Organic & Biomolecular Chemistry

REVIEW

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Carbenes from cyclopropanated aromatics†

Alexander D. Roth and Dasan M. Thamattoor *

Although a ripe old discipline by now, carbene chemistry continues to flourish as both theorists and experimentalists have shown sustained interest in this area of research. While there are numerous ways of generating carbenes, the thermal and/or photochemical decomposition of diazo compounds and diazirines remains, by far, the most commonly used method of producing these intermediates. There is no disputing the fact that these nitrogenous precursors have served carbene researchers well, but their use is not without problems. They are often sensitive and hazardous to handle and, sometimes, the desired nitrogenous precursor simply may not be available, *e.g.*, for synthetic reasons, to study the particular carbene of interest. Furthermore, there is a legitimate concern that the photochemical generation of carbenes in solution from diazo compounds and diazirines may be contaminated by reactions in the excited states (RIES) of the precursors themselves. As an alternative, several laboratories, including ours, have used cyclopropanated aromatic systems to generate a wide range of carbenes. In each case, the cheleotropic extrusion of carbenes is accompanied by the formation of stable aromatic by-products such as phenanthrene, indane, naphthalene, and 1,4-dihydronaphthalene. The emergence of these "non-traditional" carbene sources, their versatility, and promise are reviewed in this work.

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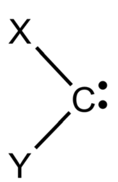
1. Introduction

Carbenes are important reactive intermediates of much interest to theoreticians, experimentalists, and the chemical industry at large.[1–8] These remarkable species have provided many critical insights into structure, bonding, and reactivity, and their study is also of much practical importance *vis-a-vis* novel materials[9–13] and organic synthesis, especially in the area of catalysis.[14–20]

Structurally, carbenes feature a neutral, divalent carbon with two nonbonded electrons. The divalent carbon is connected to two separate groups by single bonds in "saturated" carbenes (**1**), whereas in "unsaturated" carbenes (**2**), also known as vinylidenes or alkylidene carbenes, the carbene center is attached to a single group by a double bond.[21,22] In carbene **1**, the divalent carbon is approximately sp^2 hybridized with the bond angles determined by the nature of substituents and electronic structure of the carbene. The carbene center is sp hybridized in alkylidene carbenes **2**.



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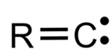

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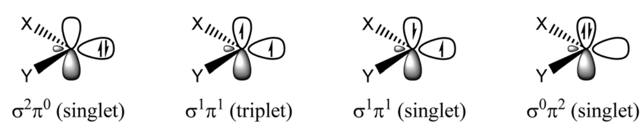
*Department of Chemistry, Colby College, Waterville, ME 04901, USA.
E-mail: dmthamat@colby.edu*

†We dedicate this paper to Miselis Professor of Chemistry Emeritus Bradford P. Mundy, a true colleague, mentor, and friend.

The two nonbonded electrons can adopt four possible electronic configurations in carbenes. These are illustrated using saturated carbene **1** as an example.



(a) Closed shell, $\sigma^2\pi^0$ singlet in which both nonbonded electrons occupy a hybrid orbital with paired spins.

(b) Triplet ($\sigma^1\pi^1$) in which one electron occupies a hybrid orbital and the other is in a p-type orbital with unpaired spins.

(c) Open shell, $\sigma^1\pi^1$ singlet which has the same occupancy as the triplets but with the electrons having paired spins.

(d) Closed shell, $\sigma^0\pi^2$ singlet in which both nonbonded electrons occupy a p-type orbital with paired spins.

Of these electronic states, the $\sigma^2\pi^0$ singlets and $\sigma^1\pi^1$ triplets are most common, although there are rare reports of excited state $\sigma^1\pi^1$ singlets[23–25] as well as $\sigma^0\pi^2$ singlets.[26,27]

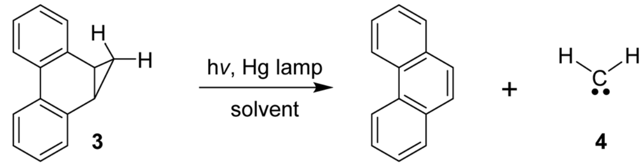
Unsaturated carbenes such as **2**, in which the electron pairs can occupy a sp-type hybrid orbital, have an overwhelming preference for the singlet ground state.[21] Recently, however, the first characterization of a triplet vinylidene has been reported.[28]

The generation of carbenes has been traditionally accomplished by the thermal and/or photochemical decomposition of diazo compounds[29,30] and diazirines.[31] Although these nitrogenous precursors have served carbene chemists well, their use is not without problems. They are often sensitive, explosive, toxic, and generally hazardous to handle.[32] There is also the possibility that the desired nitrogenous precursor simply may not be available, *e.g.*, for synthetic reasons, to study the particular carbene of interest. Furthermore, there is a legitimate concern that the photochemical generation of carbenes in solution from diazo compounds and diazirines may involve reactions in the excited states (RIES) of the precursors themselves.[33–35] In order to mitigate some of the dangers associated with diazo compounds and diazirines, considerable research has gone into investigating safer, alternative means of carbene generation including the use of *N*-sulfonylhydrazone family of salts[36,37] and metal-based approaches.[38] In this review, we discuss the emergence of cyclopropanated aromatics—derived from phenanthrene, indane, naphthalene, and 1,4-dydronaphthalene— as safe, viable, and versatile sources of carbenes. These "non-traditional" carbene precursors offer much untapped potential and can serve as alternative routes to carbenes which may not be available by other means.

2. Carbenes from cyclopropanated phenanthrenes

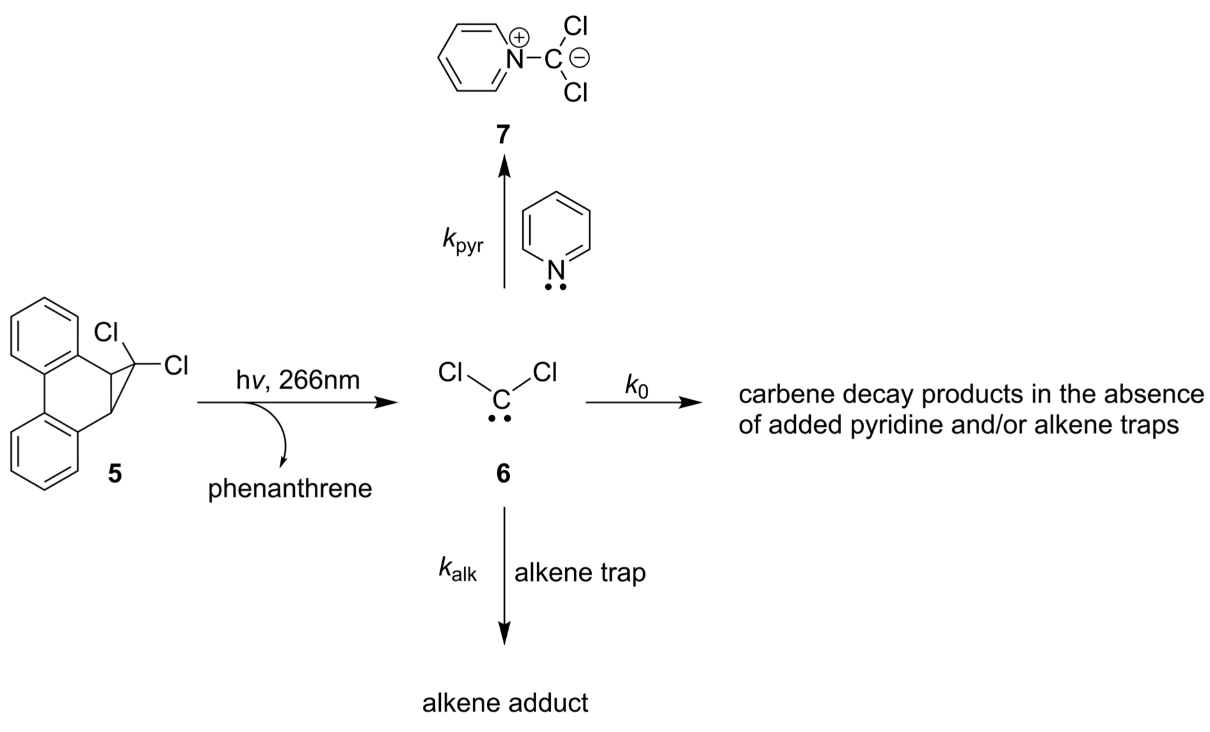
2.1 Saturated carbenes

In 1965, researchers at the Shell Oil Company reported that the photochemical decomposition of 1a,9b-dihydro-1*H*-cyclopropa[l]phenanthrene (**3**), prepared in one step by the Simmons–Smith reaction[39] of phenanthrene with CH_2I_2/Zn in 1,2-dimethoxyethane, produced phenanthrene (90% yield) and methylene (**4**). Carbene **4** underwent insertion and cyclopropanation reactions in a manner analogous to methylene derived from the photolysis of diazomethane.[40] The authors, in fact, described **3** as "a convenient, shelf-stable source of active methylene".



Quite remarkably, the generation of carbenes from precursors such as **3** was not mentioned in the literature for another 25 years when, in 1990, Chateauneuf, Johnson, and Kirchhoff published their seminal work on the absolute kinetics of dichlorocarbene (**6**) in solution using precursor **5**[41] as their source (Scheme 1).[42] Although **6** itself does not have a chromophore suitable for direct observation in time-resolved laser flash photolysis (LFP) experiments, the authors used a technique developed by Platz and coworkers[3] whereby **6** was intercepted by pyridine to form an pyridinium ylide **7** whose growth could be monitored by UV-Vis absorbance spectroscopy (Fig. 1). Steady state photolysis of **5** at 280 nm was reported to give a quantitative chemical yield of carbene **6**.

The observed rate constant, k_{obs}, for the pseudo-first order growth of the ylide at varying pyridine concentrations is a composite of two terms as shown in eqn (1), where k_{pyr} is the rate constant for the reaction of carbene with pyridine and k_0 is



Scheme 1 Kinetic studies of dichlorocarbene (**6**) photochemically generated from a phenanthrene-based precursor (**5**).[42]

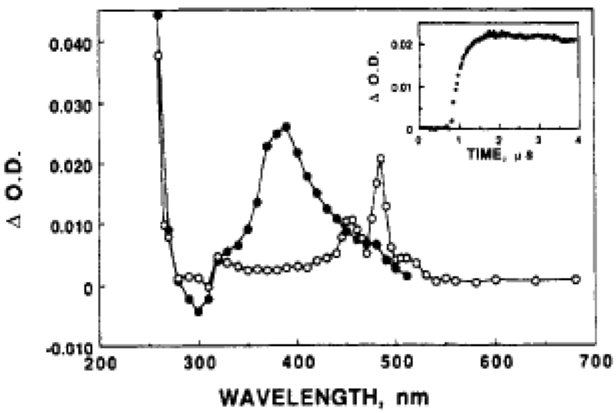


Fig. 1 LFP of precursor **5** at 266 nm in nitrogen- (●) and air-saturated (○) solutions of cyclohexene containing pyridine generates ylide **7**, whose transient absorption spectra are shown. The inset is an example of the single-exponential growth of ylide **7** monitored at 400 nm. [Reprinted, with permission, from ref. 42; Copyright 1990 American Chemical Society.]

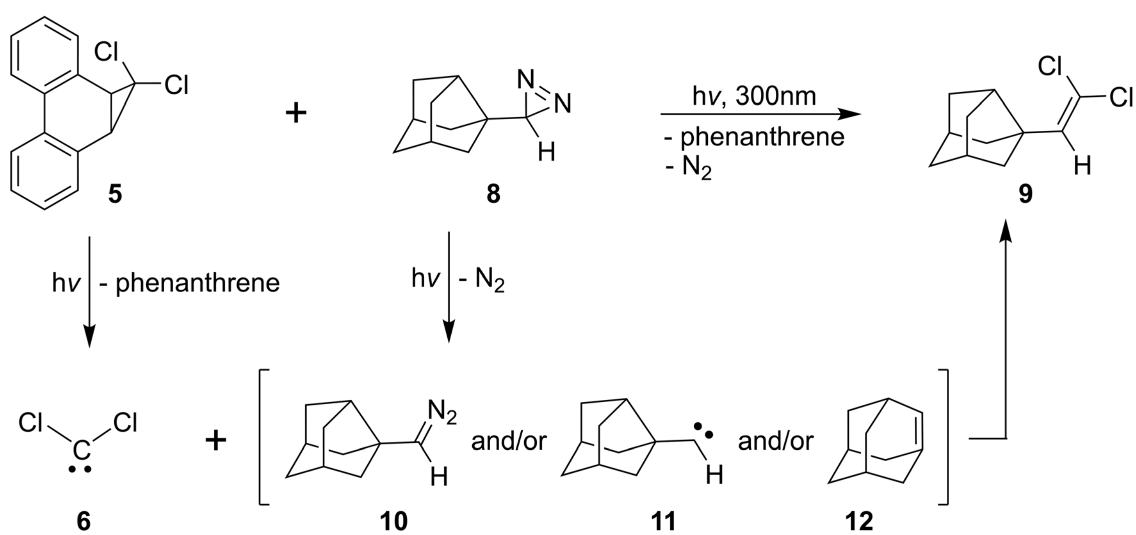
rate constant for all processes that consume the carbene other than by reaction with any added traps. Thus, a plot of k_{obs} *vs.* [pyridine] would be linear with a slope corresponding to k_{pyr} and intercept of k_0 obtained by extrapolating to zero pyridine concentration. Then, by holding the pyridine concentration constant at an optimal level, various concentrations of the alkene trap are added and a new rate constant for the growth of the ylide, $k_{obs'}$, is measured. Now $k_{obs'}$ is a composite of three terms where k_{alk} is the rate constant for the reaction of carbene with alkene (eqn (2)). As the first two terms are constant (because [pyridine] is held constant), a plot of $k_{obs'}$ *vs.* [alkene] would be linear with a slope of k_{alk} and an intercept of $k_0 + k_{py}$[pyridine].

$$k_{obs} = k_0 + k_{pyr}[\text{pyridine}] \quad (1)$$

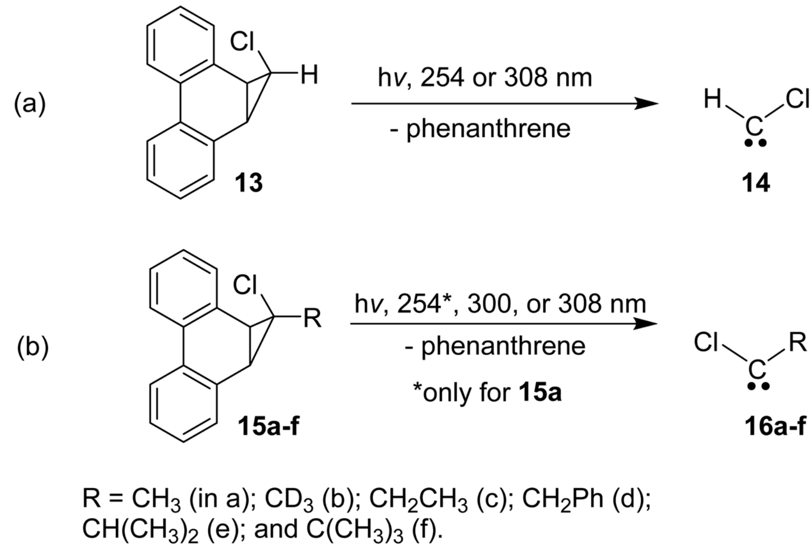
$$k_{obs'} = k_0 + k_{pyr}[\text{pyridine}] + k_{alk}[\text{alkene}] \quad (2)$$

Years later, Merrer and coworkers reported that the co-photolysis of precursor **5** with noradamantyldiazirine (**8**) produced alkene **9** (Scheme 2), albeit in a low yield of 11%.[43] Various mechanisms for the formation of **9** were discussed in terms of singlet dichlorocarbene (**6**) adding to one or more of the diazo derivative **10**, noradamantylcarbene **11**, and adamantene **12**.

