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The Stereospecific Cyclopropanation of Diarylcarbene Cation Radicals

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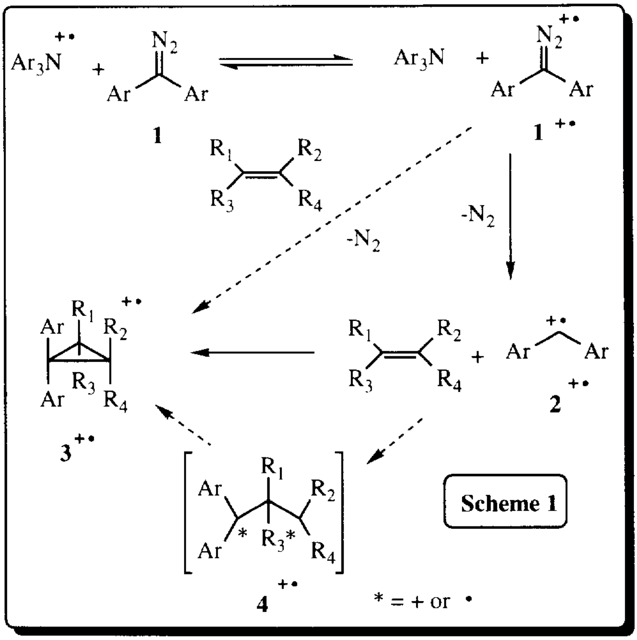
Abstract: Catalytic chemical oxidation of *p, p'*-dimethyldiphenyldiazomethane, **1**, using tris-(4-methylphenyl)aminium hexafluoroantimonate, $Ar_3N^{+\bullet}$, in the presence of excess alkene in CH_2Cl_2 yields substituted cyclopropanes, **3**, in high yield. Experiments show that cyclopropanation is stereospecific and probably proceeds via the initial formation of a 1,3 cation radical intermediate which undergoes ring closure.

The chemistry of neutral carbenes has been extensively studied over the past three decades.[1] Although carbenes undergo a myriad of chemical reactions, most are rather unselective, including those of diarylcarbenes with alkenes. In this regard, we considered whether the chemical reactions of oxidized carbenes, carbene cation radicals would be more selective. Recent work has demonstrated that diarylcarbene cation radicals can be generated in solution by the unimolecular loss of nitrogen from the corresponding oxidized diazo precursor.[2] However, only a few studies have investigated the chemistry of these highly reactive species.[2] In this communication, we wish to report on the generation and chemistry of diarylcarbene cation radicals. In particular, we have found that diarylcarbene cation radicals undergo highly efficient, stereospecific cyclopropanation with alkenes.

Catalytic chemical oxidation of *p, p'*-dimethyldiphenyldiazomethane, **1** (0.01 M), using tris-(4-methylphenyl)aminium hexafluoroantimonate, $Ar_3N^{+\bullet}$ (4 mM), in the presence of excess alkene (1.5M) in dry, argon-degassed CH_2Cl_2 for 20 min yields substituted cyclopropanes, **3**, in high yield, Table 1.[3] Additional minor products include carbene dimers and azine. The substituted cyclopropanes were characterized by GC-MS, ^1H and ^{13}C NMR and NOE studies. Each reaction yielded only one cyclopropane stereoisomer, and importantly, cyclopropanation is stereospecific (≥99%, entries 2/5, and 7/8, Table 1).[4] The relative reactivities of the various alkenes were determined by standard competition experiments, Table 1.[3,5] Catalytic chemical oxidation of *p, p'*-dichlorodiphenyldiazomethane and diphenyldiazomethane also resulted in stereospecific cyclopropanation.[6]

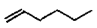
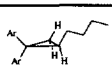
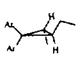
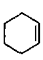
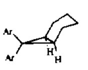
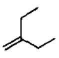
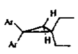
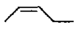
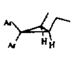
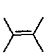
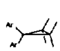
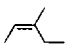
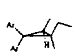
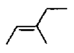
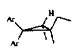
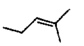
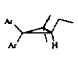
A plausible mechanism for the formation of cyclopropanes from the oxidation of diaryldiazomethanes is shown in Scheme 1. Chemical equilibration between $Ar_3N^{+\bullet}$ ($E_{ox}(Ar_3N)$ = 0.71 V vs. SCE)[7], and **1** ($E_{ox}(\mathbf{1})$ = 0.77 V vs. SCE)[7] should occur rapidly and yield $\mathbf{1}^{+\bullet}$. Subsequent unimolecular loss of nitrogen by $\mathbf{1}^{+\bullet}$



