CH_2)_3$−	methyl	LiHal	**246**	- -	- -	+ + + (dim)	0	0	> −90	THF	**229**	232
92	S−$CH_2CH_2CH_2$−	methyl	LiBr	**249**	- -	(+) [h]	- -	0	0	+25	Et_2O	**248**	261
93	$(RO)_2$*HC*−C−C−	alkyl	(diaz)	**61**	- -	+ + + (*H*−*C*)	- -	- -	0	≤ +20	THF	**54b**	86
94	C−O−*HC*−C−C−	methyl	LiBr	**249**	- -	+ + + (H−C)	- -	0	0	+25	Et_2O	**248**	261
95	C−N−*HC*−C−C−	methyl	LiBr	**249**	- -	+ + + (H−C)	- -	0	0	+25	Et_2O	**248**	261
96	1-octyl	H	(iod)	**- -**	< + +	- -	- -	0	0	0	THF + NEt_3	**118**	165
97	$-(CH_2)_5-$		LiCl	**396**	- -	0	+ + + (R′Li)	0	0	+35	Et_2O	**398**	362

Table 2 (Continued)

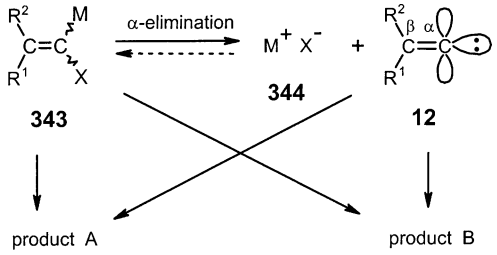
entry no.	β-substituents R²	β-substituents R¹	carbenoid[b] MX	formula no.	intramolecular reactions: FBW[c]	intramolecular reactions: 1,5-(X−Y) insertion	bimolecular reactions: nucleophiles[d]	bimolecular reactions: insertion into (X−Y)	bimolecular reactions: cycloaddns	conditions: temp, °C	conditions: solvent	source no.	ref no.
98	−$CH_2CH_2CH_2CH_2$−		KBr	**323**	−?	0	−?	0	++	+177	olefin	**322**	269
99	1-butyl	1-butyl	(iod)	**133**	--	--	+++	0	0	+25	$SAlk_2$	**132**	164
100	1-butyl	1-butyl	(iod)	**133**	+	++	++	0	0	≤ +20	THF + NEt_3	**132**	164
101	−$CH_2CH_2CH_2$−		(diaz)	**286**	+++	0	--	0	--	0?	olefin	**285**	274
102	−$CH_2CH_2CH_2$−		(diaz)	**286**	+++	0	--	--	0	0	1-butanol	**285**	274
103	−$CH_2CH_2CH_2$−		LiBr	**301**	++	0	+ (R′Li)	0	--	<0	olefin + Et_2O	**300**	283
104	−$CH_2CH_2CH_2$−		KHal	**265**	+++	0	0	--	0	+115	toluene	**264**	270
105	alkyl	alkyl	(diaz)	**(53)**	--	--	--	+++ (N−H)	0	--	HNR_2 + THF	**54a**	74
106	alkyl	alkyl	(diaz)	**(53)**	--	--	--	+++ (N−H)	0	65	HNR_2 + THF	**54b**	81
107	HC−CH_2CH_2−	−CH_2CH_2−*C*−*H*	(diaz)	**61**	--	+++ (C−H)	--	--	0	≤ +20	THF	**54a**	83
108	*H*−*C*−C−C−	methyl	KBr	**197**	+	++ (H−C)	0	+ (O−H)	0	≥ +50	none (KO*t*-Bu)	**196**	199
109	H_2C−CH_2CH_2−	methyl	LiCl	**438a**	--	++ (H−C)	+ (R′Li)	0	0	−10	THF	**437a**	369
110	*H*−*C*−CH_2CH_2−	methyl	KBr	**--**	--	+++ (H−C)	--	0	0	> −78	KHMDS in Et_2O	**192**	197
111	H_2C−CH_2CH_2−	methyl	KBr	**197**	+	+ (H−C)	0	+ (O−H)	0	≥ +50	none (KO*t*-Bu)	**196**	199
112	alkyl	H	(diaz)	**(53)**	< ++	--	--	--	0	−78	THF + HOR	**54a**	74−76
113	propyl	H	(trif)	**(29)**	< ++	--	--	--	--	0	olefin	**28**	52
114	ethyl	methyl	(heat)	**43**	+ > +	0	0	0	0	+796	none	**18**	41a
115	ethyl	methyl	(trif)	**43**	--	--	0	+ (O−H)	++	0	olefin + HO*t*-Bu	**41**	52
116	methyl	methyl	(trif)	**36**	--	--	0	+ (O−H) and ++ (Si−H)	0	0	$HSiEt_3$ + HO*t*-Bu	**35**	52
117	methyl	methyl	(trif)	**36**	--	0	+ (THF)	++ (O−H)[i]	0	0	THF	**35**	56
118	methyl	methyl	LiCl	**415**	--	0	+++[j]	--	0	≤ +20	THF	**414**	56
119	methyl	methyl	(diaz)	**36**	--	0	+++ (THF)	--	0	−78	THF	**54a**	75
120	methyl	methyl	(diaz)	**36**	--	0	--	+++ (Si−H)	0	≥ −78	$HSiEt_3$ + THF	**54a**	78
121	methyl	methyl	(diaz)	**36**	--	--	0	+++ (Si−H)	0	?	$HSiEt_3$ + benzene	**96**	108
122	methyl	methyl	(diaz)	**36**	--	0	--	--	+	−20	styrenes in THF	**54a**	205
123	methyl	methyl	LiBr	**218**	--	0	+++ (dim)	0	0	−60	THF	**217**	236
124	methyl	methyl	LiCl	**415**	--	0	+++ (R′Li)	0	0	−100	THF + Et_2O	**414**	207, 365

[a] +++ or ++ > or < +++ = formed exclusively; ++ or + > or < + = predominant; + = observed; -- = not found; ? = not finally established; 0 = not applicable. [b] α-substituents MX (or method): (iod) = from iodonium compound; (diaz) = via diazonium ylide; (trif) = from alkenyl triflate; (heat) = by thermolysis. [c] Fritsch−Buttenberg−Wiechell rearrangement: ++ > and + > + and + > (or < ++ and + < + and < +) signify that R^2 migrates faster (or slower) than R^1. [d] Substitution or dimerization (dim) or reaction with Lewis base components of the solvent, such as (THF), (DME), (NEt_3). [e] Almost stable at room temperature. [f] Solvent cyclohexene. [g] Intramolecular cycloaddition. [h] 1,6-HX insertion. [i] Into menthol. [j] Hydride transfer from mentholate.

quantum chemical computation[28] on $H_3Si-CH=C:$ referring to the gas phase might predict migratory aptitudes differing from those in solution.

