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Constrained Carbenes[‡]

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Carbenes traditionally have been used for cyclopropane synthesis but little else, since their reactions are difficult to control. However, the burgeoning discipline of supramolecular carbene chemistry−reactions in which highly reactive, divalent carbon intermediates are generated within the confines of host compounds−is making steady progress towards solving this problem. Various carbenes generated within cyclodextrins, hemicarcerands, and zeolites demonstrate increased selectivities and lifetimes since their usual decay pathways are blocked.

1. Introduction

Herein, various supramolecular modifications of carbenes and their precursors are reviewed. The reactivity/stability of a carbene@host inclusion complex (IC) can be markedly different from that of the unconstrained carbene. Indeed, there are instances in which carbenes persist for days, that is, bottleable carbenes.[1] The results of these reactions should help physical organic chemists better understand the detailed mechanisms by which carbenes decay.

1.1. Carbenes

Carbenes are neutral molecules that have divalent carbon atoms (Figure 1) and react in various ways to complete their valence shells,[2] for example, by (1) intramolecular rearrangements (Scheme 1) and (2) intermolecular C–H σ-bond insertions and C–C π-bond additions (Scheme 2). They are often generated as short-lived reaction intermediates during the thermolysis/photolysis of nitrogenous precursors,[3] such as diazo compounds[4] and 3*H*-diazirines,[5] which sometimes undergo rearrangement in the excited state (RIES), circumventing carbene intermediacy.[6–8] Despite their electron-deficient character, carbenes can also act as Brønsted–Lowry bases. Carbenium ions may be formed by protonation of carbenes (Scheme 1),[9–11] but also by protonation of diazo compounds[12] and 3*H*-diazirines.[13] Typically, carbenes have a short lifetime (τ), but they can be detected transiently if they are paramagnetic[14] or possess

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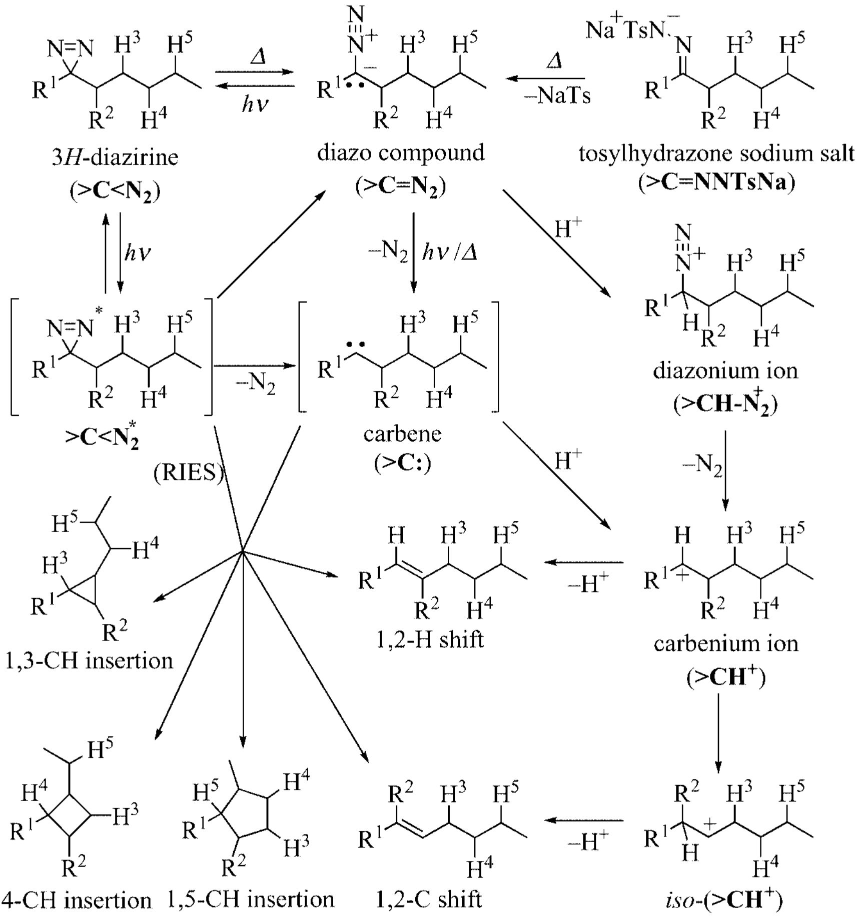


Scheme 1. Generation of a hypothetical carbene (>**C:**)/carbenium ion (>**CH⁺**) conjugate pair from nitrogenous precursors and their subsequent intramolecular reactions: Ts = *p*-$SO_2C_6H_4CH_3$.

chromophores.[15] Their fleeting presence may also be observed spectroscopically using ylide-forming Lewis bases,[16] such as pyridine (Scheme 2).[17]

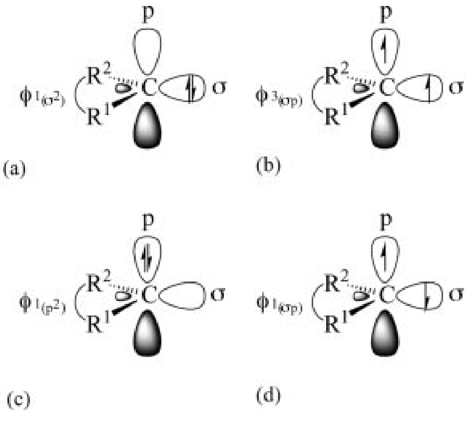
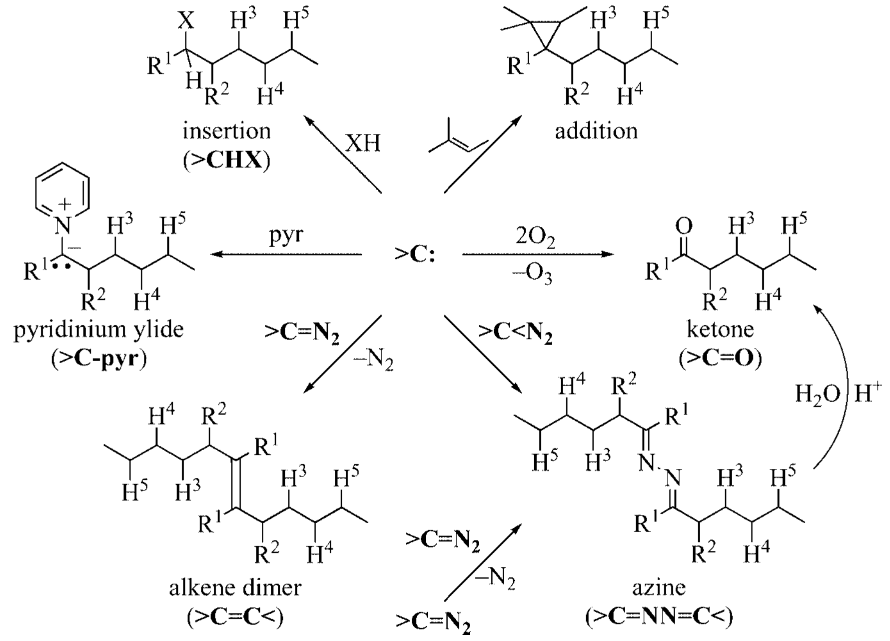


Figure 1. Structure and spin multiplicities of the four types of carbenes: (a) typical singlet (S), (b) typical triplet (T), (c) atypical p^2 singlet, and (d) atypical open-shelled singlet.

The spin multiplicity of a carbene is dependent upon whether or not its nonbonding electrons are magnetically paired (Figure 1). The spin states of carbenes are important since singlet and triplet carbenes do not react in the same manner. For instance, a singlet carbene adds to C–C double bonds with retention of the substrate's geometric configuration, whereas a triplet carbene reacts without stereospecificity under nonconcerted conditions.[18] In fact, triplet carbenes,[19,20] which are geminate diradicals,[15b] behave much like other organic free radicals, for example, they can abstract hydrogen atoms from organic solvents.[21] Moreover, electron spin resonance (ESR) spectroscopy can be used to detect triplet carbenes since they are paramagnetic.[14,22]

Unless a triplet photosensitizer is used, all carbenes are generated as singlet species because the precursors and byproducts are closed-shell species.[23] Therefore, a nascent carbene having a triplet ground state (GS) is electronically excited and needs to undergo intersystem crossing (ISC) to relax. For gaseous $^1CH_2$, collisional deactivation to $^3CH_2$ is facilitated by increased N_2 pressure.[24] Owing to their comparatively large molar masses,[25] a similar mechanism for ISC may be provided by cavitand (3D) hosts. Supramolecular inclusion of a carbene having a triplet GS could therefore increase the yield of radical-type reactions, for example, hydrogen abstraction/recombination. Exciting new chemistry might also be fostered from carbenes having ground and excited states of unlike spin multiplicity that are close in energy, for example, ΔE_{ST} = 1–2 kcal mol^{-1}.[15a,26] For such carbenes, the dormant and reacting spin states might be reversed since constraint could



Scheme 2. Intermolecular reactions of a hypothetical carbene (>**C:**): XH = H_2O, AcOH, MeOH, iPrOH, n-C_nH_{2n+2}, c-C_nH_{2n}, etc.

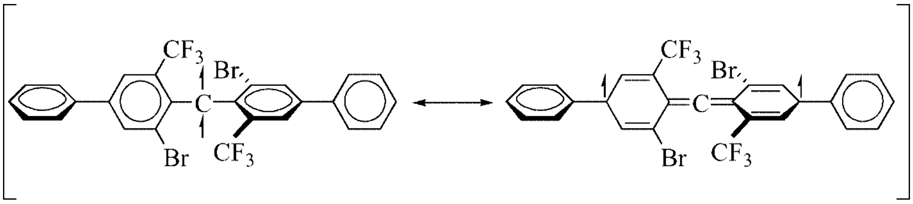


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Figure 2. Persistent triplet carbene ($t_{1/2} \approx 40$ min).

alter the carbene's bond angle (φ), which is a major factor that determines carbene ground and excited spin states.[27]

Much time and effort has been spent in recent years seeking stable carbenes.[1,28] This flurry of activity has had notable success in the form of persistent triplet carbenes.[1a,19,29] For example, triplet bis(3-bromo-5-trifluoromethyl-1,1′-biphenyl-4-yl)carbene (**1**) has a half-life ($t_{1/2}$) of around 40 min and was detected in degassed solution at room temperature even after 24 hours (Figure 2).[30] The longevity of carbene **1** is attributed to judicious placement of the bulky and inert –Br and –CF_3 groups that shield the carbene center and impede its direct dimerization to the corresponding alkene atropisomers. Of course, carbene **1** has several resonance forms, so it is not a typical geminate diradical.

Another promising area of research involves ylide-like singlet carbenes (Figure 3),[31] such as thiazol-2-ylidenes (**2**),[32] imidazolidin-2-ylidenes (**3**),[33,34] imidazolin-2-ylidenes (**4**),[28a,34,35] and cyanine-like cyclopropenylidenes (**5**).[36] Again, such intrinsically stabilized species are not representative of the majority of carbenes. Thus, extrinsic stabilization of carbenes by host compounds is warranted.

1.2. Hosts

1.2.1. Cyclodextrins

Cyclodextrins (CyDs), or Schardinger dextrins,[37] have been known for over 100 years.[38] They are formed by *Bacillus macerans*, a bacteria that macerate starch using the enzyme cyclomaltodextrin gluconotransferase.[39] A CyD is a nonreducing, cyclic oligosaccharide molecule composed of α-D-glucopyranose (α-D-Glc*p*) monomers linked at the 1- and 4-glycosidic positions. The general structure of CyDs is shown in Figure 4. Their prefixes depend on the number of pyranose units present: six (α-CyD), seven (β-CyD), and eight (γ-CyD).[40]

A variety of guest molecules can reside within the nonpolar cavities of these toroidal hosts. There are several driving forces responsible for CyD IC formation: (1) van der Waals (London dispersion) forces, (2) hydrophobic interactions, (3) dipole–dipole (electrostatic) interactions, (4) hydrogen (O–H···N, O–H···O, and/or O–H···F) bonding, (5) release of CyD distortional energy by the merging guest, and (6) expulsion of "high-energy water" from the CyD cavity upon IC formation.[41] The strength of the noncovalent interac-

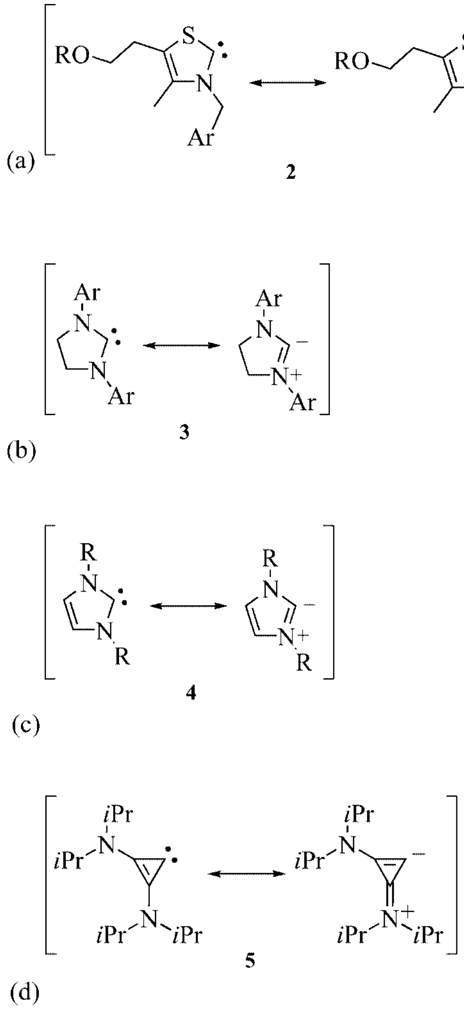
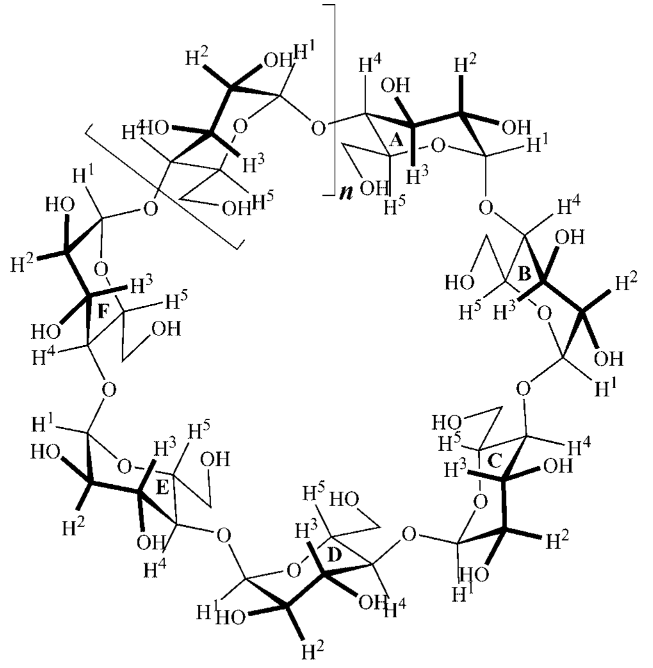


Figure 3. Stable ylide-like singlet carbenes.



