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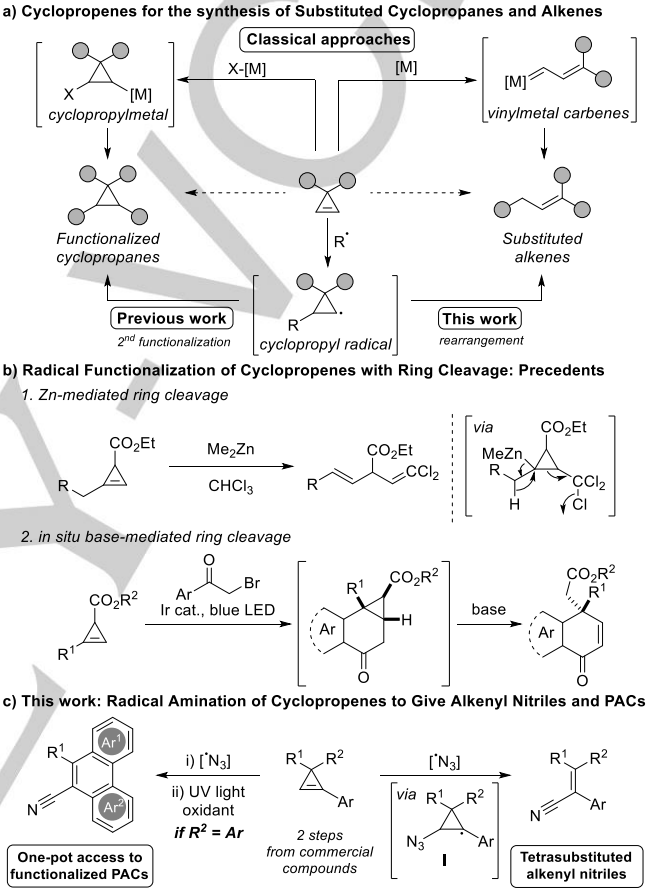
Azide Radical Initiated Ring Opening of Cyclopropenes Leading to Alkenyl Nitriles and Polycyclic Aromatic Compounds

Bastian Muriel and Jerome Waser*[a]

Abstract: We report herein a radical-mediated amination of cyclopropenes. The transformation proceeds through a cleavage of the three-membered ring after the addition of an azide radical on the strained double bond and leads to tetrasubstituted alkenyl nitrile derivatives upon loss of N_2. With 1,2-diaryl substituted cyclopropenes, this methodology could be extended to a one pot synthesis of highly functionalized polycyclic aromatic compounds (PACs). This transformation allows the synthesis of nitrile-substituted alkenes and aromatic compounds from rapidly accessed cyclopropenes using only commercially available reagents.

Alkenyl nitriles and polycyclic aromatic compounds (PACs) are important scaffolds in organic chemistry, material sciences and medicine.[1] Alkenyl nitriles are key structural motifs in pharmaceuticals such as Entacapone used in the treatment of Parkinson's disease,[2] or the reverse transcriptase inhibitor Rilpivirine.[3] In addition, they are valuable synthetic intermediates that have been used as electrophilic partners in conjugate additions.[4] PACs are also present in biologically active compounds,[5] and have found many applications as organic materials for semiconductors[6] and light-emitting diodes.[7]. For these reasons, developing new methods for the synthesis of PACs has been the focus of intensive research.[8] Nevertheless, there is still a strong demand for modular methods to access selectively polysubstituted PACs.

Cyclopropenes have emerged in the past decades as important three-carbon building blocks, due to efficient methods for their synthesis combined with a versatile reactivity.[9] Reaction at the double bond with organometallic intermediates or transition metal catalysts gives access to either functionalized cyclopropanes[10] or substituted alkenes after ring-opening via vinyl carbene intermediates[11] (Scheme 1, a). The formation of a reactive cyclopropyl radical intermediate upon the addition of a radical onto the alkene has been less explored. Nakamura and co-workers reported in 1994 the hydrostannation of cyclopropenes.[12] Several reports have later described the addition of carbon-centered radicals, with a functionalization of the resulting cyclopropyl radical through C-S bond formation,[13] H-abstraction,[14] or a second C-C bond forming event.[15] We recently developed a photoredox-mediated (3+2) annulation with cyclopropylanilines to access bicyclo[3.1.0]hexanes.[16] In contrast, examples of a radical functionalization of cyclopropenes leading to a cleavage of the three-membered ring are scarce (Scheme 1, b). Miyata and co-workers reported a ring opening rearrangement after the addition of a trichloromethyl radical to alkyl-substituted cyclopropenes, followed by trapping of the radical by dimethyl zinc (Scheme 1, b) 1.).[14a] Landais and co-workers developed a radical-mediated dicarbofunctionalization of cyclopropenes, followed by a base-mediated fragmentation of the *in situ* formed cyclopropane (Scheme 1, b) 2.).[17]



Scheme 1. Synthetic strategies towards functionalized cyclopropanes and substituted alkenes from cyclopropenes (a). Previous reports leading to a cleavage of the three-membered ring after a radical functionalization of cyclopropenes (b). This work: radical amination of cyclopropenes with an azide radical for the synthesis of alkenyl nitriles and substituted PACs (c).