The suspected dependence of reactivity on the β-substituents entails reservations concerning the following kind of comparisons. Only by paying attention to the actual substituent pattern is it possible to understand that the insertion process can compete with the FBW migrations of chlorine (entry 3), sulfonyl (entries 9 and 10), amido (entry 22), alkyl (entries 27, 100, 108, and 111), and some heteroalkyl groups (entries 33 and 38−40). But bromine (entry 2), benzenesulfinyl (entry 11), and phenylthio (entry 11) migrate distinctly faster, whereas the FBW shift is much slower than 1,5-CH insertion for silyloxy (entry 14). Similar comparisons of the FBW rearrangement with competing bimolecular (instead of unimolecular) reactions indicate modest migratory aptitudes for 4-nitrophenyl (entry 47) and cyclopropyl (entries 71, 72, and 74−76, but see also entries 73 and 77) yet no such inclination for azido[131] (entries 18 and 19). Unfortunately, even careful interpretation with due regard to the β-substituents may not always be directly reliable. It will be reliable within the model of Scheme 3 for processes starting from

Scheme 3. Interconnection of Alkylidenecarbenoids (343), Alkylidenecarbenes (12), and Their Products



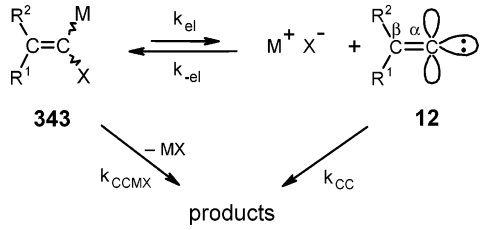
the alkylidenecarbene **12** to give products A and B in the absence of MX (**344**). However, with an alkylidenecarbenoid **343** as the source, formation of products A and B has to compete with the α-elimination of MX giving **12**, and this may raise uncertainties as follows. If product A were formed from the carbenoid **343** only but product B from the carbene **12** only (vertical arrows in Scheme 3), then the rate of generation of product A relative to that of simple α-elimination (if irreversible, **343** → **344** plus **12**) would determine the product ratio A/B and this might be mistaken to represent the selectivity of product formation from carbenoid **343** directly. This event may occur not only in comparing any two of the four title reactions of this article but also in contrasting two FBW processes (namely, the anti and syn modes), in which case the products A and B would represent the two isotopomers emanating from a labeled source. Product development would be different if the α-elimination were readily reversible: the product ratio A/B might then increase with growing concentrations of M^+X^- in the solution, because formation of B via **12** would become inhibited, as explained in the next section. However, this test has apparently never been applied; so its practicability cannot be guaranteed. The interpretation will become much more difficult if the products A and B are formed via both intermediates **343** and **12**, as envisaged for $R_2C=CLiHal$ (**230**) and $R_2C=C:$ (**234**) in section 3.2. Therefore, a reliable assessment of relative rates of FBW processes and their substituent dependence is not always a simple task.

Considering further MX derivatives with due reservations in the spirit of Scheme 3, it is worth noting that the relative rates of FBW alkyl migration and of 1,5-CH insertion observed for $Bu_2C=C:$ (**133** → **140** plus **141**, entry 100)[164] were smaller than those for **Br,K**-alkylidenecarbenoids at elevated temperatures (**197** with KO*t*-Bu, no solvent, entry 111),[199] while in cooled solutions (KHMDS in Et_2O, entry 110)[197] the FBW alkyl shift became too slow for competing with 1,5-CH insertion, as also observed for the **Cl**,**Li**-alkylidenecarbenoid $Me_2C=CH-(CH_2)_3-C(Me)=CLiCl$ in THF (**438a**, entry 109).[369] Likewise, the purported FBW shift of $R_2CH-O-CH_2-$ in comparison with the competing 1,5-CH insertion reaction appeared to show a higher rate ratio in the **Br,Li**-alkylidenecarbenoid[261] $R_2\mathbf{C}H-O-CH_2-C(Me)=CLiBr$ (**255**) in diethyl ether (entry 33) than in the related alkylidenecarbene[98] $(RR'\mathbf{C}H-O-CH_2)_2-C=C:$ (**78**). On the other hand, the expected 1,5-CH insertions could not compete with FBW migrations of primary alkyl > secondary alkyl in Cl,Zn-alkylidenecarbenoids **392** (entries 67, 68, and 70) and perhaps also in I,Zr-alkylidenecarbenoids **386** (entries 44, 69, and 90).

4.1.2. Are Rate Measurements Useful, and Do Reactivities Depend on the Solvent?

Aside from product ratios, mechanistically more promising direct rate measurements are possible owing to the following properties. Alkylidenecarbenoids are domesticated forms of the alkylidenecarbenes, moderated through an incomplete satisfaction of their ambiphilic character by coordination to MX. This view was supported by higher-level quantum chemical calculations on FBW hydrogen migrations which indicated a very low activation barrier of roughly 1.5 kcal/mol for the carbene $H_2C=C:$ in the gas phase (section 2.1)[17,18] but a much higher value of 14.0 kcal/mol for the solvated carbenoid $H_2C=CLiI$ (**227** in section 3.1).[224] Such behavior is also experimentally evident from the observation that alkylidenecarbenoids in THF solution are kinetically stable ("persistent") at very low temperatures whereas alkylidenecarbenes are not. Consequently, the rates of consumption may be measured directly for alkylidenecarbenoids at suitable temperatures. For plain bimolecular reactions lacking rate-controlling intermediates, these rates will be proportional to the concentrations of both the carbenoid **343** and a reagent (nucleophile or olefin, for examples) and to the second-order rate constant k_{CCMX} in Scheme 4, so that rate = k_{CCMX}[**343**][reagent]. However, such second-order kinetics are compatible also with a mobile preequilibrium of α-elimination ($k_{-el}[M^+X^-] \gg k_{CC}$[reagent]) in Scheme 4 involving the carbenoid **343** and the carbene **12**: With the reversibly formed intermediate **12** as the only species reacting with the partner reagent (assume that $k_{CCMX} \approx 0$), the rate of