α-CyD: ***n*** = 0
β-CyD: ***n*** = 1
γ-CyD: ***n*** = 2

Figure 4. Structure of cyclodextrin (CyD) depicting the O^1–C^4 α-linkage of D-glucopyranose monomers and inward pointing H^3 and H^5 atoms.

tion is evaluated by an association constant (K),[42] which can be measured in various ways, for example, by spectrofluorometric methods based on competition experiments.[43] Recently, induced circular dichroism (ICD) was introduced to assess K for 3*H*-diazirine@CyD ICs.[44]

The host–guest stoichiometries of CyD ICs are difficult to predict because CyDs are versatile hosts that can act either as nonstoichiometric channel-forming inclusion compounds or as stoichiometric cage-forming clathrates. Therefore, direct proof of a guest@host IC should be obtained so that structural information, such as host–guest stoichiometry and reactant orientation,[45] can be ascertained. This can be achieved by using well-developed methods: IR spectroscopy; NMR spectroscopy,[46] including ^{1}H nuclear Overhauser effect (NOE) difference spectroscopy, ^{1}H two-dimensional rotating-frame Overhauser effect spectroscopy (2D ROESY),[47] solid-state ^{13}C cross-polarization/magic angle spinning (CP/MAS) spectroscopy,[48] induced circular dichroism (ICD),[44] powder and single-crystal X-ray diffraction,[44c,49] and fast atom bombardment mass spectrometry (FAB MS).[50]

1.2.2. Zeolites

Zeolites have been known for 250 years.[51] There are many naturally occurring forms.[52] Faujasite (FAU) zeolites are crystalline, highly polar, multicameral aluminosilicates wherein guest molecules may be entrapped. There are two types, that is, X and Y, which are characterized by a tetrahedrally arranged network of interconnected sodalite cages (Figure 5).[53] The voids that are created are called supercages. Positively charged counterions, which balance $(AlO_2)^-$ moieties, are found within the FAU lattice. They can also be a source of acidity, for example, H^+ ions. These cations may be exchanged,[54] thereby allowing the free volume of the supercages to be altered by choosing ions of certain radii.[55] The loading factor (‹s›) is a measure of the ratio of guest molecules to supercages and can be determined experimentally.[56] Shape selectivity (vide infra) has been demonstrated within FAU zeolites. For example, *meta* selectivity was observed in the NaY-mediated Friedel–Crafts alkylation of benzyl chloride (BnCl) with itself.[57]

1.2.3. Hemicarcerands

Carceplex chemistry was pioneered by Cram and coworkers.[58] A carceplex is an IC formed when a guest molecule is imprisoned within the inner phase of a carcerand host, which consists of two hemispherical cavitand molecules linked together. Later, hemicarcerand (HC) variants were introduced (Figure 6),[59] for example, Pac-Man®-

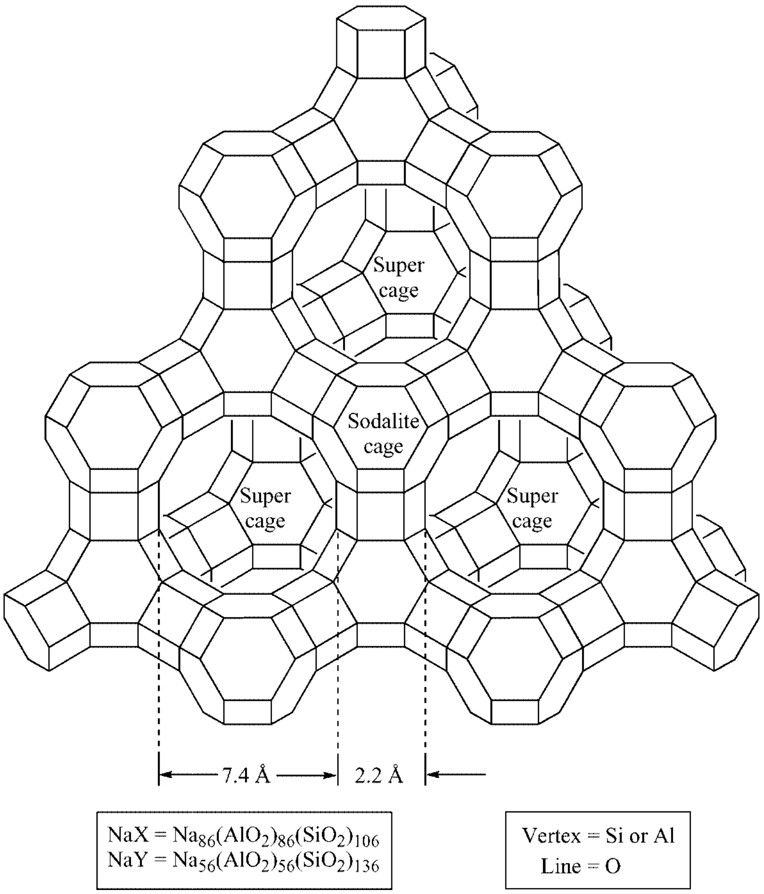


Figure 5. Structure of multicameral faujasite (FAU) zeolites X and Y depicting 13-Å diameter supercages and the tetrahedral arrangement of 7.4-Å apertures, cf. the diamond structure.

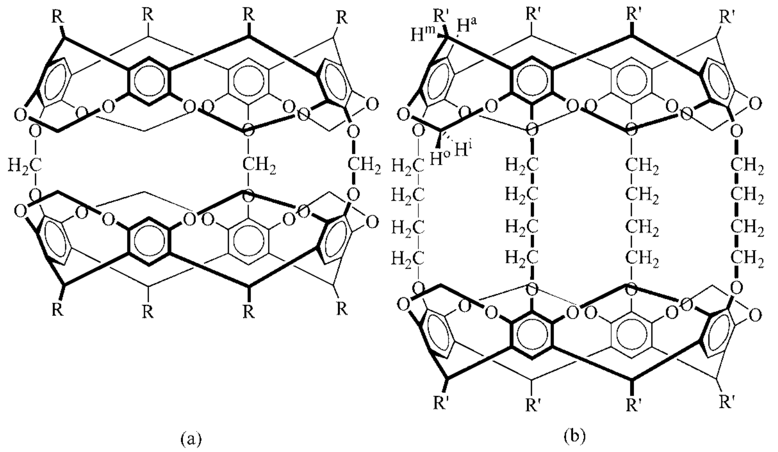


Figure 6. Hemicarcerand (HC) structures: (a) Pac-Man®-shaped, for example, R = CH_2CH_2Ph (phenethyl), and (b) bird-cage-shaped, for example, R′ = n-C_5H_{11} (pentyl), depicting the host's hydrogen atoms.

shaped HCs "gobble" guest molecules at high temperatures and retain them when the temperature is lowered. A milestone in organic chemistry was achieved when 1,3-cyclobutadiene was "tamed" within a HC.[60] Similarly, the generation of *o*-benzyne within a HC has been reported.[61] Like 1,3-cyclobutadiene, strained *o*-benzyne is a very unstable reactive intermediate.[62] Its τ was limited, however, by unwelcomed innermolecular Diels–Alder reactions with its HC host and also by the presence of adventitious water molecules.

1.2.4. Fullerenes

Fullerenes are polyhedral allotropes of carbon that can accommodate metal atoms and clusters. Buckminsterfullerene [(C_{60}–I_h)[5,6]fullerene] has 60 identical carbon atoms that are bonded to each other in the shape of a truncated icosahedron, cf. a soccer ball, in which a carbon atom occupies each vertex (Figure 7a). The 20 hexagonal and 12 pentagonal faces form two distinct ring fusions: (1) 6,6-ring junctions and (2) 5,6-ring junctions. The C–C bonds at the 6,6-ring junctions behave like alkene moieties whereby fullerenes undergo addition reactions with diazo compounds[8,63,64] and carbenes.[63,65] Indeed, multiple additions can occur.

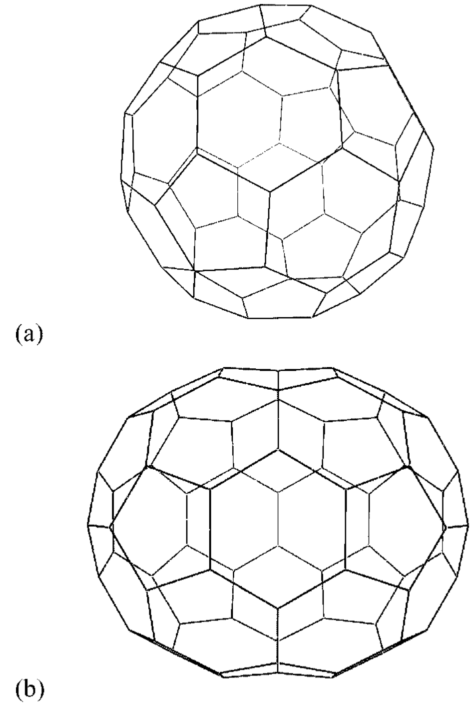


Figure 7. Structures of (a) (C_{60}–I_h)[5,6]fullerene and (b) (C_{70}–$D_{5h(6)}$)-[5,6]fullerene.

1.2.5. Crystals

Carbenes have been generated in the crystalline solid phase of their precursors at both ambient temperature and below.[66,67] Reaction selectivities are markedly different from those found in solution at various temperatures and within rigid glassy matrixes at very low temperatures because various conformers can exist in liquid solutions and amorphous solids.

1.2.6. Argon Matrixes

Carbenes have been routinely generated within cryogenic argon matrixes.[68,69] Their motions are so restricted at T = 10 K that annealing the matrix to around T = 35 K is usually required to allow the constrained carbene to adopt its most stable geometry.[30,70] Diffusion of trapping reagents, like O_2 or HCl, is also promoted by annealing. At such low temperatures, classical decay pathways, even those with small activation enthalpies, are unattainable. So, nonclassical transformations due to quantum mechanical (QM) tunneling can predominate under frozen argon matrix conditions.[71]

1.2.7. Phase Transfer Catalysts

During the 1970s, carbene reactions were performed in the presence of micelles, for example, quaternary ammonium salts, and crown ethers (Figure 8).[72] However, carbene@host ICs were not formed, nor were they sought. Instead, these systems enable phase-transfer catalysis (PTC) of Lewis acid/Lewis base reactions.

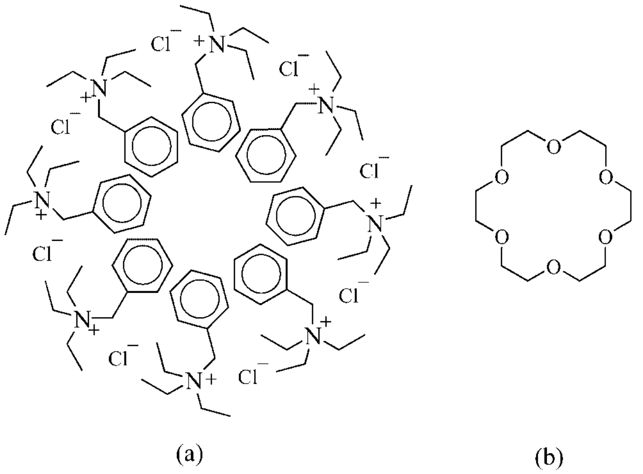


Figure 8. (a) Triethyl(benzyl)ammonium chloride (TEBA) micelle and (b) 18-crown-6 crown ether.

1.3. Supramolecular Chemistry

In 1987, supramolecular chemistry attained worldwide recognition when the Nobel Prize in Chemistry was awarded to Cram,[73] Pedersen,[74] and Lehn "for their development and use of molecules with structure-specific interactions of high selectivity."[75] Supramolecular chemistry involves the use of host compounds to entrap guest molecules.[76] Carbenes have been generated in multicameral inclusion compounds, such as FAU zeolites, and in cage compounds (clathrates), such as CyDs and HCs.

Clathrates act like molecular straitjackets.[77] They can exert a positive cage effect on entrapped reactive intermediates.[56,78] Intermolecular reactions can thus be controlled.[79] Moreover, clathrates can shield certain reaction sites during radical recombination.[79,80] The ability of a host compound to bind a specific type of guest, particularly from a mixture, is known as molecular recognition,[81] which is reminiscent of Fischer's "lock and key" metaphor used to describe the specificity of enzymes.[82] Indeed, supramolecular hosts are often called enzyme mimics,[83] because shape selectivity can bias competition reactions to favor one product over the other.

Since carbene intermediates are high in energy, their decay processes often are spontaneous and mostly indiscriminant. Indeed, with a low enthalpic barrier, that is, $\Delta H^{\ddagger} \approx 0$ (but $\Delta G^{\ddagger} \neq 0$) for most carbene reactions, the entropic term $T\Delta S^{\ddagger}$ can become decisive in bimolecular reactions. Not surprisingly, the decay rate of a carbene in a nonviscous organic solvent is often diffusion limited, cf. k_d(MeOH) =

1.20×10^{10} $\text{M}^{-1}\,\text{s}^{-1}$ at 25 °C.[9b] However, the diffusion/percolation of a guest molecule within a host compound is much less than in conventional solvents.[56] So, reactants are mostly isolated from one another and intermolecular reactions are diminished. In addition, limited guest mobility also prolongs the τ of a carbene having no intramolecular modes of decay.

