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TUTORIAL REVIEW

Activation of aminocyclopropanes via radical intermediates

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Aminocyclopropanes are versatile building blocks for accessing high value-added nitrogen-containing products. To control ring-opening promoted by ring strain, the Lewis acid activation of donor-acceptor substituted systems is now well established. Over the last decade, alternative approaches have emerged proceeding via the formation of radical inermediates, alleviating the need for double activation of the cyclopropanes. This tutorial review summarizes key concepts and recent progress in ring-opening transformations of aminocyclopropanes via radical intermediates, divided into formal cycloadditions and 1,3-difunctionalizations.

Key learning points

The readers of this review will learn about:

(1) The modern ways of generating nitrogen-centered radicals or radical cations.

(2) The activation of less reactive aminocyclopropanes such as *N*-cyclopropylamides.

(3) The recent development of formal (3+2) cycloadditions of aminocyclopropanes.

(4) The efficient 1,3-difunctionalization of aminocyclopropanes in a one-pot fashion.

(5) The role of asymmetric catalysis in controlling stereochemistry in ring-opening reactions of aminocyclopropanes.

1. Introduction

Aminocyclopropanes, as an important class of nitrogen-containing compounds, have been intensively studied both as rigid structural elements in medicinal chemistry[1] and as precursors for accessing more complex scaffolds.[2] Despite the significant amount of strain energy inherent to the cyclopropyl ring, aminocyclopropanes are usually stable under standard conditions of temperature and pressure. Therefore, reagents or catalysts are required to promote C-C bond cleavage. Early studies mainly focused on Lewis acid (LA) activation of Donor-Acceptor (DA) systems (Scheme 1A)[3] or transition-metal catalysts[4, 5] (Scheme 1B). The former is usually based on heterolytic bond activation, whereas the latter involves directing group-mediated oxidative addition onto the C-C bond. Established since a long time but neglected for synthetic applications, formation of a nitrogen-centered radical (Scheme 1C) has also been shown to promote rapid opening of the cyclopropyl ring, with a rate constant of $>10^7$ s^{-1}.[6-8] This reaction has been used as a radical clock to detect nitrogen-centered radical cations in enzymatic amine oxidations and related chemical systems.[9-18] Radical processes involving the ring-opening of aminocyclopropanes also play a significant role in regulating biological functions. For instance, single electron oxidation of 1-aminocyclopropanecarboxylic acid (ACC) by the enzyme ACC oxidase produces ethylene in plants, which is an important phytohormone.[19-21] Another example is the antidepressant drug *trans*-2-phenylcyclopropylamine, which functions by reaction of a primary radical formed after a ring-opening reaction to form a covalent bond with oxidative enzymes.[22-27]

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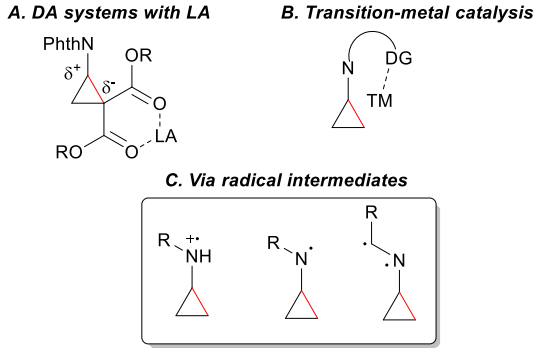
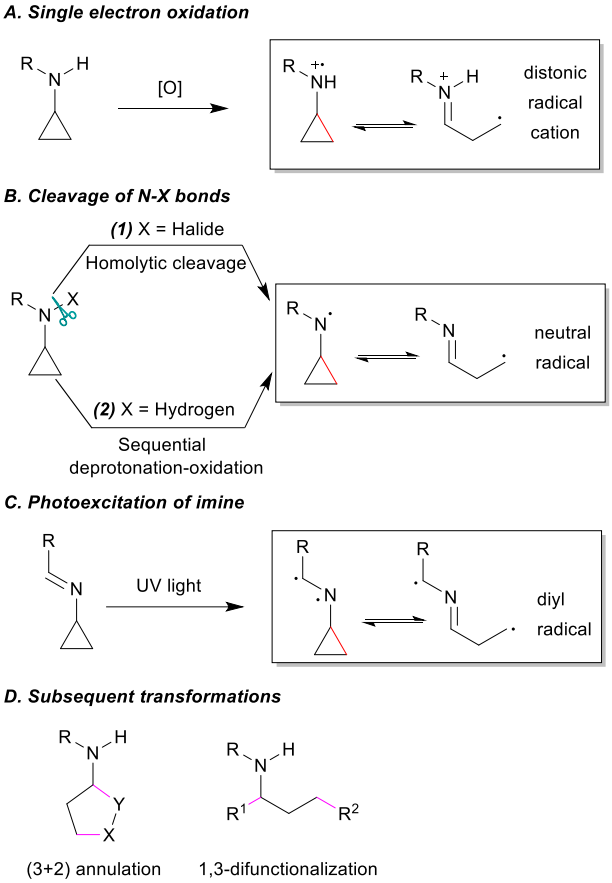


Scheme 1 Current strategies for the activation of aminocyclopropanes

In the last two decades, synthetic chemists have finally realized the potential of radical-mediated ring opening of aminocyclopropanes to develop new reactions for the synthesis of building blocks. Various approaches for generating a nitrogen-centered radical or radical cation species have been developed depending on the substrate structure (Scheme 2): A) Single electron oxidation of the nitrogen atom by a stoichiometric chemical oxidant or photoredox/electrochemical catalysis; B) Homolytic cleavage of a weak N-X bond or sequential deprotonation-oxidation; C) Photoexcitation of a cyclopropyl imine to its diyl state. Initiated by the nitrogen-centered radical or radical cation, a facile ring opening then takes place spontaneously to afford a distonic radical cation, a carbon neutral radical or a diyl radical. Then these carbon radicals can participate in formal (3+2) cycloadditions with π systems to form five-membered products or 1,3-difunctionalization reactions with radical trapping reagents and suitable nucleophiles to yield α,γ-difunctionalized amines (Scheme 2D).