Scheme 4. Rate Constants Describing Bimolecular and Unimolecular Consumption of Alkylidenecarbenoids (343)



carbenoid consumption will be proportional to the small equilibrium concentration of carbene **12** and hence (by the equilibrium quotient) to the concentrations of carbenoid **343** and of the reagent, as above:

$$\text{rate} = k_{CC}[\mathbf{12}][\text{reagent}] = k_{CC}k_{el}[\mathbf{343}][\text{reagent}]/(k_{-el}[M^+X^-])$$

The latter situation might be recognized through observation of decreased rates in the presence of increased M^+X^- concentrations; but attempts to verify this concept have not come to the attention of this author. The possibility of trapping (k_{-el}) by M^+X^- has been demonstrated[208,313] (section 3.4.1) with the carbene $MeCH(CH_2CH_2)_2C{=}C:$ (**9**), which has no proclivity for unimolecular conversions (FBW or 1,5-CH insertion). Within the model of Scheme 4, detection of this inhibitory effect constitutes evidence for the participation of carbene **12** in product formation, whereas absence of such deceleration by M^+X^- under second-order kinetics points to a direct reaction (k_{CCMX}) of carbenoid **343** with the reagent. But when carbene **12** is consumed much faster by conversion to products than by the addition to M^+X^-, so that $k_{CC}[\text{reagent}] \gg k_{-el}[M^+X^-]$ ($\gg k_{el}$), then the inhibitory effect of M^+X^- will vanish because the α-elimination step k_{el} becomes essentially irreversible and the preequilibrium gets heavily disturbed. Any such rapid product-determining step occurring after a rate-determining α-elimination (slower k_{el}) can no longer influence the measured rate $= k_{el}$[**343**] of carben*oid* consumption: In bimolecular reactions, the detection of this first-order kinetic behavior (namely, zeroeth order with respect to the reagent) would provide an independent piece of evidence for the formation of an intermediate (surmised to be the carbene **12**) on the way from the carbenoid to product.

The latter argumentation cannot be used with unimolecular conversions (FBW rearrangement or intramolecular insertion) of the carbenoid **343**, of course. These will exhibit first-order kinetics both with and without the carbene intermediate **12**, as may be gleaned from the kinetic relations and rate equations given above but with the concentration term [reagent] omitted: The decay of carbenoid **343** can take place directly (rate $= k_{CCMX}$[**343**]) or via carbene **12** in a mobile preequilibrium with rate $= k_{CC}k_{el}$[**343**]$/(k_{-el}[M^+X^-])$. Hence, the involvement of readily reversible α-elimination may again be recognized experimentally from the inhibitory effect of increasing M^+X^- concentrations. But the practicability of this technique cannot be guaranteed because the lifetimes of alkylidenecarbenes in solution should be in the range of 10^{-12} s (for H migration) to 10^{-5} s (for alkyl migration and 1,5-CH insertion), so that it may be difficult to find a sufficiently fast bimolecular MX addition reaction (discussed in section 3.4.1) that can diminish the decay rate of carbenoid **343**: the product-determining steps could still occur much faster, so that this technique fails because still $k_{CC} \gg k_{-el}[M^+X^-]$ ($\gg k_{el}$). Simple α-elimination (k_{el}) will then become the rate-determining step, so that rate $= k_{el}$[**343**] as above, which cannot be distinguished from rate $= k_{CCMX}$[**343**], of course. In this case, confirmation or rejection of carbene intermediacy in unimolecular reactions cannot be sought by rate measurements.

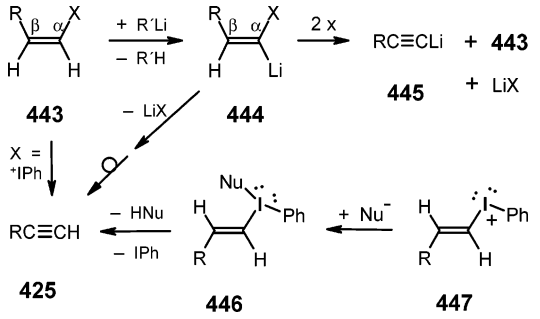
Thus, it may be concluded that kinetics might give clearer answers than selectivity alone and hence provide a powerful (albeit not infallible) tool for the differentiation of the pathways in Scheme 4. More general rate expressions have been collated[368] for situations more complicated than those discussed above (such as $k_{CC} \approx k_{-el}[M^+X^-]$). Identification of a kinetically detected intermediate requires auxiliary information such as selectivity studies in comparison with the corresponding bona fide carbene. When the selectivities are different, the kinetic intermediate cannot be the carbene alone, whereas coinciding selectivities are a necessary albeit not sufficient criterion which, however, might be strengthened or weakened by the combination with rate data: The intermediate being trapped by M^+X^- (causing deceleration) *and* having carbene selectivity should probably be the carbene, provided that the parent carbenoid was shown not to interact with M^+X^-. Indeed, a most important prerequisite of all (even qualitative) kinetic investigations is the continuous control of the integrity of the starting carbenoid. For instance, optically active cyclobutylidenecarbenoids of type $XCH(CH_2)_2C{=}CMHal$ (generated from **282c**−**f**) might afford chiral products such as **283c**−**f** (if unimolecular) or $XCH(CH_2)_2C{=}CH{-}Nu$ (if bimolecular) either in optically active form or as racemic mixtures. Initial α-elimination to give the achiral carbene $XCH(CH_2)_2C{=}C:$ must also furnish racemic products, so that a mechanistic differentiation in the latter case has to rely on rate measurements, provided that racemization of the starting carbenoid could be excluded: Evidence for an (achiral or racemic) intermediate in a bimolecular process might then be obtained from observation of reversible second-order kinetics with deceleration by M^+Hal^- or from irreversible first-order kinetics (zeroeth order in the reagent), as explained above. The absence of an intermediate in the rate-controlling steps would be indicated by irreversible second-order kinetics, in which case formation of the racemic products as stipulated above would have to be explained by nonselective conversion.