2. Results and Discussion

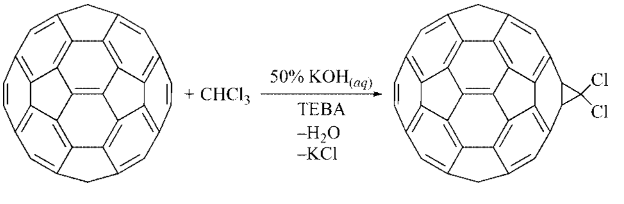
2.1. Methylene

In the early 1980s, the conversion of MeOH to gasoline over synthetic zeolite catalysts was studied. One set of experiments using MeOH@H-ZSM-5 led to the hypothesis that carbenes, like CH_2, were involved in this industrially important process.[84] However, a more explanatory mechanism was proposed,[85] and by the decade's end a rigorous study of this reaction using MAS ^{13}C NMR spectroscopy showed carbon monoxide (CO) to be the key intermediate.[86] Recently, the precise role of H-ZSM-5 in this conversion has been questioned.[87]

The formation of the $CH_2@(C_{70}–D_{5h(6)})$[5,6]fullerene IC by the Krätschmer–Huffman method was recently communicated,[88] although not independently confirmed. The putative fullerene IC was isolated in >90% purity by HPLC and characterized by ESR and IR spectroscopy. To rule out the formation of an exohedral fullerene, such as 3′*H*-cyclopropa[1,2]$(C_{70}–D_{5h(6)})$[5,6]fullerene or 3′*H*-cyclopropa[2,12]$(C_{70}–D_{5h(6)})$[5,6]fullerene, $(C_{70}–D_{5h(6)})$[5,6]fullerene was independently treated with diazomethane and the resulting adduct's spectra were compared with those of the fullerene IC. Indeed, the formation of 1,2(*endo*)-3′*H*-cyclopropa[2,12]$(C_{70}–D_{5h(6)})$[5,6]fullerene by an innermolecular reaction of CH_2 with the concave endohedral surface of the fullerene cage is expected to be slow as a result of poor orbital overlap.[61d] Moreover, the resulting cyclopropane is highly energetic since two of its carbon atoms comprise a flattened geometry. It is therefore not surprising that, according to the authors, the fullerene IC harbored the usually short-lived CH_2 intermediate for months.[88]

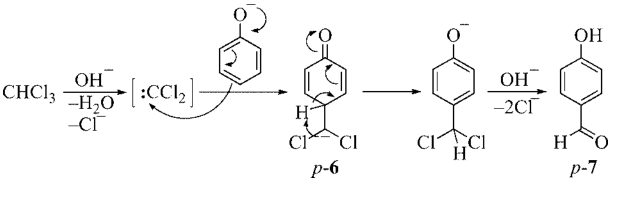
2.2. Dichlorocarbene

Carbene chemistry was revolutionized after Mąkosza's discovery of the biphasic generation of dichlorocarbene (CCl_2) in the presence of catalytic amounts of triethyl(benzyl)ammonium chloride (TEBA).[89–91] Previously, CCl_2 could only be generated under strictly anhydrous conditions, for example, by the Doering–Hoffmann method,[92] since CCl_2 is rapidly decomposed by H_2O to CO–particularly in the presence of base.[93] It is doubtful, however, that carbenes are generated within TEBA micelles.[94] Rather, this system exemplifies PTC leading to carbene formation,[89] for example, the addition of CCl_2 to $(C_{60}–I_h)$[5,6]fullerene (Scheme 3).[65] Like micelles, crown ethers have been used as phase-transfer catalysts during the biphasic generation of CCl_2 from $CHCl_3$.[95] Sometimes, the aqueous phase itself may be omitted because ionic compounds, like *t*BuOK, experience enhanced solubility in organic solvents doped with crown ethers, cf. polar aprotic solvents.



Scheme 3. Formation of 3′,3′-dichloro-3′*H*-cyclopropa[1,9]-$(C_{60}–I_h)$[5,6]fullerene by PTC.

Enhanced regioselectivity was observed when the Reimer–Tiemann reaction[96] was conducted in the presence of CyDs (Scheme 4).[97] The dehydrochlorination of $CHCl_3$ by OH^- was retarded owing to the formation of armored $CHCl_3@CyD$ ICs. Thus, the overall yield of *p*-hydroxybenzaldehyde (**7**) was even lower than usual. Indeed, at pH = 13, CyDs were unprotonated to some extent and behaved much like anionic micelles, which cannot transport the electrically repulsive OH^- base needed for $CHCl_3$ dehydrochlorination, thereby inhibiting CCl_2 formation.[98] However, α-elimination of $CHCl_3$ by the deprotonated CyD host itself was inexplicably deemed to be "less important."[97b] Encapsulation of CCl_2 within the CyD hydrophobic cavity is expected to impede hydrolysis of the carbene to CO. No innermolecular chlorination of the CyD hydroxy groups of the $CCl_2@CyD$ ICs occurred,[97b] which should have been possible.[94a] Instead, the aryl end of the phenolate anions (PhO^-) dipped into the nonpolar cavity of the CyD and reacted with the ordinarily short-lived CCl_2 intermediates. Thus, increased *para* selectivity was observed, that is, *p*-**7**/*o*-**7** = 4.65. In the absence of α-CyD, *p*-**7**/*o*-**7** = 0.71,[97b] which is close to the theoretical limit of 0.50.



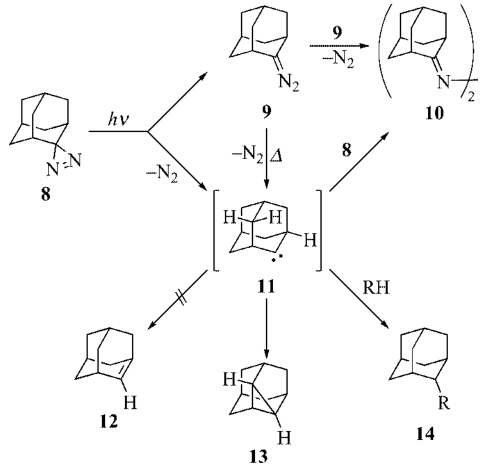
Scheme 4. Enhanced *para* selectivity was observed for the Reimer–Tiemann reaction inside α-CyD.

2.3. Cycloalkylidenes

2.3.1. 1,3-CH Insertion

The constraint of 2-adamantanylidene (**11**) by CyDs markedly alters its chemistry.[99–101] Its precursor, 2-aziadamantane (**8**),[102] has been widely studied.[103,104] Believed to have a singlet GS,[105] carbene **11** does not readily undergo a 1,2-H shift to form the strained anti-Bredt compound singlet adamantene (**12**) (Scheme 5).[106] Thus, other rearrangements of carbene **11** can flourish. Indeed, carbene

11 undergoes 1,3-CH insertion to 2,4-didehydroadamantane (**13**) exclusively in the gas phase.[107] In contrast, only traces of **13** are formed by photolysis of diazirine **8** in solution,[99] because bimolecularly derived products predominate, for example, azine **10** and adducts **14d**,**e** (Scheme 5). Likewise, photolysis of diazirine **8** in the solid phase yields no detectable **13**.[99] So, it is not surprising that less than 1% of **13** was formed during the photolysis of a physical mixture of diazirine **8** and β-CyD.[99] However, the increased yield of **13**, that is, 10–30%,[99,108] when **8**@CyD ICs are photolyzed is demonstrative of the powerful influence clathrates can have on reaction outcomes. Since there are no solvent molecules with which supramolecular carbene **11** can react and 1,2-H shift by carbene **11** is prohibited, decay by 1,3-CH insertion is greatly enhanced. The formation of the three-membered ring of **13** is indicative of the intramolecular 1,3-CH insertion of carbene **11**. Indeed, more **13** may have formed had the rims of CyD hosts been inert.



Scheme 5. Generation of 2-adamantanylidene (**11**) and its subsequent reactions: RH = (a) α-CyD, (b) β-CyD, (c) H_2O, (d) MeOH, (e) n-C_7H_{16}.

According to reversed-phase (RP) HPLC, FAB MS, MS/MS, and H/D exchange in D_2O, carbene **11** inserts into all three types of the β-CyDs 21 OH groups, but predominantly into the primary OH group, to give covalently bound *O*-(adamantan-2-yl)-β-cyclodextrin (**14b**) host–guest adducts.[99] Indeed, bis(2-adamantanyl) adducts were formed, putatively by the innermolecular insertion of two carbene **11** intermediates into two OH groups of one β-CyD. This finding, in addition to the observation that much azine **10** was formed, indicates that a 2:2 host–guest IC (**8**@β-CyD)$_2$ was responsible.[49] Similarly, it was found that a 2:1 host–guest IC **8**@(α-CyD)$_2$[49] gave 2-*O*-(2-adamantanyl)-α-cyclodextrin (2–**14a**) and 3-*O*-(2-adamantanyl)-α-cyclodextrin (3–**14a**), which are formed by chemoselective O–H insertions by encapsulated carbene **11** into the wider rims only (Figure 9).[109] Although innermolecular insertion products from β-CyD (T = 30 °C) were isolated in only 35% yield, as much as 58% of 2– and 3–**14a** were formed within the smaller confines of α-CyD.[109] However, the yield of the intramolecular insertion product **13** remains unchanged at around 10%. Innermolecular insertion products 2– and 3–**14a** were separated by RP-HPLC and identified by 600 MHz pulsed-field gradient-enhanced ^{1}H-detected ^{1}H–^{13}C heteronuclear correlation through binary quantum coherence (HMBC) NMR spectroscopy and FAB MS.[109]

Finally, carbene **11** generated within NaX zeolite gave **13** in 45% yield after correction for in situ decomposition of **13** to **14c** by hydrolysis,[48] which demonstrates that a significant amount of H_2O remains inside thermally activated NaX. The primary yield represents a 225-fold increase when compared with the reaction in n-C_7H_{16} solution.[48]

Proper orbital alignment plays a crucial role in carbene rearrangements,[110] such as 1,2-H shifts.[110,111] But host-induced topological distortion of a pliable carbene guest could misalign its frontier orbitals and reduce their overlap. Hence, its usual reactions would be foiled.[112] Indeed, intramolecular hydride and alkyl shifts might be tunable even in the absence of bystander effects.[113] To determine whether the selectivity of a flexible cycloalkylidene is altered by supramolecular constraint, 1-azi-2-methylcyclohexane (**18**)[114,115] was photolyzed within CyDs to gauge the reactivity of 2-methylcyclohexylidene (**19**), which can also be generated by the Bamford–Stevens reaction[116] of the 2-methylcyclohexanone *p*-tosylhydrazone sodium salt (**15**) (Scheme 6).[115,117]

The formation of azine **17** was inhibited in MeOH solution as well as in α- and β-CyD ICs.[115] Rapid protonation of diazo compound **16**, which was transiently observed,[115] to the corresponding diazonium ion (**16**H$^+$) by the protic media's –OH groups could account for this.[4a,12] However, molecular confinement is more likely responsible since small amounts of azine **17** were formed in the larger γ-CyD clathrates due to two molecules of **18** being included within one γ-CyD. Indeed, if the tight fit within α- and β-CyD clathrates force carbene **19** to adopt its more compact axial conformation, that is, **19**$_{ax}$, then the hydrogen atom at the C^2 position will assume an equatorial position (Figure 10b). Misalignment of the filled C–H orbital (HOMO) with the empty divalent carbon orbital (LUMO) would suppress the formation of 1-methylcyclohexene (**21**). Thus, the less substituted alkene 3-methylcyclohexene (**22**) could proliferate (Scheme 6). Moreover, the axially positioned –CH_3 group in **19**$_{ax}$, would be more susceptible to a 1,3-CH insertion, cf. **11** → **13** (Scheme 5), and yield bicyclo[4.1.0]heptane (**20**). Conformational control over carbene **19** inside CyD cavities would therefore alter its regioselectivity and chemoselectivity (Figure 10).

Statistically, the amount of alkene **21** formed through a 1,2-H shift of carbene **19** should be half that of alkene **22** because of the 1:2 ratio of hydrogen atoms at the respective migration origins. Of course, this is not the case due to the unequal inherent migratory aptitudes of each hydrogen atom,[118] cf. Saytzeff's rule. Thus, the **21**:**22** ratio from the 2-methylcyclohexyl cation (**19**H$^+$) is around 5.4,[119] although the microwave-induced dehydration of the **23c**@NaY FAU IC gave **21**:**22** = 2.2.[120] The **21**:**22** ratios for the conjugate base, that is, carbene **19**, in solution were

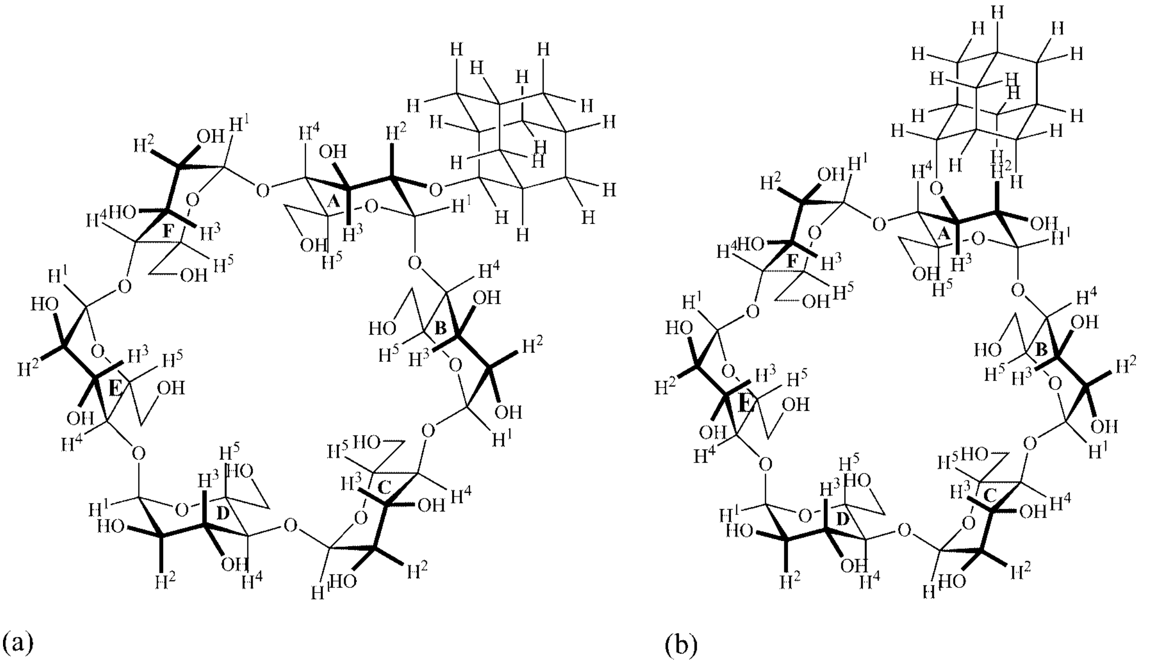
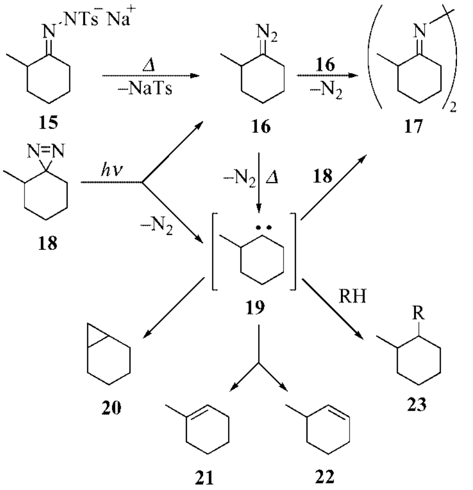


Figure 9. Innermolecular insertion products: (a) 2-*O*-(2-adamantanyl)-α-cyclodextrin (2–**14a**) and (b) 3-*O*-(2-adamantanyl)-α-cyclodextrin (3–**14a**).



Scheme 6. Generation of 2-methylcyclohexylidene (**19**) and its subsequent reactions: RH = (a) CyD, (b) MeOH, (c) H_2O, (d) n-C_5H_{12}.