Although examples of amination reactions of cyclopropenes have been reported in the presence of transition metals or lanthanides combined with electrophilic,[18] or nucleophilic sources of nitrogen,[19] the addition of *N*-centered radicals has not been reported to date. We report herein a ring-opening reaction initiated by the addition of an azide radical (Scheme 1, c). This transformation led to the formation of alkenyl nitriles after the rearrangement of a putative azido-cyclopropyl radical (**I**). With 1,2-diaryl substituted cyclopropenes we developed a one-pot radical amination / oxidative photocyclization to access highly substituted PACs. While azide radicals have already been used for the synthesis of alkenyl nitriles through C-H or C-C bond cleavage of alkenes and alkynes, these processes were limited to

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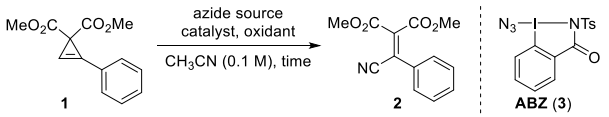
the synthesis of trisubstituted olefins and cyclopropenes were not reported as substrates.[20]

Our investigations started with cyclopropene **1** employing ABZ (**3**) as safe azidation reagent under mild photoredox-catalyzed conditions known to generate azide radicals (Table 1).[21] Under green LED irradiation with $Cu(dap)_2Cl$ as photocatalyst, alkenyl nitrile **2** was formed in 82% yield (entry 1). When reducing the equivalents of ABZ from 2.0 to 1.4, **2** was obtained in 78% yield (entry 2). In the presence of inexpensive $CuCl_2$ and ABZ (**3**) without irradiation, **2** was formed in 62% yield (entry 3). Employing 2 equivalents of PIDA and TMS-N_3 as commercial reagents,[22] **2** was obtained in 56% yield after 30 minutes of reaction (entry 4). Adding 10 mol% of $CuCl_2$ led to a high yield of 94% (entry 5).[23] While going from 2.0 to 1.5 equivalent led to a decrease in yield to 85% (entry 6), we found 1.8 equivalent to be optimal combined with a reduced loading of $CuCl_2$ to 5 mol% (entry 7). Under these conditions, **2** could be isolated in 88% yield.

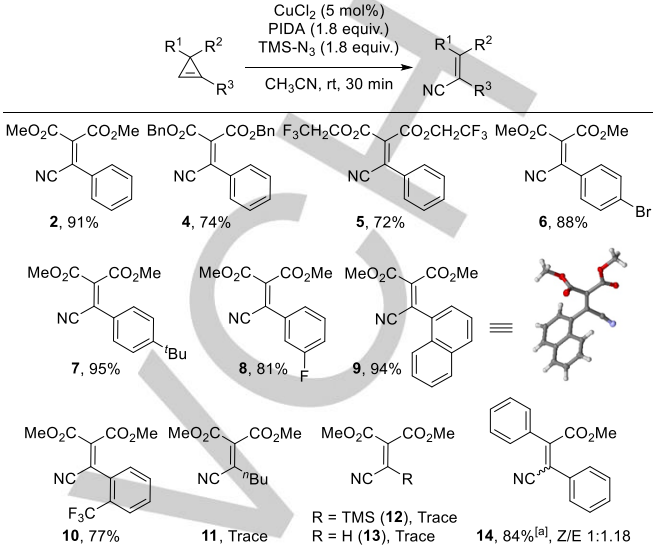
Table 1. Discovery and optimization of the radical amination.[a]