Using the pyridinium ylide method, Platz, Johnson, and coworkers also measured the kinetics of monochlorocarbene (**14**), generated from photolysis of **13** at 308 nm, in various solvents (Scheme 3a).[44] Precursor **13** was synthesized by the low-temperature treatment of **5** with butyllithium and subsequent quenching with methanol. The authors were able to determine the solvent-dependent lifetimes of **14**, and, using a Stern–Volmer type analysis, obtained absolute rate constants for the reactions of **14** with various alkenes. When the photolysis of **13** was performed at 254 nm in the presence of cyclohexene, carbene **14** could be intercepted as a cyclopropane adduct by the alkene in yields of ~86%. In a subsequent study, a similar approach was taken to measure the kinetics of various alkylchlorocarbenes, **16a–f**, generated from the corresponding cyclopropanated phenanthrenes (at 308 nm), **15a–f** (Scheme 3b).[45] These studies seemed to indicate that using diazirines to photochemically generate carbenes **16a–f** is fraught with reactions happening in the excited states of the precursors, which can be avoided by using phenanthrene-based carbene sources **15a–f**. A later, more specific comparative study of the kinetics of benzylchlorocarbene (**16d**) from **15d** and a diazirine precursor further implicated the incursion of excited state precursor chemistry with the nitrogenous source.[46] Synthesis of **15a–d** could be readily accomplished by treating **5** at low temperatures with butyllithium followed by addition of the appropriate alkyl halide.[45] To prepare **15e** and **15f**, the dichloro adduct **5** was treated with isopropyl-



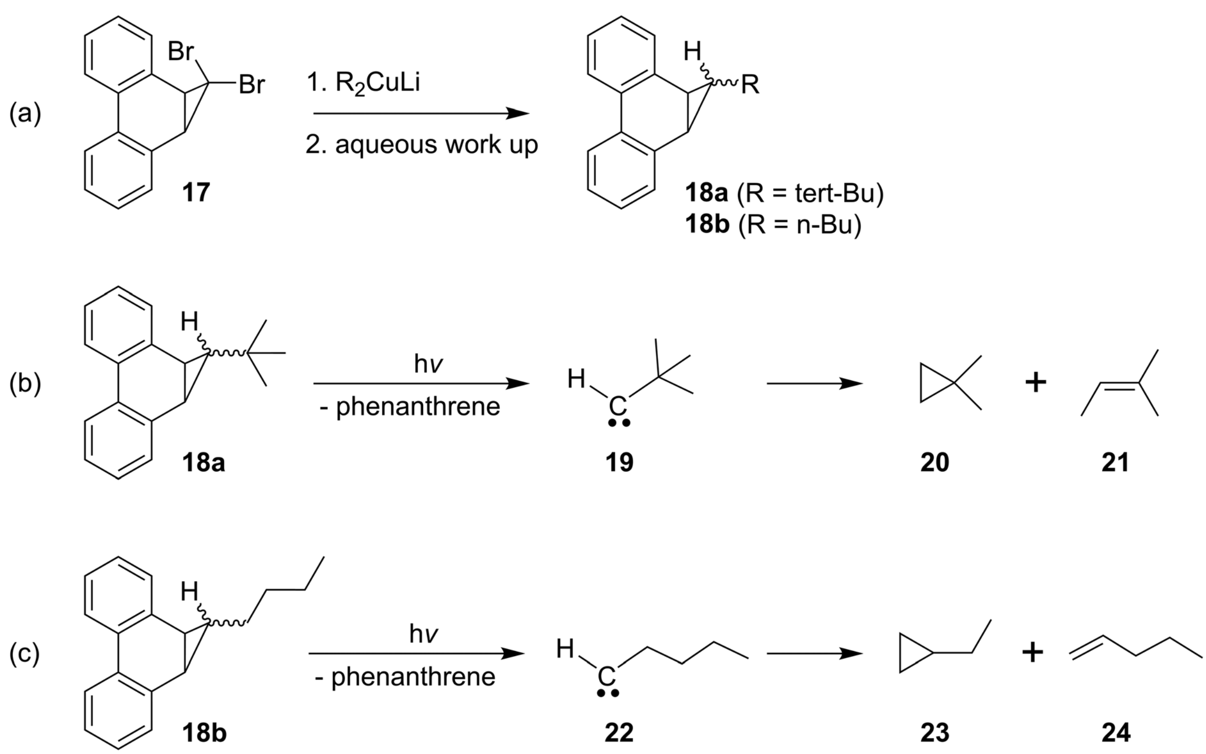
Scheme 2 Formation of alkene **9** from the co-photolysis of precursor **5** and noradamantyldiazirine (**8**).[43]



Scheme 3 Generation of chlorocarbene (**14**)[44] and alkylchlorocarbenes (**16a–f**)[45] from phenanthrene-based precursors.

magnesium bromide and lithium bis(*tert*-butyl)cuprate respectively, followed by quenching with a solution of chlorine in tetrachloromethane. Photolysis of **15a–f** at 300 nm in the presence of cyclohexene gave the corresponding carbene—alkene adducts in yields that varied depending on the carbene substituents. A similar photolysis of **15a** at 254 nm gave the methylchlorocarbene adduct of cyclohexene in up to ~83% yield within 30 minutes.

Jones and coworkers were the first to demonstrate the utility of cyclopropanated phenanthrene systems to generate alkyl carbenes (Scheme 4).[47] They synthesized stereoisomers of precursors **18a** and **b** (Scheme 4a) by a Hiyama reaction[48,49] in



Scheme 4 (a) Synthesis of precursors **18a** and **b**; (b) photochemical generation and rearrangements of *tert*-butylcarbene (**19**) from **18a**; and (c) photochemical generation and rearrangements of butylcarbene (**22**) from **18b**.[47]

which **17**,[50,51] the dibromo analog of **5**, is treated with the appropriate lithium dialkylcuprate, followed by an aqueous work up. Photolysis of **18a** produced *tert*-butylcarbene (**19**), which subsequently rearranged into 1,1-dimethylcyclopropane (**20**) by intramolecular C–H insertion and 2-methyl-2-butene (**21**) by 1,2-methyl shift (Scheme 4b). The ratio of **20** : **21** was temperature dependent (~90 : 10 @ 25 °C and ~100 : 0 @ −78 °C) and consistent with those observed from sources that generate the "real" carbene **19** but at odds with the ratio (~50 : 50) observed from photolysis of *tert*-butyldiazomethane or *tert*-butyldiazirine. These results further implicated precursor chemistry, *via* RIES (*vide supra*), in the photolysis of nitrogenous sources to **19**. In a similar manner, photolysis of **18b** gave the corresponding butylcarbene (**22**), which rearranged into the ethylcyclopropane (**23**) by intramolecular C–H insertion, and 1-butene (**24**) which could, in principle, be produced from a 1,2-shift of either a hydrogen or the propyl chain (Scheme 4c).[47] The ratio of **23** to **24** was found to be ~25 : 75. Carbene **22** was also trapped, albeit in low yield, with cyclohexene.

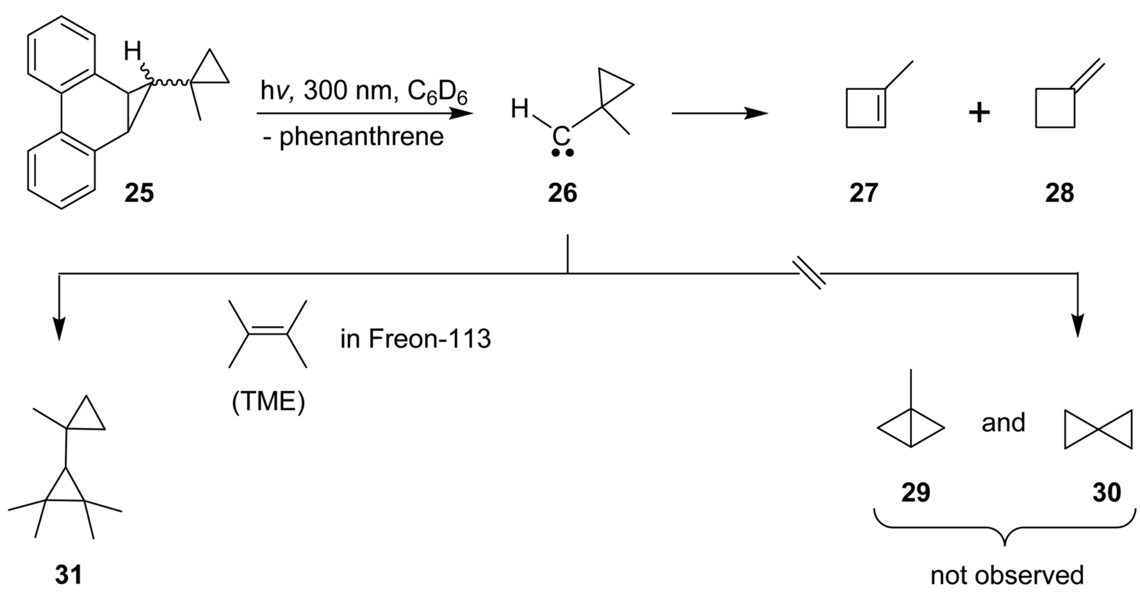
In a subsequent report, Ruck and Jones disclosed that the **20** : **21** ratio, obtained when carbene **19** is generated from precursor **18a** (as well as from *tert*-butyldiazomethane), was perturbed by solvents.[52] Solvents capable of forming ylides with the carbene showed a higher proportion of **21** relative to **20**, an effect attributed to 1,2-methyl shift within the ylide.

Photolysis of both the *exo* and *endo* isomer of **25** in benzene-*d*6 generated the corresponding (1-methylcyclopropyl) carbene (**26**), which yielded 1-methylcyclobutene (**27**) as the major product and methylenecyclobutane (**28**) in smaller amounts (Scheme 5).[53] The ring-expansion of **26** into **27** was accelerated by the "bystander" methyl substituent, although the origin of **28** was not ascertained. No C–H insertion products, **29** and **30**, were detected. Carbene **26** added to tetramethylethylene (TME) in 1,1,2-trichlorotrifluoroethane (Freon-113) to produce the bicyclopropyl adduct **31**. Using a double-reciprocal plot of 1/[**31**] *vs*. 1/[**TME**] at various TME concentrations, the lifetime of carbene **26** was estimated to be 12 ns in Freon-113. The experimental results were found to be consistent with density functional theory (DFT) calculations, which indicated that the methyl group helps stabilize the incipient positive charge on the adjacent carbon that develops in the transition state during ring expansion.

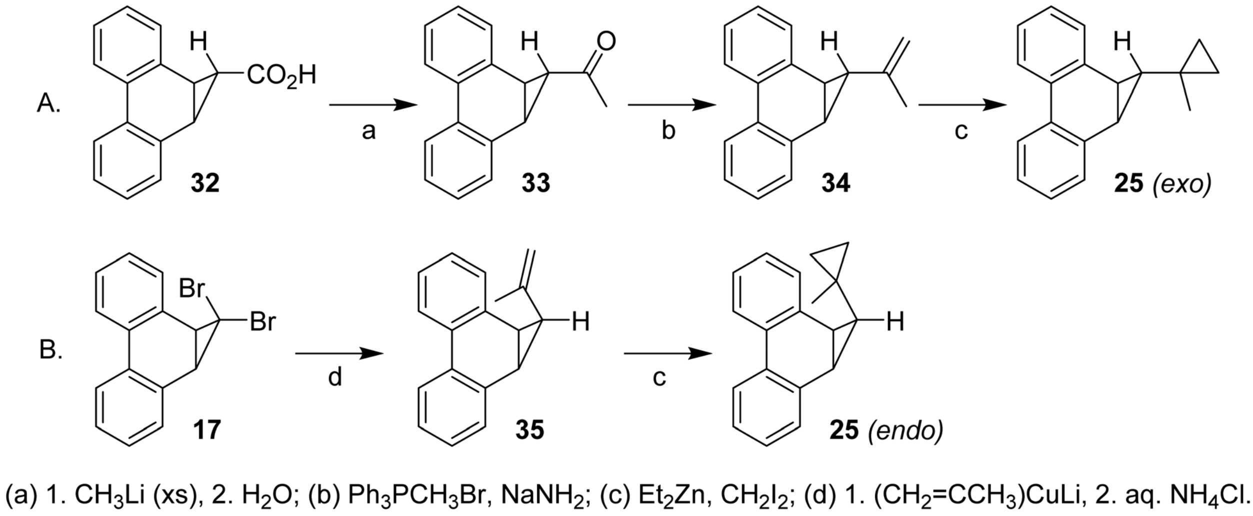
Synthesis of *exo* and *endo* **25** was carried out as shown in Scheme 6.[53] The *exo* precursor was synthesized (Scheme 6A) by converting the known carboxylic acid **32**[54] into the methyl ketone **33**, followed by a Wittig reaction to access **34**. Cyclopropanation of **34** then led to *exo*-**25**. To prepare *endo*-**25**, the Hiyama reaction mentioned previously was adapted to prepare the isopropenyl derivative **35** from **17**, which was subsequently cyclopropanated (Scheme 6B).

Photolysis of precursor **36** in the presence of TME led to products **38** and **39** that are attributable to the trapping of (1-norbornyl)carbene **37** (Scheme 7).[55] The combined yield of **38** and **39** was reported to be 28% relative to the phenanthrene byproduct. In the absence of TME, carbene **37** was shown to ring-expand to the strained, anti-Bredt olefin **40**, which underwent a retro Diels–Alder reaction to the triene **41**. Triene **41** made up 15% of the product mixture when the photolysis was done at 60 °C and was the only product upon photolyzing at 100 °C. Synthesis of precursor **36** was accomplished in one step from **5** using a Hiyama reaction with lithium bis(1-norbornyl)cuprate and an aqueous work up.[55]

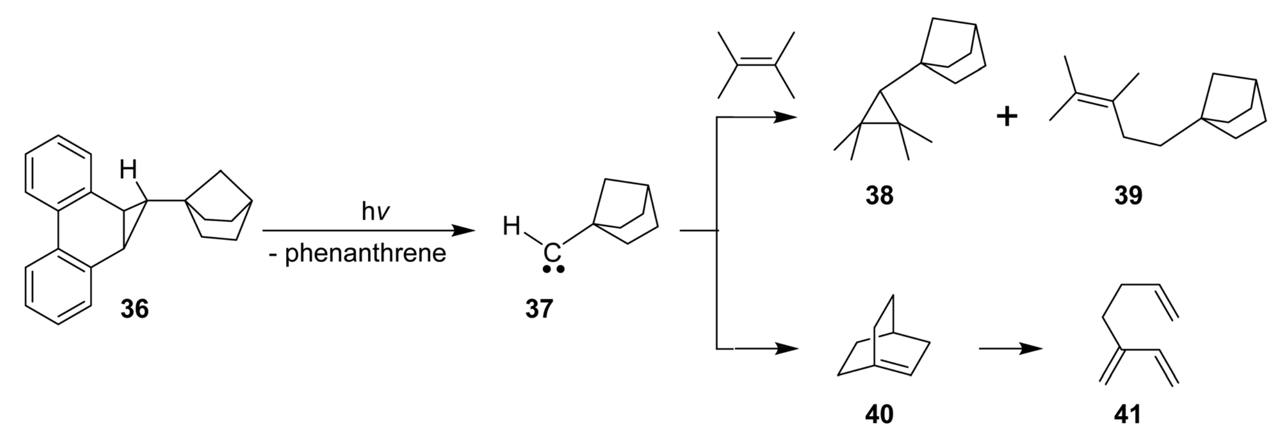
As noted earlier, the chemistry of *tert*-butylcarbene (**19**) is dominated by 1,3-hydrogen insertion and the 1,2-methyl shift is formed as a minor product or not at all.[47] In contrast, photolysis of precursor **42** generated the carbene 2-hydroxy-2-methylpropylidene (**43**), which showed a strong preference for a 1,2-



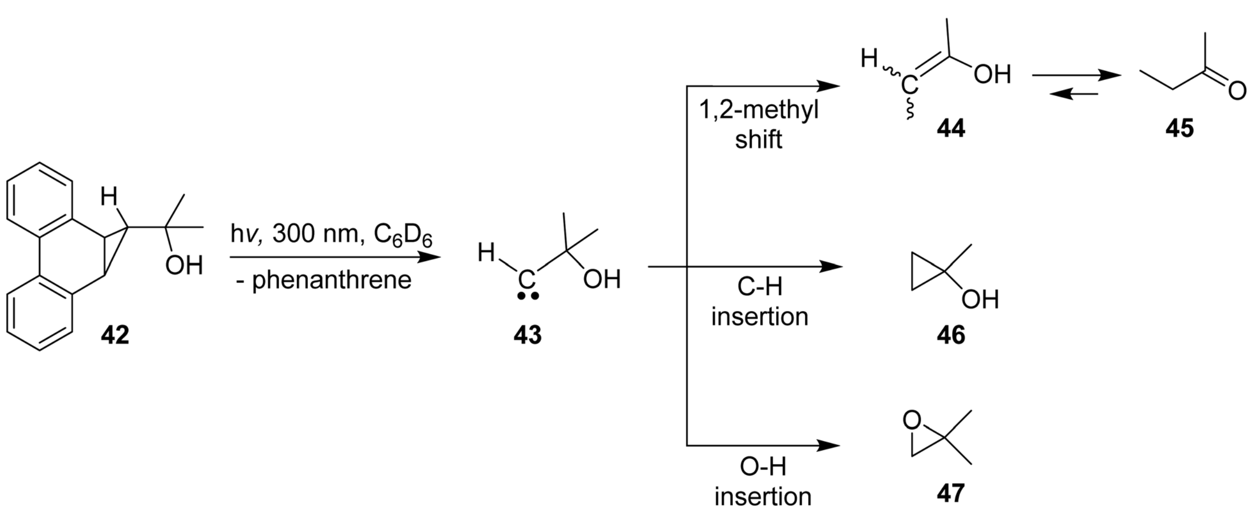
Scheme 5 Solution chemistry of (1-methylcyclopropyl)carbene (**26**) generated from precursor **25**.[53]



Scheme 6 Synthesis of the *exo* and *endo* precursors **25** to (1-methylcyclopropyl)carbene (**26**).[53]



Scheme 7 Generation, trapping, and rearrangement of (1-norbornylyl)carbene **37**.[55]



Scheme 8 Generation of 2-hydroxy-2-methylpropylidene (**43**), from the cyclopropanated phenanthrene precursor **42**, and its rearrangement reactions.[56]

methyl shift to produce the enol **44**, which subsequently tautomerized to 2-butanone (**45**) (Scheme 8).[56] C–H insertion to form 1-methylcyclopropanol (**46**) and O–H insertion to produce 2,2-dimethyloxirane (**47**) were minor products. The relative ratio of **45** : **46** : **47** was 69 : 28 : 3, with a combined yield of 55%. Clearly, substituting one of the methyl groups in **19** with an OH group as in **43** accelerated the methyl shift. DFT calculations confirmed the stabilizing effect of the β-hydroxy group on the transition state connecting **43** and **44**. Precursor **42** was synthesized by the reaction of methyllithium with **33** followed by an aqueous work up.[56]

When the two methyl groups in **42** were replaced with ring systems, as in **48a** and **b**, photolysis in benzene-*d*6 produced the corresponding carbenes **49a** and **b**, which rearranged exclusively by alkyl shifts to give the ring-expanded enols **50a** and **b** respectively (Scheme 9).[57] Tautomerization of **50a** and **b** gave the observed products cyclobutanone (**51a**) and cyclopentanone (**51b**) respectively. In this case, no C–H or O–H insertion products were detected.