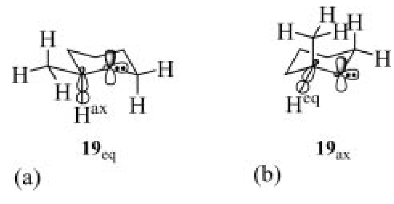
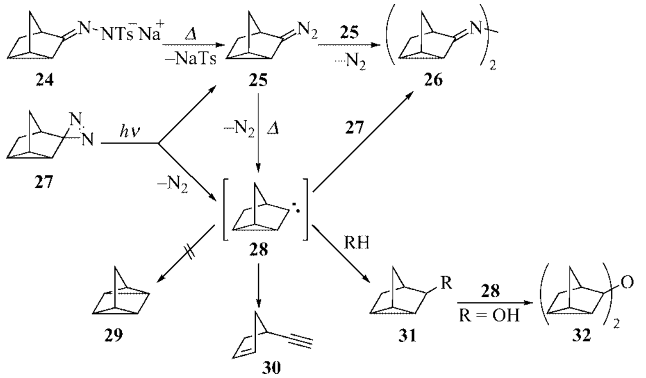


Figure 10. Two conformeric isomers of carbene **19**.

around 1.8–2.3 and 1.9–2.6 for **19**@CyD ICs.[115] Moreover, trace amounts of the 1,3-CH insertion product **20** were produced only by the thermal Bamford–Stevens reaction[116] in *N*-methyl-2-pyrrolidinone.[117] These findings indicate that the more stable conformer $\mathbf{19}_{\mathrm{eq}}$ (Figure 10a) predominates both in conventional media and inside CyDs.

2.3.2. 1,4-CH Insertion

The Bamford–Stevens reaction[116] of the 3-nortricyclanone *p*-tosylhydrazone sodium salt (**24**) (Scheme 7) generates 3-nortricyclanylidene (**28**).[121] Quadricyclane (**29**) was anticipated from an intramolecular C–H insertion of carbene **28** but was not observed. Instead, 4-ethynylcyclopentene (**30**) was formed by cyclopropylcarbene fragmentation,[122] a process similar to the well-known Eschenmoser fragmentation.[123] The carbene rearrangement is believed to proceed through a coarctate transition state (TS) that requires strict orbital alignment of the divalent carbon with the cyclopropane ring.[124] A bilateral symmetry and an endocyclic configuration are required—both of which are exemplified by carbene **28**.[125]



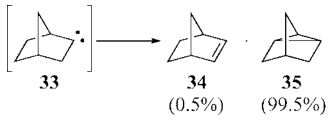
Scheme 7. Generation of 3-nortricyclanylidene (**28**) and its subsequent reactions: RH = (a) α-CyD, (b) β-CyD, (c) MeOH, (d) *i*PrOH, (e) AcOH, (f) H_2O, (g) c-C_6H_{12}.

In lieu of the unsuitable Bamford–Stevens reagent **24**, 3-azinortricyclane (**27**)[126] was used as a precursor of carbene **28**. The CyD ICs were determined to be **27**@(α-CyD)$_2$ and

($(\mathbf{27}@\beta\text{-CyD})_2$) by structural analysis.[44,46,47,126] Indeed, the results are in agreement with these structures. No azine **26** was formed upon photolysis of the sandwich-like $\mathbf{27}@(\alpha\text{-CyD})_2$ IC because of complete encapsulation of the reactive guest. However, bimolecular reaction of the guests within the $(\mathbf{27}@\beta\text{-CyD})_2$ dimer produced azine **26** by virtue of their geminated assemblage. Of the two possible intramolecular products, **29** and **30** (Scheme 7), only enyne **30** was observed after photolysis of the **27**@CyD ICs. Control experiments with **29**@CyD showed it to be stable under the reaction conditions. Thus, no **29** was formed by photolysis of the ICs of **27**. In addition to intramolecular fragmentation to **30**, innermolecular reaction of carbene **28** with the O–H bonds of both CyDs predominated, giving *O*-substituted CyDs (**31a** and **31b**) detected by FAB MS analysis.[126]

Photolysis of the diazirine **27**@NaY FAU IC (‹s› = 0.25) yielded some **30** but no **29**, which was found to be stable under the reaction conditions. The principal formation of 3-nortricyclanol (**31f**, 76%), which is also stable within NaY,[127] by hydrolysis of carbene **28** demonstrates that a significant amount of H_2O remains inside thermally activated NaY as well. The presence of bimolecularly derived azine **26** and ether **32** indicates some diffusion of ephemeral carbene **28** within the lightly loaded FAU zeolite.

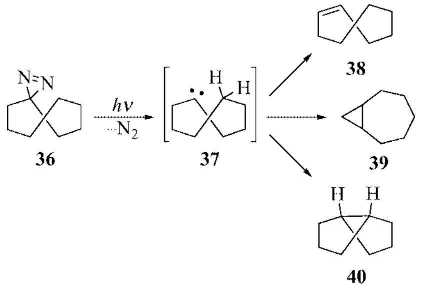
Confinement of carbene **28** within CyDs and FAU zeolites did not hamper its fragmentation to enyne **30** and awaken the dormant 1,4-CH insertion to **29**. Apparently, there is still enough space within the hosts' cavities for the unraveling process. Moreover, 1,4-CH insertions are too slow to compete due to improper orbital alignment.[128,129] The absence of C–H insertion by carbene **28** is noteworthy because 2-norbornanylidene (**33**), which merely lacks the C^2–C^6 zero-atom bridge in **28**, undergoes C–H insertion to nortricyclane (**35**) almost exclusively (Scheme 8).[128,130]



Scheme 8. Intramolecular reactions of 2-norbornanylidene (**33**).

2.3.3. 1,5-CH Insertion

The effect of molecular confinement on reactant conformation can be astounding. If a reactive intermediate is deprived of its normal decay route then new reaction alternatives may flourish. This is the case with cyclooctylidene (**37**) (Scheme 9).[4b,129,131,132] Upon photolysis of azicyclooctane (**36**), *cis*-cyclooctene (**38**) is readily formed, but so too are products derived from intramolecular C–H insertions of carbene **37**. Of special interest is bicyclo[3.3.0]octane (**40**). Created from a 1,5-CH insertion within carbene **37**,[133] *cis*-fused **40** needs space to form. Since the free volume of a CyD depends on the number of monomer units of which it is comprised (Figure 4), it is not surprising that these factors conspire to limit the formation of **40** when diazirine **36** is photolyzed within α-CyD.[131] The occurrence of a transannular C–H insertion becomes less probable as the cavity within the molecular reaction vessel gets smaller (Table 1).



Scheme 9. Competing intramolecular reactions of cyclooctylidene (**37**).

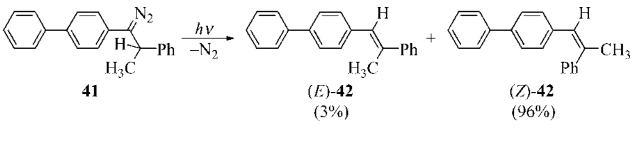
Table 1. Propensity of transannular 1,5-CH insertion of cyclooctylidene (**37**) within CyDs decreases as the size of the host cavity decreases.

CyD	Free volume [Å^3][a]	Yield of **40** [%][b]
γ	427	42
β	262	37
α	174	29

[a] See ref.[41b]. [b] See ref.[131].

2.4. Alkyl(aryl)carbenes

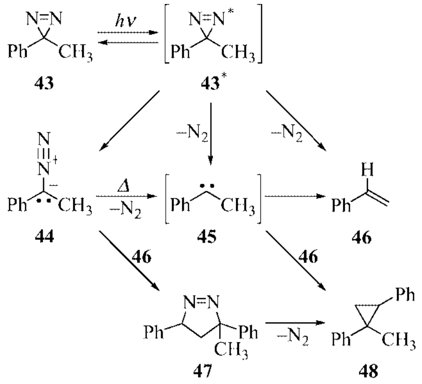
Photolysis of 1-(1,1′-biphenyl-4-yl)-1-diazo-2-phenylpropane (**41**) in solution yields products derived from 1,2-H and 1,2-Ph shifts and intermolecular reaction of the corresponding carbene. In contrast, only a 1,2-H shift, leading to 1-(1,1′-biphenyl-4-yl)-2-phenylpropene (**42**), is observed when polycrystalline **41** is photolyzed in the solid phase (Scheme 10).[67a–67d] Moreover, the 1,2-H shift is highly stereoselective in the solid phase as a result of conformational constraints and orbital alignment,[110] and the more sterically crowded stereoisomer (*Z*)-**42** was formed almost exclusively ($\lambda > 380$ nm). However, RIES within the diazo compound[6] could not be fully discounted.



Scheme 10. High stereoselectivity for the (*Z*) isomer is observed in polycrystalline media.

2.4.1. Methyl(phenyl)carbene

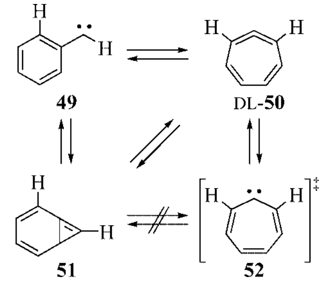
With the intention of selectively derivatizing CyDs,[134] nitrogenous carbene precursors have been enlisted as labile guests.[135] The involvement of supramolecular carbenes was inferred based on intramolecular products stemming from 1,2-H shifts and intermolecular additions to these products. However, 3*H*-diazirines that possess relatively weak α-C–H bonds are susceptible to RIES.[7a,b] During the photolysis of 3-methyl-3-phenyl-3*H*-diazirine (**43**), RIES of **43*** and/or a 1,2-H shift of methyl(phenyl)carbene (**45**) produces styrene (**46**), which undergoes a secondary reaction to give *cis*- and *trans*-1-methyl-1,2-diphenylcyclopropanes (**48**) (Scheme 11).[135a] Of course, these three-atom rings are not necessarily formed by carbene **45** addition to **46**. Homolytic scission of pyrazoline **47**,[136] which may be formed by the facile [3+2] dipolar addition of diazo compound **44** to alkene **46**, can give cyclopropanes **48** (Scheme 11). The participation of carbenes was also surmised from the formation of the innermolecular O–H insertion products of CyDs that were originally sought. The innermolecular products, that is, *O*-(1-phenylethyl)cyclodextrins, can also be explained without invoking carbenes. Since most of the diazo compounds that were used decomposed during CyD IC formation,[135c] CyD derivatization may have occurred by a diazonium ion route.[4a,12]



Scheme 11. Formation of styrene (**46**) and 1-methyl-1,2-diphenylcyclopropane (**48**) within CyDs.

2.4.2. Phenylcarbene

The intramolecular rearrangement of phenylcarbene (**49**) to 1,2,4,6-cycloheptatetraene (**50**) is a well-known transformation (Scheme 12).[137,138] When carbene **49** was generated within the confines of a HC,[61e,139] innermolecular C–H insertion was mostly observed. However, allene **50** was formed in low yield by photochemical ring expansion ($\lambda >$ 416 nm) of carbene **49**. Incarcerated allene **50** was protected from dimerization, so the 2D ^{1}H NOESY NMR spectrum of **50**@HC was obtainable.



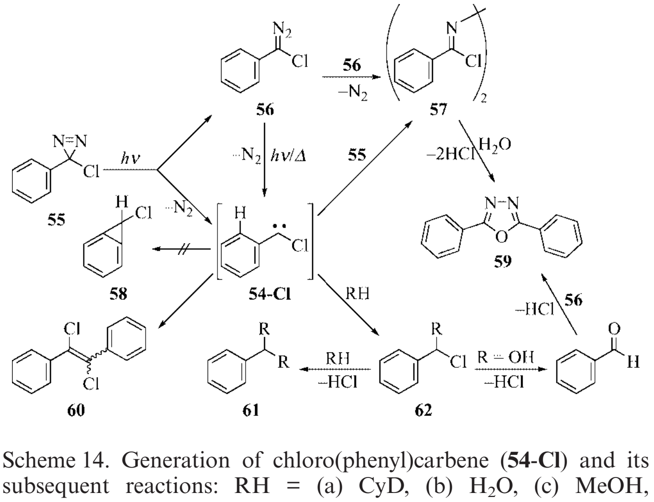
Scheme 12. Phenylcarbene (**49**) ring expansion.

2.5. (Aryl)halocarbenes

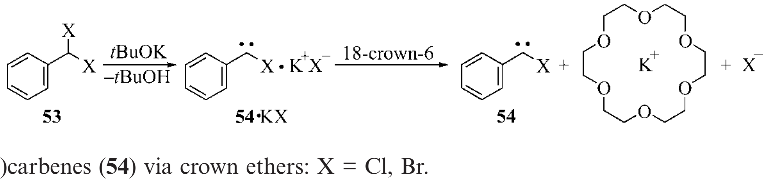
Base-induced α-eliminations of benzal halides (**53**) were performed in the presence of 18-crown-6 (Scheme 13).[140] However, it was not the carbenes, but rather the alkali metal cations, that were ensconced within the coronand (2D) hosts. The halo(phenyl)carbenes (**54**) produced in this manner behaved much like those arising from 3-halo-3-phenyl-3*H*-diazirines, which are reported to yield free carbenes. Since crown ethers are known to encompass the cations of the salt byproducts,[141] it was reasoned that a transformation from carbenoid to carbene character was being observed.

2.5.1. Chloro(phenyl)carbene

Photolysis of neat 3-chloro-3-phenyl-3*H*-diazirine (**55**)[142] yields azine **57** as the sole product (Scheme 14).[143] In solution, chloro(phenyl)carbene (**54-Cl**) inserts into solvent molecules to give **62**;[144] indeed, no azine **57** is formed in either THF or alcohols.[143] In anhydrous alcohols, transformation of α-chloro ethers **62c**,**d** provides the acetals **61c**,**d** exclusively. However, base is required to neutralize the HCl byproduct and quench subsequent hydrolysis, which leads to benzaldehyde (PhCHO). Finally, the formal carbene dimer **60** is formed in minor amounts (up to 5%) only in nonpolar solvents.[143]

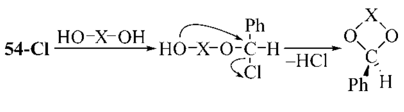


Scheme 14. Generation of chloro(phenyl)carbene (**54-Cl**) and its subsequent reactions: RH = (a) CyD, (b) H_2O, (c) MeOH, (d) *i*PrOH, (e) HCl, (f) *n*-C_5H_{12}, (g) *c*-C_6H_{12}, (h) THF, (i) $CHCl_3$, (j) PhH, (k) PhCH(OH)CH(OH)Ph.

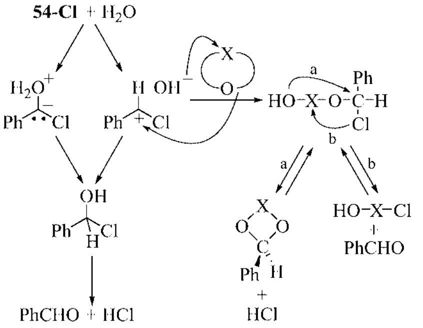


Scheme 13. Free halo(phenyl)carbenes (**54**) via crown ethers: X = Cl, Br.