Is the medium an important parameter? The lifetimes of Hal,Li-alkylidenecarbenoids $R_2C{=}CLiHal$ (**230**) are shorter[228,237] in diethyl ether solution than in the more polar THF; but it is not clear whether the successful application of the nonpolar solvent hexane[238] to promote the FBW rearrangement of (R′—

$C{\equiv}C)_2C{=}CLiBr$ (section 3.2) was due to an accelerating medium effect or to avoidance of destructive proton transfer from an ethereal solvent. The alkylidenecarbenes **156** generated by "Michael addition" of $PhSO_2^-$ to Alk−C≡C−I^+−Ph (**104**) revealed only small changes[134] of their 1,5-CH insertion versus "FBW" ratios upon solvent changes from water to THF and to benzene. Thus, the choice of a solvent does not appear to be an efficient tool for controlling a selection between at least these two reactions. This disappointing trait will probably extend to the alkylidenecarbenoids, but a systematic investigation has not come to the attention of this author. In a noncoordinating solvent such as hexane, lithium cations are believed[6,7] to be inclined to assist the separation of halide anion from their shared C-α atom more readily than in the coordinating solvent THF, but it is not known whether such cation assistance will accelerate simple α-elimination more than the FBW rearrangement (or other processes) of the carbenoid. In competition with FBW ring expansion, the Br,Li-cyclobutylidenecarbenoid $(CH_2)_3C{=}$CLiBr (**301**) could be substituted by PhLi in Et_2O[283] (**301** → **303** → **305**) but not by an excess of *n*-BuLi in hexane.[286] However, this observation alone does not provide evidence for a solvent-dependent selectivity of **301** in bimolecular substitution, because it may have resulted from the weaker nucleophilicity of organollithium reagents when dissolved in a hydrocarbon. The solvent dependence of global rates of multistep sequences[2,198,208,270,272,321] such as **264** → **265** → **268** → **269** does not allow one to draw straightforward conclusions. Thus, the role played by the solvent has received relatively little attention; nevertheless, simple comparison of published selectivities should be meaningful because at present they do no appear to be very sensitive to the medium.

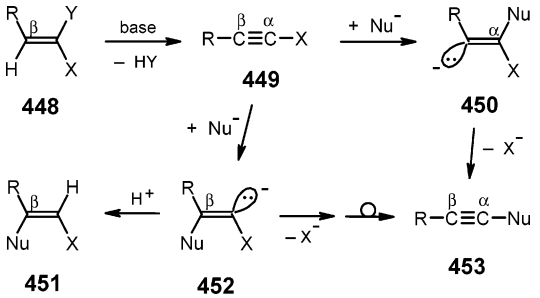
4.1.3. FBW Rearrangements Feigned by β-Elimination or by Competing Species

Formation of an alkyne from a possible precursor of an alkylidenecarbenoid or alkylidenecarbene cannot always be taken as evidence for an FBW rearrangement. The carbenoid **444** (R = phenyl; X = chlorine), obtained by deprotonation of the terminal (*Z*)-chloroolefin **443**, was reported[325] to decompose in THF/Et_2O even at −110 °C by bimolecular[229,325] anti-β elimination, affording the acetylide **445** along with an equivalent amount of re-formed (*Z*)-β-chlorostyrene (**443**). Acceleration of the conversion by additional *n*-BuLi[229,325] supported this mechanism. The (*E*)-isomer of **443** furnished the corresponding products (**445** and re-formed (*E*)-β-chlorostyrene) only at a higher temperature (−60 °C),[325] which would allow the (*E*) → (*Z*) conversion of the carbenoid **444**, as proven[242] for Ph−C(Me)=CLiCl (**353**) at a similar temperature. In this way, kinetic evidence should also be used to qualify (or disqualify) other alkyne formations as FBW processes. For example, the formation[265,376] at −10 °C within 15 min of an acetylide RC≡CLi (**445**) from RCH=CLiX (**444**, generated by the much faster[376] α-lithiation of **443**) carrying X = O−C(=O)−N(*i*-Pr)$_2$ in diethyl ether could have been qualified as an FBW rearrangement by establishing *uni*molecular consumption of **444** at a rate that was independent of excess[376] *t*-BuLi. Stoichiometry does not differentiate these cases because the FBW product **425** is sufficiently acidic to protonate **444** rapidly, leading to the same mixture of **445** and **443** as in the bimolecular β-elimination. The alkynes R−C≡CH (**425**) arising from sulfoxides[366] (**423**) via R−CH=CLiCl (**424**) may also result from bimolecular β-elimination with excess *t*-BuLi, feigning the FBW process. Further possible examples[262,263] have been mentioned before.



For X = $^+$I−Ph as the nucleofuge in (*Z*)-iodonium compounds **443**, anti-β elimination occurs so readily that these cations with β-hydrogen are notoriously unstable, converting to alkynes **425** even in acidic solutions.[377] Moreover, it was emphasized in section 2.4.2 that a corresponding (*E*)-isomer **447** may also decompose to an alkyne **425** by conversion to **446** (a 10-I-3 compound)[143] followed by a syn-β elimination, as depicted previously for Alk−CH=CH−IClPh (**113**) → Alk−C≡CH (**116**). It appears possible to distinguish these processes from FBW rearrangements by the investigation of deuterated specimens as explained for 1-octyl−CD=CH−I^+−Ph (**120**).