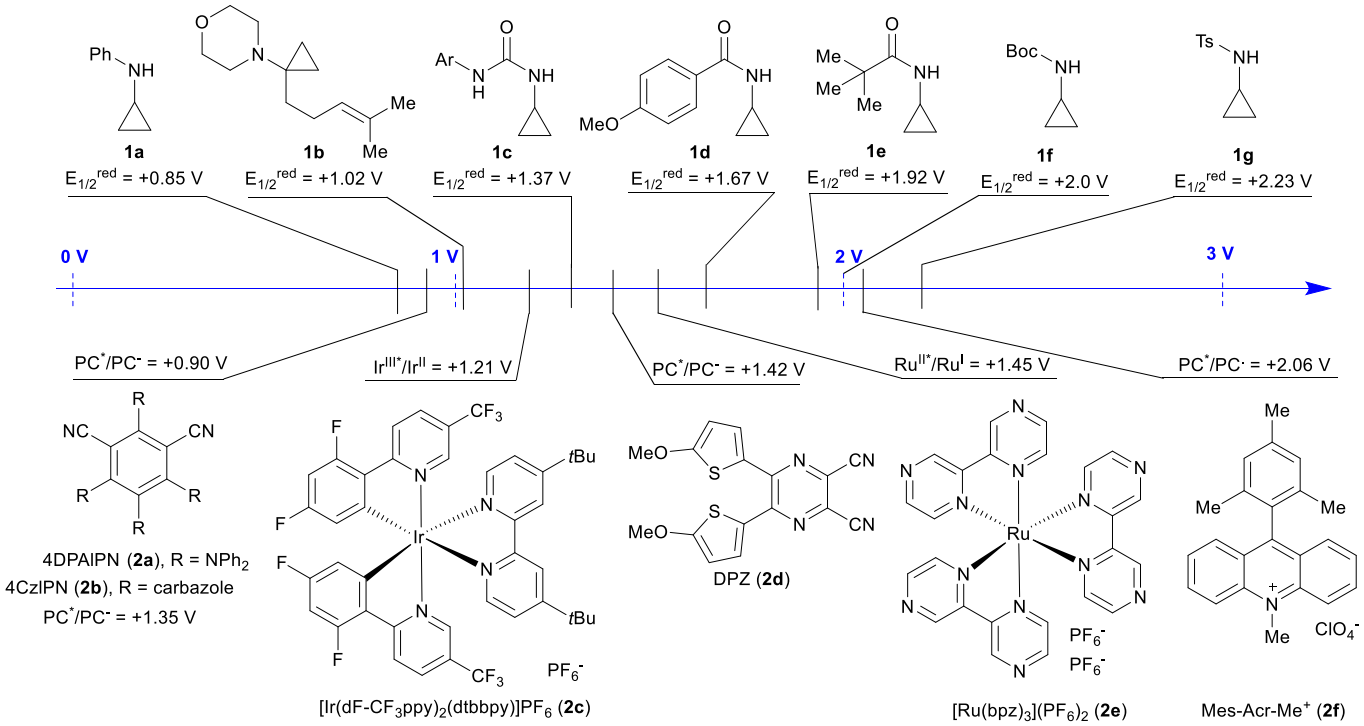


Scheme 2 Activation of aminocyclopropanes and major types of transformations via radical intermediates.

From the three different approaches, the first one has been most often applied. It is indeed known that amino groups can be easily oxidized to radical cationic species, especially when the substituents on the nitrogen atom are aryl or alkyl groups.[28] For example, the redox potential of *N*-cyclopropylaniline **1a** was measured to be + 0.85 V vs SCE in MeCN[29] (Scheme 3), indicating that it is easy to be oxidized to form a nitrogen-centered radical cation. In fact, exposure of *N*-cyclopropylanilines to air under ambient conditions is known to cause oxidation and fragmentation.[30] The redox potential of morpholine substituted cyclopropane **1b** was measured to be +1.02 V.[31] However, when the nitrogen atom is protected in the form of a urea (**1c**), amide (**1d-e**) or carbamate (**1f**), its redox potential increases substantially.[32,33] Therefore, if photocatalytic methods are used, photoredox catalysts **2a-f** with increasing oxidation potentials are needed**.** For the most electron-poor substrates such as sulfonamide (**1g**) ($E_{1/2}$ = +2.23V),[34] the deprotonation-oxidation strategy illustrated in Scheme 2B was usually employed. The sulfonamide anion obtained after deprotonation can then be more easily oxidized by a photocatalyst.

This review will describe the evolution of radical-based methods for the activation of aminocyclopropanes, starting with pioneering works and focusing then on the most recent breakthroughs. While early efforts in this field focused mainly

on *N*-aryl or *N*-alkyl substituted aminocyclopropanes, the activation of more challenging substrates such as *N*-acyl, *N*-sulfonyl or *N*-carbamate aminocyclopropanes has been successful recently. Moreover, catalytic reactions have been realized and, in some cases, enantioselective variants were developed. The review is structured based on the two major types of reactions that have been developed: (3+2) formal cycloadditions will be described first, followed by 1,3-difunctionalization reactions giving non-cyclic products.

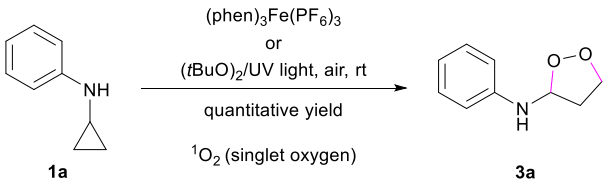


Scheme 3 Redox potentials of representative aminocyclopropanes and photoredox catalysts discussed in this review

2. Formal (3+2) cycloadditions

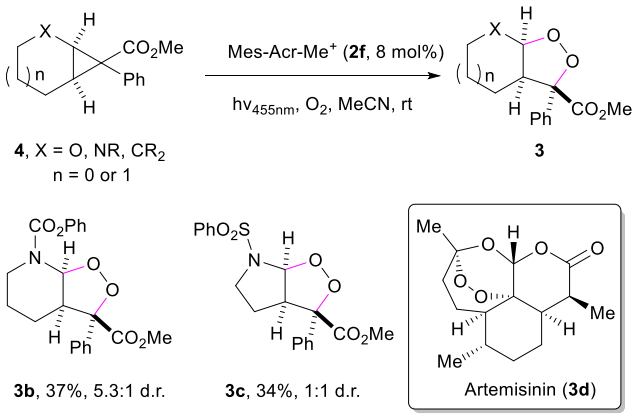
2.1 (3+2) Annulations with singlet oxygen

A 1,2-dioxolane species, arising from a formal (3+2) cycloaddition between an *N*,*N*-dialkyl substituted aminocyclopropane and molecular oxygen, was first proposed as a likely intermediate in 1975 for explaining the formation of ring-expanded epoxy ketones.[35,36] However, it was not isolated until 2001 when the Wimalasena group employed an iron(III) catalyst as single-electron oxidizing reagent for the (3+2) cycloaddition of **1a** and oxygen to give peroxide **3a** (Eq. 1).[37] Interestingly, the Six group found in 2003 that purification of *N*-(4-phenoxyphenyl)aminocyclopropane by flash column chromatography on silica gel can also afford the corresponding α-amino endoperoxide, probably due to the activating effect of silica gel.[38] Electrochemical aerobic oxidation was employed in 2007 by the Six and Buriez group to realize the same transformation. The advantage of this method is that the applied potential can be finely adjusted for each substrate.[39]



Equation 1 Formal (3+2) cycloaddition of *N*-cyclopropyl aniline (**1a**) with molecular oxygen.

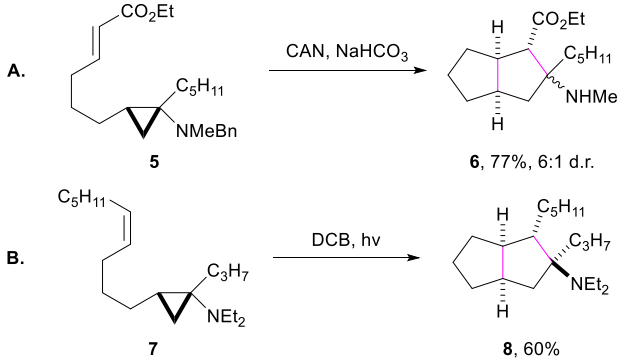
In 2020, the Reiser group found that a series of DA cyclopropanes can be oxidized by 9-mesityl-10-methylacridinium perchlorate (Mes-Acr-Me$^+$, **2f**) under blue light irradiation.[40] In this work, DA aminocyclopropanes **4** could be used, affording polycyclic endoperoxides **3b-c** as products (Scheme 4). The obtained endoperoxides might be interesting in medicinal chemistry, given their close analogy to the active principle of approved drugs such as artemisinin (**3d**).