The structures of the **55**@CyD ICs were found to be **55**@(α-CyD)$_2$ and (**55**@β-CyD)$_2$.[143] Photolysis of **55**@CyD ICs in the solid phase produced azine **57**, PhCHO, and HCl. But when the **55**@CyD ICs were photolyzed as slurries in alkaline buffer (pH = 9.3), RP-HPLC and FAB MS revealed the presence of derivatized CyDs.[143] Their structures were not fully ascertained, but FAB MS analysis ruled out 6^A,6^B-*O*-(benzylidene)cyclodextrins[145] and related isomers (Scheme 15). Upon formation, carbene **54-Cl** immediately reacts with H_2O to form a zwitterion or ion pair,[10,11] which yields the hydrolysis products PhCHO and HCl (Scheme 16). However, ring scission of the CyD host by the ion pair would yield an α-chloro ether capable of eliminating (a) HCl to form CyD-PhCHO and (b) PhCHO to form CyD-HCl.



Scheme 15. Derivatized CyDs, such as the isomers 2,3- and 6^A,6^B-*O*-(benzylidene)cyclodextrins, were not formed by **54-Cl**@CyD innermolecular insertion: HO–X–OH = CyD (as polyol).

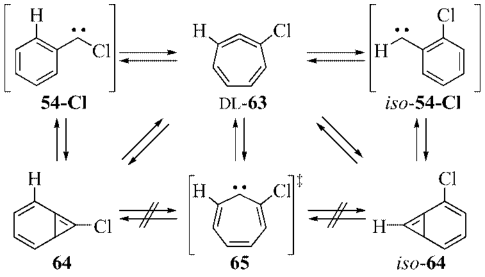


Scheme 16. Hydrolysis within **54-Cl**@CyD ICs likely precedes innermolecular reaction: XO = CyD (as polyether).

Photolysis of **54-Cl**@FAU ICs also gave azine **57**, PhCHO, and HCl as the major products.[143] The formation of the carbene **54-Cl** hydrolysis products demonstrates that a significant amount of H_2O remains inside thermally activated FAUs. Carbene **54**@FAU ICs were also studied by transient diffuse reflectance UV/Vis spectroscopy and laser flash photolysis (LFP) using 4,4′-bipyridine.[146] The τ of carbene **54-Cl** was measured within Y-type FAUs exchanged with group 1 cations. Though never exceeding 3.2 µs, it was found to depend on the counterion's Lewis acidity and increases in the series LiY < NaY < KY < RbY < CsY. Thermolysis of the **55**@NaY FAU IC resulted in PhCHO and 2,5-diphenyl-1,3,4-oxadiazole (**59**), which is usually formed by the hydrolysis of azine **57**. Note that **59** was also formed after photolysis of diazirine **55** in neat PhCHO, likely by aldehyde trapping of diazo compound **56**.[143,147]

Carbene **54-Cl** was shown by LFP to be insensitive to the presence of $^3O_2$ in solution.[15b,148,149] Similarly, no reaction with H_2 (by abstraction/recombination) in an H_2-doped argon matrix was observed.[150] However, singlet carbene **54-Cl** reacted slowly with $^3O_2$ in a spin-forbidden process when it was photolytically generated in an argon matrix.[147a,151] Indeed, carbene **54-Cl** may be capable of inner-sphere electron transfer (IS-ET).[152] Nevertheless, pronounced matrix effects on carbene **54-Cl**, like increased hydrogen-abstraction by QM tunneling, are unlikely.[68,153]

The τ of carbene **54-Cl** is reported to be around 3.6 µs (λ_{max} = 310 nm;[154] 2,2,4-trimethylpentane), as determined by LFP of diazirine **55**.[148,155] At T = 10 K, matrix-isolated **54-Cl** completely undergoes ring expansion to 1-chloro-1,2,4,6-cycloheptatetraene (DL-**63**) when exposed to short wavelength irradiation (λ > 254 nm) (Scheme 17). Neither 7-chlorobicyclo[4.1.0]hepta-2,4,6-triene (**64**) nor 2-chloro-2,4,6-cycloheptatrien-1-ylidene (**65**) was observed during prolonged irradiation (λ > 338 nm) of carbene **54-Cl**.[137c,156] Hence, cyclic allene DL-**63** apparently derives from a direct 1,2-C shift within the frozen argon matrix.[112,157] However, if **64** were to lie in a shallow potential energy well then it would be very fleeting and perhaps unobservable.[137d,e] (2-Chlorophenyl)carbene (*iso*-**54-Cl**) also rearranges to cyclic allene DL-**63**.[137c,151] According to one study, the two carbenes do not interconvert,[151] since carbene **54-Cl** has a singlet GS and carbene *iso*-**54-Cl** likely has a triplet GS. In another report, irradiation (λ > 212 nm) of cyclic allene DL-**63** (produced from *iso*-**54-Cl**) did generate some carbene **54-Cl**.[137c] Finally, the 1,3-CH insertion of carbene **54-Cl** to 1-chloro-1*H*-cyclopropabenzene (**58**) has never been observed (Scheme 14).



Scheme 17. Ring expansion of chloro(phenyl)carbene (**54-Cl**).

2.5.2. *([1,1′-Biphenyl]-4-yl)chlorocarbene*

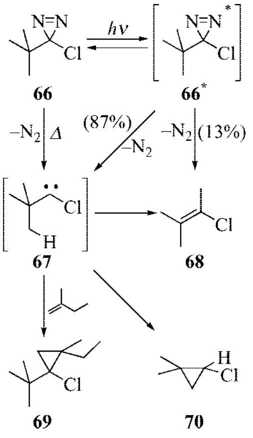
Photolysis of crystalline diazirine *p*-Ph-**55** yields the corresponding azine as the sole product.[67f] As mentioned earlier, similar results were found with neat liquid diazirine **55**.[143] Since azines are likely formed via carbene–diazirine ylides,[158] the carbene τ becomes crucial. The τ of ([1,1′-biphenyl]-4-yl)chlorocarbene (*p*-Ph-**54-Cl**) was determined to be 24.7 µs (λ_{max} = 360 nm; 2,2,4-trimethylpentane) by LFP of 3-([1,1′-biphenyl]-4-yl)-3-chloro-3*H*-diazirine (*p*-Ph-**55**).[155]

2.6. (*tert*-Alkyl)halocarbenes

Like carbene **54-Cl** and other (aryl)halocarbenes, (*tert*-alkyl)halocarbenes cannot undergo a 1,2-H shift. Nevertheless, other types of intramolecular rearrangements can flourish.

2.6.1. *(tert-Butyl)chlorocarbene*

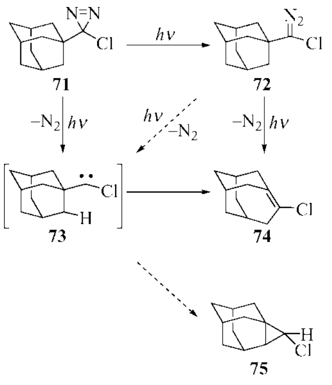
The decomposition of 3-*tert*-butyl-3-chloro-3*H*-diazirine (**66**), by either thermolysis or photolysis (Scheme 18), yields mainly 1-chloro-2,2-dimethylcyclopropane (**70**).[159] 2-Chloro-3-methyl-2-butene (**68**) is also formed, but to a lesser extent.[160] Cyclopropane **70** stems from a 1,3-CH insertion of (*tert*-butyl)chlorocarbene (**67**) ($\tau \approx 1.1\ \mu s$; $\tau_{uncorr.} \approx 90$ ns[16]).[17,113d,160–162] In fact, the C–H insertion product **70** was observed even at $T = 11$ K and was likely formed by QM tunneling.[161,163]



Scheme 18. (*tert*-Butyl)chlorocarbene (**67**) mostly undergoes 1,3-CH insertion.

2.6.2. *(Adamantan-1-yl)chlorocarbene*

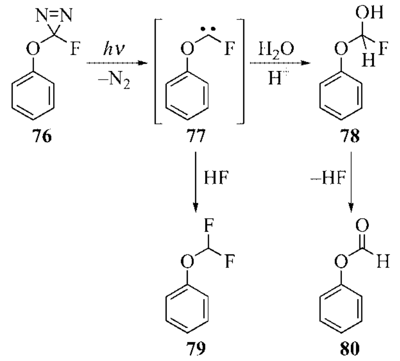
In a related case, photolysis of 3-(adamantan-1-yl)-3-chloro-3*H*-diazirine (**71**) in an argon matrix at $T = 10$ K yields both 1-[chloro(diazo)methyl]adamantane (**72**) and (adamantan-1-yl)chlorocarbene (**73**) as primary photoproducts (Scheme 19).[164] It was not clear, however, which reactive intermediate formed anti-Bredt 4-chlorotricyclo[4.3.1.1^{3,8}]undec-3-ene (**74**) by a 1,2-C shift, that is, ring expansion. The formation of minor amounts of 4-chlorotetracyclo[4.3.1.1^{3,8}.0^{3,5}]undecane (**75**) by 1,3-CH insertion could not be ruled out. Nevertheless, the predominance of a 1,2-C shift is in sharp contrast to the 1,3-CH insertion featured with CH_3-bearing carbene **67**, which can also be considered an unscaffolded version of carbene **73**.



Scheme 19. (Adamantan-1-yl)chlorocarbene (**73**) may undergo a 1,2-C shift.

2.7. (Aryloxy)halocarbenes

Most recently, spectroscopic characterization of a singlet carbene@HC IC was achieved as a result of supramolecular carbene τ enhancement. Photolysis of 3-fluoro-3-phenoxy-3*H*-diazirine (**76**) within a HC (Figure 6b) generates fluoro(phenoxy)carbene (**77**), an electronically stabilized carbene that does not undergo innermolecular reaction inside the HC host.[165] However, adventitious water molecules destroyed carbene **77** (Scheme 20). When pyridine was added as base to inhibit this acid-catalyzed reaction, carbene **77** persisted for days within its HC cage. NMR spectroscopy was used to characterize incarcerated carbene **77** and its spectrum indicated that the carbene adopts a more compact cisoid conformation within the clathrate even though this conformer is less stable than the transoid form.



Scheme 20. Formation of fluorophenoxycarbene (**77**) within a HC and reaction with adventitious H_2O.

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[1] a) *Chem. Eng. News* **1999**, *77*, 19; b) S. S. Krishnamurthy, *Curr. Sci.* **1991**, *60*, 619–620; c) See also refs.[19,28–36].

[2] a) J. Hine, *Divalent Carbon*, Ronald, New York, **1964**; b) W. Kirmse, *Carbene, Carbenoide und Carbenanaloge*, Verlag Chemie, Weinheim, **1969**; c) W. Kirmse, *Carbene Chemistry*, 2nd ed., Academic Press, New York, **1971**; d) M. Jones Jr., R. A. Moss (Eds.), *Carbenes*, Wiley, New York, **1973**, vol. 1; e) M. Jones Jr., R. A. Moss (Eds.), *Carbenes*, Wiley, New York, **1975**, vol. 2; f) M. Jones Jr., *Sci. Am.* **1976**, *234*, 101–113; g) W. M. Jones, U. H. Brinker in *Pericyclic Reactions* (Eds.: A. P. Marchand, R. E. Lehr), Academic Press, New York, **1977**, vol. 1, chapter 3; h) M. Regitz (Ed.), *Methoden der Organischen Chemie (Houben-Weyl)*, Thieme, Stuttgart, **1989**, vol. E19b; i) U. H. Brinker (Ed.), *Advances in Carbene Chemistry*, JAI Press, Greenwich, CT, **1994**, vol. 1; j) U. H. Brinker (Ed.), *Advances in Carbene Chemistry*, JAI Press, Stamford, CT, **1998**, vol. 2; k) U. H. Brinker (Ed.), *Advances in Carbene Chemistry*, Elsevier, Amsterdam, **2001**, vol. 3; l) H. E. Helson, W. L. Jorgensen, *J. Org. Chem.* **1994**, *59*, 3841–3856; m) R. A. Moss, M. S. Platz, M. Jones Jr (Eds.), *Reactive Intermediate Chemistry*, Wiley,

New York, **2004**; n) G. Bertrand (Ed.), *Carbene Chemistry: From Fleeting Intermediates to Powerful Reagents*, Marcel Dekker, New York, **2002**.

[3] a) E. Schmitz, D. Habisch, A. Stark, *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 548; b) H. Dürr, A.-M. A. Abdel-Wahab in *Organic Photochemistry and Photobiology* (Ed.: W. M. Horspool), CRC Press, Boca Raton, FL, **1995**, pp. 954–983.

[4] a) S. Patai (Ed.), *The Chemistry of Diazonium and Diazo Groups*, Wiley, New York, **1978**, vols. 1–2; b) W. J. Baron, M. R. DeCamp, M. E. Hendrick, M. Jones Jr., R. H. Levin, M. B. Sohn in *Carbenes* (Eds.: M. Jones Jr., R. A. Moss), Wiley, New York, **1973**, vol. 1, chapter 1.

[5] a) M. T. H. Liu (Ed.), *Chemistry of Diazirines*, CRC Press, Boca Raton, FL, **1987**, vols. 1–2; b) E. Schmitz, *Adv. Heterocycl. Chem.* **1963**, *1*, 83–130; c) E. Schmitz, *Adv. Heterocycl. Chem.* **1979**, *17*, 63–107; d) E. Schmitz, *Angew. Chem. Int. Ed. Engl.* **1964**, *3*, 333–341; e) E. Schmitz in *Methoden der Organischen Chemie (Houben-Weyl)* (Ed.: D. Klamann), Thieme, Stuttgart, **1992**, vol. E16c, pp. 678–728.

[6] S. Çelebi, S. Leyva, D. A. Modarelli, M. S. Platz, *J. Am. Chem. Soc.* **1993**, *115*, 8613–8620.

[7] a) W. R. White III, M. S. Platz, *J. Org. Chem.* **1992**, *57*, 2841–2846; b) D. A. Modarelli, S. Morgan, M. S. Platz, *J. Am. Chem. Soc.* **1992**, *114*, 7034–7041; c) N. Yamamoto, F. Bernardi, A. Bottoni, M. Olivucci, M. A. Robb, S. Wilsey, *J. Am. Chem. Soc.* **1994**, *116*, 2064–2074.

[8] T. Wakahara, Y. Niino, T. Kato, Y. Maeda, T. Akasaka, M. T. H. Liu, K. Kobayashi, S. Nagase, *J. Am. Chem. Soc.* **2002**, *124*, 9465–9468.

[9] a) J. E. Chateauneuf, *Res. Chem. Intermed.* **1994**, *20*, 249–263; b) J. Peon, D. Polshakov, B. Kohler, *J. Am. Chem. Soc.* **2002**, *124*, 6428–6438.

[10] a) W. Kirmse in *Advances in Carbene Chemistry* (Ed.: U. H. Brinker), Elsevier, Amsterdam, **2001**, vol. 3, pp. 1–51; b) W. Kirmse, T. Meinert, *J. Chem. Soc., Chem. Commun.* **1994**, 1065–1066; c) W. Kirmse, N. Knöpfel, K. Loosen, R. Siegfried, H.-J. Wroblowsky, *Chem. Ber.* **1981**, *114*, 1187–1191.

[11] a) W. Kirmse in *Advances in Carbene Chemistry* (Ed.: U. H. Brinker), JAI Press, Greenwich, CT, **1994**, vol. 1, pp. 1–57; b) D. Bethell, A. R. Newall, G. Stevens, D. Whittaker, *J. Chem. Soc. B* **1969**, 749–751; c) D. Bethell, A. R. Newall, D. Whittaker, *J. Chem. Soc. B* **1971**, 23–31.