Entry	Azide Source (equiv.)	Cat. (mol%)	Oxidant (equiv.)	Time	Yield[b]
1[c]	ABZ (2)	$Cu(dap)_2Cl$ (1)	-	O/N	82%
2[c]	ABZ (1.4)	$Cu(dap)_2Cl$ (1)	-	O/N	78%
3	ABZ (1.4)	$CuCl_2$ (10)	-	O/N	62%
4	TMS-N_3 (2)	-	PIDA (2)	30 min	56%
5	TMS-N_3 (2)	$CuCl_2$ (10)	PIDA (2)	30 min	94%
6	TMS-N_3 (1.5)	$CuCl_2$ (10)	PIDA (1.5)	30 min	85%
7	TMS-N_3 (1.8)	$CuCl_2$ (5)	PIDA (1.8)	30 min	90% (88%[d])

[a] Reaction conditions: 0.1 mmol scale, O/N: overnight. dap = 2,9 - bis(para-anisyl) - 1,10 - phenanthroline. [b] Yields determined by ^1H NMR using CH_2Br_2 as internal standard. [c] Reaction performed under Green LED irradiation. [d] Isolated yield on 0.1 mmol scale.

With optimized conditions in hands, we carried some preliminary scope investigations (Scheme 2). On a 0.3 mmol scale, cyclopropene **1** delivered alkenyl nitrile **2** in 91% yield. Dibenzyl- and ditrifluoroethyl-ester substituted cyclopropenes gave products **4** and **5** in 74% and 72% yield, respectively. Both electron-donating and -withdrawing groups in *para*-position on the aromatic substituent of the cyclopropene were compatible with the reaction (products **6** and **7**).[24] *Meta*-substitution was also tolerated (product **8**, 81% yield). The reaction proceeded as well with a 2-naphthyl substituent, delivering **9** in 94% yield. For **9**, an X-Ray structure could be obtained.[25] An *ortho*-CF_3 substituted cyclopropene led to the formation of **10** in 77% yield. As shown with examples **11**, **12** and **13** for which only traces of the alkenyl nitriles were observed, having an aryl-substituent on the unsaturated bond was essential. With aryl groups both in position 1 and 2 of the cyclopropene ring, the reaction proceeded in high yield, with **14** isolated in 84% yield on a 1.6 mmol scale, albeit with almost no stereoselectivity.



Scheme 2. Preliminary scope investigations of the radical amination. Reaction conditions: 0.3 mmol scale. [a] Yield on 1.6 mmol scale.

Alkenyl nitrile **2** could be obtained in 92% yield on gram scale (Scheme 3). Taking advantage of the electrophilic nature of **2**, it was successfully engaged in several transformations. A Corey–Chaykovsky cyclopropanation led to **15** in 54% yield.[26] Alkene **2** underwent a (3+2) annulation with allenoate **16**, delivering cyclopentene **17** in 89% yield.[27] **2** could also be engaged in a Diels-Alder cycloaddition with Danishefsky's diene **18**,[28] leading to cyclohexenone **19** after acidic deprotection in 64% yield. We then investigated the possibility to engage cyano-stilbene derivatives such as **14** into an oxidative photocyclization.[29] Under irradiation, *E* to *Z* isomerization would occur, allowing converting both isomers to the product. While straightforward methods now exist for the synthesis of simple disubstituted stilbenes,[30] accessing tetrasubstituted stilbenes with four different substituents as obtained in our work still constitutes an important challenge.[31] In the presence of 1.1 equivalent of DDQ in acetonitrile (0.05 M) under UV irradiation (365 nm) for 20 hours, cyano-phenanthrene **20** could be isolated in 74% yield.

A one-pot process from 1,2-diaryl substituted cyclopropenes allowed to directly access the corresponding PACs (Scheme 4, see SI for details). On a 0.3 mmol scale, **20** could be isolated in 80% yield. A *tert*-butyl ester, a ketone and a trifluoromethyl group in position 1 of the cyclopropene led to phenanthrenes **21**, **22** and **23** in 51-75% yields. Both electron-donating and -withdrawing substituents in *para* position of both aromatic groups were well tolerated, delivering products **24**-**27**. Substitutions in *ortho* and *meta* positions were also tolerated (**28**-**31**). A 1-thienyl substituted cyclopropene gave heteroaromatic product **32** in 61% yield.