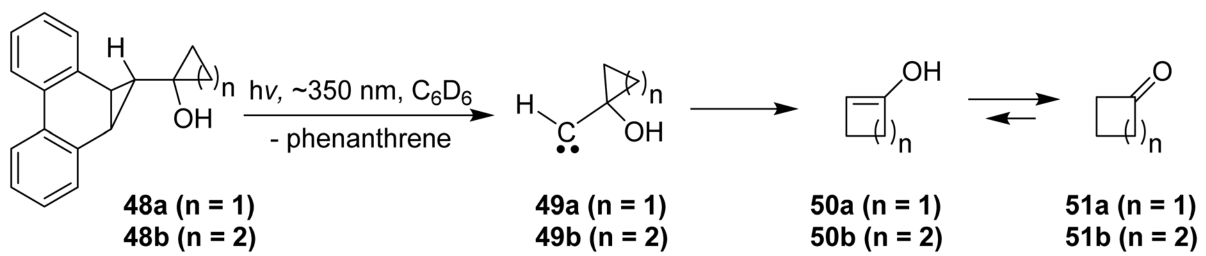
Synthesis of **48a** was accomplished in one step from the known ester **52**[54] as shown in Scheme 10A. Likewise, precursor **48b** was prepared directly from the known monobromo derivative **53**[51,58] (Scheme 10B).

In another related example, 2-ethoxyethylidene (**55**), generated in benzene-*d*6 from precursor **54**, was shown to rearrange into ethyl vinyl ether (**56**) in 43% yield (Scheme 11).[58] In principle, ether **56** can be produced by a 1,2-shift of either the hydrogen or the alkoxy group, but a deuterium labeling experiment and calculations showed that it was the hydrogen that moved preferentially, evidently due to the activating effect of the oxygen. Precursor **54** was obtained by treating **53** with *tert*-butyllithium and quenching with $ClCH_2OEt$.[58]

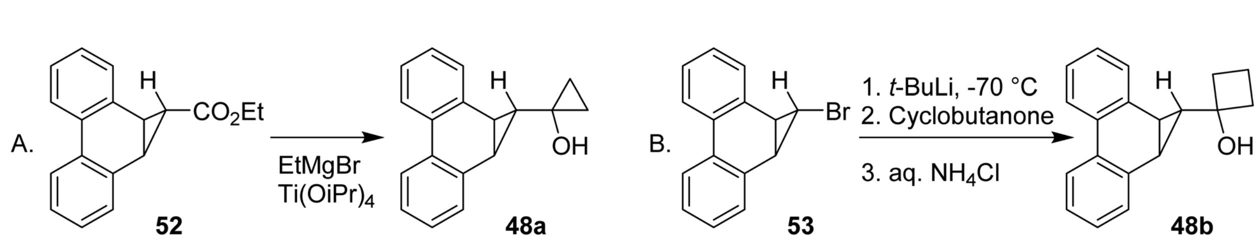
2.2 Unsaturated carbenes

In 2012, the Thamattoor laboratory reported the first instance of a cyclopropanated phenanthrene precursor used to generate an alkylidene carbene (Scheme 12).[59] They demonstrated that the photolysis of methylenecyclopropane derivative **57** led to a quantitative formation of phenylacetylene **59**. Presumably, precursor **57** photolyzed cleanly and efficiently to benzylidenecarbene (**58**). A subsequent Fritsch–Buttenberg–Wiechell (FBW)-type rearrangement[60–62] converted **58** into phenylacetylene (**59**) in quantitative yield. Although **59** can be formed by the 1,2-shift of either hydrogen or the phenyl ring in **58**, use of the ^{13}C-labeled precursor **57*** demonstrated that **59*** was formed from **58*** exclusively by a 1,2-H shift.

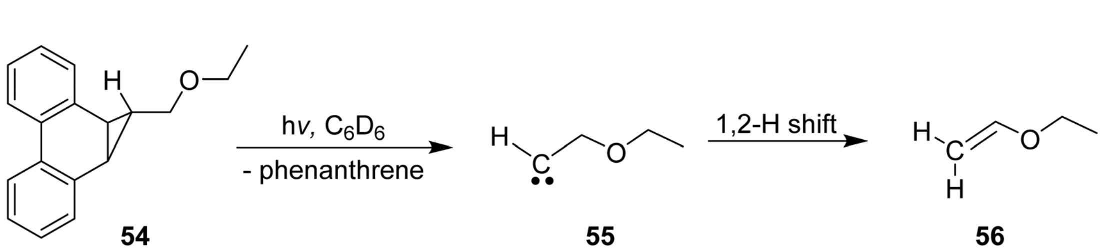
Synthesis of precursor **57** was accomplished by first converting **17** into the benzyl derivative **60**, followed by a base-induced dehydrobromination (Scheme 13). The ^{13}C-labeled



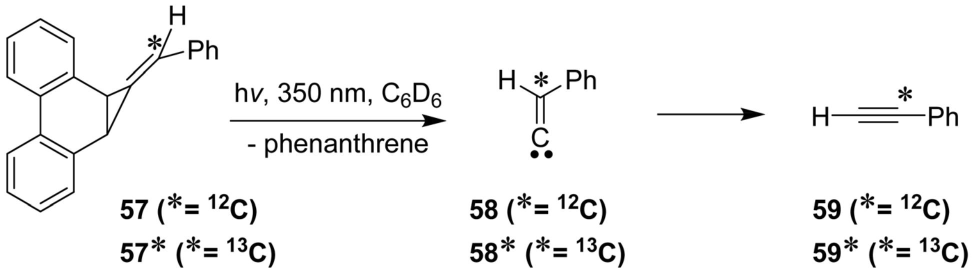
Scheme 9 Formation of ketones **51a** and **b** from photolysis of **48a** and **b** respectively.[57]



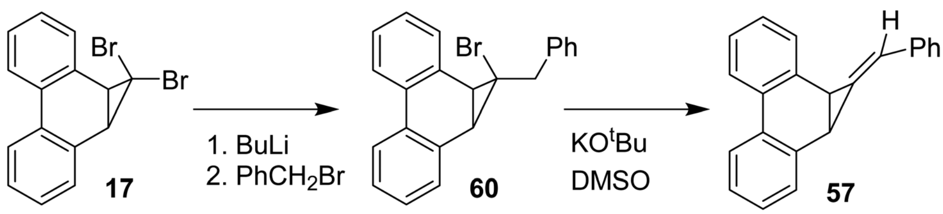
Scheme 10 Synthesis of precursors **48a** and **b**.[57]



Scheme 11 Generation and rearrangement of 2-ethoxyethylidene (**55**).[58]



Scheme 12 Generation and rearrangement of benzylidenecarbene (**58**/**58***).[59]



Scheme 13 Synthesis of precursor **57**.[59]

precursor **57*** could be synthesized in an analogous manner by using benzyl bromide labeled at the benzylic carbon.[59]

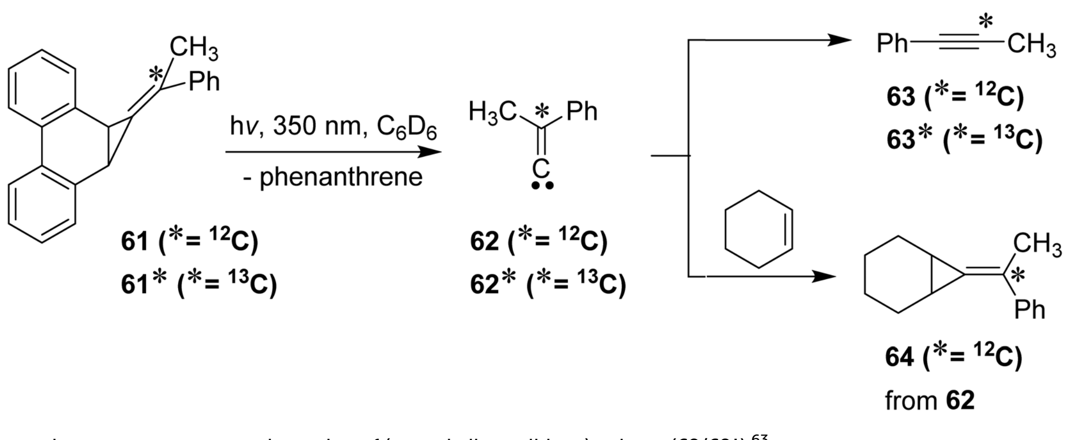
The 1,2-H shift in of **58**, calculated to be an essentially barrier-free process, was too facile for the carbene to be intercepted by external alkene traps. When precursor **61** was photolyzed, however, the generated (α-methylbenzylidene)carbene **62** not only underwent a FBW rearrangement to 1-phenylpropyne (**63**) in 73% yield but could also be intercepted by cyclohexene to form the adduct **64** (Scheme 14) albeit in a low yield of 1.5%.[63] Interestingly, generating the ^{13}C-labeled **62***, from precursor **61***, gave **63***, indicating that it is the phenyl ring that preferentially migrates rather than the methyl. Calculations indicate that the barrier to phenyl migration is only about 3.8 kcal mol^{-1} as compared to 11.9 kcal mol^{-1} for the methyl shift.

Precursor **61** was synthesized by the Petasis reaction[64] of **53** using acetophenone as the ketone (Scheme 15). By using acetophenone containing a ^{13}C-label at the carbonyl position, the labeled precursor **61*** was prepared.

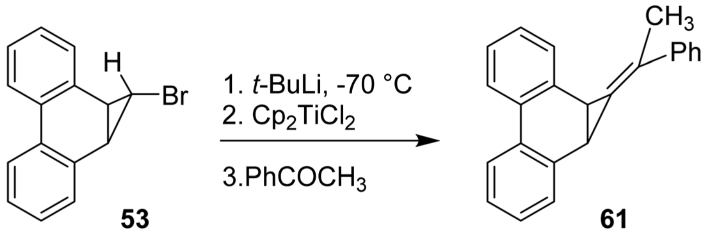
Singlet **62** also became the first alkylidene carbene to be directly observed by femtosecond transient absorption (fs-TA) spectroscopy.[65] Irradiation of **61** in acetonitrile at 267 nm gave the singlet excited state of the precursor, which extruded the carbene in ∼4 ps. The carbene then decayed over a period of ∼13.3 ps.

Photolysis of precursor **65** in cyclohexene has been also reported to give the adduct **67** in a 23% yield (Scheme 16).[66] Evidently, **65** extrudes dimethylvinylidene (**66**), which subsequently cyclopropanates the alkene to form **67**. Precursor **65** was synthesized by using acetone as the ketone in the procedure shown in Scheme 15.[66]

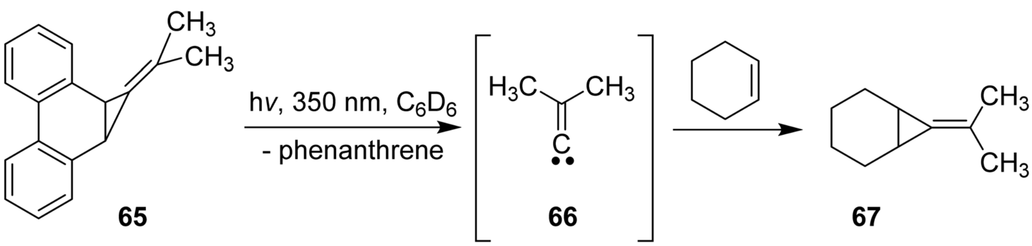
Thamattoor and coworkers subsequently photolyzed precursors **68a** and **b** in benzene-*d*6 to generate the corresponding alkylidene carbenes, **69a** and **b**, in each of which the double



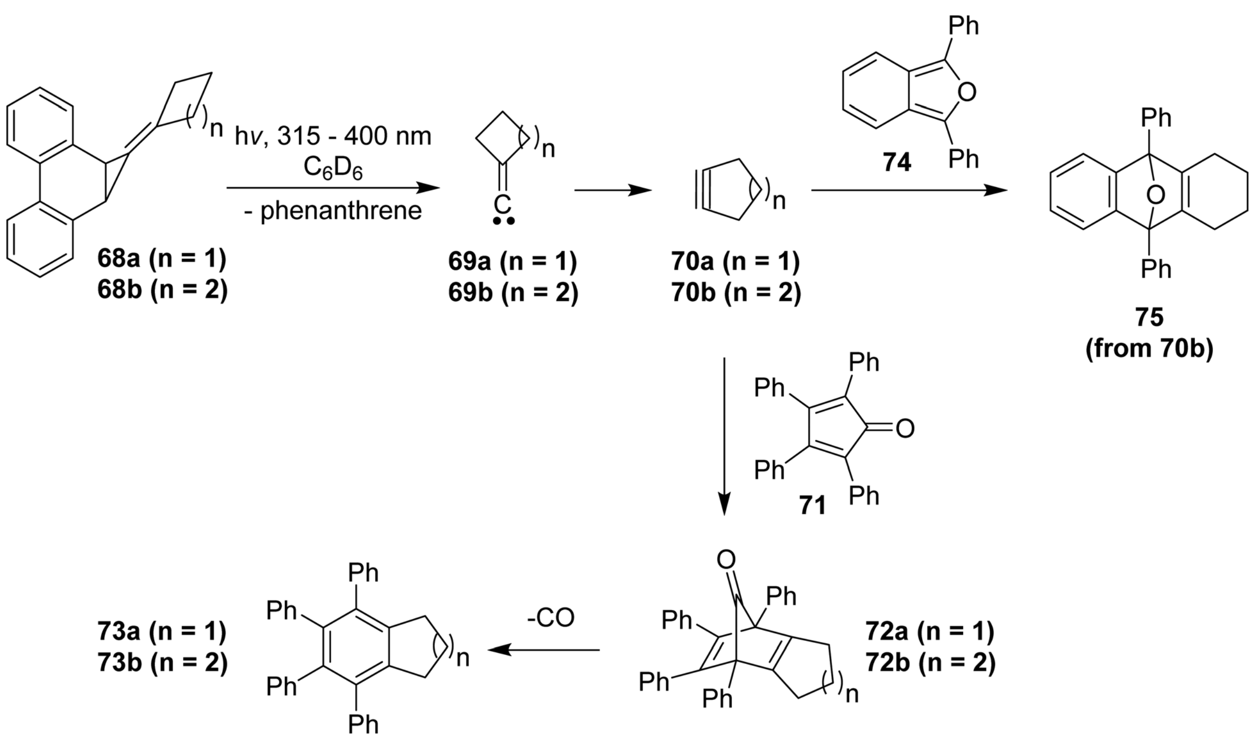
Scheme 14 Generation, rearrangement, and trapping of (α-methylbenzylidene)carbene (**62**/**62***).[63]



Scheme 15 Synthesis of precursor **61**.[64]



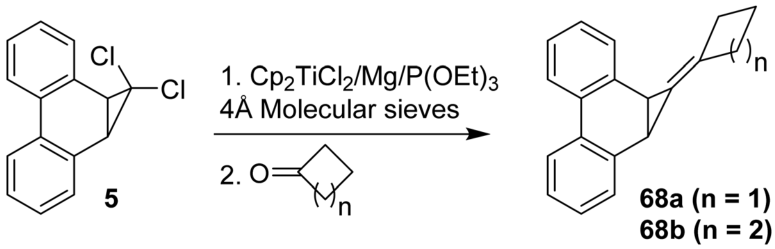
Scheme 16 Generation and trapping of dimethylvinylidene (**66**).[66]



Scheme 17 Generation of cyclopentyne and cyclohexyne from the FBW rearrangement of cyclic alkylidene carbenes, and their trapping reactions.[67]

bond is exocyclic to a ring (Scheme 17).[67] FBW rearrangement of **69a** and **b** led to cyclopentyne (**70a**) and cyclohexyne (**70b**) respectively. Interception of **70a** by tetraphenylcyclopentadienone (**71**) gave the adduct **73a** after loss of CO from the initially-formed Diels–Alder product **72a**. Similarly, **70b** was trapped with **71** to obtain **73b** *via* **72b**. The yields of **73a** and **b** were reported to be 27% and 43% respectively. It was also possible to trap **70b** with 1,3-diphenylisobenzofuran (**74**) to produce the adduct **75** in 65% yield. The activation barriers for the ring expansion of carbenes **69a** and **b** were computed to be 1.6 and 9.1 kcal mol^{-1} respectively.

Synthesis of precursors **68a** and **b** could be carried out by using cyclobutanone and cyclopentanone respectively, instead of acetophenone, in the Petasis procedure shown in



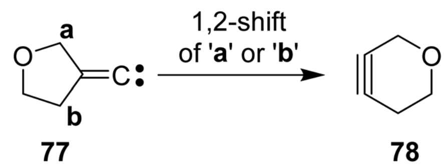
Scheme 18 An alternative approach to synthesizing precursors **68a** and **b** by using the Takeda reaction.[67,68]

Scheme 15. Alternatively, **68a** and **b** could be prepared in one step from **5** by adapting the Takeda reaction[68] as shown in Scheme 18.