Scheme 1

produces the carbene cation radical $\mathbf{2}^{+\bullet}$, which can then react with the alkene to form cyclopropane $\mathbf{3}^{+\bullet}$. Electron transfer from Ar_3N or **1** to $\mathbf{3}^{+\bullet}$ ($E_{ox}(\mathbf{3}) \geq 1.5$ V vs. SCE)[7] gives cyclopropane **3** and regenerates either the catalyst $Ar_3N^{+\bullet}$ or $\mathbf{1}^{+\bullet}$.

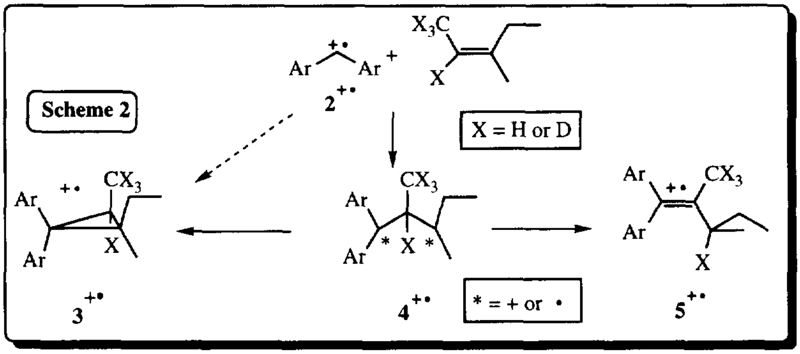
Table 1. Oxidative Cyclopropanation Reactions of 1 with Alkenes[3]

Entry	Alkene	Product	Yield	Relative Reactivity
1			61%	0.47
2			63%	0.57
3			62%	1.0
4			73%	1.43
5			76%	1.67
6			75%	1.99
7			83%	2.19
8			81%	2.41
9			87%	2.70

An alternative mechanism for the formation of **3** may involve the reaction of $\mathbf{1}^{+\bullet}$ directly with alkene and then loss of nitrogen. Diphenyldiazomethane cation radicals have been previously postulated to be involved in carbene dimer formation.[2h,i] This pathway can be readily distinquished from that described above by the kinetics for the disappearance of $\mathbf{1}^{+\bullet}$. Whereas the disappearance of $\mathbf{1}^{+\bullet}$ to form $\mathbf{2}^{+\bullet}$ should be independent of alkene, the direct reaction should have a first order dependence on alkene. The kinetics of $\mathbf{1}^{+\bullet}$ disappearance can be measured by absorption spectroscopy ($\lambda_{max}(\mathbf{1}^{+\bullet})$ = 680 nm).[7a] The first order rate constant for disappearance of $\mathbf{1}^{+\bullet}$ is 32 s^{-1}. Importantly, under these reaction conditions in which high yields of cyclopropanes **3** are observed, the rate constant is independent of cyclohexene concentration (0-2.5 M). This observation indicates that the decay of $\mathbf{1}^{+\bullet}$ does not result from a reaction with alkene but rather from a unimolecular process, most probably the loss of nitrogen.[7b,c]

The reaction of singlet carbenes with alkenes is commonly thought to be concerted and hence stereospecific, whereas that of triplet carbenes is stepwise and non-stereospecific. Although the reaction of diarylcarbene cation radicals $\mathbf{2}^{+\bullet}$ with alkenes is stereospecific, is the reaction concerted or stepwise, proceeding via a 1,3 cation radical intermediate $\mathbf{4}^{+\bullet}$? Some mechanistic insight was gained from the reaction of *cis*- and *trans*-3-methyl-2-pentene with **1**, entries 7 and 8, Table 1. In addition to the stereospecific cyclopropanes, a rearrangement product **5** was also formed in low yield, ≤ 8%.[3] This product can possibly be formed via a 1,2 hydrogen rearrangement of intermediate $\mathbf{4}^{+\bullet}$ to $\mathbf{5}^{+\bullet}$, followed by reduction, Scheme 2. This 1,2 hydrogen rearrangement is well documented for other 1,3 cation radicals.[8] In fact, previous mechanistic work by Bauld et. al. on the cyclopropanation reaction of alkene cation radicals with ethyldiazoacetate suggested that such 1,3 cation radicals were involved.[2e,f]