Scheme 4 Formal (3+2) cycloaddition of DA cyclopropanes **4** with molecular oxygen.

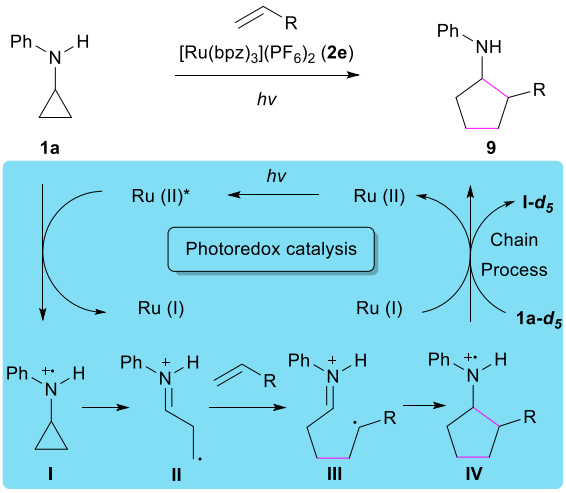
2.2 (3+2) Annulations with alkenes

In 1998, the Iwata group and the Cha group independently reported intramolecular (3+2) annulations of *N,N*-dialkyl substituted aminocyclopropanes with a pendant π C = C bond.[41, 42] The Iwata group used several equivalents of ceric ammonium nitrate (CAN) as oxidant and the *N*-benzyl group in **5** was shown to be crucial in this reaction – its rapid cleavage gave rise to the secondary amine **6** as product, which is more resistant to further oxidative decomposition (Scheme 5A). The Cha group used 1.5 equivalents of 1,4-dicyanobenzene (DCB) under irradiation with a medium-pressure mercury lamp as the oxidizing system and a tertiary amine **8** was obtained as product (Scheme 5B).



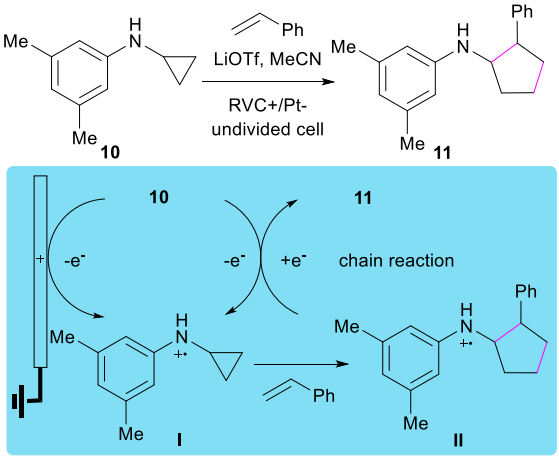
Scheme 5 Intramolecular formal (3+2) cycloaddition of *N,N*-dialkyl aminocyclopropanes **5** and **7** with a tethered alkene.

In 2012, the Zheng group reported a photocatalytic intermolecular (3+2) annulation of cyclopropyl anilines with alkenes (Scheme 6).[29] A photoredox process was initially proposed for this reaction: Under visible light irradiation, $[Ru(bpz)_3]^{2+}$ is excited and takes one electron from substrate **1a** to form radical cation **I**. The following β-scission gives a distonic radical cation **II**, which further reacts with an alkene to yield **III**. After intramolecular addition of the carbon radical to the iminium, the resulting radical cation **IV** oxidizes $[Ru(bpz)_3]^{+}$ to $[Ru(bpz)_3]^{2+}$ and closes the catalytic cycle to give **9**.



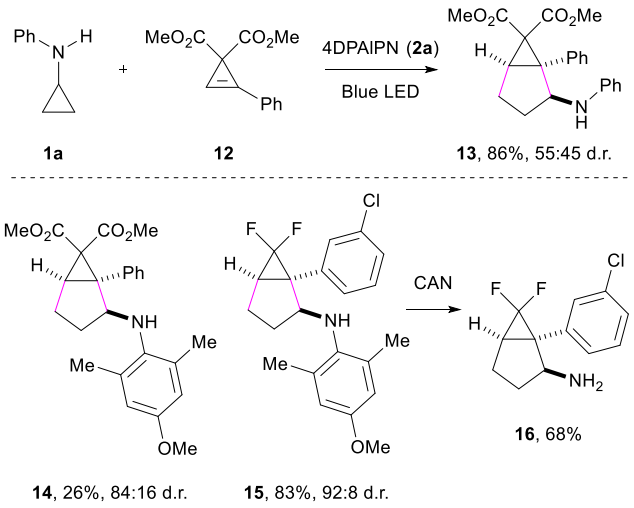
Scheme 6 Formal (3+2) cycloaddition of cyclopropyl aniline **1a** with olefins enabled by photoredox catalysis.

In 2017, the Zheng group collaborated with the Chen group to study the detailed mechanism of this reaction by electrospray ionization mass spectrometry (ESI-MS) in combination with online laser irradiation of the reaction mixture.[43] Radical cations **I** and **II**, as well as the reduced photocatalyst $Ru(I)(bpz)_3^{+}$ were all detected and their structure supported by high-resolution MS. Moreover, by mixing the post-irradiation reaction solution with deuterated cyclopropyl aniline **1a-*d*$_5$** from a second channel without light irradiation, the product arising from the isotope-labelled substrate **I-*d*$_5$** was detected, thus indicating the involvement of radical chain mechanism in the (3+2) annulation (Scheme 6). In 2021, these two groups further collaborated with the Zare group to study an electrochemical process for the annulation of cyclopropane **10** with styrene to give **11** (Scheme 7).[44] Similar to the visible-light-mediated (3+2) annulation, mechanistic studies performed on an electrochemistry/mass spectrometry (EC/MS) platform suggested a chain mechanism.



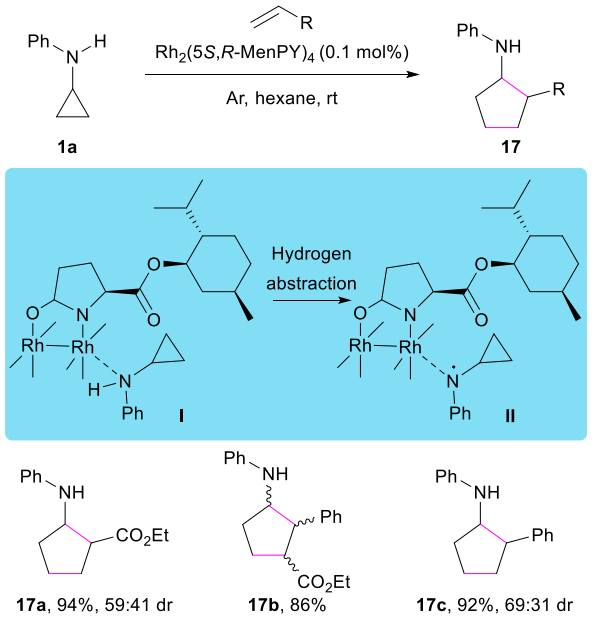
Scheme 7 Electrochemical process for the (3+2) annulation of *N*-cyclopropyl aniline **10** with styrene.