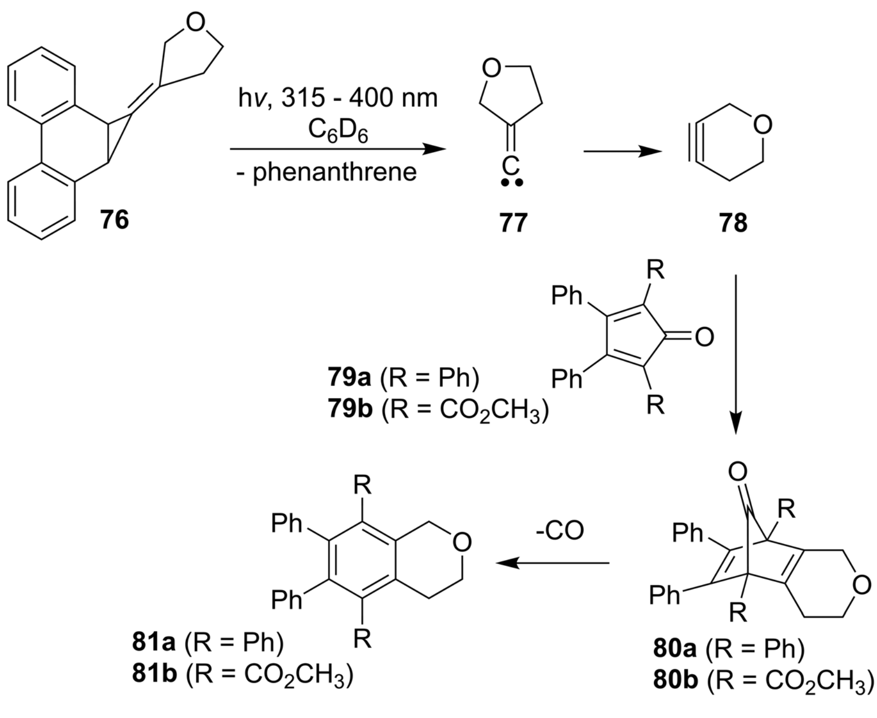
Heterocycloalkynes, such as the oxacyclohexyne **78**, could be also generated by following an analogous approach (Scheme 19).[69] Thus, precursor **76**, synthesized by using dihydro-3-furanone as the ketone in Scheme 18, was photolyzed in benzene-*d*6 to produce the alkylidene carbene **77**, which rearranged into **78**. Reaction of **78** with cyclopentadienones **79a** and **b** gave the corresponding initial adducts **80a** and **b**, which subsequently lost carbon monoxide to form **81a** (20%) and **81b** (16%) respectively.

When precursor **76** was photolyzed in acetonitrile, the generated carbene **77** formed ylide **82** with the solvent (Scheme 20), which could be directly observed by fs-TA spectroscopy.[70] The ylide **82** had a broad absorption in the visible region (λ_{max} of 450 nm) and a lifetime of ~13.5 ps.

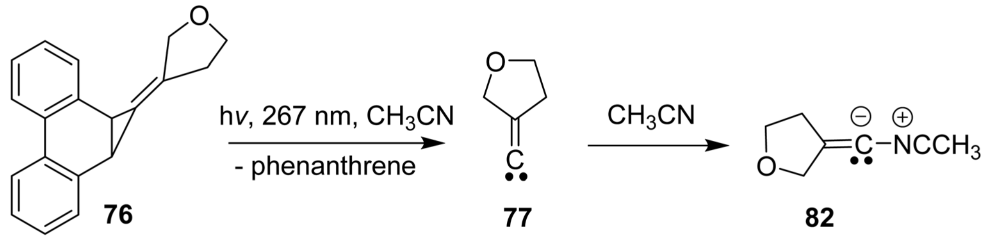
Unlike carbenes **69a** and **b**, **77** is asymmetrical. Thus, the ring expansion of **77** into **78** can proceed by one of two distinct pathways as either the allylic carbon attached to the oxygen (marked as **a**) or the other allylic carbon (marked as **b**) could be involved in the FBW rearrangement to give the same product **78** (see below).



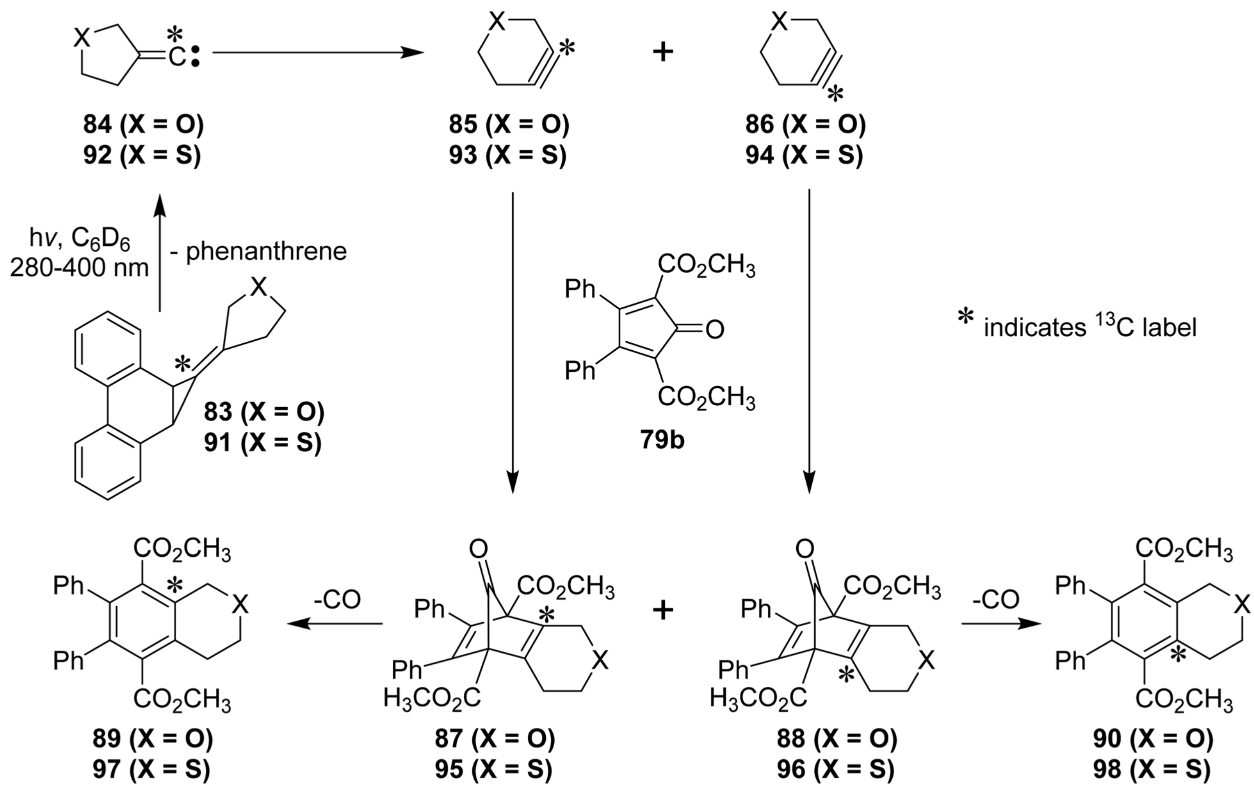
To determine the relative migratory aptitudes of the two different allylic carbons, ^{13}C-labeled precursor **83** was synthesized from the corresponding, labeled **5**, and photolyzed to form the labeled carbene **84** (Scheme 21).[71] Rearrangement of **84** gave isotopomers **85** and **86** which were trapped with the cyclopentadienone **79b** to give a mixture of **89** and **90** *via* **87** and **88** respectively. The relative ratio of **89 : 90** was found to be 92 : 8 (in a combined yield of 30%) indicating an overwhelming



Scheme 19 Generation of oxacyclohexyne **78** and its trapping reactions.[69]



Scheme 20 Ylide formation between carbene **77** and solvent acetonitrile.[70]



Scheme 21 ^{13}C labeling studies to determine relative migratory aptitudes in carbenes **84** and **92**.[71]

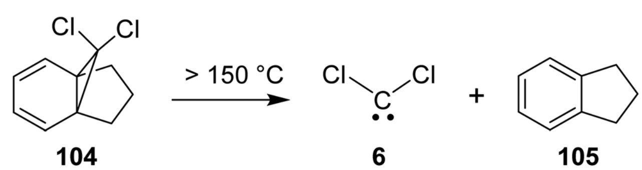
preference for the oxygen-bound allylic carbon to migrate in **84**, a result consistent with calculations. An analogous series of reactions, performed with the sulfur variant (**91** → **92** → **93**/**94** → **95**/**96** → **97**/**98**) gave a **97** : **98** ratio of 61 : 39 (combined yield 3%).[71] Thus, it appears that although the migration of the sulfur-bound allylic carbon is still favorable in **92**, the preference is not as strong as in the oxygen analog **84**, a result that is also supported by calculations. Precursor **91** was synthesized in a manner similar to **83**.

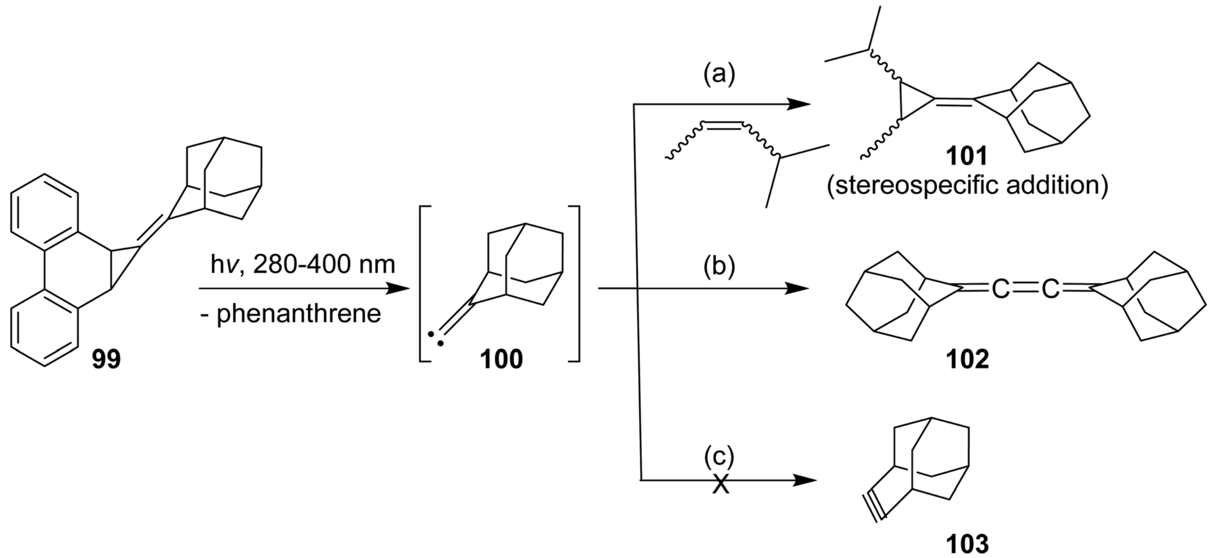
In a more recent study (Scheme 22), adamantylidenecarbene (**100**), generated from precursor **99**, was shown to cyclopropanate *E*- and *Z*-4-methyl-2-pentene in a stereospecific fashion to form adducts **101** (in yields of 14% from *cis* and 15% from *trans* alkene), and dimerize, in the absence of traps, to the cumulene **102** (21% yield).[72] In this case, no FBW ring expansion to homoadamantyne **103** was observed. Precursor **99** was synthesized using 2-adamantanone as the ketone in Scheme 18.[72]

3. Carbenes from cyclopropanated indanes

3.1 Saturated carbenes

The first mention of a cyclopropanated indane serving as a carbene source appeared as a footnote in a paper published by Vogel and coworkers.[73] The authors reported that the dichloro derivative **104** released dichlorocarbene (**6**) and indane (**105**) when heated to temperatures above 150 °C.

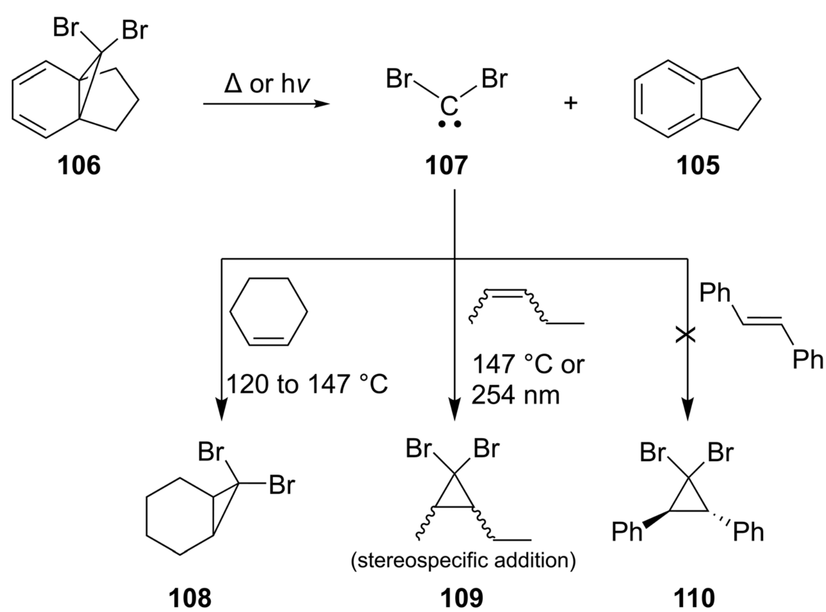




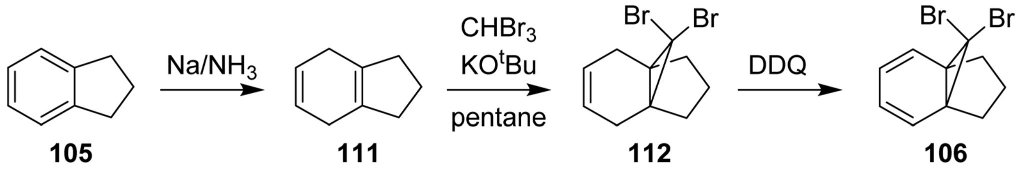
Scheme 22 Generation of adamantylidenecarbene (**100**) and its reactions. [Adapted from ref. 72 with permission under CC-BY 4.0.; Copyright 2023. The Authors. Published by the American Chemical Society.].

Some twenty years later, Warner and coworkers disclosed that photolysis or pyrolysis of **106** produced dibromocarbene (**107**) and indane (**105**) as shown in Scheme 23.[74] The carbene could be trapped by cyclohexene to yield norcarane **108** in yields ranging from 10% at 120 °C to 56% at 147 °C. Trapping by *cis*- or *trans*-2-pentene occurred in a stereospecific fashion to afford the cyclopropanated adducts (**109**). The *cis* and *trans* adducts were formed in 40% and 55% yields respectively from pyrolysis (147 °C), and 90% and 75% yields respectively from photolysis (254 nm). Attempts to trap **107**, generated from both bromoform under basic conditions and **106**, in *trans*-stilbene, showed no evidence of the expected cyclopropane (**110**). Pyrolysis of **106** in increasing concentrations of cyclohexene did not change the pseudo-first order rate constant of precursor decomposition, suggesting that the extrusion of **107** was a unimolecular process.

The synthesis of **106**, as shown in Scheme 24,[74] was accomplished by initially performing a Birch reduction on indane (**105**) to synthesize the diene **111**.[75] Subsequent addition of dibromocarbene to **111** occurred predominantly at the more nucleophilic, tetra-substituted double bond to form **112**.[75] Finally, oxidation of **112** with 2,3-dichloro-5,6-dicyano-1,4-



Scheme 23 Generation of dibromocarbene (**107**) *via* pyrolysis and photolysis of **106**, and related trapping studies.[74]

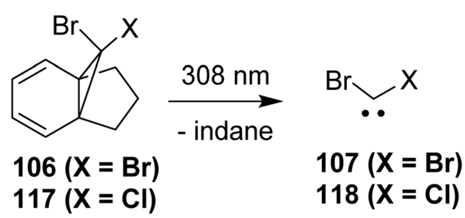


Scheme 24 Synthesis of precursor **106**.[74]

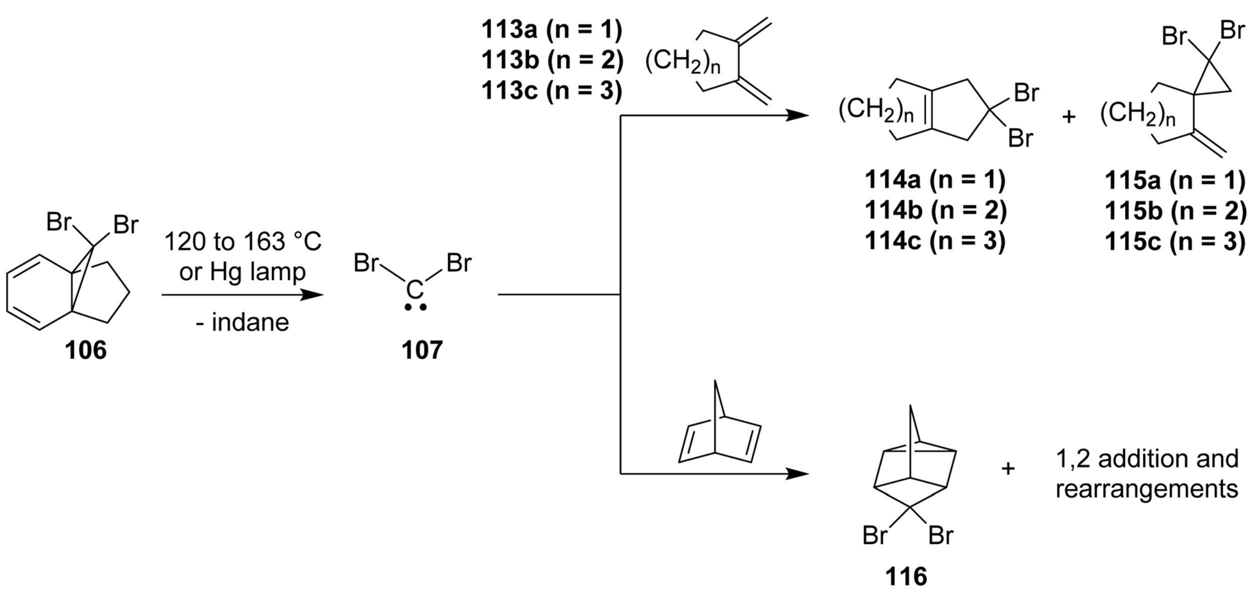
benzoquinone (DDQ) delivered the desired precursor **106**.[74] Due to the relative ease of synthesizing **106**, and its similar or improved ability to generate **107** compared to naphthalene-based analogues (see section 4), Warner and coworkers noted that the indane-based method for generating carbenes showed particular promise.[74]

Jones and coworkers also generated **107** from **106**, photochemically and thermally, in the presence of 1,4-dienes of various sizes (**113a–c**), as shown in Scheme 25. They found the very uncommon products of 1,4 addition (**114a–c**), albeit in low yields of 2–22% relative to the expected products of cyclopropanation (**115a–c**).[76] Furthermore, **107** underwent a homo 1,4 addition in the presence of norbornadiene, forming the adduct **116** (relative yield of 20% from photolysis and 24% from thermolysis) along with the products of cyclopropanation and rearrangements.[76] While 1,2 addition was the major process in all experiments (ranging from 78–98% of the total product), the formation of **114a–c** and **116** from "free" **107** marked the first conclusive evidence of a singlet carbene undergoing an intermolecular 1,4- and homo 1,4-additions respectively.