If the product **5** is formed from $\mathbf{4}^{+\bullet}$, does the stereospecific cyclopropanation also proceed via $\mathbf{4}^{+\bullet}$? An induced kinetic isotope effect study was conducted to ascertain whether $\mathbf{4}^{+\bullet}$ is indeed a common intermediate in the formation of $\mathbf{3}^{+\bullet}$ and $\mathbf{5}^{+\bullet}$. Simply, if the ratio of **3** to **5** using 3-methyl-2-pentene-d_4,[9] (X=D, Scheme 2), is different than that using 3-methyl-2-pentene, (X=H), $\mathbf{4}^{+\bullet}$ must be a common intermediate in the reaction. Under identical reaction conditions, the ratio of **3** to **5** was 50.0 ± 4.2 using the d_4 alkene, and 23.1 ± 3.1 using the d_0 alkene. Neglecting secondary isotope effects, the ratio of ratios yields a primary isotope effect of 2.16 for the 1,2 hydrogen rearrangement of $4^{+\bullet}$. This observed induced isotope effect requires that $4^{+\bullet}$ be a common intermediate which presumably undergoes both ring closure to $3^{+\bullet}$ and rearrangement to $5^{+\bullet}$ faster than C-C bond rotation, which would have produced the stereoisomeric cyclopropane. Although the reactions of **1** with the other alkenes do not give rearrangement products in appreciable amounts, and so cannot be subjected to the same mechanistic scrutiny, it is reasonable to assume that they all proceed via 1,3 cation radical intermediates $4^{+\bullet}$.[10]



The chemistry of diarylcarbenes **2** and diarylcarbene cation radicals, $2^{+\bullet}$, is indeed quite different. First, the reactions of diarylcarbenes with alkenes often involve both singlet and triplet spin states and are quite complicated. Stereospecific cyclopropanation is usually not observed.[1] Cyclopropanes are formed in low yields and the major products are usually C-H insertion products.[11] In contrast, cyclopropanes are formed stereospecifically and in high yield from a single doublet spin state of $2^{+\bullet}$. Second, diarylcarbenes typically react as nucleophiles rather than electrophiles.[12] However, their oxidation to $2^{+\bullet}$ increases the electrophilicity as indicated by the weak correlation between the reactivity of $2^{+\bullet}$ with increasing nucleophilicity of the alkene, Table 1. Third, triplet carbenes usually undergo stepwise, non-stereospecific cyclopropanation via 1,3 triplet biradicals. Ring closure of this biradical to ground state cyclopropane is highly exothermic, but it is spin forbidden, and so C-C bond rotation competes with intersystem crossing. In contrast, although ring closure and rearrangement of the 1,3 cation radical $4^{+\bullet}$ are not highly exothermic, they occur rapidly, i.e. faster than C-C bond rotation.[13]

In conclusion, diarylcarbene cation radicals $2^{+\bullet}$ undergo stereospecific cyclopropanation with electron rich alkenes. Mechanistic studies indicate that the reaction proceeds via the initial formation of a 1,3 cation radical intermediate, which can undergo ring closure and rearrangement. Future work will examine other diarylcarbene cation radicals and their reactions with alkenes and other nucleophiles.

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2. (a) Bethell, D.; Parker, V. D. *Acc. Chem. Res..* **1988**, *21*, 400, and references therein. (b) Parker, V. D.; Bethell, D. *J. Amer. Chem. Soc.* **1987**, *109*, 5066. (c) Schuster, G. B.; Little, C. B. *J. Amer. Chem. Soc.*