Inspired by the work from the Zheng group, we reported in 2019 an intermolecular (3+2) annulation of cyclopropyl aniline **1a** with cyclopropene **12** for the synthesis of bicyclo[3.1.0]hexane **13** (Scheme 8).[45] 4DPAIPN (**2a**), a less oxidizing ($E_{1/2}$ (*PC/PC$^-$) = +0.90) but stronger reducing ($E_{1/2}$ (PC/PC$^-$) = −1.65) photocatalyst than the more frequently used 4CzIPN (**2b**), was found to be the most general catalyst for the reaction. For most substrates, low to moderate diastereoselectivity was observed like for **13**. However, by putting two methyl groups at the *ortho* position and a methoxy group at the *para* position of the aniline, the diastereoselectivity was increased significantly when comparing **14** to **13**. The diastereoselectivity and yield were further increased when difluorocyclopropenes were used as a reaction partner, as shown in the case of **15**. The advantage of this protecting group is that it can be easily removed by oxidative cleavage with CAN, releasing free amines like **16**.



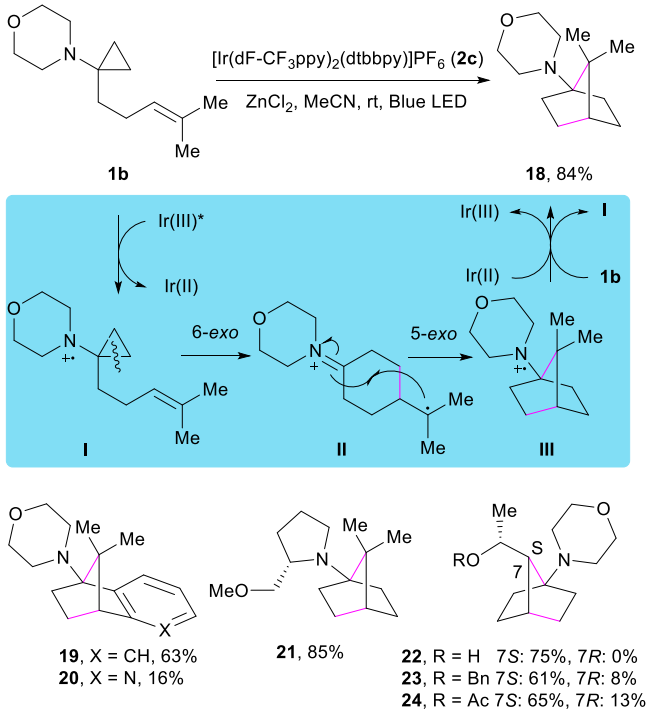
Scheme 8 Photoredox catalyzed formal (3+2) cycloaddition of *N*-cyclopropyl anilines with cyclopropenes.

In 2018, the Wang group disclosed a (3+2) annulation between *N*-cyclopropyl aniline (**1a**) and alkenes to give cyclopropylamines **17**, resulting from a new activation mode with a dirhodium (II) complex (Scheme 9).[46] In their studies, UV/VIS spectra showed a shift from 665 to 592 nm for the characteristic band of Rh_2 π* to Rh_2 σ*, indicating that there was a coordination of dirhodium (II) to **1a**. In addition, UV/vis spectra analysis showed no change in the oxidative state of dirhodium (II). Therefore, they suggested that the formation of complex **I** may decrease the bond dissociation energy of the N-H bonds in *N*-cyclopropyl aniline (**1a**), facilitating the N-H bond cleavage. The author proposed that a hydrogen atom abstraction would occur on complex **II** from an unidentified radical generated from **1a,** yielding *N*-centered radical **II**, which would undergo the formal cycloaddition. Several different types of alkenes are well tolerated in this reaction, including acrylates and styrenes (products **17a-c**). Although Rh_2(5*S*,*R*-MenPY)$_4$ is a chiral catalyst, the obtained products are optically inactive.



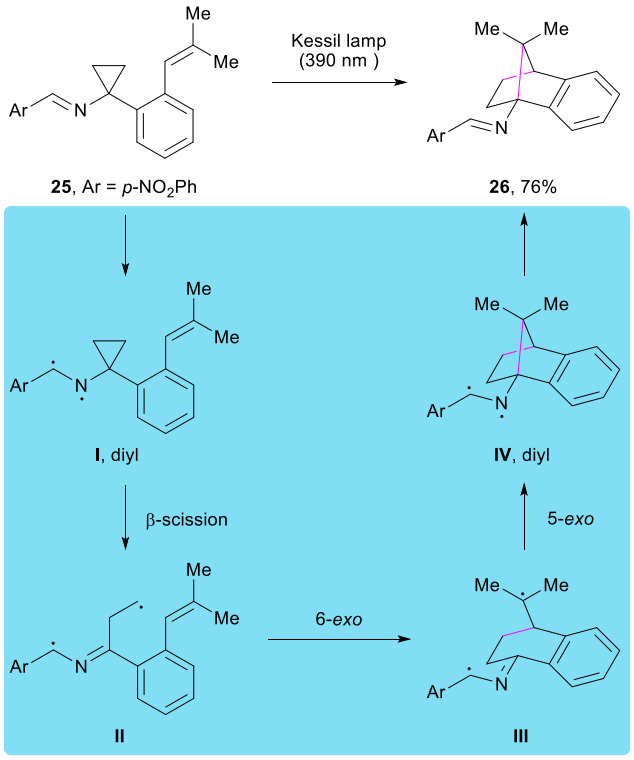
Scheme 9 Dirhodium(II)-catalyzed formal (3+2) cycloaddition of **1a** with alkenes.

Interestingly, by tethering an alkene to the C1 position of aminocyclopropanes and modifying the length of the alkyl chain, the Stephenson group synthesized 1-aminonorbornanes via a formal (3+2) cycloaddition in 2019 (Scheme 10).[31] A commonly-used iridium complex, [Ir(dF-CF$_3$ppy)$_2$dtbbpy]PF$_6$ (**2c**), was selected as the photoredox catalyst to oxidize **1b** after photoexcitation under blue light irradiation. Ring-opening of radical cation I will give **II**. After radical cyclization, the radical cation **III** could be reduced to the final product **18**. The addition of 20 mol% of the Lewis acid $ZnCl_2$ enhanced the conversion and delivered **18** in 84% yield. Other annulated 1-aminonorbonanes such as **19-20** can be accessed albeit with lower yields. The substituents on nitrogen can vary from morpholine (**18**-**20**, **22**-**24**) to pyrrolidine (**21**) or azetidine. The author also discovered that the configuration at C7 in **22-24** could be controlled by the external stereocenter. Complete selective towards 7*S* over 7*R* was observed in substrate **22** bearing a free hydroxy group.