[12] J. March, *Advanced Organic Chemistry*, 4th ed., Wiley, New York, **1992**, p. 355.

[13] a) E. Schmitz in *Chemistry of Diazirines* (Ed.: M. T. H. Liu), CRC Press, Boca Raton, FL, **1987**, vol. 1, chapter 3 (see pp. 79–84); b) S. D. Isaev, G. G. Zhalnina, Z. N. Murzinova, S. I. Lastovenko, A. G. Yurchenko, *J. Org. Chem. USSR* **1988**, *24*, 126–131 (Transl. of *Zh. Org. Khim.*); c) S. D. Isaev, N. I. Kulik, A. G. Yurchenko, *Theor. Exp. Chem.* **1993**, *29*, 213–216 (Transl. of *Teor. Eksp. Khim.*).

[14] a) A. R. Forrester, J. S. Sadd, *J. Chem. Soc., Chem. Commun.* **1976**, 631–632; b) A. R. Forrester, J. S. Sadd, *J. Chem. Soc., Perkin Trans. 2* **1982**, 1273–1278.

[15] a) G. L. Closs, B. E. Rabinow, *J. Am. Chem. Soc.* **1976**, *98*, 8190–8198; b) R. A. Moss, N. J. Turro in *Kinetics and Spectroscopy of Carbenes and Biradicals* (Ed.: M. S. Platz), Plenum Press, New York, **1990**, pp. 213–238.

[16] J. E. Jackson, M. S. Platz in *Advances in Carbene Chemistry* (Ed.: U. H. Brinker), JAI Press, Greenwich, CT, **1994**, vol. 1, pp. 89–160.

[17] a) J. E. Jackson, N. Soundararajan, M. S. Platz, *J. Am. Chem. Soc.* **1988**, *110*, 5595–5596; b) R. Bonneau, M. T. H. Liu, M. T. Rayez, *J. Am. Chem. Soc.* **1989**, *111*, 5973–5974.

[18] a) P. S. Skell, R. C. Woodworth, *J. Am. Chem. Soc.* **1956**, *78*, 4496–4497 (Correction: *J. Am. Chem. Soc.* **1956**, *78*, 6427); b) R. C. Woodworth, P. S. Skell, *J. Am. Chem. Soc.* **1959**, *81*, 3383–3386; c) P. S. Skell, *Tetrahedron* **1985**, *41*, 1427–1428; d) M.-D. Su, *J. Phys. Chem.* **1996**, *100*, 4339–4349.

[19] H. Tomioka in *Reactive Intermediate Chemistry* (Eds.: R. A. Moss, M. S. Platz, M. Jones Jr), Wiley, New York, **2004**, chapter 9.

[20] For open-shelled singlet carbenes see Figure 1d and ref.[138].

[21] G. Wu, M. Jones Jr., R. Walton, P. M. Lahti, *J. Org. Chem.* **1998**, *63*, 5368–5371.

[22] a) N. J. Turro, *Modern Molecular Photochemistry*; University Science Books, Mill Valley, CA, **1991**, pp. 551–552; b) C. Wentrup, *Reactive Molecules*; Wiley, New York, **1984**, pp. 46–48, 176–180.

[23] E. Wigner, E. E. Witmer, *Z. Phys.* **1928**, *51*, 859–886.

[24] F. A. Matsen, D. J. Klein, *Adv. Photochem.* **1969**, *5*, 1–55 (see pp. 29–32).

[25] C. Wentrup, *Reactive Molecules*; Wiley, New York, **1984**, pp. 182–183.

[26] a) D. Griller, A. S. Nazran, J. C. Scaiano, *Tetrahedron* **1985**, *41*, 1525–1530; b) C. Wentrup, *Reactive Molecules*; Wiley, New York, **1984**, pp. 190–191.

[27] R. Hoffmann, G. D. Zeiss, G. W. Van Dine, *J. Am. Chem. Soc.* **1968**, *90*, 1485–1499.

[28] a) *Chem. Eng. News* **1991**, *69*, 19–20; b) R. Dagani, *Chem. Eng. News* **1994**, *72*, 20–22; c) C. Buron, H. Gornitzka, V. Romanenko, G. Bertrand, *Science* **2000**, *288*, 834–836; d) *Chem. Eng. News* **2001**, *79*, 22; e) *Chem. Eng. News* **2000**, *78*, 57; f) G. Bucher, M. Winkler, *Nachr. Chem.* **2002**, *50*, 289–293; g) J. M. Hopkins, M. Bowdridge, K. N. Robertson, T. S. Cameron, H. A. Jenkins, J. A. C. Clyburne, *J. Org. Chem.* **2001**, *66*, 5713–5716.

[29] a) H. Tomioka, E. Iwamoto, H. Itakura, K. Hirai, *Nature* **2001**, *412*, 626–628; b) M. Freemantle, *Chem. Eng. News* **2001**, *79*, 11; c) K. Hirai, H. Tomioka, *J. Am. Chem. Soc.* **1999**, *121*, 10213–10214; d) H. Tomioka in *Advances in Carbene Chemistry* (Ed.: U. H. Brinker), JAI Press, Stamford, CT, **1998**, vol. 2, pp. 175–214; e) H. Tomioka, *Acc. Chem. Res.* **1997**, *30*, 315–321; f) H. Tomioka, T. Watanabe, K. Hirai, K. Furukawa, T. Takui, K. Itoh, *J. Am. Chem. Soc.* **1995**, *117*, 6376–6377.

[30] a) T. Itoh, Y. Nakata, K. Hirai, H. Tomioka, *J. Am. Chem. Soc.* **2006**, *128*, 957–967; b) *Chem. Eng. News* **2006**, *84*, 41.

[31] a) P. Chen in *Advances in Carbene Chemistry* (Ed.: U. H. Brinker), JAI Press, Stamford, CT, **1998**, vol. 2, pp. 45–75; b) J. Warkentin in *Advances in Carbene Chemistry* (Ed.: U. H. Brinker), JAI Press, Stamford, CT, **1998**, vol. 2, pp. 245–295.

[32] a) R. Breslow, *J. Am. Chem. Soc.* **1957**, *79*, 1762–1763; b) R. Breslow, *J. Am. Chem. Soc.* **1958**, *80*, 3719–3726; c) H.-W. Wanzlick, H.-J. Kleiner, *Angew. Chem. Int. Ed. Engl.* **1964**, *3*, 65; d) R. A. Olofson, J. M. Landesberg, K. N. Houk, J. S. Michelman, *J. Am. Chem. Soc.* **1966**, *88*, 4265–4266; e) R. W. Hoffmann, B. Hagenbruch, D. M. Smith, *Chem. Ber.* **1977**, *110*, 23–36; f) H. Sugimoto, K. Hirai, *Tetrahedron Lett.* **1985**, *26*, 883–886; g) R. Kluger, *Chem. Rev.* **1987**, *87*, 863–876.

[33] a) H.-W. Wanzlick, H.-J. Kleiner, *Angew. Chem.* **1961**, *73*, 493; b) H.-W. Wanzlick, E. Schikora, *Chem. Ber.* **1961**, *94*, 2389–2393; c) H. W. Wanzlick, *Angew. Chem. Int. Ed. Engl.* **1962**, *1*, 75–80; d) H.-W. Wanzlick, H. Ahrens, *Chem. Ber.* **1964**, *97*, 2447–2450; e) D. M. Lemal, R. A. Lovald, K. I. Kawano, *J. Am. Chem. Soc.* **1964**, *86*, 2518–2519; f) R. W. Hoffmann, *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 754–765; g) N. Wiberg, *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 766–779; h) D. M. Lemal in *The Chemistry of the Amino Group* (Ed.: S. Patai), Wiley, New York, **1968**, chapter 12; i) A. J. Arduengo III, J. R. Goerlich, W. J. Marshall, *J. Am. Chem. Soc.* **1995**, *117*, 11027–11028.

[34] H. E. Winberg, J. E. Carnahan, D. D. Coffman, M. Brown, *J. Am. Chem. Soc.* **1965**, *87*, 2055–2056.

[35] a) A. J. Arduengo III, R. L. Harlow, M. Kline, *J. Am. Chem. Soc.* **1991**, *113*, 361–363; b) A. J. Arduengo III, H. V. R. Dias, D. A. Dixon, R. L. Harlow, W. T. Klooster, T. F. Koetzle, *J. Am. Chem. Soc.* **1994**, *116*, 6812–6822; c) R. A. Olofson, W. R. Thompson, J. S. Michelman, *J. Am. Chem. Soc.* **1964**, *86*, 1865–1866; d) H. A. Staab, H. Irngartinger, A. Mannschreck, M.-T. Wu, *Justus Liebigs Ann. Chem.* **1966**, *695*, 55–64; e) M. Regitz,

Angew. Chem. Int. Ed. Engl. **1996**, *35*, 725–728; f) W. A. Herrmann, C. Köcher, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2162–2187; g) A. J. Arduengo III, R. Krafczyk, *Chem. Unserer Zeit* **1998**, *32*, 6–14.

[36] V. Lavallo, Y. Canac, B. Donnadieu, W. W. Schoeller, G. Bertrand, *Science* **2006**, *312*, 722–724.

[37] F. Schardinger, *Wien. Klin. Wochenschr.* **1904**, *17*, 207–209.

[38] A. Villiers, *C. R. Hebd. Seances Acad. Sci.* **1891**, *112*, 536–538.

[39] a) J. Szejtli, *Chem. Intell.* **1999**, 5, 38–45; b) M. C. Feiters in *Comprehensive Supramolecular Chemistry* (Ed.: J.-M. Lehn), Pergamon Press, New York, **1995**, vol. 10, chapter 11.

[40] a) V. T. D'Souza, K. B. Lipkowitz (Eds.), "Cyclodextrins" in *Chemical Reviews*, American Chemical Society, Washington DC, **1998**, vol. 98, no. 5, pp. 1741–2076; b) G. Wenz, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 803–822; c) W. Saenger, *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 344–362; d) M. L. Bender, M. Komiyama, *Cyclodextrin Chemistry*, Springer, Berlin, **1978**.

[41] a) K. Kano, Y. Tamiya, S. Hashimoto, *J. Inclusion Phenom. Mol. Recognit. Chem.* **1992**, *13*, 287–293; b) J. Szejtli in *Biotechnology of Amylodextrin Oligosaccharides* (Ed.: R. Friedman), ACS Symposium Series 458, American Chemical Society, Washington, DC, **1991**, chapter 1.

[42] F. Cramer, F. M. Henglein, *Chem. Ber.* **1957**, *90*, 2561–2571.

[43] O. S. Tee, T. A. Gadosy, J. B. Giorgi, *Can. J. Chem.* **1996**, *74*, 736–744.

[44] a) D. Krois, U. H. Brinker, *J. Am. Chem. Soc.* **1998**, *120*, 11627–11632; b) M. M. Bobek, D. Krois, U. H. Brinker, *Org. Lett.* **2000**, *2*, 1999–2002; c) J.-L. Mieusset, D. Krois, M. Pacar, L. Brecker, G. Giester, U. H. Brinker, *Org. Lett.* **2004**, *6*, 1967–1970; d) D. Krois, U. H. Brinker in *Handbook of Cyclodextrins and Their Complexes* (Ed.: H. Dodziuk), Wiley, New York, **2006**, pp. 289–298.

[45] A guest must have an electronegative group, like –F or –OH, to effect an opposite inclusion orientation within CyDs in the aqueous versus solid phase. See refs.[47,49].

[46] a) B. Casu, M. Reggiani, G. G. Gallo, A. Vigevani, *Tetrahedron* **1966**, *22*, 3061–3083; b) P. V. Demarco, A. L. Thakkar, *J. Chem. Soc. D* **1970**, 2–4; c) D. D. MacNicol, *Tetrahedron Lett.* **1975**, *16*, 3325–3326; d) W.-S. Chung, N. J. Turro, J. Silver, W. J. le Noble, *J. Am. Chem. Soc.* **1990**, *112*, 1202–1205; e) Z. H. Qi, V. Mak, L. Diaz, D. M. Grant, C.-J. Chang, *J. Org. Chem.* **1991**, *56*, 1537–1542; f) D. Salvatierra, C. Jaime, A. Virgili, F. Sánchez-Ferrando, *J. Org. Chem.* **1996**, *61*, 9578–9581.

[47] a) J. L. Alderfer, A. V. Eliseev, *J. Org. Chem.* **1997**, *62*, 8225–8226; b) P. M. Ivanov, D. Salvatierra, C. Jaime, *J. Org. Chem.* **1996**, *61*, 7012–7017.

[48] R. Kupfer, M. D. Poliks, U. H. Brinker, *J. Am. Chem. Soc.* **1994**, *116*, 7393–7398.

[49] M. M. Bobek, G. Giester, H. Kählig, U. H. Brinker, *Tetrahedron Lett.* **2000**, *41*, 5663–5667.

[50] a) V. A. Pokrovskii, V. V. Mosin, *Theor. Exp. Chem.* **1987**, *23*, 58–73 (Transl. of *Teor. Eksp. Khim.*); b) R. D. Voyksner, F. P. Williams, C. S. Smith, D. L. Koble, H. H. Seltzman, *Biomed. Environ. Mass Spectrom.* **1989**, *18*, 1071–1078; c) G. Pocsfalvi, M. Liptak, P. Huszthy, J. S. Bradshaw, R. M. Izatt, K. Vekey, *Anal. Chem.* **1996**, *68*, 792–795.

[51] A. F. Cronstedt, *K. Sven. Vetenskapsakad. Handl., Stockholm* **1756**, *17*, 120–123.

[52] R. Manly, J. Holmes, *New Sci.* **1989**, *121*, 39–43.

[53] V. Ramamurthy in *Photochemistry in Organized and Constrained Media* (Ed.: V. Ramamurthy), VCH, New York, **1991**, chapter 10.

[54] V. Ramamurthy, D. R. Corbin, N. J. Turro, Z. Zhang, M. A. Garcia-Garibay, *J. Org. Chem.* **1991**, *56*, 255–261.

[55] V. Ramamurthy, N. J. Turro, *J. Inclusion Phenom. Mol. Recognit. Chem.* **1995**, *21*, 239–282.

[56] M. A. Garcia-Garibay, Z. Zhang, N. J. Turro, *J. Am. Chem. Soc.* **1991**, *113*, 6212–6218.

[57] H. W. G. van Herwijnen, U. H. Brinker, *J. Org. Chem.* **2001**, *66*, 2874–2876.

[58] D. J. Cram, S. Karbach, Y. H. Kim, L. Baczynskyj, K. Marti, R. M. Sampson, G. W. Kalleymeyn, *J. Am. Chem. Soc.* **1988**, *110*, 2554–2560.

[59] R. Warmuth, J. Yoon, *Acc. Chem. Res.* **2001**, *34*, 95–105.