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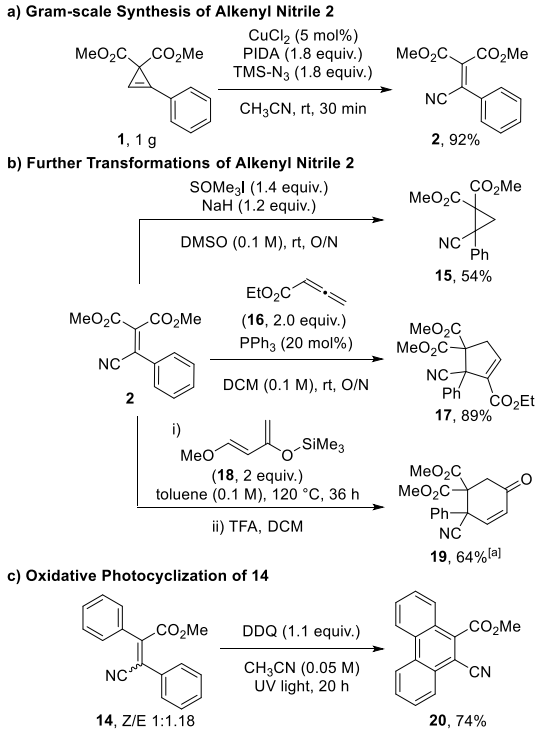
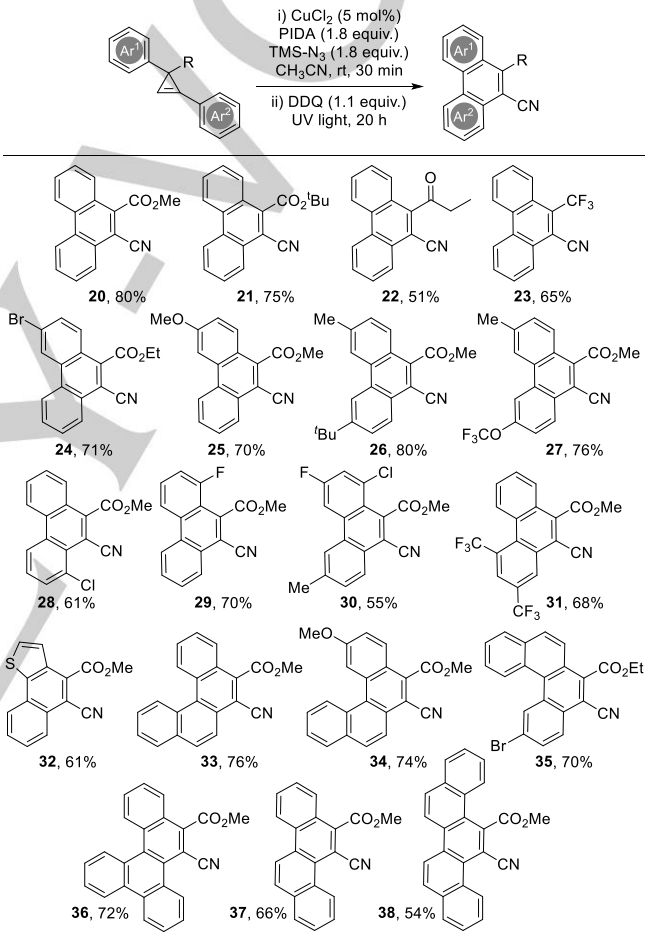


Scheme 3. Gram-scale synthesis of **2** and further functionalizations of alkenyl nitriles **2** and **14**. [a] Isolated as a 4.2:1 mixture of regioisomers, major regioisomer drawn.

We then investigated the synthesis of extended PACs. Cyclopropenes substituted with 2-naphthyl groups gave functionalized [4]helicenes **33**-**35** in good yields. Chrysene and benzo[g]chrysene derivatives could also be accessed (products **36** and **37**). Substituted picene **38** was obtained in a slightly lower yield of 54%. For all the substrates, full conversion of the starting material towards the corresponding alkenyl nitriles was observed. Hence when lower yields were obtained, the oxidative photocyclization was the limiting step.