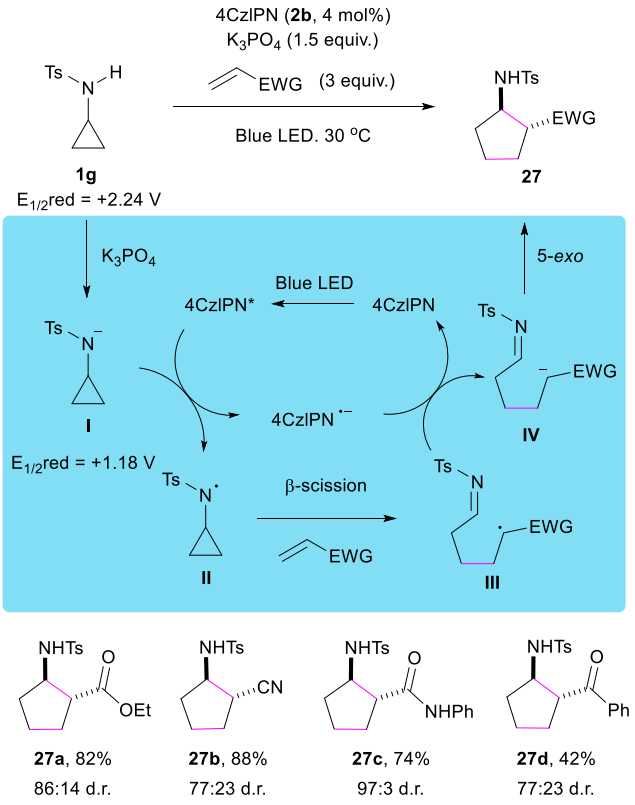
Scheme 10 Intramolecular (3+2) annulation for the synthesis of 1-aminonorbornanes **18**-**24**.

Also in 2019, they reported another method for the synthesis of 1-aminonorbornanes **26** by exploiting imine photochemistry for generating N-centered radicals (Scheme 11).[47] Previous studies from the Campos group showed that *N*-cyclopropylimines easily undergo photochemical rearrangement to form 1-pyrrolines.[48] Further mechanistic studies revealed that this rearrangement involves the generation of an excited state diradical, whose decay leads to 1-pyrrolines as well as cyclopropylamine isomers.[49] The Stephenson group discovered that, however, by tethering a π C=C bond at C1 position, a formal (3+2) cycloaddition could outcompete the rearrangement to form 1-aminonorbonanes. Imine **25** can be excited by violet light to give an excited state diyl **I** (Scheme 11), whose nitrogen-centered radical character was employed to facilitate the homolytic fragmentation of the cyclopropane ring. Two new C-C bonds were formed through subsequent 6-*exo* and 5-*exo* radical cyclization steps to give **26**. This methodology requires no photocatalyst and 1-aminonorbornanes with a free amino group can be easily synthesized after removal of the Schiff base. These two complementary reports from the Stephenson group represent to date the most efficient and flexible access to 1-aminonorbornanes, which can be potentially useful in medicinal chemistry. In 2020 the Stephenson group also utilized the masked N-centered radical approach for the synthesis of aminocyclopentanes through an intermolecular (3+2) annulation between cyclopropylimines and alkenes.[50]



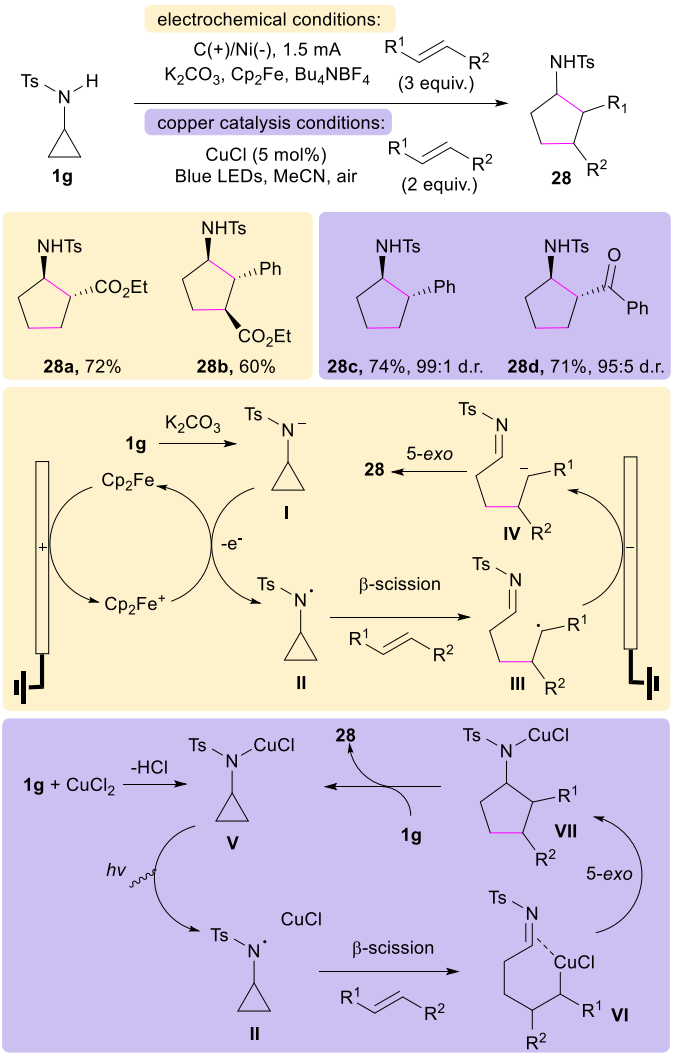
Scheme 11 Exploiting the diyl state **I** of *N*-cyclopropylimine **25** for the synthesis of 1-aminonorbornane **26**.

In 2021, the Aggarwal group reported a highly diastereoselective photoredox-catalyzed (3+2) cycloaddition of *N*-sulfonyl aminocyclopropane **1g** with electron-deficient olefins (Scheme 12).[51] Inorganic bases such as K_3PO_4 were key for success in this reaction. By performing cyclic voltammetry experiments for *N*-tosyl aminocyclopropane **1g** and its deprotonated form **I**, they found the redox potential of **1g** dropped significantly when K_3PO_4 was added (from $E_{1/2}$red = +2.24 V vs SCE in MeCN to $E_{1/2}$red = +1.18 V vs SCE in MeCN). Together with other mechanistic studies, these results suggested the single-electron oxidation of the aza-anion **I** by photoexcited 4CzIPN (**2b**) to yield a neutral nitrogen-centered radical **II**. After ring opening and radical addition, electron-poor radical **III** would be further reduced to the stabilized carbanion **IV** by the photocatalyst. A Mannich-type reaction would then give aminocyclopentane **27**. Only sulfonylated aminocyclopropanes can be used, but the alkene scope is more general, including acrylates, acrylonitriles, acrylamides and enones (products **27a-d**).



Scheme 12 Diastereoselective photoredox-catalyzed (3+2) annulation of **1g** with electron-deficient alkenes.