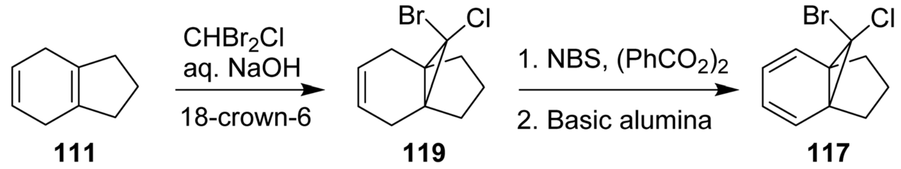
Precursor **106** (along with the 1,4-dihydronaphthalene-based **184b**, see section 4) was used in the first-ever study of dibromocarbene (**107**) by nanosecond LFP methods.[77] The same study also reported on the kinetics of the "mixed" dihalocarbene, bromochlorocarbene (**118**), generated from precursor **117**. Using the pyridinium ylide method described previously and a Stern–Volmer type analysis, the lifetimes of **107** and **118** and their k_{alk} in various alkenes were elucidated. A comparison of the Stern–Volmer rate constants indicated that dibromocarbene (**107**) was far less selective than dichlorocarbene (**6**)[42] and slightly less selective than bromochlorocarbene (**118**), and that the absolute reactivity of **118** was more akin to **107** than **6**. These observations were explained by invoking the greater electronic stabilization effect provided to the carbene by chlorine than bromine.[77]



The synthesis of **117** was achieved as shown in Scheme 26.[77] Thus, the phase transfer catalyzed addition of bromochlorocarbene to **111** produced the adduct **119**. Allylic bromination of **119** followed by a dehydrobromination on basic alumina gave precursor **117**.



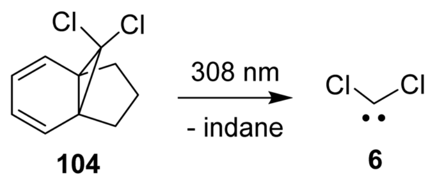
Scheme 25 Use of **106** to generate free **107**, which was trapped *via* both 1,2 and 1,4 addition to 1,4 dienes. A homo 1,4-addition to norbornadiene was also observed.[76]



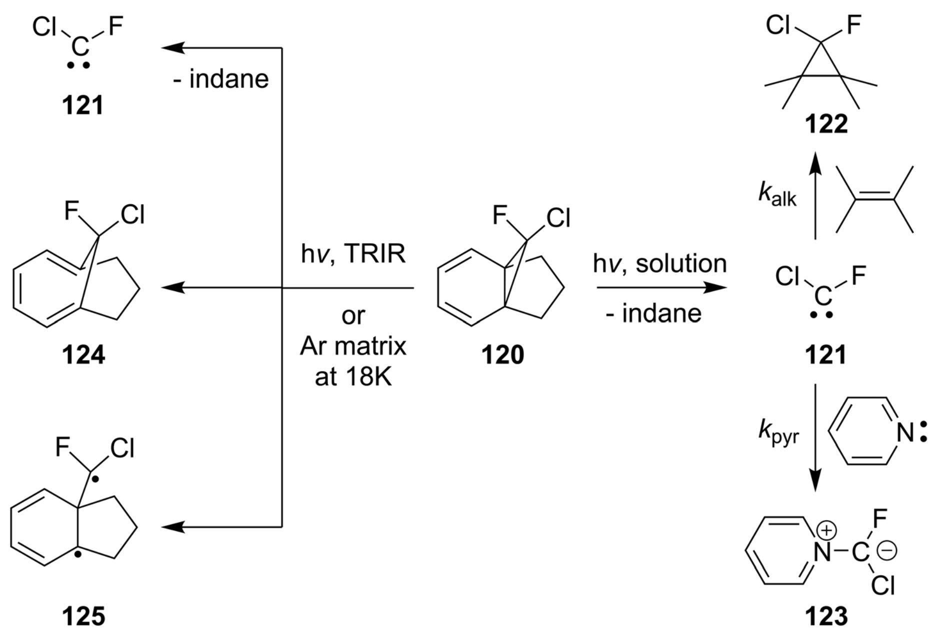
Scheme 26 Synthesis of precursor **117**.[77]

To continue probing the effects of different halogens on dihalocarbenes, Tippmann and Platz synthesized **120** by treating **104** with butyllithium at −78 °C, followed by quenching with the electrophilic fluorinating agent *N*-fluorobenezenesulfonimide.[78] The dichloro derivative **104** itself was prepared by replacing bromoform with chloroform in the route outlined in Scheme 24. Photolysis of **120** in the presence of TME at 300 nm yielded the expected cyclopropane **122** from the interception of chlorofluorcarbene **121** by the alkene (Scheme 27). LFP of **120** conducted in pyridine formed the corresponding ylide **123** at a near-diffusion controlled rate, a finding in agreement with work done on monochlorocarbene (**14**)[44] and dichlorocarbene (**6**).[42] The rate constant for the reaction of **121** with TME, k_{alk}, was determined to be about an order of magnitude less than for **6**, although the lifetimes of **121** and **6** were comparable. Time-Resolved IR (TRIR) spectroscopy with 266 nm irradiation, and Matrix Isolation studies using 300 nm light yielded three transient C–F stretches; using DFT calculations, the authors assigned two stretches to **121** and triene **124**, and the third (hesitantly) to biradical **125**.[78] The lifetime of **121** and the rate constant for its reaction with TME, as measured by TRIR, was comparable to the values obtained by LFP.

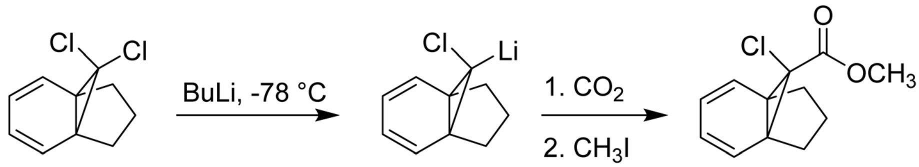
Precursor **104** was used in a LFP study, by the pyridinium ylide method, to investigate specific solvation of dichlorocarbene (**6**) by ethereal solvents.[79] LFP experiments on **104** were performed in solutions of Freon-113, tetrahydrofuran (THF), and 1,4-dioxane containing pyridine and TME. The rates of ylide and cyclopropane formation were found to be similar across all solvents (with ethereal solvents actually lowering the lifetime of **6**), indicating that specific solvation of **6** by the ethereal solvents does not occur.[79]



In the early 2000s, the Platz laboratory remained the primary group investigating the generation of carbenes from indane-based precursors, with much of their work focused on halogen-substituted carbenes. For example, in 2001, the Platz group reported the use of precursor **127** in an extensive study of carbomethoxychlorocarbene (**128**), a carbonylcarbene with a singlet ground state (Scheme 29).[80] Synthesis of **127** was accomplished by treating **104** with butyllithium at low temp-



Scheme 27 Investigation of chlorofluorocarbene (**121**) from precursor **120**.[78]



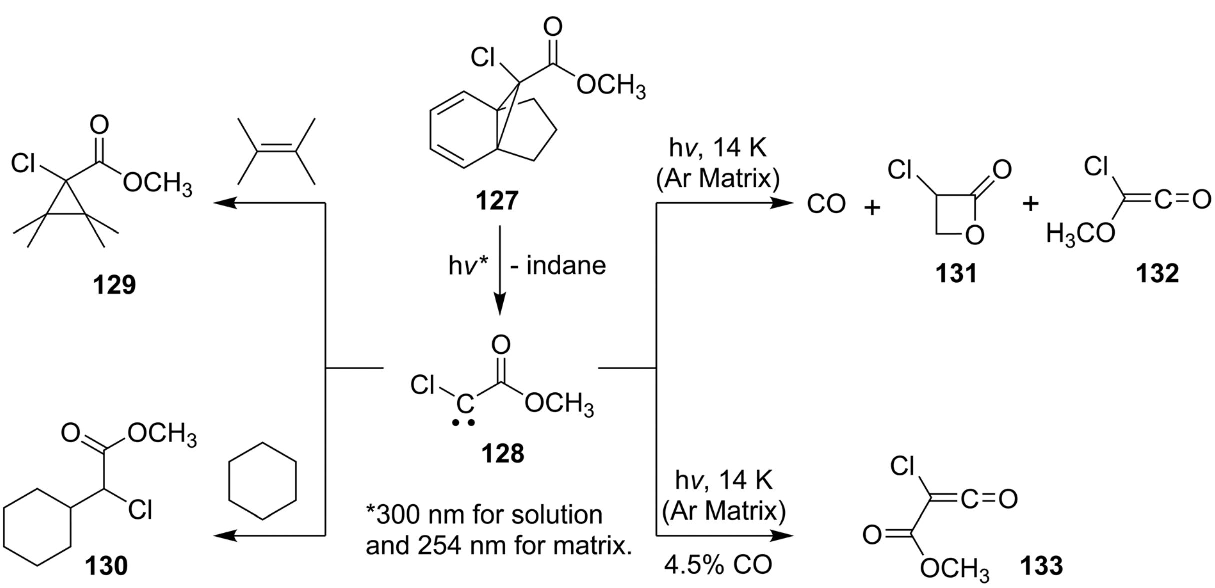
Scheme 28 Synthesis of precursor **127**.[80]

erature, and quenching the lithiated species **126** with Dry Ice followed by iodomethane (Scheme 28).[80]

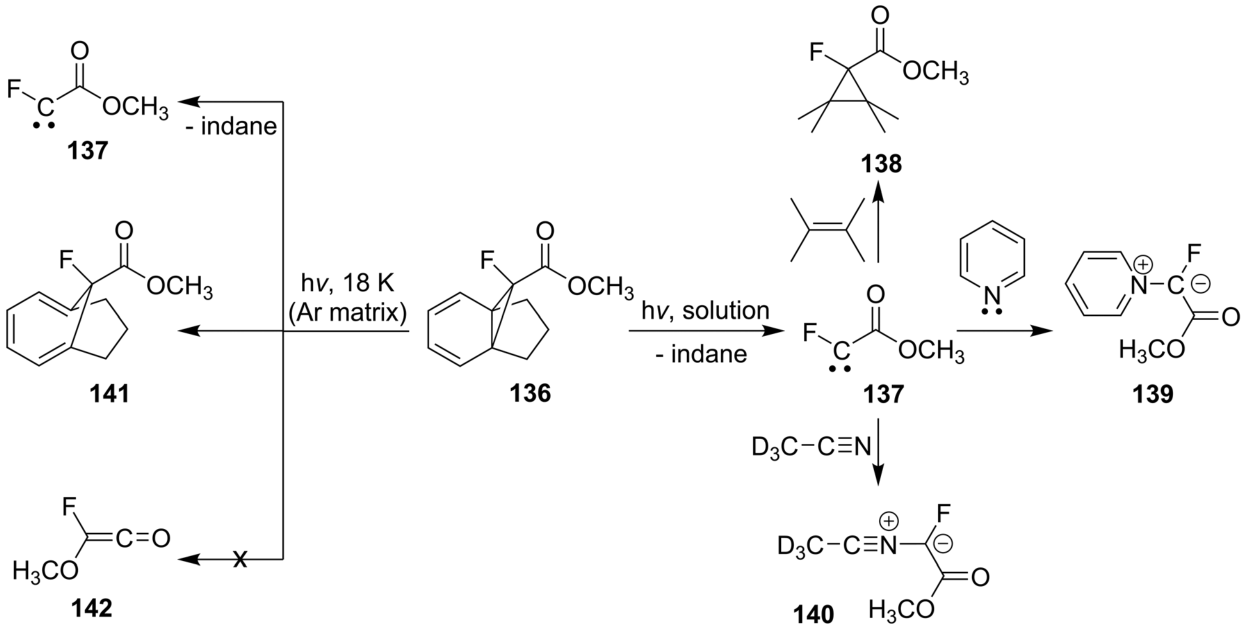
Photolysis (300 nm) of **127** in TME and in cyclohexane produced cyclopropane **129** and the insertion product **130** respectively, implicating the intermediacy of carbene **128** (Scheme 29). The yields of **129** and **130** were measured to be 85% and 16% relative to the indane byproduct. Photolysis (254 nm) of **127** in argon at 14 K, and monitoring by IR and UV-vis spectroscopy, showed evidence of **128** and carbon monoxide. Further irradiation of the matrix at 350 or 650 nm led to bleaching of the carbene signal and appearance of additional bands attributable to the β-lactone **131** and ketene **132** (product of Wolff Rearrangement). When photolysis was performed in an argon matrix doped with 4.5% CO, the yield of the carbene decreased and a new IR stretch was observed, which was attributed to ketene **133** formed from the trapping **128** by CO. All spectroscopic assignments were consistent with DFT calculations.

LFP experiments using the pyridinium ylide method were also performed using precursor **127**.[80] In Freon-113, the lifetime of carbene **128** was estimated to be 114 ns at ambient temperature, and the absolute rate constant for its reaction with pyridine (k_{pyr}) was found to be 2×10^9 M^{-1} s^{-1}. This value of k_{pyr} (in Freon-113) was subsequently used to estimate the lifetime of **128** in various other solvents. In addition to standard LFP experiments (pyridinium ylide/Stern–Volmer analysis with TME), LFP trials in different solvents – α,α,α-trifluorotoluene, Freon-113, and perfluorohexane – and at different temperatures, were conducted to allow for an Arrhenius treatment of the data. The barrier for carbene disappearance in the three solvents was estimated to be 5.4, 10.9, and 24.7 kJ mol^{-1} respectively. While the authors were unable to prove that Wolff Rearrangement was the sole means by which **128** is consumed, suggesting that the carbene might additionally react with solvent, they did provide a lower bound of ≥24.7 kJ mol^{-1} for the rearrangement **128** into ketene **132**, based on their studies in perfluorohexane (in which the carbene has a lifetime of 364 ns at 293 K).[80]

Shortly thereafter, Platz and coworkers reported their work on the photolysis of **134**, a precursor to chlorocyanocarbene **135** (see below).[81] The synthesis of **134** was achieved by quenching **126** with tosyl cyanide. While **134** generated indane when photolyzed in cyclohexane, benzene, and TME, products attributable to the reaction of **135** with solvents were made in very low yield and not isolable. LFP of **134** in Freon-113, cyclohexane, cyclohexane-d_{12}, benzene, and acetonitrile with pyridine generated the expected ylide, and the lifetime of **135** in each solvent was determined as usual. The lifetime of **135** was

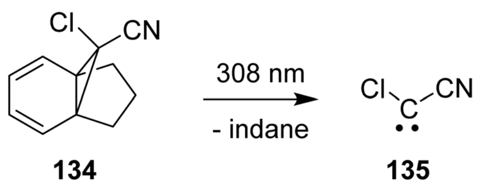


Scheme 29 Solution chemistry and matrix isolation studies of carbomethoxychlorocarbene **128** generated from the indane-based precursor **127**.[80]



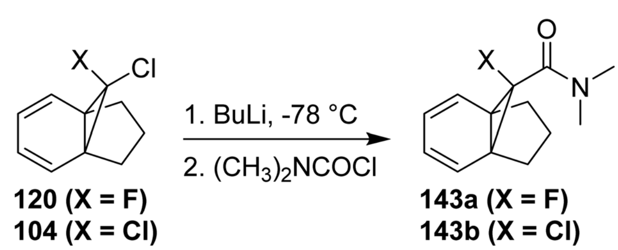
Scheme 30 Solution chemistry and matrix isolation studies of carbomethoxyfluorocarbene **137** generated from the indane-based precursor **136**.[82]

shorter than that of the carbene **128**, which the authors attributed to the greater electron-withdrawing effect of the cyano group and its lack of carbene-stabilizing interactions. LFP experiments of **134** in oxygenated Freon-113 showed no signs of a detectable oxide, which suggested that **135** likely did not have a triplet ground state.[81]