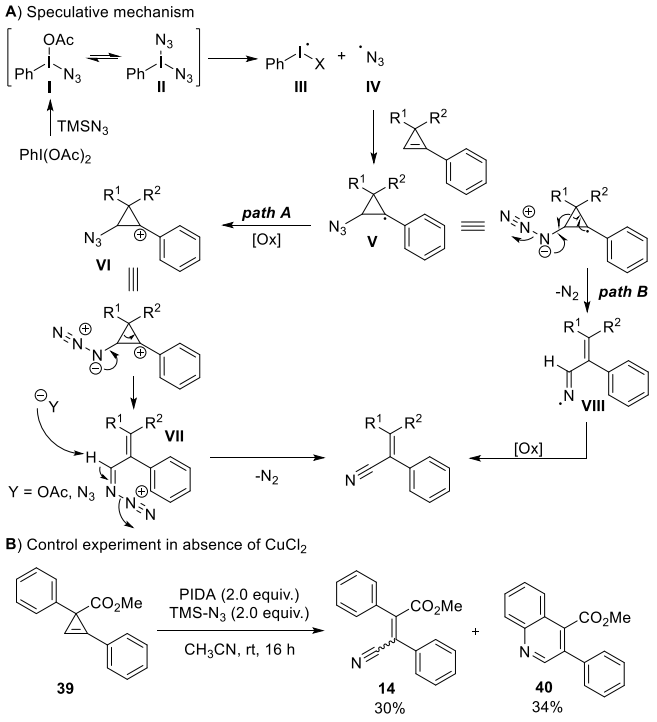
Based on experimental observations and literature precedence in the use of azides to generate nitrile-containing compounds,[32] a speculative mechanism can be proposed (Scheme 5A). The reaction of PIDA with TMS-N_3 would lead to the formation of unstable hypervalent iodine compounds **I** and **II**, which will dissociate into a iodanyl and an azide radical **III** and **IV**.[22, 33] **IV** would most likely add onto the C-C double bond of the cyclopropene to generate azido-cyclopropyl radical **V**.[34] Two different paths can then be proposed. In path A, cyclopropyl radical **V** would be oxidized to cyclopropyl cation **VI**, probably by an hypervalent iodine intermediate. From the latter a ring-opening rearrangement initiated by the azide group would occur, leading to the formation of **VII**. From **VII**, a base-mediated (azide or acetate)[35] fragmentation would then lead to the alkenyl nitrile upon loss of nitrogen.[36] Another possibility from intermediate **V** would be a direct rearrangement triggered by the azide group with loss of nitrogen to give iminyl radical **VIII** (path b).[37] The rearrangement of cyclopropyl to allyl radicals is a relatively easy process, with an energy barrier of only 22 kcal/mol for the cyclopropyl radical.[38] In this case, coupling it with nitrogen release may even lower further the activation energy, although this remains highly speculative. From this intermediate, oxidation, most probably by hypervalent iodine reagent intermediates **I** or **II**, would give the nitrile product.[39]

The role of the copper catalyst is still unclear. When the reaction was performed with cyclopropene **39** in absence of $CuCl_2$ (Scheme 5B), alkenyl nitrile **14** could be still isolated in 30% yield, but quinoline **40** was also obtained in 34%. Quinoline **40** may be formed by addition of the iminyl radical in intermediate **VIII** onto the benzene ring, followed by oxidation and rearomatization. Its formation therefore further support path **b** of the proposed mechanism. One role for copper may be to recombine with the imine radical, preventing cyclization and facilitating formation of the nitrile via deprotonation, eventually after oxidation by the hypervalent iodine reagent.[40]



Scheme 4. Scope of the one-pot radical amination / oxidative photocyclization. Reaction conditions: 0.3 mmol scale.

In conclusion, we have developed a radical amination/ring-opening of cyclopropenes using azides as nitrogen source. This transformation constitutes the first example of addition of an *N*-centered radical onto cyclopropenes and is one of the few reports of a ring-opening event after a radical functionalization of the unsaturated bond. The obtained tetrasubstituted alkenyl nitriles could be further engaged in several transformations. In the case of 1,2-diaryl-substituted cyclopropenes, a one-pot process could be developed to access highly functionalized PACs. This methodology therefore provides a new way to use cyclopropenes as starting materials for the synthesis of valuable nitrile-containing scaffolds using commercially available reagents.



Scheme 5. Speculative mechanism and control experiment in absence of copper catalyst with cyclopropene **39**.

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Keywords: cyclopropenes • amination • radicals • nitriles • polycyclic aromatic compounds

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[25] The structure of **9** was confirmed by X-ray analysis. Deposition Number 2027422 (for **9**) contain the supplementary crystallo-graphic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

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[40] We thank a reviewer for suggesting us this pathway for the conversion of the imine radical to the nitrile product.

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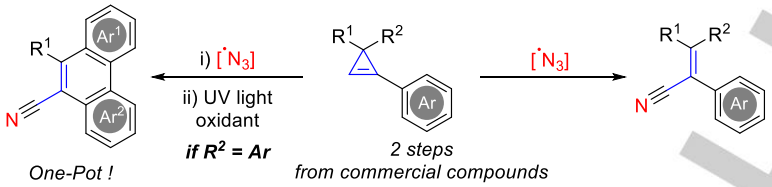

A radical amination of cyclopropenes has been developed. The transformation proceeds through a cleavage of the three-membered ring and provides access to alkenyl nitriles, without the need of an external cyanide source. With 1,2-diaryl substituted cyclopropenes, a one-pot process could be developed to access a wide range of highly functionalized polycyclic aromatic compounds.

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