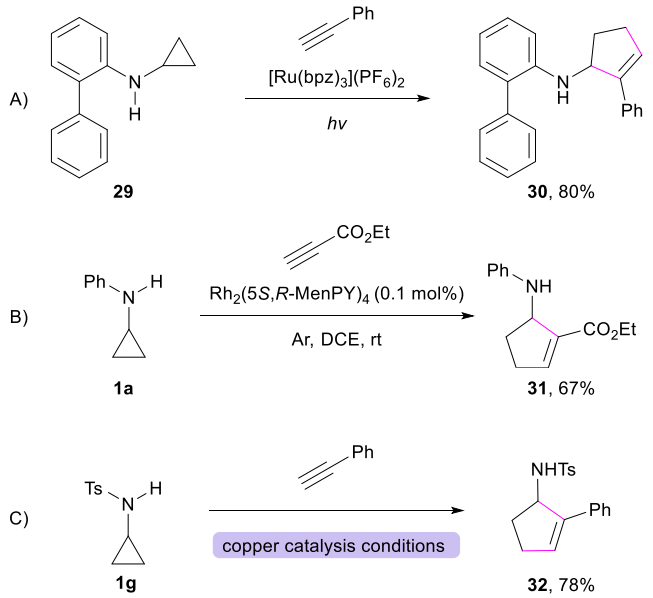
Very recently, the Banerjee group and the Reiser/Verma group independently reported a (3+2) cycloaddition of *N*-sulfonyl aminocyclopropanes with various olefins through an electrochemical strategy and visible-light-accelerated copper catalysis, respectively (Scheme 13).[52, 53] In both cases, the aminocyclopentane products **28a-d** were obtained in high diastereoselectivity and good yield. For the electrochemical process, mechanistic studies show that there was a significant improvement in the catalytic current in the presence of ferrocene (Cp_2Fe), indicating that it is probably a mediator for electron transfer. Again, a base was needed for this reaction. Similar to the mechanistic hypothesis depicted in Scheme 12, they proposed that N-centered radical **II** is formed via oxidation of the sulfonamide anion **I** by a ferrocene cation. In the work of Reiser/Verma, it was assumed that Cu(II) is the catalytically active species, which could form a transient complex **V** with **1g**. Then **V** could undergo visible light-induced homolysis to produce the N-centered radical **II**, which further recombines with CuCl and reacts with alkene to give **VI** after ring opening. Coordination of Cu(II) by the imine may account for the high diastereoselectivity of the ring-closure step.



Scheme 13 Electricity-mediated and visible-light-accelerated copper-catalyzed (3+2) annulation of **1g** with alkenes.

2.3 (3+2) Annulations with alkynes

In order to avoid the diastereoselective issue observed in the formal (3+2) cycloaddition of aminocyclopropanes with alkenes, alkynes can be used as reaction partners. In 2014, under similar conditions as in their previously disclosed intermolecular (3+2) annulation of aminocyclopropanes with alkenes, the Zheng group extended this transformation to alkynes for the synthesis of aminocyclopentene **30** (Scheme 14A).[54] In 2019, the Wang group also extended their dirhodium (II) complex catalysed (3+2) annulation of *N*-cyclopropyl aniline (**1a**) to include alkynes (product **31**, Scheme 14B).[55] The visible-light-accelerated copper-catalysis was also successful for the (3+2) cycloaddition of **1g** with alkynes (product **32**, Scheme 14C).[53]

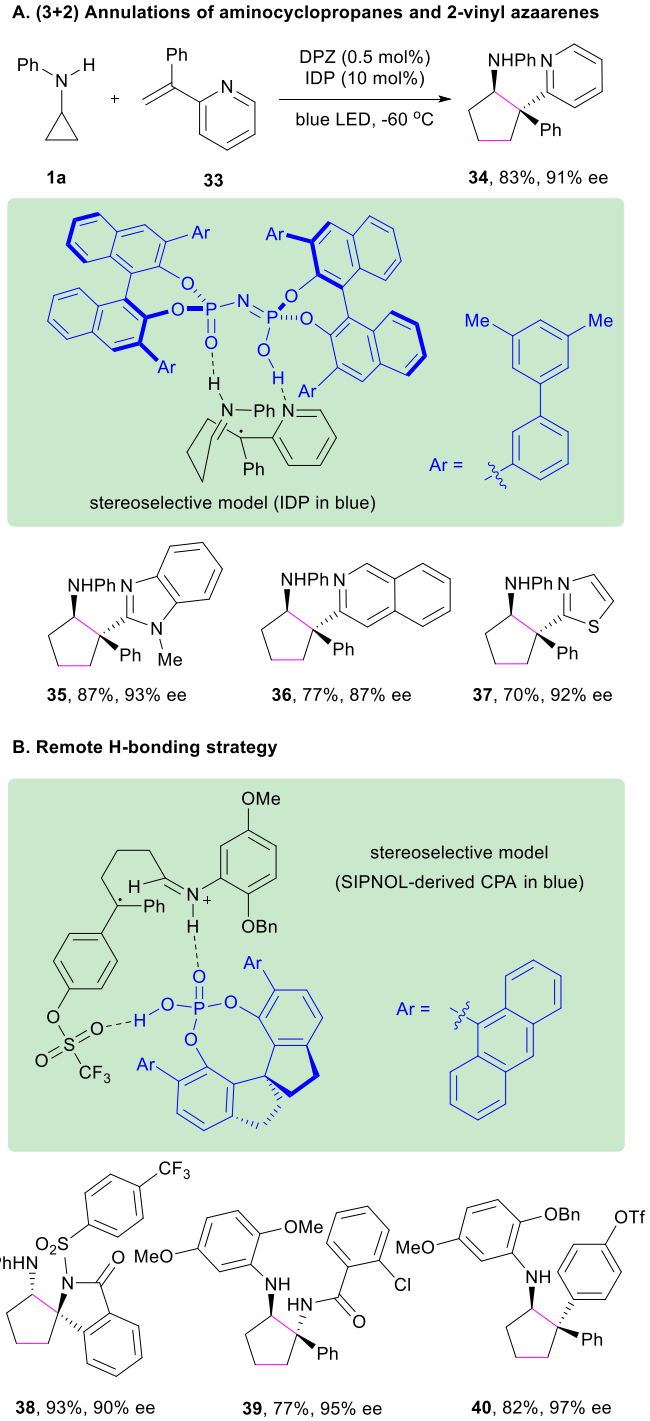


Scheme 14 (3+2) Annulations of *N*-cyclopropyl amines with alkynes.

2.4 Asymmetric (3+2) annulations with alkenes

Although racemic (3+2) annulation reactions between aminocyclopropanes and alkenes have been developed for more than two decades, their enantioselective version was not known until 2020, when the Jiang/Huang group and the Ooi group concurrently reported an asymmetric version of the formal (3+2) cycloaddition.[32,56] The lack of asymmetric catalysis in this area was probably due to the fact that it is difficult to control facial selectivity when highly reactive radical intermediates are formed.