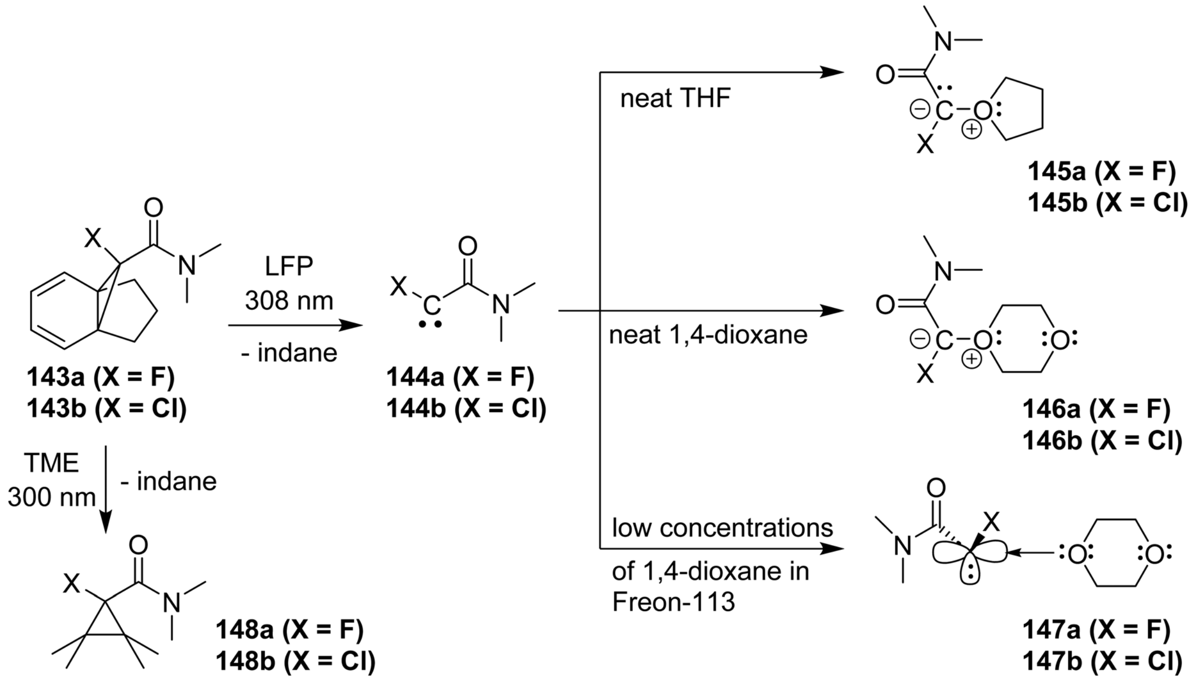


The Platz group also studied carbomethoxyfluorocarbene (**137**), the fluorine-substituted analog of **128**, using precursor **136** (Scheme 30).[82] Synthesis of **136** was carried out by the procedure outlined in Scheme 28 but starting with **120** instead of **104**. Photolysis of **136** in TME at 300 nm afforded the expected cyclopropanation product **138** in 27% yield, and LFP of **136** at 308 nm using pyridine and deuterated acetonitrile yielded the spectroscopically active ylides **139** and **140** respectively. The value of k_{pyr} was 3.2 times larger for **137** than **128**, and the former's lifetime was half as long, a finding that contradicted the trends found in aryl- and alkylhalocarbenes. To reconcile the fact that the fluorine-substituted carbene was clearly more reactive than its chlorine counterpart, the authors showed, using DFT calculations, that the carbenic carbon in **137** is more electrophilic than in **128**. Apparently, the electronegativity of fluorine is more influential in determining reactivity than is its π back-bonding, though the authors could not explain why only ester-substituted carbenes exhibit this effect.[82] Deposition and photolysis of **136** in an argon matrix at 254 nm, and monitoring by IR spectroscopy, revealed C–F stretches which the authors assigned to the carbene **137** and the triene **141**. There was, however, no evidence for the formation of ketene **142** that might have been expected from a Wolff Rearrangement in **137**.

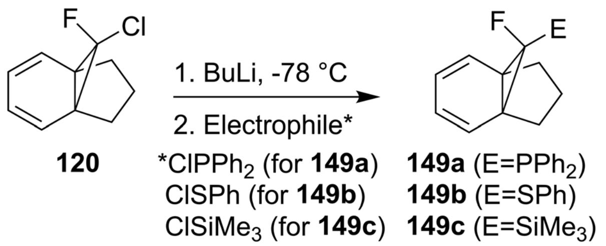
The amide analogs of **128** and **137** have been generated from indane-based precursors **143a** and **b**, which were synthesized as shown in Scheme 31.[83] Photolysis of **143a** and **b** produced fluoro- and chlorocarbene amides **144a** and **b** respectively that were investigated by the pyridinium ylide LFP method, TRIR techniques, and computational approaches (Scheme 32). In particular, the ability of coordinating solvents to specifically solvate the carbenes was examined. It was concluded that in neat THF, carbenes **144a** and **b** gave the ylides **145a** and **b** respectively, whereas the corresponding ylides **146a** and **b** were obtained in neat 1,4-dioxane. In the presence of small amounts of 1,4-dioxane in Freon-113, however, there appeared to be evidence for the formation of complexes **147a** and **b**, indicating specific solvation of the carbenes. Photolysis of **143a** and **b** in TME gave adducts **148a** (29%) and **148b** (60%) respectively.



Scheme 31 Synthesis of precursors **143a** and **b**.[83]



Scheme 32 Chemistry of haloamide carbenes **144a** and **b**.[83]

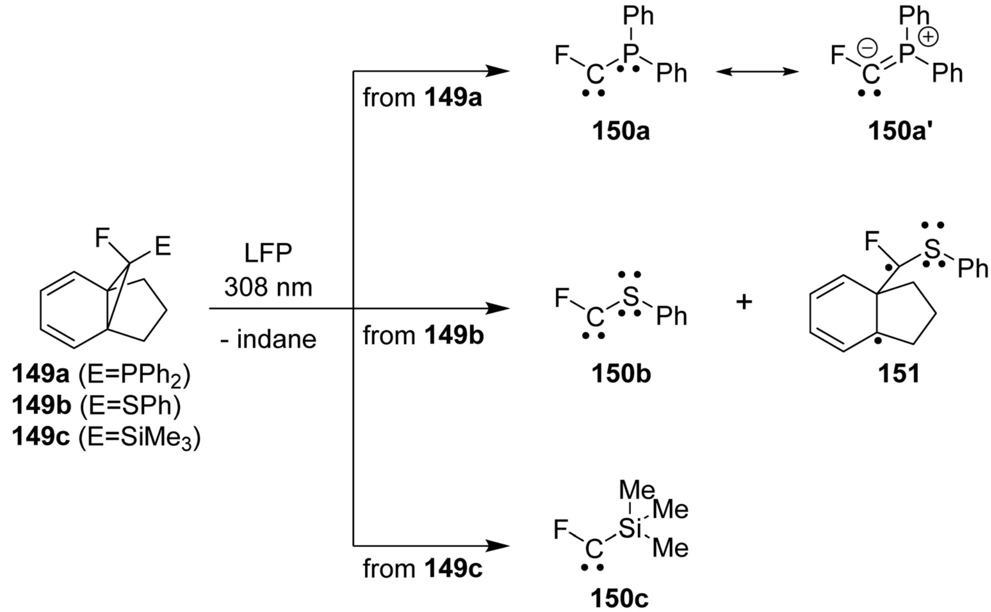


Scheme 33 Synthesis of precursors **149a–c** to various fluorocarbenes.[84]

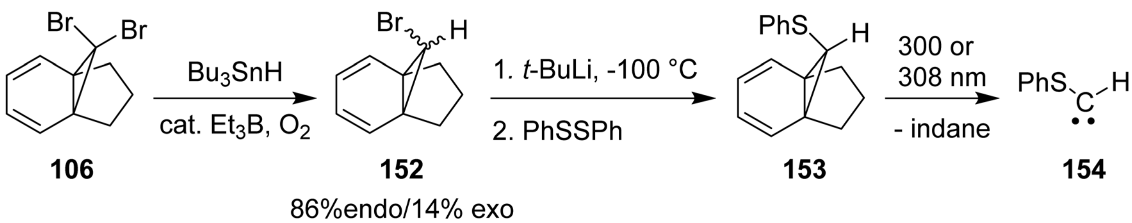
Indane-based precursors **149a–c** were also synthesized as shown in Scheme 33.[84] Photolysis of **149a–c** at 308 nm generated the corresponding carbenes (**150a–c**) substituted by a fluorine and a Period 3 heteroatom-attached moiety (Scheme 34).[84] Although standard LFP experiments with pyridine gave the expected ylides whose growth could be monitored for kinetic studies, carbene **150a** could be also directly observed as it had a usable absorption at 325 nm. LFP of **149a** in solvents of varying polarities demonstrated that **150a** was strongly stabilized in polar solvents, with lifetimes about a magnitude longer in dichloromethane (9.8 μs) than in cyclohexane (1.0 μs). However, there was no evidence for the specific solvation of **150a** as was observed in the case of **144a** and **b** (*vide supra*). With the support of DFT calculations, the authors attributed the general longevity of **150a** to the strong stabilizing contribution of mesomeric structure **150a′**. Carbene **150b** was shown to have a lifetime of 1.0 μs in cyclohexane at ambient temperature, but the LFP of **149b** also showed another absorption that was affected appreciably by the presence of oxygen. The authors attributed this absorption to the biradical **151**.[84] Curiously, similar biradicals were not observed from **149a** and **c**. Carbene **150c** was found to have a much shorter lifetime of 33 ns.

The Platz group then synthesized **153** from **106**, *via* **152**, as shown in Scheme 35.[85] Photolysis of **153** at 300 nm in TME produced the expected cyclopropane adduct of **154** in 80% yield. LFP experiments at 308 nm irradiation, performed with pyridine and TME, allowed the determination of the lifetime of **154** and the rate constants for its reaction with pyridine (k_{pyr}) and alkene (k_{alk}). Carbene **154** had a substantially longer lifetime, and lower k_{pyr} and k_{alk}, than monochlorocarbene (**14**), but its k_{pyr} and k_{alk} were about a magnitude greater than that of **150b** even though the lifetimes were the same. DFT calculations indicated that the longevity and nucleophilicity of **154** might be due to substantial π back-bonding from the sulfur into the carbene, which gave the carbenic carbon a natural charge of −0.54.[85]

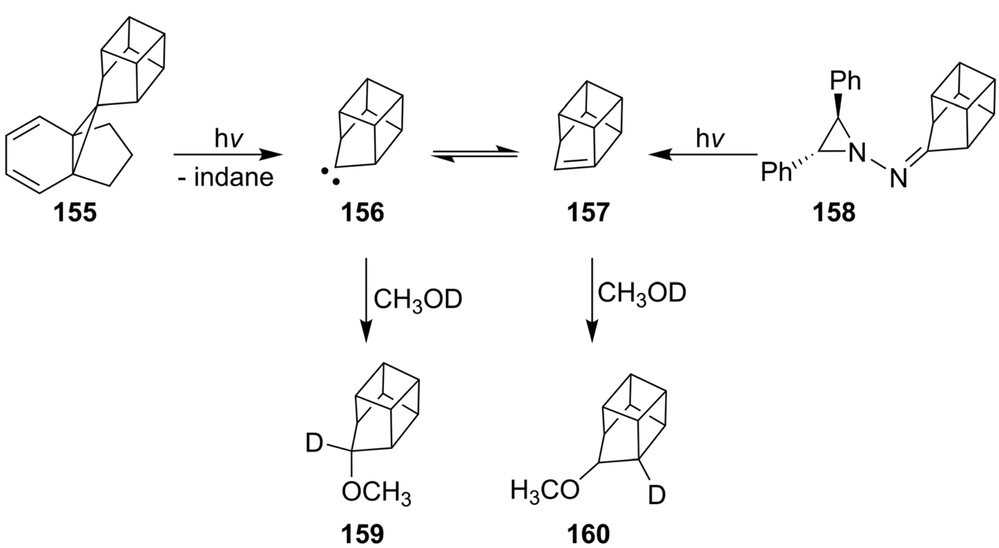
The first example of a dialkylcarbene being generated from an indane-based precursor was presented in a 1989 report by Jones and Chen, which described the photochemical extrusion of homocuban-9-ylidene (**156**) from **155** (Scheme 36).[86] While **156** had been generated previously from the nitrogenous source **158**, it was a product of rearrangement of the initially formed alkene **157**; thus, carbene **156** had never been formed directly.[87,88] Photolysis of **155** in the presence of deuterated methanol afforded the addition products of both the carbene *and* the bridgehead alkene (**159** and **160** respectively). Photolyzing **155** in increasing concentrations of CH_3OD linearly increased the ratio of **159** : **160**, indicating that carbene **156** was indeed the direct product of photolysis. This finding,



Scheme 34 Generation of the fluoro carbenes **150a–c** from precursors **149a–c**.[84]



Scheme 35 Synthesis of precursor **153** and its photolysis to produce carbene **154**.[85]



Scheme 36 The generation of homocuban-9-ylidene (**156**) from **155**, its rearrangement into bridgehead alkene **157**, and the products of trapping.[86]

coupled with the previous determination that **158** generated **157**, meant that the **156–157** system was the first example of an equilibrating carbene-bridgehead alkene pair.[86]

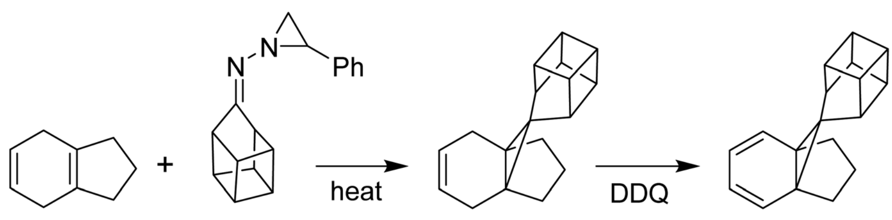
In an extension of the previous work, Jones, Platz, and coworkers used **155** and a diazirine precursor to **157** to investigate the equilibrium constant between **156** and **157**.[89] By means of conventional product analysis from trapping experiments, LFP methods, and Stern–Volmer quenching studies, they established that the equilibrium constant between **156** and **157** is close to unity at 20 °C, although they could not determine which species was favored at equilibrium.[89] They also determined that the reaction of **156** and **157** with deuterated methanol occurred within an order of magnitude from diffusion-controlled rates.[89]

The synthetic route to **155** is shown in Scheme 37.[89] Thus, the diene **111** was heated with the aziridylimine **161** to form adduct **162.** Subsequent DDQ oxidation of **162** delivered the desired precursor **155.**

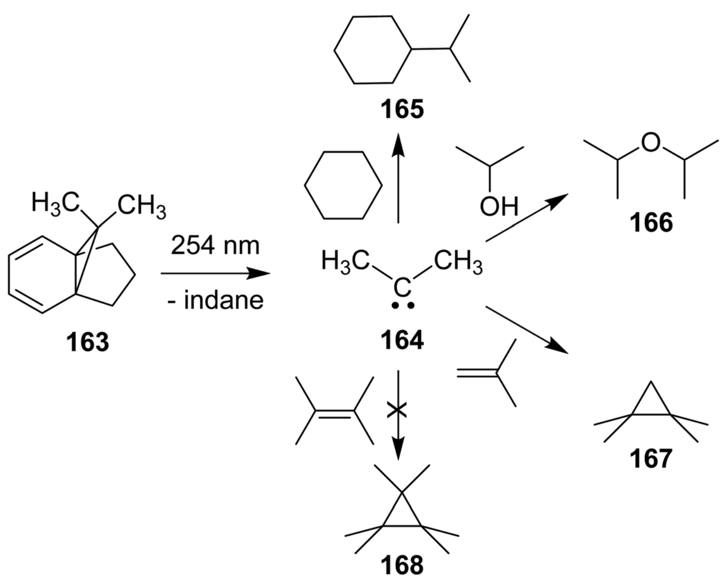
In 2001, Platz and coworkers reported that the indane-based precursor **163** could serve as a photochemical precursor to dimethylcarbene (**164**), the simplest dialkylcarbene.[90] When generated from a diazirine source, **164** rearranged into propene rather than undergoing intermolecular reactions, an outcome attributed to the incursion of RIES.[91] In contrast, photolysis of **163** in cyclohexane, isopropanol, and isobutylene gave the products of C–H insertion (**165**), O–H insertion (**166**), and cyclopropanation (**167**) respectively, though the overall yield of each process was poor (Scheme 38). Attempts to trap **164** with TME showed no evidence of cyclopropane **168**, presumably due to unfavorable steric interactions between the carbene and alkene. Despite the low yields, the presence of the trapped carbene demonstrated that **164** *was* sufficiently long-lived to undergo bimolecular reactions.[90] Synthesis of **163** was accomplished by the Hiyama reaction[48,49] of **106** with lithium dimethylcuprate followed by quenching with iodomethane, a procedure analogous to that shown in Scheme 4a.