[60] a) D. J. Cram, M. E. Tanner, R. Thomas, *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1024–1027; b) B. R. Arnold, J. Michl, *J. Phys. Chem.* **1993**, *97*, 13348–13354.

[61] a) R. Warmuth, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1347–1350; b) R. Warmuth, *Chem. Commun.* **1998**, 59–60; c) D. Bradley, *Chem. Br.* **1998**, *34*, 16; d) R. Warmuth, *J. Inclusion Phenom. Macrocycl. Chem.* **2000**, *37*, 1–38; e) R. Warmuth, *Eur. J. Org. Chem.* **2001**, 423–437.

[62] S. G. Wierschke, J. J. Nash, R. R. Squires, *J. Am. Chem. Soc.* **1993**, *115*, 11958–11967.

[63] F. Diederich, L. Isaacs, D. Philp, *Chem. Soc. Rev.* **1994**, *23*, 243–255.

[64] a) T. Suzuki, Q. Li, K. C. Khemani, F. Wudl, *J. Am. Chem. Soc.* **1992**, *114*, 7301–7302; b) J. Almy, A. Herrera, N. Martín, C. Seoane, T. Suzuki, F. Wudl, *J. Chem. Educ.* **1996**, *73*, A105–A106; c) A. B. Smith III, R. M. Strongin, L. Brand, G. T. Furst, W. J. Romanow, K. G. Owens, R. C. King, *J. Am. Chem. Soc.* **1993**, *115*, 5829–5830; d) Y. Niino, T. Wakahara, T. Akasaka, M. T. H. Liu, K. Kobayashi, S. Nagase, *ITE Lett.* **2002**, 3, C60–C63.

[65] A. Hildebrand, U. Hilgers, R. Blume, D. Wiechoczek, *J. Chem. Educ.* **1996**, *73*, 1066–1067.

[66] T. Sugawara, H. Tukada, A. Izuoka, S. Murata, *J. Am. Chem. Soc.* **1986**, *108*, 4272–4278.

[67] a) S. H. Shin, A. E. Keating, M. A. Garcia-Garibay, *J. Am. Chem. Soc.* **1996**, *118*, 7626–7627; b) *Chem. Eng. News* **1996**, *74*, 34; c) S. H. Shin, D. Cizmeciyan, A. E. Keating, S. I. Khan, M. A. Garcia-Garibay, *J. Am. Chem. Soc.* **1997**, *119*, 1859–1868; d) A. E. Keating, S. H. Shin, K. N. Houk, M. A. Garcia-Garibay, *J. Am. Chem. Soc.* **1997**, *119*, 1474–1475; e) M. A. Garcia-Garibay, S. Shin, C. N. Sanrame, *Tetrahedron* **2000**, *56*, 6729–6737; f) C. N. Sanrame, C. P. Suhrada, H. Dang, M. A. Garcia-Garibay, *J. Phys. Chem. A* **2003**, *107*, 3287–3294.

[68] H. Tomioka, Y. Ozaki, Y. Koyabu, Y. Izawa, *Tetrahedron Lett.* **1982**, *23*, 1917–1920.

[69] a) T. Bally in *Reactive Intermediate Chemistry* (Eds.: R. A. Moss, M. S. Platz, M. Jones Jr.), Wiley, New York, **2004**, chapter 17; b) R. S. Sheridan in *Organic Photochemistry and Photobiology* (Ed.: W. M. Horspool), CRC Press, Boca Raton, FL, **1995**, pp. 999–1006.

[70] See ref.[19], p. 390.

[71] H. Tomioka, "Tunneling Insertion Reaction of Carbenes" in *Springer Series on Atomic, Optical, and Plasma Physics* **2004**, vol. 36 (Atom Tunneling Phenomena in Physics, Chemistry and Biology), pp. 147–172; [*Chem. Abstr.* **2004**, *140*, 303107].

[72] F. Montanari, S. Quici, S. Banfi in *Comprehensive Supramolecular Chemistry* (Ed.: J.-M. Lehn), Pergamon Press, New York, **1995**, vol. 10, chapter 13.

[73] a) A. L. Byrum, *Chem. Eng. News* **2001**, *79*, 38–40; b) A. Byrum, *Chem. Eng. News* **2001**, *79*, 10.

[74] H. E. Schroeder, C. J. Pedersen, *Pure Appl. Chem.* **1988**, *60*, 445–451.

[75] 1987 Nobel Prize lectures: a) D. J. Cram, *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1009–1020; b) C. J. Pedersen, *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1021–1027; c) J.-M. Lehn, *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 89–112.

[76] J.-M. Lehn (Ed.), *Comprehensive Supramolecular Chemistry*, Pergamon Press, New York, **1995**, vols. 1–11.

[77] D. Bradley, *Chem. Br.* **1992**, *28*, 870.

[78] N. J. Turro, *Acc. Chem. Res.* **2000**, *33*, 637–646.

[79] a) R. N. Bantu, R. Kupfer, U. H. Brinker, *Tetrahedron Lett.* **1994**, *35*, 5117–5120; b) K. Takahashi, *Chem. Rev.* **1998**, *98*, 2013–2033 (see p. 2029).

[80] a) M. S. Syamala, B. Nageswer Rao, V. Ramamurthy, *Tetrahedron* **1988**, *44*, 7234–7242; b) K. Pitchumani, M. Warrier, V. Ramamurthy, *J. Am. Chem. Soc.* **1996**, *118*, 9428–9429; c) R.-

Q. Xie, Y.-C. Liu, X.-G. Lei, *Res. Chem. Intermed.* **1992**, *18*, 61–69; d) K. Pitchumani, P. Velusamy, M. C. Durai Manickam, C. Srinivasan, *Proc. Indian Acad. Sci. Chem. Sci.* **1994**, *106*, 49–57.

[81] a) J. Rebek Jr., *Chem. Commun.* **2000**, 637–643; b) A. D. Hamilton, *J. Chem. Educ.* **1990**, *67*, 821–828.

[82] a) E. Fischer, *Ber. Dtsch. Chem. Ges.* **1894**, *27*, 2985–2993; b) D. K. Smith, *J. Chem. Educ.* **2005**, *82*, 393–400.

[83] a) R. Breslow, *Science* **1982**, *218*, 532–537; b) L. Liu, R. Breslow, *J. Am. Chem. Soc.* **2002**, *124*, 4978–4979; c) *Chem. Eng. News* **2002**, *80*, 34.

[84] C. D. Chang, C. T.-W. Chu, *J. Catal.* **1982**, *74*, 203–206.

[85] J. H. C. van Hooff, *J. Catal.* **1983**, *79*, 242–243.

[86] M. W. Anderson, J. Klinowski, *Nature* **1989**, *339*, 200–203.

[87] M. Jacoby, *Chem. Eng. News* **2002**, *80*, 5.

[88] a) L. Dunsch, P. Georgi, M. Krause, C.-R. Wang, T. Kai, T. Tomiyama, T. Okazaki, H. Shinohara, *Abstr. Pap.-Electro-Chem. Soc. 201st* **2002**, 955; b) R. Dagani, *Chem. Eng. News* **2002**, *80*, 32–35.

[89] M. Mąkosza, M. Wawrzyniewicz, *Tetrahedron Lett.* **1969**, *10*, 4659–4662.

[90] a) I. Tabushi, Z.-I. Yoshida, N. Takahashi, *J. Am. Chem. Soc.* **1970**, *92*, 6670–6672; b) E. V. Dehmlow, J. Schönefeld, *Justus Liebigs Ann. Chem.* **1971**, *744*, 42–50; c) E. V. Dehmlow, M. Lissel, *Tetrahedron Lett.* **1976**, *17*, 1783–1786.

[91] a) S. L. Regen, A. Singh, *J. Org. Chem.* **1982**, *47*, 1587–1588; b) L. Xu, F. Tao, *Synth. Commun.* **1988**, *18*, 2117–2121; c) L. Xu, W. B. Smith, U. H. Brinker, *J. Am. Chem. Soc.* **1992**, *114*, 783–784; d) L. Xu, U. H. Brinker in *Synthetic Organic Sonochemistry* (Ed.: J.-L. Luche), Plenum Press, New York, **1998**, pp. 344–345.

[92] a) A. Geuther, *Ann. Chem. Pharm.* **1862**, *123*, 121–122; b) J. Hine, *J. Am. Chem. Soc.* **1950**, *72*, 2438–2445; c) J. Hine, A. M. Dowell Jr., *J. Am. Chem. Soc.* **1954**, *76*, 2688–2692; d) W. v. E. Doering, A. K. Hoffmann, *J. Am. Chem. Soc.* **1954**, *76*, 6162–6165.

[93] J. R. Pliego Jr., W. B. De Almeida, *J. Phys. Chem.* **1996**, *100*, 12410–12413.

[94] a) I. Tabushi, Z.-I. Yoshida, N. Takahashi, *J. Am. Chem. Soc.* **1971**, *93*, 1820; b) G. C. Joshi, N. Singh, L. M. Pande, *Tetrahedron Lett.* **1972**, *13*, 1461–1464.

[95] D. Landini, A. M. Maia, F. Montanari, F. M. Pirisi, *Gazz. Chim. Ital.* **1975**, *105*, 863–874.

[96] a) H. Wynberg, *Chem. Rev.* **1960**, *60*, 169–184; b) H. Wynberg, E. W. Meijer, *Org. React. (NY)* **1982**, *28*, 1–36; c) A. Hassner, C. Stumer, *Organic Syntheses Based on Name Reactions and Unnamed Reactions*, Pergamon Press, Tarrytown, NY, **1994**, p. 314; d) J. March, *Advanced Organic Chemistry*, 4th ed., Wiley, New York, **1992**, pp. 544–545.

[97] a) M. Ohara, J. Fukuda, *Pharmazie* **1978**, *33*, 467; b) M. Komiyama, H. Hirai, *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2053–2056; c) M. Komiyama, H. Hirai, *J. Am. Chem. Soc.* **1983**, *105*, 2018–2021.

[98] G. C. Joshi, N. Singh, L. M. Pande, *Tetrahedron Lett.* **1972**, *13*, 1461–1464.

[99] U. H. Brinker, R. Buchkremer, M. Kolodziejczyk, R. Kupfer, M. Rosenberg, M. D. Poliks, M. Orlando, M. L. Gross, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1344–1345.

[100] U. H. Brinker, M. G. Rosenberg in *Advances in Carbene Chemistry* (Ed.: U. H. Brinker), JAI Press, Stamford, CT, **1998**, vol. 2, pp. 29–44.

[101] W. Kirmse, *Angew. Chem. Int. Ed.* **2005**, *44*, 2476–2479.

[102] S. D. Isaev, A. G. Yurchenko, F. N. Stepanov, G. G. Kolyada, S. S. Novikov, N. F. Karpenko, *J. Org. Chem. USSR* **1973**, *9*, 745–748 (Transl. of *Zh. Org. Khim.).*

[103] R. A. Moss, M. J. Chang, *Tetrahedron Lett.* **1981**, *22*, 3749–3752.

[104] a) H. Bayley, J. R. Knowles, *Biochemistry* **1978**, *17*, 2420–2423; b) H. Bayley, J. R. Knowles, *Biochemistry* **1980**, *19*, 3883–3892; c) B. Erni, H. G. Khorana, *J. Am. Chem. Soc.* **1980**, *102*, 3888–3896; d) J. Brunner, H. Senn, F. M. Richards, *J. Biol. Chem.* **1980**, *255*, 3313–3318; e) M. Nassal, *Liebigs Ann. Chem.* **1983**, 1510–1523.

[105] a) T. Bally, S. Matzinger, L. Truttman, M. S. Platz, S. Morgan, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1964–1966; b) S. D. Isaev, N. I. Kulik, A. G. Yurchenko, *Theor. Exp. Chem.* **1993**, *29*, 80–83 (Transl. of *Teor. Eksp. Khim.*).

[106] a) J. Michl, G. J. Radziszewski, J. W. Downing, K. B. Wiberg, F. H. Walker, R. D. Miller, P. Kovačič, M. Jawdosiuk, V. Bonačič-Koutecký, *Pure Appl. Chem.* **1983**, *55*, 315–321; b) R. T. Conlin, R. D. Miller, J. Michl, *J. Am. Chem. Soc.* **1979**, *101*, 7637–7638; c) D. J. Martella, M. Jones Jr., P. v. R. Schleyer, *J. Am. Chem. Soc.* **1978**, *100*, 2896–2897; d) M. Jones Jr., in *Advances in Carbene Chemistry* (Ed.: U. H. Brinker), JAI Press, Stamford, CT, **1998**, vol. 2, pp. 77–96; e) G. V. Shustov, M. T. H. Liu, *Can. J. Chem.* **1998**, *76*, 851–861.

[107] S. D. Isaev, A. G. Yurchenko, F. N. Stepanov, G. G. Kolyada, S. S. Novikov, *J. Org. Chem. USSR* **1973**, *9*, 436 (Transl. of *Zh. Org. Khim.*).

[108] D. Krois, L. Brecker, A. Werner, U. H. Brinker, *Adv. Synth. Catal.* **2004**, *346*, 1367–1374.

[109] D. Krois, M. M. Bobek, A. Werner, H. Kählig, U. H. Brinker, *Org. Lett.* **2000**, *2*, 315–318.

[110] A. Nickon, A. G. Stern, M. C. Ilao, *Tetrahedron Lett.* **1993**, *34*, 1391–1394.

[111] M. T. H. Liu, *Acc. Chem. Res.* **1994**, *27*, 287–294.

[112] U. H. Brinker, L. König, *Chem. Lett.* **1984**, 45–48.

[113] a) A. Nickon, *Acc. Chem. Res.* **1993**, *26*, 84–89; b) R. A. Moss, W. Ma, *Tetrahedron Lett.* **1999**, *40*, 5101–5104; c) R. A. Moss, W. Ma, S. Yan, F. Zheng, *Tetrahedron Lett.* **2001**, *42*, 8923–8926; d) D. C. Merrer, R. A. Moss in *Advances in Carbene Chemistry* (Ed.: U. H. Brinker), Elsevier, Amsterdam, **2001**, vol. 3, pp. 53–113.

[114] J. J. Fuchs, US Patent 3287354, **1966** [*Chem. Abstr.* **1967**, *66*, 65453].

[115] M. G. Rosenberg, S. M. Kam, U. H. Brinker, *Tetrahedron Lett.* **1996**, *37*, 3235–3238.

[116] W. R. Bamford, T. S. Stevens, *J. Chem. Soc.* **1952**, 4735–4740.

[117] J. W. Wilt, W. J. Wagner, *J. Org. Chem.* **1964**, *29*, 2788–2789.

[118] The inherent migratory aptitude of a group depends mainly on three factors: (1) the intrinsic migratory aptitude, (2) the bystander substituent on the migration origin, and (3) the spectator substituent on the migration terminus. For reviews, see: a) ref.[113a], b) ref.[113d] (see pp. 80–91).