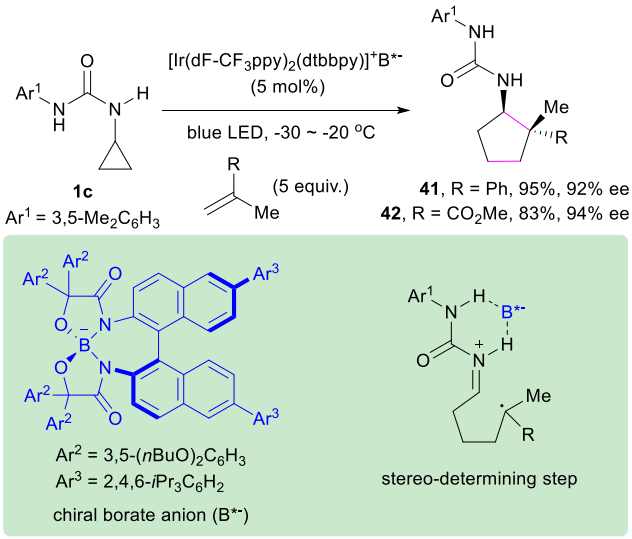
To create a more rigid chiral environment, the Jiang/Huang group chose 2-vinylazaarenes **33** as reaction partner, whose nitrogen atom can participate in hydrogen bonding interactions with a chiral Brønsted acid catalyst (Scheme 15A).[56] Under cooperative photoredox and chiral Brønsted acid catalysis, cyclopropyl anilines are oxidized by a dicyanopyrazine-derived dye (DPZ, **2d**) and the final C-C bond forming step was controlled by a C2-symmetric iminodiphosphoric acid (IDP). The azaarene in the alkene partner includes pyridine, benzimidazole, (iso)quinoline and thiazole among others. A series of cyclopentylamine derivatives **34**-**37** featuring all-carbon quaternary stereocenters α to azaarenes have been synthesized in high yields and enantioselectivities. More recently, they managed to extend the scope to electron-rich and electron-neutral olefins by developing a remote H-bonding induction strategy (Scheme 15B).[57] After extensive catalyst screening, a SPINOL-based chiral phosphoric acid (CPA) was found to be the optimal catalyst for this reaction. Various types of olefins, such as 3-methylene-isoindolin-1-one (**38**), α-phenyl ethenamine (**39**) and 1,1-diarylethlene (**40**), are well tolerated in this catalytic system although reaction conditions need to be optimized in each case.



Scheme 15 A. Asymmetric (3+2) annulation between aminocyclopropane **1a** and 2-vinyl azaarenes. B. Remote H-bonding strategy for the asymmetric (3+2) annulation between aminocyclopropanes and electron-rich/neutral olefins.

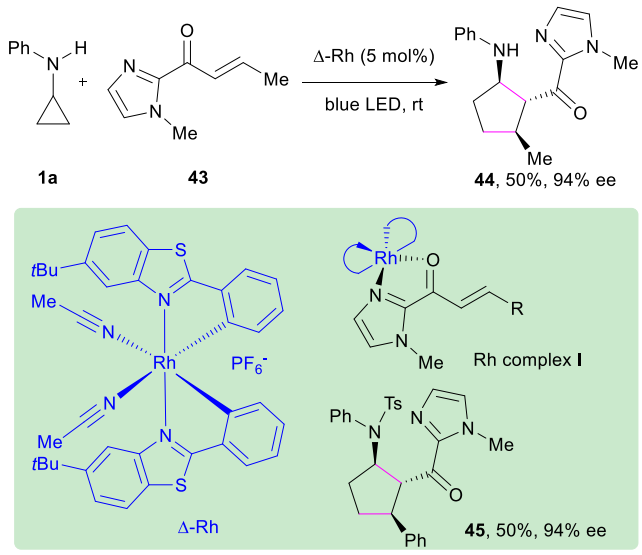
The Ooi group introduced a urea on aminocyclopropane (**1c**), which acts as a redox-active directing group with anion-binding ability (Scheme 16).[32] The design and synthesis of an iridium polypyridyl complex with a weakly coordinating chiral borate anion led to stereoselective C-C bond formation in the ring closure step through ionic interactions. This system tolerated

electron-rich alkenes (e.g. α-alkylstyrene in **41**) as well as electron-deficient ones such as α-alkyl acrylate (**42**),[58] giving access to aminocyclopentanes with quaternary stereocenters.



Scheme 16 Enantioselective (3+2) annulation between *N*-cyclopropylureas **1c** and alkenes.

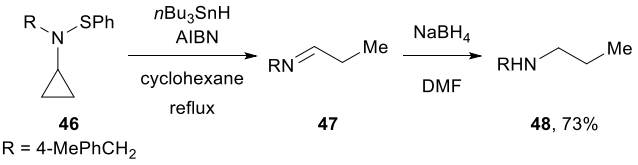
The Aleman group recently employed a chiral-at-Rhodium catalyst for an enantioselective (3+2) annulation between *N*-cyclopropyl aniline **1a** and α,β-unsaturated acyl imidazole **43** (Scheme 17).[59] This type of electron-deficient olefins coordinate to the rhodium catalyst Δ-Rh via a N,O-chelate (Rhodium complex **I**), which is the photoactive species in the system ($E[Rh^{III*}/Rh^{II}]$ = +1.38 V).[60] Products featuring three contiguous stereogenic centers such as **44** and **45** were obtained in medium yields but with high enantioselectivities. The success of this reaction depended on the substrate-catalyst complex to participate in both the photoactivation and ring closure steps.



Scheme 17 Asymmetric (3+2) cycloadditions of aniline cyclopropane **1a** enabled by a chiral-at-Rhodium catalyst.

3. 1,3-Difunctionalizations

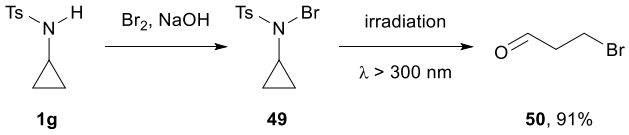
Compared to the (3+2) annulations of aminocyclopropanes with singlet oxygen, alkenes or alkynes, intercepting the distonic radical cation/neutral radical with a radical trapping reagent and a nucleophile for 1,3-difunctionalization has been less explored. In 1990s the Bowman group reported that formal dihydrogenation of N-cyclopropyl sulfenamide **46** can be achieved through homolytic cleavage of the N-S bond with radical generating reagents such as tributyltin hydride (Scheme 18).[61, 62] The nitrogen-centered radical initiated β-scission and the resulting carbon-centred radical was trapped by tributyltin hydride to form an imine product **47**, which was further reduced to **48** by $NaBH_4$ in order to facilitate its isolation. This transformation is not synthetically practical, as it is less straightforward than the classical Pd-catalysed hydrogenation conditions.



Scheme 18 Homolytic cleavage of the N-S bond in aminocyclopropane **46** using nBu_3SnH/AIBN.

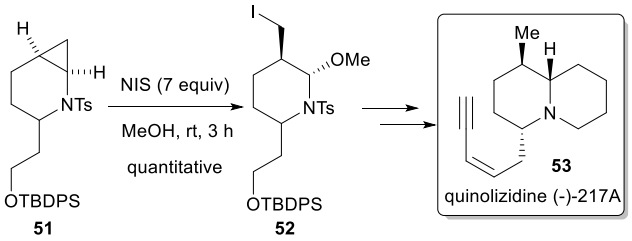
3.1 Bromination/iodination

In 1978 Dekker *et al.,* reported the photolysis of *N*-cyclopropyl-*N*-bromosulfonamide **49**, and 3-bromopropanal **50** was isolated as a result of solvolysis of the unstable imine intermediate (Scheme 19).[63] This work however, suffers from: 1) the need of one extra step for preparing the *N*-brominated substrate from **1g**; 2) requiring UV light irradiation; 3) the loss of the valuable nitrogen moiety.