3.2 Unsaturated carbenes

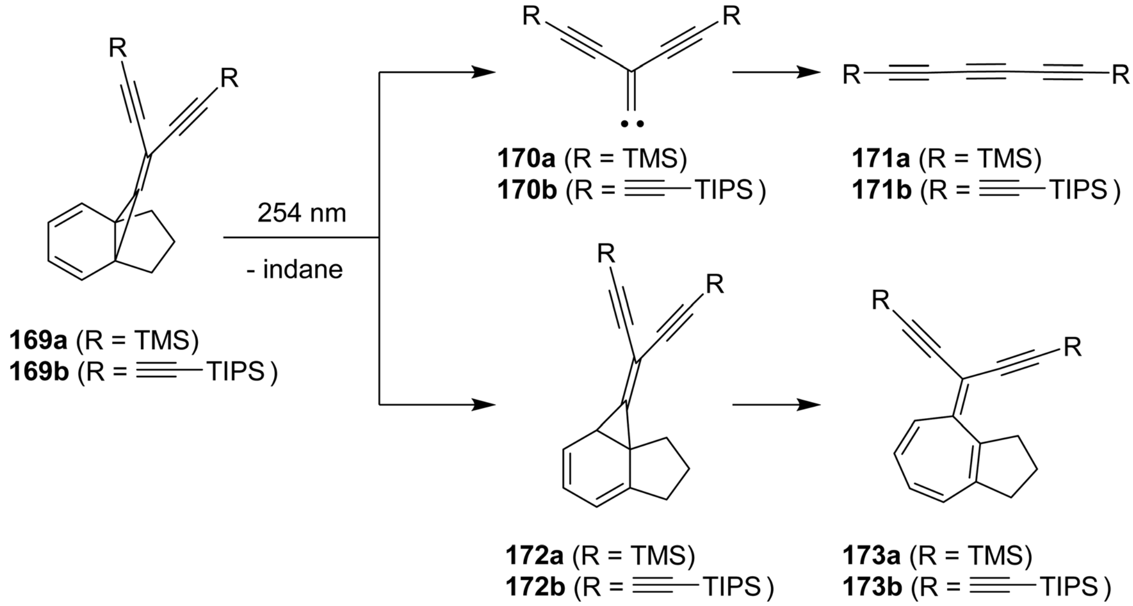
There is but a solitary report of unsaturated carbenes being generated from indane-based precursors.[92] In this report, Tobe and coworkers disclosed that photolysis of precursors **169a** and **b** produced the unsaturated carbenes **170a** and **b** respectively, which subsequently rearranged into the corresponding linear polyynes **171a** and **b** (Scheme 39). Interestingly, the ring-expanded isomers of the precursors, **173a** and **b**, were also



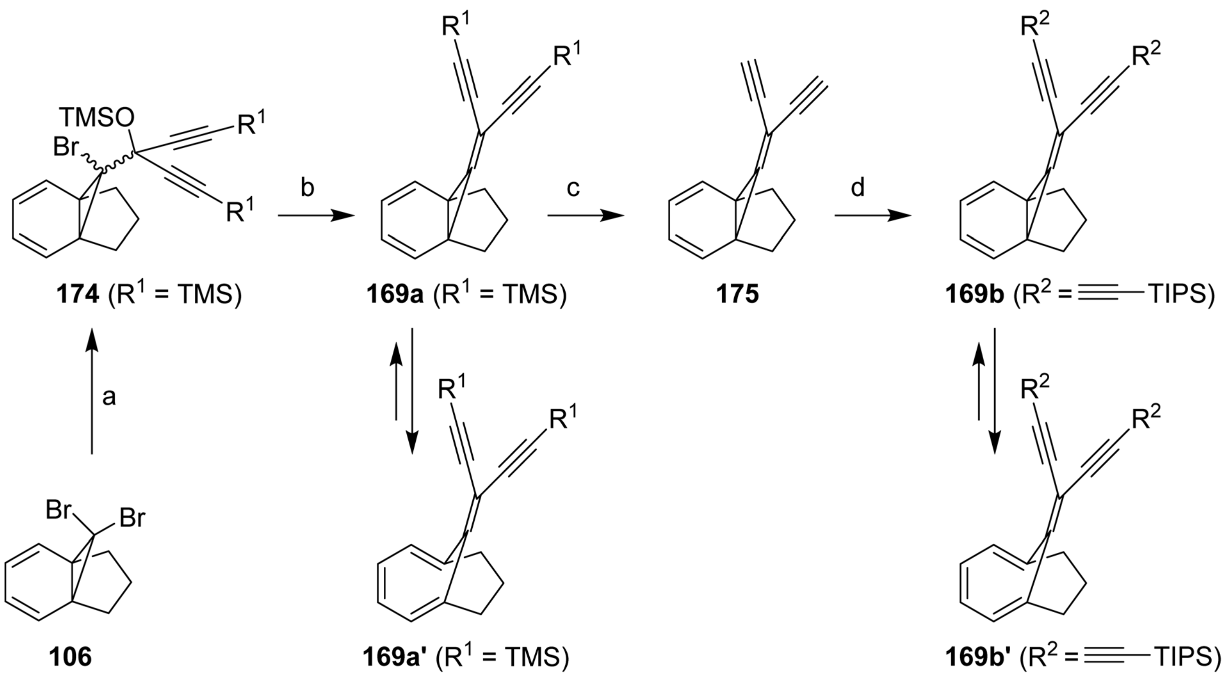
Scheme 37 Synthesis of precursor **155**.[89]



Scheme 38 Generation of dimethylcarbene (**164**) from precursor **163**, and its intermolecular reactions.[90]



Scheme 39 Indane-based precursors **169a** and **b** produce linear polyynes **171a** and **b** respectively *via* the corresponding unsaturated carbenes **170a** and **b** upon photolysis. Precursors **169a** and **b** also undergo isomerization to **173a** and **b**.[92]



(a) 1. BuLi, -100 °C, 2. (TMS-C≡C)$_2$C=O, -70 °C, 3. TMSCl; (b) 1. *t*-BuLi, -110 °C, 2. TMSCl; (c) LiOH.H$_2$O; (d) TIPS-C≡C-Br, CuCl, NH$_2$OH.HCl, aq. EtNH$_2$.

Scheme 40 Synthesis of precursors **169a** and **b**.[92]

found in these reactions. A 1,5-sigmatropic shift in **169a** and **b** leading to **172a** and **b** respectively, followed by an electrocyclic ring opening, accounts for the formation of **173a** and **b**. Analogous rearrangements have been also reported during the generation of alkylidene carbenes from some of the phenanthrene-based systems described above.[66,72]

Synthesis of precursors **169a** and **b** was accomplished as outlined in Scheme 40.[92] The first step was the conversion of

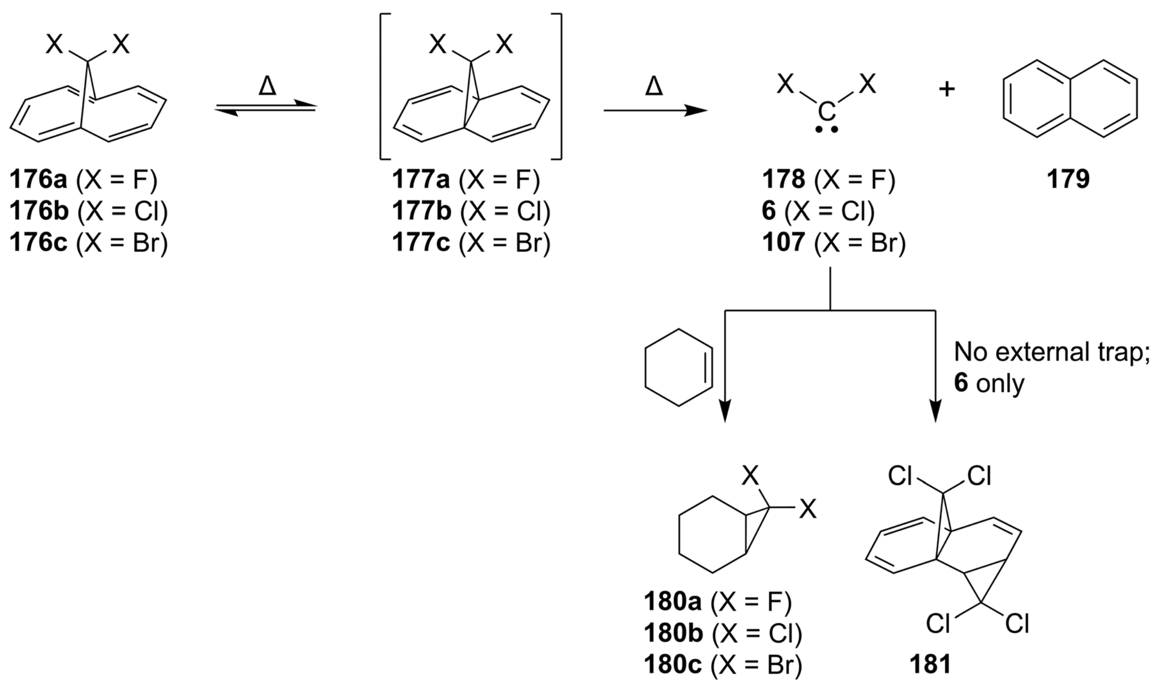
106 into the diyne **174**. A Peterson-like elimination from **174** then gave **169a**. Removal of the TMS group from **169a** to produce **175**, followed by a coupling reaction, led to **169b**. Both **169a** and **b** appear to be more stable in the ring-opened form **169a′** and **169b′** respectively.

4. Carbenes from cyclopropanated naphthalenes and related systems

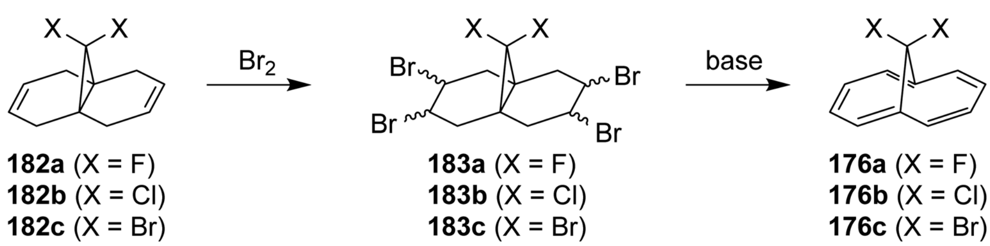
The use of cyclopropanated naphthalenes as carbene sources was first reported in 1968 by Vogel and coworkers, who described the pyrolysis of 11,11-dihalogeno-1,6-methano-[10] annulenes **176a–c** to give the respective dihalocarbene (**178**, **6**, **107**) and naphthalene (**179**) (Scheme 41).[73] The authors invoked the rearrangement of **176a–c** into the corresponding ring-closed isomers **177a–c**, and subsequent fragmentation of the cyclopropyl ring, to explain the observed products. When performed in an excess of cyclohexene, the pyrolysis cleanly generated the expected dihalonorcaranes (**180a–c**) in high yields. Interestingly, the authors noted that in the absence of cyclohexene, the dichlorocarbene (**6**) generated from this system was apparently trapped by the precursor, giving the norcaradiene derivative **181**. No evidence for the formation of the fluorine or bromine analogues of **181** was mentioned.[73] Dichlorocarbene (**6**) generated from **176b** was also reported to cyclopropanate *cis*- and *trans*-butenes in a stereospecific fashion.[73]

Synthesis of precursors **176a–c** was carried out as shown in Scheme 42.[73] The first step was the exhaustive bromination of **182a–c** to produce tetrabromides **183a–c**. Complete dehydrobromination of **183a–c** under basic conditions yielded **176a–c**.

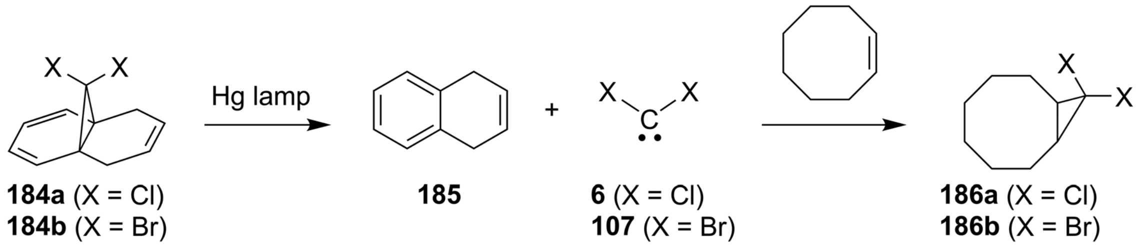
As was the case with phenanthrene-based carbene precursors, many years passed before this novel means of carbene generation was expanded to different systems. It was not until 1986 (almost two decades later!) that Jones and coworkers reported on their use of the partially hydrogenated precursors **184a** and **b**, which were attractive alternatives to **176b** and **c** because of their relative ease of synthesis.[93] Synthesis of **184a** and **b** was accomplished by partial oxidation of **182c** and **b**,



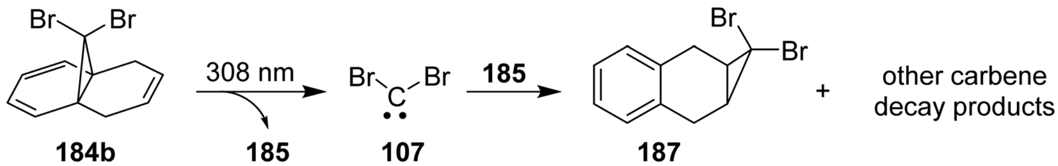
Scheme 41 Thermal generation of dihalocarbenes **178**, **6**, and **107** from naphthalene-based precursors **176a–c**.[73]



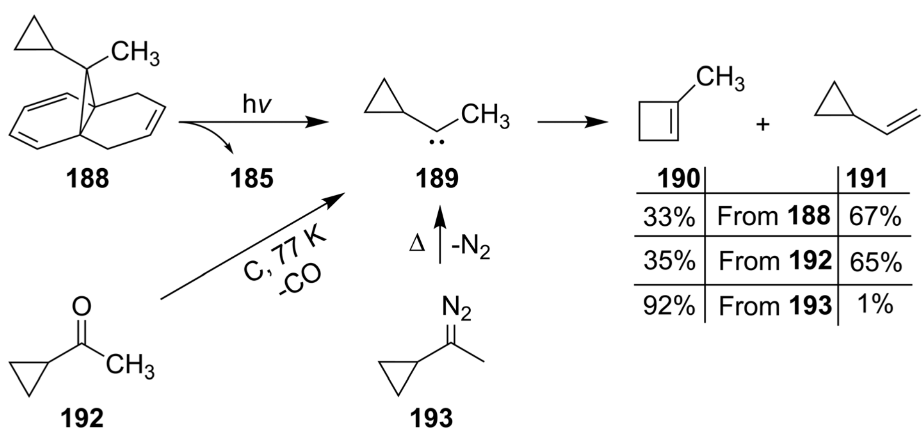
Scheme 42 Synthesis of precursors **176a–c**.[73]



Scheme 43 Photochemical generation of dihalocarbenes **6** and **107** from a 1,4-dihydronaphthalene-based precursors and trapping studies.[93]



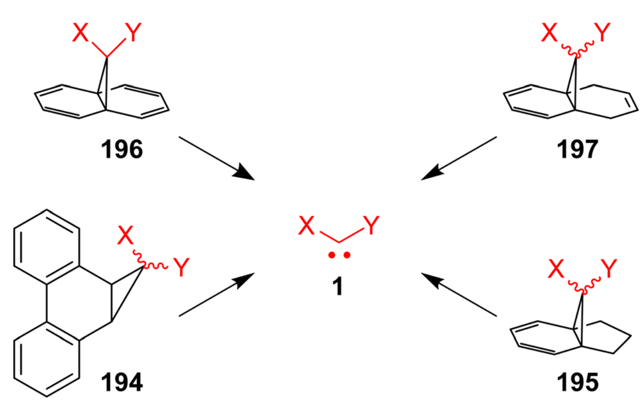
Scheme 44 Generation of dibromocarbene (**107**) from precursor **184b** and trapping by 1,4-dihydronaphthalene (**185**).[77]



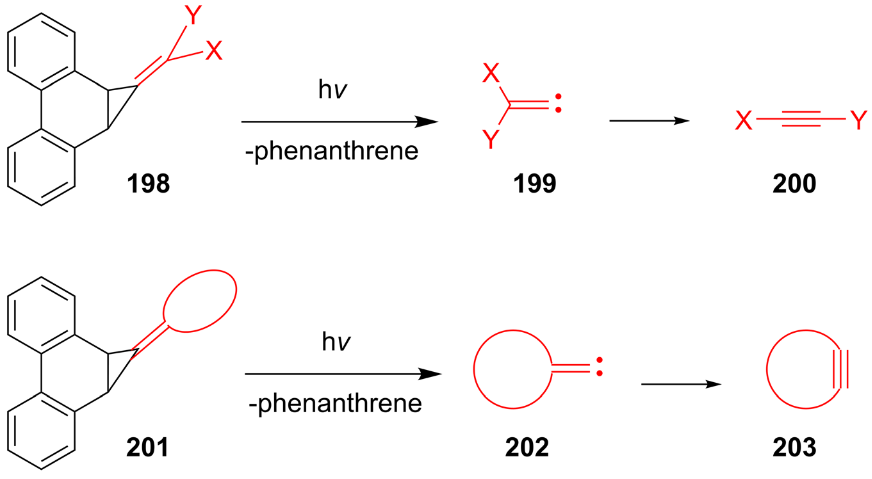
Scheme 45 The use of precursors **188**, **192**, and **193** to generate cyclopropylmethylcarbene **189**, and its rearrangement into **190** and **191**.[94]

respectively, with DDQ.[93] Upon photolysis with a medium-pressure Hg lamp at room temperature, both **184a** and **b** generated the respective dihalocarbenes (**6** and **107**) in addition to 1,4-dihydronaphthalene (**185**) as shown in Scheme 43. Photolysis in the presence of *cis*-cyclooctene yielded the expected cyclopropanation products, **186a** and **b** in about 80% yield. The selectivity indices of **107** with several olefin traps was comparable whether the precursor was **184b** or bromoform under basic phase-transfer-catalytic conditions, leading the authors to suggest that **107** has similar electronic states in both cases.[93]

Subsequently, kinetic experiments on dibromocarbene (**107**) were performed using both **106** and **184b** as precursors, the findings of which have been discussed in section 3.1.[77] In the same publication, the authors reported the effect of the re-addition of **107** to **185** (forming **187**) on the lifetime of the



Scheme 46 Generation of saturated carbenes from cyclopropanated aromatics. X and Y may or may not be identical.