[119] a) R. L. Taber, W. C. Champion, *J. Chem. Educ.* **1967**, *44*, 620; b) C. C. Price, *J. Am. Chem. Soc.* **1939**, *61*, 1847–1849; c) G. Vavon, M. Barbier, *Bull. Soc. Chim. Fr.* **1931**, *49*, 567–582 (see pp. 569, 576); d) J.-B. Senderens, *Ann. Chim. (Paris)* **1922**, *18*, 117–145 (see p. 141); e) J.-B. Senderens, *Ann. Chim. Phys.* **1912**, *25*, 449–529 (see pp. 500–501); f) W. Ipatiew, *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 3383–3387; g) M. Murat, *Ann. Chim. Phys.* **1909**, *16*, 108–126 (see p. 121); h) P. Sabatier, A. Mailhe, *Ann. Chim. Phys.* **1907**, *10*, 527–574 (see pp. 549–550, 572); i) P. Sabatier, J.-B. Senderens, *Ann. Chim. Phys.* **1905**, *4*, 319–488 (see p. 374).

[120] J. Ipaktschi, M. Brück, *Chem. Ber.* **1990**, *123*, 1591–1593.

[121] a) S. J. Cristol, J. K. Harrington, *J. Org. Chem.* **1963**, *28*, 1413–1415; b) D. M. Lemal, A. J. Fry, *J. Org. Chem.* **1964**, *29*, 1673–1676; c) J. Arct, U. H. Brinker in *Methoden der Organischen Chemie (Houben-Weyl)* (Ed.: M. Regitz), Thieme, Stuttgart, **1989**, vol. E19b, pp. 337–375; d) L. K. Sydnes, U. H. Brinker in *Methoden der Organischen Chemie (Houben-Weyl)* (Ed.: M. Regitz), Thieme, Stuttgart, **1989**, vol. E19b, pp. 542–576; e) R. H. Shapiro, *Org. React. (NY)* **1976**, *23*, 405–507; f) P. K. Freeman, D. E. George, V. N. M. Rao, *J. Org. Chem.* **1963**, *28*, 3234–3237; g) W. Kirmse, N. Knöpfel, *J. Am. Chem. Soc.* **1976**, *98*, 4672–4674.

[122] a) P. B. Shevlin, M. L. McKee, *J. Am. Chem. Soc.* **1989**, *111*, 519–524; b) R. A. Moss, W. Liu, K. Krogh-Jespersen, *J. Phys. Chem.* **1993**, *97*, 13413–13418; c) R. A. Moss, *Pure Appl.*

Chem. **1995**, *67*, 741–747; d) H. Huang, M. S. Platz, *Tetrahedron Lett.* **1996**, *37*, 8337–8340; e) H. Huang, M. S. Platz, *J. Am. Chem. Soc.* **1998**, *120*, 5990–5999; f) J. R. Ammann, R. Subramanian, R. S. Sheridan, *J. Am. Chem. Soc.* **1992**, *114*, 7592–7594; g) T. V. Levashova, O. V. Semeikin, E. S. Balenkova, *J. Org. Chem. USSR* **1980**, *16*, 53–56 (Transl. of *Zh. Org. Khim.*); h) R. K. Murray Jr., T. M. Ford, *J. Org. Chem.* **1977**, *42*, 1806–1808; i) P. K. Freeman, J. K. Pugh, *J. Am. Chem. Soc.* **1999**, *121*, 2269–2273; j) R. G. Bergman, V. J. Rajadhyaksha, *J. Am. Chem. Soc.* **1970**, *92*, 2163–2164; k) M. S. B. Wills, R. L. Danheiser, *J. Am. Chem. Soc.* **1998**, *120*, 9378–9379.

[123] a) W. Kirmse, *Eur. J. Org. Chem.* **1998**, 201–212; b) J. March, *Advanced Organic Chemistry*, 4th ed., Wiley, New York, **1992**, p. 1037; c) A. Hassner, C. Stumer, *Organic Syntheses Based on Name Reactions and Unnamed Reactions*, Pergamon Press, Tarrytown, NY, **1994**, p. 110; d) B. P. Mundy, M. G. Ellerd, *Name Reactions and Reagents in Organic Synthesis*, Wiley, New York, **1988**, pp. 72–73.

[124] a) R. Herges, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 255–276; b) compare pseudopericyclic vs. coarctate reactions: D. M. Birney, *J. Am. Chem. Soc.* **2000**, *122*, 10917–10925.

[125] Diazirine RIES that mimics the result of cyclopropylcarbene fragmentation has been postulated. For examples, see: a) ref.[122d,122e]; b) D. M. Thamattoor, M. Jones Jr., W. Pan, P. B. Shevlin, *Tetrahedron Lett.* **1996**, *37*, 8333–8336.

[126] M. G. Rosenberg, U. H. Brinker, *J. Org. Chem.* **2001**, *66*, 1517–1522.

[127] a) B. I. Azbel', N. F. Gol'dshleger, Ya. I. Isakov, E. T. Épel'baum, Yu. Yu. Yampol'skii, Kh. M. Minachev, *Bull. Acad. Sci. USSR Div. Chem. Sci.* **1986**, *35*, 1122–1125 (Transl. of *Izv. Akad. Nauk SSSR, Ser. Khim.*); b) B. I. Azbel', N. F. Gol'dshleger, Ya. I. Isakov, E. T. Épel'baum, Yu. Yu. Yampol'skii, M. L. Khidekel', Kh. M. Minachev, *Dokl. Chem.* **1984**, *276*, 197–199 (Transl. of *Dokl. Akad. Nauk SSSR, Ser. Khim.*).

[128] L. Friedman, H. Shechter, *J. Am. Chem. Soc.* **1961**, *83*, 3159–3160.

[129] G. F. Bradley, W. B. L. Evans, I. D. R. Stevens, *J. Chem. Soc., Perkin Trans. 2* **1977**, 1214–1220.

[130] a) P. K. Freeman, D. E. George, V. N. M. Rao, *J. Org. Chem.* **1964**, *29*, 1682–1684; b) W. Kirmse, T. Meinert, D. A. Modarelli, M. S. Platz, *J. Am. Chem. Soc.* **1993**, *115*, 8918–8927.

[131] R. Kupfer, U. H. Brinker, *Liebigs Ann.* **1995**, 1721–1725.

[132] For a review, see: L. K. Sydnes, U. H. Brinker in *Methoden der Organischen Chemie (Houben-Weyl)* (Ed.: M. Regitz), Thieme, Stuttgart, **1989**, vol. E19b, p. 601.

[133] a) L. Wojnárovits, T. Szondy, E. Szekeres-Bursics, G. Földiák, *J. Photochem.* **1982**, *18*, 273–276; b) L. Wojnárovits, *J. Chem. Soc., Perkin Trans. 2* **1984**, 1449–1451; c) A. C. Cope, M. Brown, G. L. Woo, *J. Am. Chem. Soc.* **1965**, *87*, 3107–3110.

[134] a) A. M. Aquino, C. J. Abelt, K. L. Berger, C. M. Darragh, S. E. Kelley, M. V. Cossette, *J. Am. Chem. Soc.* **1990**, *112*, 5819–5824; b) M. F. Acquavella, M. E. Evans, S. W. Farraher, C. J. Névoret, C. J. Abelt, *J. Org. Chem.* **1994**, *59*, 2894–2897.

[135] a) C. J. Abelt, J. M. Pleier, *J. Org. Chem.* **1988**, *53*, 2159–2162; b) C. J. Abelt, J. S. Lokey, S. H. Smith, *Carbohydr. Res.* **1989**, *192*, 119–130; c) S. H. Smith, S. M. Forrest, D. C. Williams Jr., M. F. Cabell, M. F. Acquavella, C. J. Abelt, *Carbohydr. Res.* **1992**, *230*, 289–297; d) C. J. Abelt, *Minutes 6th Int. Symp. Cyclodextrins,* **1992**, 649–654; [*Chem. Abstr.* **1994**, *121*, 83794].

[136] C. Wentrup, *Reactive Molecules*, Wiley, New York, **1984**, pp. 139–142.

[137] a) See ref.[2g], pp. 137–159; b) W. M. Jones, R. C. Joines, J. A. Myers, T. Mitsuhashi, K. E. Krajca, E. E. Waali, T. L. Davis, A. B. Turner, *J. Am. Chem. Soc.* **1973**, *95*, 826–835; c) R. J. McMahon, C. J. Abelt, O. L. Chapman, J. W. Johnson, C. L. Kreil, J.-P. LeRoux, A. M. Mooring, P. R. West, *J. Am. Chem. Soc.* **1987**, *109*, 2456–2469; d) M. W. Wong, C. Wentrup, *J. Org. Chem.* **1996**, *61*, 7022–7029; e) P. R. Schreiner, W. L. Karney, P. v. R. Schleyer, W. T. Borden, T. P. Hamilton, H. F. Schaefer III, *J. Org. Chem.* **1996**, *61*, 7030–7039; f) S. Matzinger, T. Bally, *J. Phys. Chem. A* **2000**, *104*, 3544–3552; g) C. M. Geise, C. M. Hadad, *J. Org. Chem.* **2002**, *67*, 2532–2540.

[138] cf. Rearrangement of phenylnitrene (an atypical open-shelled singlet) to 1-aza-1,2,4,6-cycloheptatetraene: a) N. P. Gritsan, M. S. Platz, *Adv. Phys. Org. Chem.* **2001**, *36*, 255–304; b) M. S. Platz, N. P. Gritsan, *Abstr. 222nd Pap.-Am. Chem. Soc.* **2001**, ORGN 242; c) M. S. Platz, *Acc. Chem. Res.* **1995**, *28*, 487–492; d) A. Marcinek, E. Leyva, D. Whitt, M. S. Platz, *J. Am. Chem. Soc.* **1993**, *115*, 8609–8612.

[139] a) R. Warmuth, M. A. Marvel, *Angew. Chem. Int. Ed.* **2000**, *39*, 1117–1119; b) R. Warmuth, M. A. Marvel, *Chem. Eur. J.* **2001**, *7*, 1209–1220; c) C. Kemmis, R. Warmuth, *J. Supramol. Chem.* **2001**, *1*, 253–267.

[140] R. A. Moss, F. G. Pilkiewicz, *J. Am. Chem. Soc.* **1974**, *96*, 5632–5633.

[141] a) C. J. Pedersen, *J. Am. Chem. Soc.* **1967**, *89*, 2495–2496; b) C. J. Pedersen, *J. Am. Chem. Soc.* **1967**, *89*, 7017–7036.

[142] a) W. H. Graham, *J. Am. Chem. Soc.* **1965**, *87*, 4396–4397; b) A. Padwa, M. J. Pulwer, T. J. Blacklock, *Org. Synth.,* **1990**, *Coll. Vol. VII*, 203–206; c) R. A. Moss, J. Włostowska, W. Guo, M. Fedorynski, J. P. Springer, J. M. Hirshfield, *J. Org. Chem.* **1981**, *46*, 5048–5050; d) R. A. Moss, *Acc. Chem. Res.* **2006**, *39*, 267–272.

[143] M. G. Rosenberg, U. H. Brinker, *J. Org. Chem.* **2003**, *68*, 4819–4832.

[144] M. T. H. Liu, K. Toriyama, *J. Phys. Chem.* **1972**, *76*, 797–801.

[145] M. Yoshinaga, Jpn. Patent 0532704, **1993**; [*Chem. Abstr.* **1993**, *119*, 10738].

[146] R. Moya-Barrios, F. L. Cozens, *Org. Lett.* **2004**, *6*, 881–884.

[147] a) G. A. Ganzer, R. S. Sheridan, M. T. H. Liu, *J. Am. Chem. Soc.* **1986**, *108*, 1517–1520; b) A. K. Mal'tsev, P. S. Zuev, O. M. Nefedov, *Bull. Acad. Sci. USSR Div. Chem. Sci.* **1985**, *34*, 1999 (Transl. of *Izv. Akad. Nauk SSSR, Ser. Khim.*).

[148] N. J. Turro, J. A. Butcher Jr., R. A. Moss, W. Guo, R. C. Munjal, M. Fedorynski, *J. Am. Chem. Soc.* **1980**, *102*, 7576–7578.

[149] a) N. J. Turro, G. F. Lehr, J. A. Butcher Jr., R. A. Moss, W. Guo, *J. Am. Chem. Soc.* **1982**, *104*, 1754–1756; b) I. R. Gould, N. J. Turro, J. Butcher Jr., C. Doubleday Jr., N. P. Hacker, G. F. Lehr, R. A. Moss, D. P. Cox, W. Guo, R. C. Munjal, L. A. Perez, M. Fedorynski, *Tetrahedron* **1985**, *41*, 1587–1600.

[150] P. S. Zuev, R. S. Sheridan, *J. Am. Chem. Soc.* **2001**, *123*, 12434–12435.

[151] W. W. Sander, *Spectrochim. Acta, Part A* **1987**, *43*, 637–646.

[152] M. B. Jones, V. M. Maloney, M. S. Platz, *J. Am. Chem. Soc.* **1992**, *114*, 2163–2169.

[153] H. Tomioka, Y. Ozaki, Y. Izawa, *Chem. Lett.* **1982**, 843–846.

[154] R. S. Sheridan, *Inter-Amer. Photochem. Soc. News.* **2000**, *23*, 39–48.

[155] I. Naito, A. Oku, N. Otani, Y. Fujiwara, Y. Tanimoto, *J. Chem. Soc., Perkin Trans. 2* **1996**, 725–729.

[156] Singlet **65** is computed to lie at the TS between (*R*)-**63** and (*S*)-**63**. For an account of the related enantiomerization of DL-**50**, see ref.[61e], p. 432.

[157] a) W. M. Jones in *Rearrangements in Ground and Excited States* (Ed.: P. de Mayo), Academic Press, New York, **1980**, vol. 1, chapter 3; b) W. Kirmse, S. Kopannia, *J. Org. Chem.* **1998**, *63*, 1178–1184.

[158] R. Bonneau, M. T. H. Liu, *J. Phys. Chem. A* **2000**, *104*, 4115–4120.

[159] R. A. Moss, R. C. Munjal, *J. Chem. Soc., Chem. Commun.* **1978**, 775–776.

[160] R. A. Moss, G.-J. Ho, *J. Am. Chem. Soc.* **1990**, *112*, 5642–5644.

[161] R. A. Moss, *Pure Appl. Chem.* **1995**, *67*, 741–747.

[162] a) R. A. Moss, W. Liu, *J. Chem. Soc., Chem. Commun.* **1993**, 1597–1599; b) R. A. Moss in *Advances in Carbene Chemistry* (Ed.: U. H. Brinker), JAI Press, Greenwich, CT, **1994**, vol. 1, pp. 59–88.
[163] P. S. Zuev, R. S. Sheridan, *J. Am. Chem. Soc.* **1994**, *116*, 4123–4124.
[164] G. Yao, P. Rempala, C. Bashore, R. S. Sheridan, *Tetrahedron Lett.* **1999**, *40*, 17–20.
[165] a) X. Liu, G. Chu, R. A. Moss, R. R. Sauers, R. Warmuth, *Angew. Chem. Int. Ed.* **2005**, *44*, 1994–1997; b) R. Dagani, *Chem. Eng. News* **2005**, *83*, 12.

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