Competing species are those which imitate alkylidenecarbenes (and the carbenoids) instead of allowing them to become the actual intermediates. For instance, terminal olefins **448** carrying a β-hydrogen atom and two nucleofugal groups (X, Y) may be the precursors of alkynes **449,** the substitution of which by a nucleophile (Nu^-) must also be considered[378] to be mechanistically ambiguous. For a sufficiently



electron-withdrawing β-substituent R in **449**, nucleophilic attack at C-α and expulsion of the nucleofuge X^- from the intermediate **450** would furnish the substitution product **453** by the conventional addition−elimination mechanism without FBW rearrangement. On the other hand, attack of Nu^- at C-β of **449** may be anticipated if the nucleofugal group X can provide for a better preliminary stabilization of the negative charge. If the resulting carbenoid anion **452** can be trapped to give **451**, it

would appear rather probable that **452** without trapping will produce the FBW product **453**. It can be seen that positive evidence for this FBW rearrangement from ^{13}C-labeling will emerge only if R (but not Nu) migrates to C-α (assuming carbenium rearrangements to be out of the question). Further examples of feigned FBW events comprise the formation of alkynes AlkC≡CH (**116**) from iodine(III) compounds Alk−CH=CH−ICl_2Ph^- (**114**) or Alk−CH=CH−I^+−Ph (**111**) by β-elimination. Alkynes may also arise from iodonium cations by heterolysis with concerted carbenium rearrangement **102** → **106** (section 2.4.1) and subsequent deprotonation, as exemplified by formation of 6-phenyl-2-hexyne from $Ph(CH_2)_3$−C(Me)=CH−I^+−Ph (**126**). The (9-fluorenylidene)methanediazonium ion (section 3.4.2) can simulate the corresponding carbene in ring expansion[332] to give 9-chlorophenanthrene.

4.1.4. Unimolecular Insertion Reactions

Intramolecular 1,5-CH insertion is certainly the most important synthetic achievement in the field, owing to its extreme regio- and stereospecificity and reliability for the preparation of cyclopentene derivatives. These properties were discovered during mechanistic investigations and exploited in numerous syntheses[65,67,69,85−87,98,100,175,184−187,197] of natural products and otherwise interesting target molecules. As repeatedly emphasized, the regiospecificity in the types of compounds currently being considered is even narrowed inasmuch as 1,5-CH insertion into sp^2-CH bonds is practically out of the question. Under the special constitutional conditions shown in **176** → **177** (section 2.4.3), 1,5-insertion into N−H was faster[188] than that into C−H bonds. The following other modes are extremely rare: 1,4-CH (**179** → **180**),[190] 1,6-CH (**371**),[334] 1,6-OSi, and 1,7-OSi (section 2.3.2).[101] Two products of formal 1,5-NC insertion were obtained[87] in poor yield.

Alkylidenecarbenes HX−CH_2CH_2−C(R^1)=C: (**61**) exhibited the impressive 1,5-CH insertion selectivity[83] 1:30:240 for *prim*-/*sec*-/*tert*-C−H bonds, shown also by the carbenes RR′CH−CH_2CH_2−C(Me)=C: (**200**) that were presumably formed by KBr elimination from RR′CH−CH_2CH_2−C(Me)=C**KBr** (**197**). On the contrary, H_3C−O−CH_2−C(Alk)=C**KCl** was found[67] to be distinctly more selective than the corresponding carbene; therefore, simple α-elimination (Scheme 4) of KCl is thought to be slower than the 1,5-CH insertion occurring within this carbenoid. The selectivity difference was less than dramatic, but it is difficult to draw further conclusions about X,M-alkylidenecarbenoids because their selectivities have been insufficiently explored. The Cl,Li-alkylidenecarbenoid Me_2C=CH−$C(Me)_2$−$(CH_2)_3$−C(Me)=CLiCl was reported[369] to undergo 1,5-CH insertion already at −60 °C in THF; but intermediacy of the corresponding alkylidenecarbene was not excluded for any of the **Cl**,**Li**-alkylidenecarbenoids.

4.1.5. Bimolecular Insertion, Substitution, Addition, and Cycloaddition Reactions

Bimolecular X−Y insertions are disfavored by their concentration dependence and by usually negative activation entropies. A glance at Table 2 shows that only the fastest bimolecular X−Y insertions can be successful: Si−H, O−H, and in more concentrated solutions also N−H, but hardly ever[78] any kind of simple C−H functions (except in the case[354] of the long-lived and unselective carbene F_2C=C:, this even at < −243 °C[16]). The mechanism of an apparent insertion into the aldehydic C−H bond of 2-methylpropanal[109] is not known. Surprisingly, quantum chemical calculations suggested an activation barrier of 15.9 kcal/mol[379] for an *inter*molecular insertion of H_2C=C: into the primary C−H bond of ethane and a similar barrier[380] for insertion into methane. This means that *all* other reaction modes of alkylidenecarbenes must face significantly lower barriers because the more reactive *sec*-C−H bonds are abundant in almost all of the solvents in use but do not react. However, O−H in small concentrations can compete with *intra*molecular 1,5-CH insertion (entries 108 and 111) or with the decelerated FBW migration of 4-nitrophenyl (entry 47),[76] whereas the FBW and intramolecular 1,5-CH insertion reactions of amido groups[93] (**69** in section 2.3.1 and entry 22) occur faster than bimolecular O−H insertion. Free 2-butylidenecarbene Et−C(Me)=C: (**43**) was shown,[52] as described in section 2.2, to be probably the active species inserting into the H−O bond of HO*t*-Bu.

Vinylic nucleophilic substitution (possibly in-plane $S_NV\sigma$) at alkylidenecarbenoids was presented in detail in sections 3.2 and 3.4.3. It has been known for a much longer period of time than the recently established (section 2.4.2) $S_NV\sigma$ process at primary alkenyliodonium cations Alk−CH=CH−I^+−Ph (**111**), which does not involve alkylidenecarbenes. It occurs very rapidly with organolithium compounds and with similarly strong nucleophiles by attack at C-α of Hal,Li-alkylidenecarbenoids, affording diverse stereochemical results, often at low temperatures that do not encourage the formation of carbenes by α-elimination of LiHal. Therefore, S_NV will probably take place at Hal,Li-alkylidenecarbenoids before these can generate the corresponding alkylidenecarbenes. Disappointing inversion/retention selectivities were also observed[56] for the hydride transfer (entry 118) from alcoholates to alkylidenecarbenoids (**436** → **434** → → **435**) described in section 3.4.3. There has been very little study of the solvent dependence because the organolithium compounds were usually applied in ethereal media. For example, substitution of optically active $MeCH(CH_2CH_2)_2$C=CLiCl (**403**) by *t*-BuLi in THF to give $MeCH(CH_2CH_2)_2$C=CLi−*t*-Bu (**8a**) had a half-reaction time[6] of roughly 90 min at −100 °C, whereas the same substitution reaction in TMEDA/pentane solvent[208] at −100 °C was distinctly faster, as judged from the half-reaction time <15 min of the initiating deprotonation of $MeCH(CH_2CH_2)_2$C=CH−Cl (**404**) followed by even faster[208] formation of the substitution products. The complete racemization[208] tentatively ascribed to TMEDA in pentane solution (section 3.4.3) does not allow one to decide between $MeCH(CH_2CH_2)_2$C=CLiCl (**403**) and $MeCH(CH_2CH_2)_2$C=C: (**9**) as the two intermediates involved. A decision might perhaps become possible by employing the much faster[6] Br/Li exchange reaction