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3. 2,6-di-*t*-butyl pyridine (0.02M) is added to prevent acid catalyzed decomposition of **1**, see Bakee, J. M.; Bethell, D.; Parker, V. D. *Acta Chim. Scand.* **1987**, B41, 253. $Ar_3N^{+\bullet}$ was prepared by the addition of 0.95 eq. of NO^+SbF6^- to a solution of 1.5 M Ar_3N in CH_2Cl_2. The reaction was stirred at room temperature for 2 hours and then diluted into 100 fold excess of diethyl ether. The purple solid was collected via filtration. The competition studies were run under identical conditions using 0.75 M cyclohexene and 0.75 M indicated alkene. The determined relative reactivity is the ratio of observed cyclopropanes from the indicated alkene to that from cyclohexene. Rearrangement product **5** was characterized by GC-MS, NMR and independent synthesis. Diazo **1** does not yield **3** in the absence of catalyst $Ar_3N^{+\bullet}$, which suggests that oxidation of **1** is required.
4. The purity of the alkenes (Wiley Organics) used was ≥ 99%. Analysis of the reaction mixtures by GC and ^1H NMR indicate that the ratio of cyclopropane stereoisomers is ≥ 99%, with the major product having the same relative stereochemistry as the alkene used.
5. Attempts to use electron-poor alkenes were unsuccessful because of competing thermal neutral reactions of the alkenes with **1**, presumably 1,3 dipolar cycloaddition reactions.
6. The reactions of the other diazo compounds with $Ar_3N^{+\bullet}$ were significantly slower, in part because of the higher oxidation potentials of the diazo compounds. We are currently investigating these reactions.
7. (a) $\mathbf{1}^{+\bullet}$ was prepared by stopped flow mixing of **1** (0.5 mM) in CH_2Cl_2 containing 2,6-di-*t*-butyl pyridine (1 mM) with tris-(4-bromophenyl)aminium hexafluoroantimonate or thianthrenium tetrafluoroborate (0.55 mM) in CH_2Cl_2. The appearance of $\mathbf{1}^{+\bullet}$ was monitored by absorption spectrsocopy at 650 nm and occured within 2 msec. The absorption spectrum of $\mathbf{1}^{+\bullet}$ was obtained by photoinduced electron transfer, see Todd et. al. *J. Amer. Chem. Soc.* **1991**, *113*, 3601. (b) Preliminary electrochemical experiments (BAS 100W) indicate that loss of nitrogen from $\mathbf{1}^{+\bullet}$ is also quite rapid. In addition, the CV trace was unaffected by the addition of alkene when the scan rate was such that the wave indicated partial reversibility in the absence of alkene.[2b] (c) The kinetics also rules out the possibility of a cation radical mediated 3+2 dipolar cycloadditon of the diazo compound with cyclohexene to form the heterocyclic cation radical which can subsequently lose nitrogen.
8. (a) Adam, W.; Sahin, C.; Sendelbach, J.; Walter, H.; Chen, G-F.; Williams, F. *J. Amer. Chem. Soc.* **1994**, *116*, 2576, and references therein. (b) Adam, W.; Walter, H.; Chen, G-F.; Williams, F. *J. Amer. Chem. Soc.* **1992**, *114*, 3007.
9. The deuterated alkene was synthesized from acetaldehyde-d_4 (Aldrich, >99% atom % D) by standard Wittig reaction using sec-butyl-triphenylphosphonium iodide. The *cis*/*trans* mixture of alkenes was characterized by GC-MS and ^1H NMR. A similar mixture of the d_4 alkene was used for these experiments.
10. The observation that similar rearrangement products are not observed with the other alkenes suggests that the rate of rearrangement of the postulated 1,3 cation radicals is slower than ring closure to form $\mathbf{3}^{+\bullet}$. For tetra substituted alkenes, an alkyl group must undergo the rearrangement. These alkyl shifts are expected to be slower than hydrogen shifts.[1] For mono and 1,2 alkyl substituted alkenes, the enthalpy for 1,2 hydrogen rearrangement is calculated to be significantly less exothermic. Alternatively, these reactions may be concerted and not proceed via 1,3 cation radicals.
11. For example, see Baron, W. J.; Hendrick, M. E. *J. Amer. Chem. Soc.* **1973**, *95*, 6286.
12. (a) Dix, E. J.; Goodman, J. L. *J. Amer. Chem. Soc.* **1973**, *95*, 6286. (b) Bethell, D.; Newall, A. R.; Whittaker, D. *J. Chem. Soc. B* **1971**, 23. (c) Kirmse, W.; Kilian, J.; Steenken, S. *J. Amer. Chem. Soc.* **1990**, *112*, 6399.
13. In fact, the the thermodynamics of ring closure of 1,3 cation radicals has received considerable attention in the literature. See Borden et. al. *Chem. Phys. Lett.* **1986**, *123*, 337.

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