Scheme 47 Generation of unsaturated carbenes from cyclopropanated aromatics. X and Y may or may not be identical.

carbene (Scheme 44). The authors determined that, indeed, the ability to add to the olefinic double bond in **185** served to shorten the lifetime of **107** when generated from **184b** as opposed to **106**; however, these effects seemed to be minimal, especially when a solvent trap was used.[77]

As shown in Scheme 45, precursor **188** has been used as a photochemical source of cyclopropylmethylcarbene **189**.[94] Synthesis of **188** was achieved by the Hiyama reaction[48,49] of **184b** with lithium dicyclopropylcuprate followed by quenching with iodomethane. When **188** is photolyzed in diglyme-d_{14}, both the ring expansion (1-methylcyclobutene, **190**) and 1,2 hydrogen shift (vinylcyclopropane, **191**) products of cyclopropylmethylcarbene (**189**) are produced. Importantly, it was observed that **191** was the major product of the photolysis, a finding consistent with products from free **189** generated by the reaction of atomic carbon with cyclopropyl methyl ketone (**192**),[95] but in sharp contrast to the ratio of pyrolysis products from precursor **193**, which was reported to yield significantly lower amounts of **191**.[96,97] While the researchers acknowledged that the temperature difference between the photolytic and pyrolytic methods may have caused the discrepancy in the ratio of products, they suggested that the comparable ratio of products from **188** and **192** may reflect the true ratio of products from the real carbene **189**. They implied that with **193**, nitrogenous precursor chemistry may be contributing to what was previously believed to be pure carbene chemistry.[94]

5. Conclusions

As shown in Scheme 46, non-traditional carbene sources such as **194**, **195**, **196**, and **197**, based on cyclopropanated aromatics, can all serve as viable alternatives to potentially hazardous diazirine and diazo precursors for the generation of saturated carbenes **1**. In each case the cheleotropic extrusion of carbenes is accompanied by the formation of stable aromatic by-products, *e.g.*, phenanthrene from **194**, indan from **195**, naphthalene from **196**, and 1,4-dihydronaphthalene from **197**.

Furthermore, methylenecyclopropanes appended to aromatic systems, *e.g.*, **198** and **201**, have been used to generate linear alkynes (**200**) and strained cycloalkynes (**203**) respectively, *via* the corresponding unsaturated carbenes **199** and **202** (Scheme 47). This is a particularly noteworthy advantage as unsaturated carbenes are typically not generated from nitrogenous sources such as diazirines and diazo compounds, which are difficult to access for synthetic reasons.

It is anticipated that the emergence of these relatively easy to synthesize, safe, stable, and versatile cyclopropanated aromatic systems will empower researchers to devise creative routes to new and unusual carbenes exhibiting interesting properties. These cyclopropanated systems are especially valuable as a complementary approach when synthetic challenges may preempt other means of generating particular carbenes.

Conflicts of interest

There are no conflicts to declare.

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References

1 *Chem. Rev.*, 2018, 118, 9455–10032.
2 *Contemporary Carbene Chemistry*, ed. R. A. Moss and M. P. Doyle, [In *Wiley Ser. React. Intermed. Chem. Biol.*, 2014; 7], John Wiley & Sons, Inc., Hoboken New Jersey, 2014.

3 M. Platz, in *Carbene chemistry: from fleeting intermediates to powerful reagents*, ed. G. Bertrand, Marcel Dekker and Fontis Media, S. A., New York and Lausanne, 2002, ch. 2, pp. 27–56.
4 *Advances in Carbene Chemistry*, ed. U. H. Brinker, Elsevier, Amsterdam, 2001.
5 *Advances in Carbene Chemistry*, ed. U. H. Brinker, Jai, Stamford, 1998.
6 *Advances in Carbene Chemistry*, ed. U. H. Brinker, Jai, Greenwich, 1994.
7 W. Kirmse and P. P. Gaspar, *Carbene chemistry*, Academic Press, New York, 2d edn., 1971.
8 Z. Yang, M. L. Stivanin, I. D. Jurberg and R. M. Koenigs, *Chem. Soc. Rev.*, 2020, **49**, 6833–6847.
9 S. Bai and Y.-F. Han, *Acc. Chem. Res.*, 2023, **56**, 1213–1227.
10 H. Song, E. Pietrasiak and E. Lee, *Acc. Chem. Res.*, 2022, **55**, 2213–2223.
11 Y. Wang, J.-P. Chang, R. Xu, S. Bai, D. Wang, G.-P. Yang, L.-Y. Sun, P. Li and Y.-F. Han, *Chem. Soc. Rev.*, 2021, **50**, 13559–13586.
12 S. Ibáñez, M. Poyatos and E. Peris, *Acc. Chem. Res.*, 2020, **53**, 1401–1413.
13 C. A. Smith, M. R. Narouz, P. A. Lummis, I. Singh, A. Nazemi, C.-H. Li and C. M. Crudden, *Chem. Rev.*, 2019, **119**, 4986–5056.
14 Y. He, Z. Huang, K. Wu, J. Ma, Y.-G. Zhou and Z. Yu, *Chem. Soc. Rev.*, 2022, **51**, 2759–2852.
15 X. Qi and Y. Lan, *Acc. Chem. Res.*, 2021, **54**, 2905–2915.
16 D. Zhu, L. Chen, H. Fan, Q. Yao and S. Zhu, *Chem. Soc. Rev.*, 2020, **49**, 908–950.
17 S. C. Sau, P. K. Hota, S. K. Mandal, M. Soleilhavoup and G. Bertrand, *Chem. Soc. Rev.*, 2020, **49**, 1233–1252.
18 Q. Liang and D. Song, *Chem. Soc. Rev.*, 2020, **49**, 1209–1232.
19 R. Jazzar, M. Soleilhavoup and G. Bertrand, *Chem. Rev.*, 2020, **120**, 4141–4168.
20 A. Doddi, M. Peters and M. Tamm, *Chem. Rev.*, 2019, **119**, 6994–7112.
21 R. Knorr, *Chem. Rev.*, 2004, **104**, 3795–3849.
22 R. S. Grainger and K. R. Munro, *Tetrahedron*, 2015, **71**, 7795–7835.
23 M. S. Platz, *J. Org. Chem.*, 2014, **79**, 2341–2353.
24 H. Lee, Y. Miyamoto and Y. Tateyama, *J. Org. Chem.*, 2009, **74**, 562–567.
25 J. Wang, J. Kubicki, E. F. Hilinski, S. L. Mecklenburg, T. L. Gustafson and M. S. Platz, *J. Am. Chem. Soc.*, 2007, **129**, 13683–13690.
26 J. P. Wagner, *J. Am. Chem. Soc.*, 2022, **144**, 5937–5944.
27 B. Chen, A. Y. Rogachev, D. A. Hrovat, R. Hoffmann and W. T. Borden, *J. Am. Chem. Soc.*, 2013, **135**, 13954–13964.
28 Y. Kutin, J. Reitz, P. W. Antoni, A. Savitsky, D. A. Pantazis, M. Kasanmascheff and M. M. Hansmann, *J. Am. Chem. Soc.*, 2021, **143**, 21410–21415.
29 H. Zollinger, *Diazo chemistry II*, VCH, Weinheim, 1995.
30 M. Regitz and G. Maas, *Diazo compounds : properties and synthesis*, Academic Press, Orlando, 1986.
31 *Chemistry of Diazirines*, ed. M. T. H. Liu, CRC Press, Boca Raton, 1987.
32 S. P. Green, K. M. Wheelhouse, A. D. Payne, J. P. Hallett, P. W. Miller and J. A. Bull, *Org. Process Res. Dev.*, 2020, **24**, 67–84.
33 L. L. Rodina, V. I. Baranovskii, O. S. Galkina, V. A. Nikolaev, N. L. Tonogina and A. V. Povolotskiy, *J. Org. Chem.*, 2017, **82**, 11399–11405.
34 V. Brusar, M. Forjan, I. Ljubić, M. Alešković, K. Becker and S. Vdović, *J. Org. Chem.*, 2023, **88**, 4286–4300.
35 M. S. Platz, H. Huang, F. Ford and J. Toscano, *Pure Appl. Chem.*, 1997, **69**, 803–808.
36 Z. Liu, P. Sivaguru, G. Zanoni and X. Bi, *Acc. Chem. Res.*, 2022, **55**, 1763–1781.
37 J. R. Fulton, V. K. Aggarwal and J. de Vicente, *Eur. J. Org. Chem.*, 2005, 1479–1492.
38 L. Zhang, B. M. DeMuynck, A. N. Paneque, J. E. Rutherford and D. A. Nagib, *Science*, 2022, **377**, 649–654.
39 H. E. Simmons and R. D. Smith, *J. Am. Chem. Soc.*, 1959, **81**, 4256–4264.
40 D. B. Richardson, L. R. Durrett, J. M. Martin, Jr., W. E. Putnam, S. C. Slaymaker and I. Dvoretzky, *J. Am. Chem. Soc.*, 1965, **87**, 2763–2765.
41 G. C. Joshi, N. Singh and L. M. Pande, *Synthesis*, 1972, 317, DOI: 10.1055/s-1972-21879.
42 J. E. Chateauneuf, R. P. Johnson and M. M. Kirchhoff, *J. Am. Chem. Soc.*, 1990, **112**, 3217–3218.
43 S. R. Hare, M. Orman, F. Dewan, E. Dalchand, C. Buzard, S. Ahmed, J. C. Tolentino, U. Sethi, K. Terlizzi, C. Houferak, A. M. Stein, A. Stedronsky, D. M. Thamattoor, D. J. Tantillo and D. C. Merrer, *J. Org. Chem.*, 2015, **80**, 5049–5065.
44 M. Robert, J. P. Toscano, M. S. Platz, S. C. Abbot, M. M. Kirchhoff and R. P. Johnson, *J. Phys. Chem.*, 1996, **100**, 18426–18430.
45 M. Robert, I. Likhotvorik, M. S. Platz, S. C. Abbot, M. M. Kirchoff and R. Johnson, *J. Phys. Chem. A*, 1998, **102**, 1507–1513.
46 M. Nigam, M. S. Platz, B. M. Showalter, J. P. Toscano, R. Johnson, S. C. Abbot and M. M. Kirchhoff, *J. Am. Chem. Soc.*, 1998, **120**, 8055–8059.
47 H. C. Glick, I. R. Likhovorik and M. Jones, Jr., *Tetrahedron Lett.*, 1995, **36**, 5715–5718.
48 K. Kitatani, T. Hiyama and H. Nozaki, *Bull. Chem. Soc. Jpn.*, 1977, **50**, 1600–1607.
49 K. Kitatani, T. Hiyama and H. Nozaki, *J. Am. Chem. Soc.*, 1976, **98**, 2362–2364.
50 J. M. Nguyen and D. M. Thamattoor, *Synthesis*, 2007, 2093–2094.
51 J. Schaeffler and J. Retey, *Angew. Chem.*, 1978, **90**, 906–907.
52 R. T. Ruck and M. Jones, Jr., *Tetrahedron Lett.*, 1998, **39**, 2277–2280.
53 D. M. Thamattoor, J. R. Snoonian, H. M. Sulzbach and C. M. Hadad, *J. Org. Chem.*, 1999, **64**, 5886–5895.
54 N. L. Drake and T. R. Sweeney, *J. Org. Chem.*, 1946, **11**, 67–74.

55 R. T. Ruck and M. Jones, Jr., *Tetrahedron Lett.*, 1998, **39**, 4433–4436.
56 R. A. Farlow, D. M. Thamattoor, R. B. Sunoj and C. M. Hadad, *J. Org. Chem.*, 2002, **67**, 3257–3265.
57 J. D. DeAngelo, S. Hatano and D. M. Thamattoor, *Aust. J. Chem.*, 2019, **72**, 890–893.
58 K. S. Graves, D. M. Thamattoor and P. R. Rablen, *J. Org. Chem.*, 2011, **76**, 1584–1591.
59 K. A. Moore, J. S. Vidaurri-Martinez and D. M. Thamattoor, *J. Am. Chem. Soc.*, 2012, **134**, 20037–20040.
60 P. Fritsch, *Justus Liebigs Ann. Chem.*, 1894, **279**, 319–323.
61 W. P. Buttenberg, *Justus Liebigs Ann. Chem.*, 1894, **279**, 324–337.
62 H. Wiechell, *Justus Liebigs Ann. Chem.*, 1894, **279**, 337–344.
63 X. Yang, K. Languet and D. M. Thamattoor, *J. Org. Chem.*, 2016, **81**, 8194–8198.
64 N. A. Petasis and E. I. Bzowej, *Tetrahedron Lett.*, 1993, **34**, 943–946.
65 L. Du, X. Lan, D. L. Phillips, W. H. Coldren, C. M. Hadad, X. Yang and D. M. Thamattoor, *J. Phys. Chem. A*, 2018, **122**, 6852–6855.
66 T. S. Hardikar, M. A. Warren and D. M. Thamattoor, *Tetrahedron Lett.*, 2015, **56**, 6751–6753.
67 D. P. Maurer, R. Fan and D. M. Thamattoor, *Angew. Chem., Int. Ed.*, 2017, **56**, 4499–4501.
68 T. Takeda, R. Sasaki and T. Fujiwara, *J. Org. Chem.*, 1998, **63**, 7286–7288.
69 R. Fan, Y. Wen and D. M. Thamattoor, *Org. Biomol. Chem.*, 2017, **15**, 8270–8275.
70 S. K. Sarkar, M. Ko, X. Bai, L. Du, D. M. Thamattoor and D. L. Phillips, *J. Am. Chem. Soc.*, 2021, **143**, 17090–17096.
71 T. E. Anderson, D. M. Thamattoor and D. L. Phillips, *Org. Lett.*, 2023, **25**, 1364–1369.
72 A. D. Roth, C. E. Wamsley, S. M. Haynes and D. M. Thamattoor, *J. Org. Chem.*, 2023, **88**, 14413–14422.
73 V. Rautenstrauch, H. J. Scholl and E. Vogel, *Angew. Chem., Int. Ed. Engl.*, 1968, **7**, 288–289.
74 P. M. Warner, S. L. Lu and R. Gurumurthy, *J. Phys. Org. Chem.*, 1988, **1**, 281–285.
75 E. Vogel, W. Wiedemann, H. D. Roth, J. Eimer and H. Günther, *Justus Liebigs Ann. Chem.*, 1972, **759**, 1–36.
76 N. A. Le, M. Jones, Jr., F. Bickelhaupt and W. H. De Wolf, *J. Am. Chem. Soc.*, 1989, **111**, 8491–8493.
77 M. Robert, J. R. Snoonian, M. S. Platz, G. Wu, H. Hong, D. M. Thamattoor and M. Jones, *J. Phys. Chem. A*, 1998, **102**, 587–592.
78 E. M. Tippmann and M. S. Platz, *J. Phys. Chem. A*, 2003, **107**, 8547–8551.
79 S. I. Presolski, A. Zorba, D. M. Thamattoor, E. M. Tippmann and M. S. Platz, *Tetrahedron Lett.*, 2004, **45**, 485–486.
80 I. Likhotvorik, Z. Zhu, E. L. Tae, E. Tippmann, B. T. Hill and M. S. Platz, *J. Am. Chem. Soc.*, 2001, **123**, 6061–6068.
81 Y. Sun, I. Likhotvorik and M. Platz, *Tetrahedron Lett.*, 2002, **43**, 7–9.
82 E. M. Tippmann, G. Holinga and M. S. Platz, *Org. Lett.*, 2003, **5**, 4919–4922.
83 E. M. Tippmann, M. S. Platz, I. B. Svir and O. V. Klymenko, *J. Am. Chem. Soc.*, 2004, **126**, 5750–5762.
84 C. Buron, E. M. Tippmann and M. S. Platz, *J. Phys. Chem. A*, 2004, **108**, 1033–1041.
85 S. E. Condon, C. Buron, E. M. Tippmann, C. Tinner and M. S. Platz, *Org. Lett.*, 2004, **6**, 815–818.
86 N. Chen and M. Jones, Jr., *Tetrahedron Lett.*, 1989, **30**, 6969–6972.
87 N. Chen and M. Jones Jr., *J. Phys. Org. Chem.*, 1988, **1**, 305–308.
88 P. E. Eaton and K. L. Hoffmann, *J. Am. Chem. Soc.*, 1987, **109**, 5285–5286.
89 N. Chen, M. Jones, Jr., W. R. White and M. S. Platz, *J. Am. Chem. Soc.*, 1991, **113**, 4981–4992.
90 I. R. Likhotvorik, E. Tippmann and M. S. Platz, *Tetrahedron Lett.*, 2001, **42**, 3049–3051.
91 F. Ford, T. Yuzawa, M. S. Platz, S. Matzinger and M. Fülscher, *J. Am. Chem. Soc.*, 1998, **120**, 4430–4438.
92 Y. Tobe, N. Iwasa, R. Umeda and M. Sonoda, *Tetrahedron Lett.*, 2001, **42**, 5485–5488.
93 J. F. Hartwig, M. Jones, R. A. Moss and W. Ławrynowicz, *Tetrahedron Lett.*, 1986, **27**, 5907–5910.
94 D. M. Thamattoor, M. Jones, W. Pan and P. B. Shevlin, *Tetrahedron Lett.*, 1996, **37**, 8333–8336.
95 The authors performed their own experiment, careful to avoid the complications involved with gas phase chemistry, and obtained the ratios shown in Scheme 20. For previous examples of real carbenes being generated by addition of carbon atoms to carbonyls, see: (*a*) B. M. Armstrong, M. L. McKee and P. B. Shevlin, *J. Am. Chem. Soc.*, 1995, **117**, 3685–3689; (*b*) P. S. Skell and J. H. Plonka, *Tetrahedron*, 1972, **28**, 3571–3582.
96 L. Friedman and H. Shechter, *J. Am. Chem. Soc.*, 1960, **82**, 1002–1003.
97 W. Kirmse, B. G. v. Buelow and H. Schepp, *Justus Liebigs Ann. Chem.*, 1966, **691**, 41–49.