of optically active $MeCH(CH_2CH_2)_2C{=}CBrCl$ (**402**) with *t*-BuLi to generate $MeCH(CH_2CH_2)_2C{=}CLiCl$ (**403**) *in pentane* (without TMEDA) at a very low temperature. Provided that carbenoid **403** under these conditions would be neither consumed by substitution nor racemized rapidly, this strategy would allow studies in nonpolar solvents: By careful control of the stereochemical integrity of optically active carbenoids such as **403** or $XCH(CH_2)_2C{=}CMHal$ (generated from the sources **282c**−**f**), the intermediacy of the corresponding achiral carbenes $MeCH(CH_2CH_2)_2C{=}C:$ (**9**) or $XCH(CH_2)_2C{=}C:$, respectively, as a prerequisite for racemization, substitution, addition, and other reactions could then perhaps be supported or disproved, as discussed in section 4.1.2. The results should also shed more light on the concept of metal-assisted ionization,[6,7] which implies that less polar solvents should activate the Hal,Li-alkylidenecarbenoids toward heterolytic Hal−C bond fission.

Carbenoid dimerizations ("dim" in Table 2) as a special kind of such S_NV reactions to give butatrienes (**245** in section 3.2) can take over at or below −60 °C already (entries 51, 91, and 123) if the alkylidenecarbenoids in sufficiently high concentrations are not consumed by rivaling reaction modes. The same dependence of S_NV rates on the concentrations of other nucleophilic reagents may entail difficulties in retrieving the relative reactivities from Table 2 because the yield of a (projected or undesired) substitution reaction may depend (in a straightforward though not always specified manner) on the mode of addition of the reagents.

Alkylidenecarbenes, being more electrophilic than alkylidenecarbenoids, can perform *addition reactions* to weaker nucleophiles such as alcoholates[56] (**37** or **430**, both in entry 117), tetrahydrothiophene[164] (**134**, entry 99), and even DME[131] (**161** in entries 18 and 19) or THF. Addition to THF was repeatedly encountered and recognized by secondary products (**38** → **40**, **57** → **58**, and **139** → **143**) that arose at a rate comparable[164] to those of 1,5-*sec*-CH insertion and FBW alkyl migration in $Bu_2C{=}C:$ (**133** → **140** + **141** + **143** in entry 100). The addition proceeds via high-energy oxonium ylides that may be considered as unstable solvent complexes of the alkylidenecarbenes and that are formed fast but reversibly, so that they are usually not troublesome (entries 105, 106, and 112). But alkylidene*carbenoids* do *not* appear to possess any proclivity toward addition to THF or diethyl ether (other than cation solvation). An alkenediazonium cation $R^1R^2C{=}CH{-}N_2^+$ (**97**) was shown[115] to simulate the carbene $R^1R^2C{=}C:$ (**12**) in the nucleophilic addition of lithium azide.

Free alkylidenecarbenes are very probably the *active species in [1 + 2] cycloaddition* reactions (sections 2.2, 2.5, and 2.6) carried out with most kinds of precursors, including Br,**K**-isopropylidenecarbenoid ($Me_2C{=}CKBr$, **216**). But although the carbene $Me_2C{=}C:$ (**36**) is energetically within reach of the carbenoids $Me_2C{=}CKBr$ (**216**) or $Me_2C{=}CLiBr$ (**218**), the latter does *perhaps* (section 2.6) undergo [1 + 2] cycloadditions without prior LiBr elimination. The solvent complex with THF does not disturb the cycloadditions of isopropylidenecarbene ($Me_2C{=}C:$ **36**, entry 122).[205] But 1,5-CH insertion can predominate over [1 + 2] cycloaddition (entry 14),[91] as can the faster types of FBW migration both in carbenes (entries 13, 53, 56, and 101) and in Br,Li-cyclobutylidenecarbenoid[283] $(CH_2)_3C{=}CLiBr$ (**301**, entry 103).

In conclusion, it appears possible that all of the diverse reaction modes of alkylidene*carbenes* might be rather similarly decelerated in the Hal,Li-alkylidene*carbenoids*, notwithstanding exceptions and significant selectivity differences of the intermediates in question. Nevertheless, this overview and Table 2 can testify to at least three intrinsic differences in the chemical behavior of such carbenoids and carbenes: The free carbenes are usually too short-lived for dimerization (except[16] for $F_2C{=}C:$); they can add to Lewis bases such as ethers, forming C−O bonds, and they form C−O bonds with potassium or lithium primary and secondary alcoholates but do not extract hydride anion[56] from these reagents. Alkylidenecarbenoids can be expected to exhibit the opposite behavior in these three regards and to be kinetically stable up to −100 °C and sometimes at even higher temperatures.

4.2. State of the Art

The ability to perform 1,5-CH insertion reactions, [1 + 2] cycloadditions, and FBW rearrangements seems to be common for alkylidenecarbenoids $R^1R^2C{=}CMX$ (**343**) and the short-lived alkylidenecarbenes $R^1R^2C{=}C:$ (**12**, Scheme 3 in section 4.1.1), the latter reacting thermally always in their singlet spin state. An apparently simple way to differentiate these two types of intermediates consists of measuring product ratios A/B of $R^1R^2C{=}CMX$ for comparison with the A/B selectivity of a corresponding bona fide alkylidenecarbene **12** generated from another source. As explained previously on several occasions, equal selectivity is only a necessary albeit not sufficient condition for the assignment of a common reactive species, whereas differing selectivities would exclude carbene **12** to be the *only* responsible intermediate. More quantitative conclusions will not be possible in general without auxiliary information. In a particularly simple situation, conservation (retention or inversion) of full optical activity in the products from an optically active precursor definitely rules out an achiral alkylidenecarbene **12** as the reactive species (if thermally equilibrated[381]) because achiral **12** cannot convey chiral information to its products. Well-founded rejection of a carbene as the (only) intermediate on account of optical activity or of divergent product mixtures from different precursors is beyond dispute and will automatically lead to imputation of a carbenoid ("what else?") as the (additional) responsible intermediate. Although the experimental conditions were often not sufficiently similar to allow a valid comparison of the differentiating selectivities, a few suitable examples could be tracked down (sections 2.5 and 2.6), and these suggested that some Br,K-alkylidenecarbenoids are very probably able to convert to their free carbenes. The latter are then the active species in [1 + 2] cycloaddition reactions even though their complexes with THF were repeat-

edly identified as equilibrium components. On the other hand, [1 + 2] cycloadditions are disfavored in the presence of β-aryl substituents that migrate rapidly *before* the Hal,M-alkylidenecarbenoids can eliminate MHal, including KBr and KCl (section 3.4.2). This issue is less clear for FBW migrations of unstrained dialkyl groups whose stereochemical inclinations have received little attention.

The issue is quite different for Br,K-cyclobutylidenecarbenoids such as $(CH_2)_3C{=}CKBr$ (**265** in entry 104 of Table 2), which are prominent for several reasons (section 3.3.1). Their FBW rearrangement, accelerated by the release of ring strain, is probably much faster than carbene formation by simple α-elimination. Because of their reluctance to form cyclopentynes as the expected FBW products, they have disclosed that their anti (**280**) and syn (**281**) alkyl migrations can proceed in the absence of coordinating solvents with comparable velocities but by different mechanistic variants. The ^{13}C-labeled product structures suggested reaction pathways with and without migration of bromide anion, but it appears desirable to extend these experiments first to ethereal solvents and then to other X,M-cyclobutylidenecarbenoids (especially M = Li, such as **301**) in a variety of solvents in order to examine whether such a notion is more generally valid. It would also be reassuring to obtain stronger evidence that key products such as **280** and **281** were indeed formed on the FBW pathway rather than by bromide addition to cyclopentynes.

Alkylidenecarbenoids $R^1R^2C{=}CMX$ can be configurationally stable at below −70 °C and for a short time even at +190 °C (section 3.4.2). However, their (*E*,*Z*) interconversion (**249**/**250**) can be catalyzed by LiBr through S_NV[242] or by residual starting material $R^1R^2C{=}CBr_2$ (**248**) through the rapid Br/Li exchange reaction. Close scrutiny in this article of quite a few mechanistic investigations has uncovered open questions concerning the control of stereochemical integrity of the starting materials during various conversions. This problem was more properly handled in some studies (section 3.4.2) of FBW aryl migrations; but migratory aptitudes in bona fide diarylmethylene*carbenes* were not determined although they would be requisite to a qualitative evaluation of the additional participation of such carbenes. A lack of corresponding studies with cyclobutylidenecarbenes was mentioned in section 4.1.1. Therefore, our present understanding of the FBW mechanisms of alkylidenecarbenoids is limited by our inability to assess the role of the corresponding free carbenes and thus to clarify how anti and syn migrations can, in contrast to common belief, occur with comparable velocities. (For examples, see the leading third of section 3.4.2.) While this trait has been supported by quantum chemical calculations of the β-hydrogen migrations within $H_2C{=}CLiI$ (**227**, with transition states **226** and **228** in section 3.1), it would be desirable to obtain also computational transition states for at least methyl migration in the syn and anti modes, with both lithium chloride and potassium bromide as MX in $R^1R^2C{=}CMX$, and both with and without solvation, in order to arrive at a more realistic assessment of the role of metal-assisted ionization,[6,7] that is by no means fully understood. Experiments in the presence of the macrobicyclus [2.2.1]cryptand or of the cyclic tetraether 12-crown-4 with the purpose of separating lithium cations from their anions might be helpful in this respect, although recent experience[382] with the nucleophile phenyllithium appears sobering. Organopotassium compounds are more reactive; but will they be able to perform vinylic substitution reactions (S_NV) at X,K-alkylidenecarbenoids?

As mentioned at the beginning of section 2.1, the computed flat energy profiles of "FBW" hydrogen migration within an alkylidenecarbene may be unsuitable for extrapolating the rate constants for the migration of other groups. Attention is also called to the experience that the calculated activation energies depend strongly on the level of computational sophistication. With these caveats, the effects of certain *stationary* β-substituents on anti and syn FBW migrations should receive theoretical in addition to experimental examination. Such studies should help to confirm or refute the proposal, built at present upon scattered reports, that FBW migration in $R^1R^2C{=}CMX$ and $R^1R^2C{=}C$: may be retarded by inductively electron-withdrawing stationary β-substituents but accelerated by a stationary inductive electron donor moiety such as LiO. It may also be discovered that these carbenoids and carbenes respond very differently to the action of certain substituents. The whole proposal implies that migratory aptitudes cannot be expressed by a general *one*-dimensional reactivity scale, as was demonstrated for several cases in this article. Instead, apparent selectivities to be expected in practice may be estimated on the basis of Table 2 and future extensions. In this table it will also be seen that the widespread habit of removing a cooling bath before quenching of a low-temperature reaction can destroy useful information on absolute reactivities, namely, the approximate reaction rate at a well-defined temperature.

Experimental rate constants can be measured for persistent alkylidenecarbenoids $R^1R^2C{=}CMX$, perhaps even at temperatures as high as 0 °C (sections 3.2 and 3.4.2), but this has been done very rarely and perhaps hardly ever for unimolecular insertion reactions and for the bimolecular processes (insertion, substitution, nucleophilic addition, and [1 + 2] cycloaddition). Identification of the rate-determining step could be achieved by the kinetic tests of concentration dependences (section 4.1.2): Especially revealing results would consist in finding a first order of reaction for a bimolecular process or in detecting kinetic inhibition by M^+X^-, because both point to the simple α-elimination pathway via the carbene intermediate **12** in Scheme 4. The normal acceleration by increasing concentrations (second-order kinetics) of a reaction partner would demonstrate this partner's involvement in one of the rate-controlling steps preceding the transition state, as discussed in section 4.1.2. For an analysis of the product-determining steps, the selectivities determined with a well-chosen pair of reactions should be compared with the selectivity of the corresponding bona fide carbene under the same conditions.

Seen from a mechanistic viewpoint, the state of the art can be held to be immature, for reliable information on the question asked in the title of this article is rather limited. While the properties of free alkylidenecarbenes appear moderately clear with respect to intra- and bimolecular insertion, nucleophilic addition, and [1 + 2] cycloaddition reactions, our knowledge of the behavior of alkylidenecarbenoids at work is quite underdeveloped in these fields and is confined to notions that mean little more than "as-if-carbenes".

The mechanistic assignments possible at this time can be recapitulated in the following tentative guidelines, which are based on fragmentary evidence and hence prone to extension and revision:

1. *FBW migrations* of aryl groups in the carbenoids ArRC=CMX are often faster than simple α-elimination of MX = LiHal or KHal, as shown by stereodivergent anti/syn product ratios (sections 3.3 and 3.4.2). However, it appears that the rates of these rearrangements may be decreased by certain stationary *β*-substituents.

2. *Intramolecular 1,5-CH insertion* can occur in carbenoids R^1R^2C=CMHal (mechanism unknown) with MHal = LiHal and KCl, whereas simple α-elimination of MHal = KBr is probably sufficiently fast for an initial generation of the carbene R^1R^2C=C:, which then performs the insertion reaction (section 2.5).

3. *Intermolecular insertion* reactions into H−Si, H−O, and sometimes H−N bonds are possible for those alkylidenecarbenes that hesitate to undergo unimolecular processes (section 4.1.4).

4. *Vinylic substitution* reactions (S_NV) by *tert*-butyllithium can occur with a Hal,Li-alkylidenecarbenoid in THF solution at −100 °C (mechanistic details unknown) more rapidly than simple α-elimination of LiHal. Likewise, these carbenoids appear to be responsible for hydride extraction from primary or secondary alcoholates (section 3.4.3) and for "dimerization" leading to butatrienes (section 3.2). But only the alkylidenecarbenes appear to be sufficiently electrophilic to add Lewis bases such as THF and other ethers (sections 2.2−2.4), generating oxonium ylides.

5. *[1 + 2] Cycloaddition* reactions of Hal,Li-alkylidenecarbenoids are probably possible but not rigorously established (section 2.6; no mechanistic conjectures known). But simple α-elimination of MHal = KBr (forming 2-adamantylidene; **206** in section 2.5) and of KO_3SCF_3 (section 2.2) or of iodobenzene (section 2.4) can be the initiating step, generating an alkylidenecarbene which will become the reactive species performing the [1 + 2] cycloaddition (section 2.6).

6. α-*Eliminations* of LiHal from several alkylidenecarbenoids in ethereal solvents appear to be coupled to one or other of the five reaction modes listed above, thus avoiding simple α-elimination. A clear-cut experimental example for the initializing formation of the free alkylidenecarbene from a **Hal**,**Li**-alkylidenecarbenoid appears to be unknown, but the destabilization observed for TMEDA containing solutions of Cl−$(CH_2)_3$−C(Me)=CLiBr (**246**) in THF[232] and of $MeCH(CH_2CH_2)_2C$=CLiCl (**403**) in pentane[208] points to facilitated α-elimination of LiHal (**344**). Hence, the use of TMEDA should be considered carefully and might account for the low yield (16%) of the reverse addition[208] of LiCl to carbene $MeCH(CH_2CH_2)_2C$=C: (**9**).

7. The active species arising from primary alkenyl triflates (section 2.2), from diazoalkenes (section 2.3.1), and from iodine(III) compounds with certain reservations (section 2.4.3) can be considered to be *alkylidenecarbenes*, responsible for insertion, nucleophilic addition, [1 + 2] cycloaddition, and FBW reactions. This tentative rule was fairly well substantiated only for bimolecular O−H insertion (**45**), for the addition of tetrahydrothiophene (**130**/**131**), and for [1 + 2] cycloaddition (**207**/**208**, and **211a**/**b** in Scheme 1); it remains to be confirmed by additional examples from the various reaction modes.

Of course, an acceptable assignment of the relevant intermediate may sometimes be possible simply owing to the sheer difficulty of formulating any convincing alternatives; for example, in the diazoalkene system R^1R^2C=CN_2 (**53**) → R^1R^2C=C: (**12**, section 2.3). The intermediacy of an alkylidenecarbene or an alkylidenecarbenoid cannot be taken as established by the bare formation of an alkyne (section 4.1.3) from a possible precursor such as Alk−CH=CH−I^+−Ph (**111**) and RCH=CXY (**443** or **448**). Differentiation of these two types of intermediates has not often been accomplished; but because they can usually create the same kinds of products, a practitioner may not care so much about the mechanistic modes, provided they lead to the desired substances. Indeed, many elegant and/or useful applications have not been cited in this article simply because they provided no basis for well-founded mechanistic considerations. Yet understanding the mechanistic details can sometimes hold the key to reach a necessary level of practicability, as shown by the impressive development[347,348] over the years of a one-pot[350] homologation of carboxylic esters rivaling the Arndt−Eistert synthesis. Moreover, the valuable cyclization reaction affording cyclopentenes by 1,5-CH insertion (section 4.1.3 and earlier) was developed on the basis of mechanism-oriented studies.

The author wishes to apologize for any scientific misjudgments or errors, especially to those readers who may feel some of the evaluations to be improper or provoking: criticism uttered in this article was meant with the intention of stimulating ideas about how to arrive at new insights.

5. Acknowledgments

I gratefully acknowledge the generous support obtained from my colleagues in the organic division of the Chemistry Department. I am also indebted to Professor Dennis N. Kevill and Dr. David S. Stephenson for their linguistic advice. Several paragraphs of this article have gained precision thanks to constructive objections raised by the Reviewers.

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CR030616H