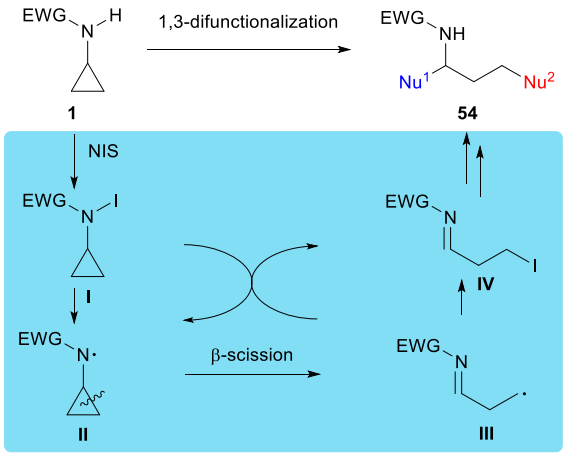
Scheme 19 Preparation and photolysis of **49**.

In 2011, during the total synthesis of quinolizidine (-)-217A (**53**), the Harrity group used excess *N*-iodosuccinimide (NIS) or *N*-bromosuccinimide (NBS) for the ring opening of aminocyclopropane **51** (Scheme 20).[64] Although a polar mechanism was suggested in analogy to the electrophilic ring-opening of cyclopropanols,[65] the reaction pathway is still uncertain due to lack of experimental or theoretical support.



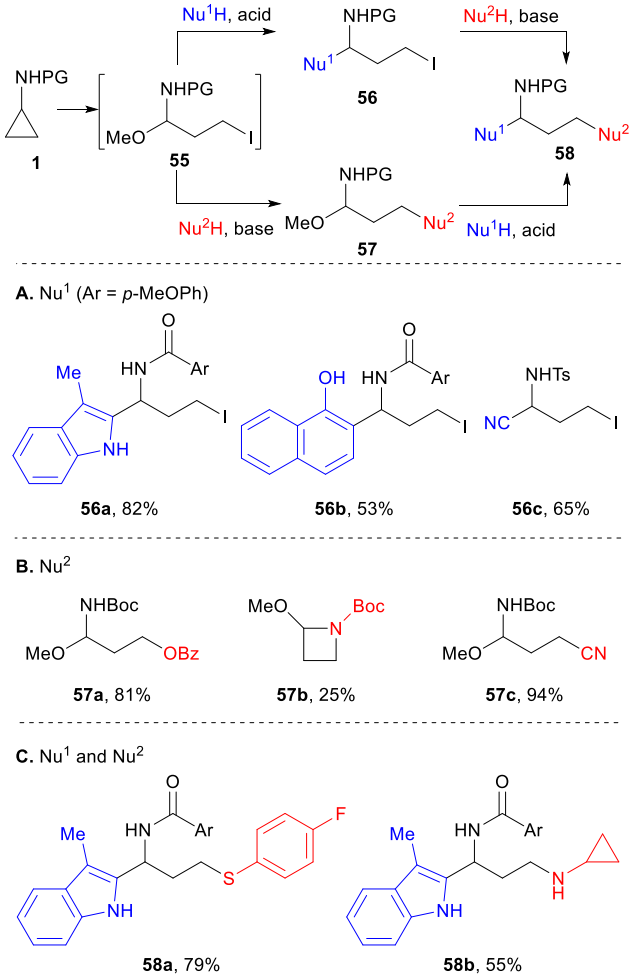
Scheme 20 Efficient ring-opening iodination in the total synthesis of quinolizidine (-)-217A (**53**).

The Hofmann-Löffler-Freytag reaction (HLF reaction) is an efficient way for the synthesis of pyrrolidines that can be carried out under mild conditions by virtue of modern modifications such as the Suárez modification.[66] The Muñiz group has also made significant contributions in this area, such as the first catalytic HLF reaction or a photoredox approach.[67, 68] In particular, the Muñiz group disclosed in 2016 an NIS promoted HLF reaction, which provided a convenient access to pyrrolidines with NIS as the only reagent.[69] In 2019, inspired by this recent progress in the HLF reaction, our group reasoned that similar conditions could be used for ring opening 1,3-difunctionalizations of aminocyclopropanes.[70] Indeed, we found that *N*-acyl, *N*-sulfonyl or *N*-carbamate protected aminocyclopropanes **1**, which are challenging substrates for single electron oxidation, can be converted into unstable N-halogenated cyclopropane **I** by mixing with NIS or NBS (Scheme 21). N-X bond cleavage would give N-centered radical **II**, followed by β-scission to **III** and recombination to give imine **IV**. It has to be mentioned that although **I** and **IV** are observed and isolated in some cases, they are unstable, and addition of nucleophiles is usually done directly *in situ* to give multi-functionalized product **54**. The radical species **II** or **III** were not detected due to their short life time. However, the ring-opening process with NBS was dependant on ambient light exposure and no diastereoselectivity was observed for the reaction with a 2-methyl substituted aminocyclopropane. These observations are indicative of a radical pathway.



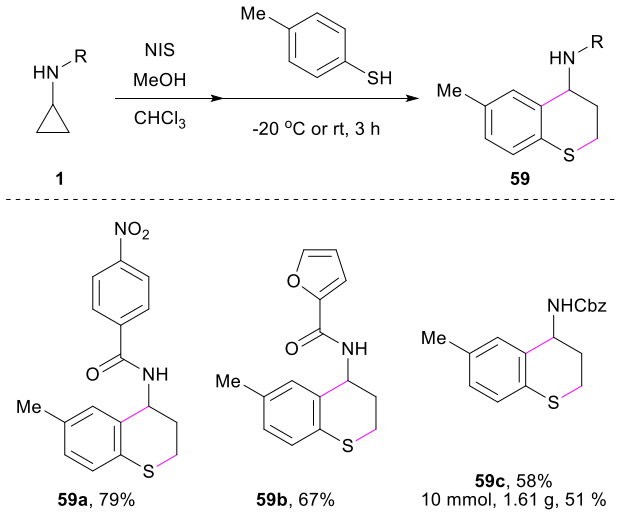
Scheme 21 NIS-promoted ring-opening 1,3-difunctionalization of aminocyclopropanes **1**.

In the presence of methanol, the unstable imine intermediates **III** are isolated in the form of hemiaminals **55**, which can be seen as biscationic synthons (Scheme 22): the methoxy group can be selectively replaced by nucleophiles under slightly acidic conditions to form iodides **56a-c** (Schemee 22A), while the iodide can be substituted by nucleophiles under basic conditions through a S_N2 pathway to form hemiaminals **57a-c** (Scheme 22B). Sequential substitution by two different nucleophiles to form 1,3-difunctionalized products **58a,b** was also possible, showing the potential of this facile ring-opening iodination for accessing rapidly multi-functionalized building blocks (Scheme 22C).



Scheme 22 Generation of biscationic synthons **55** and its use in the ring-opening 1,3 difunctionalization of aminocyclopropanes **1**.

In 2020, we further reported an efficient synthesis of 4-amino thiochromans by adding thiophenols to the in-situ formed biscationic synthon **55** (Scheme 23).[71] This transformation involves an interesting rearrangement of the isolable N,S-acetal to the final product **59**. Thiochromans **59a-c** were obtained in 51-79% yield.



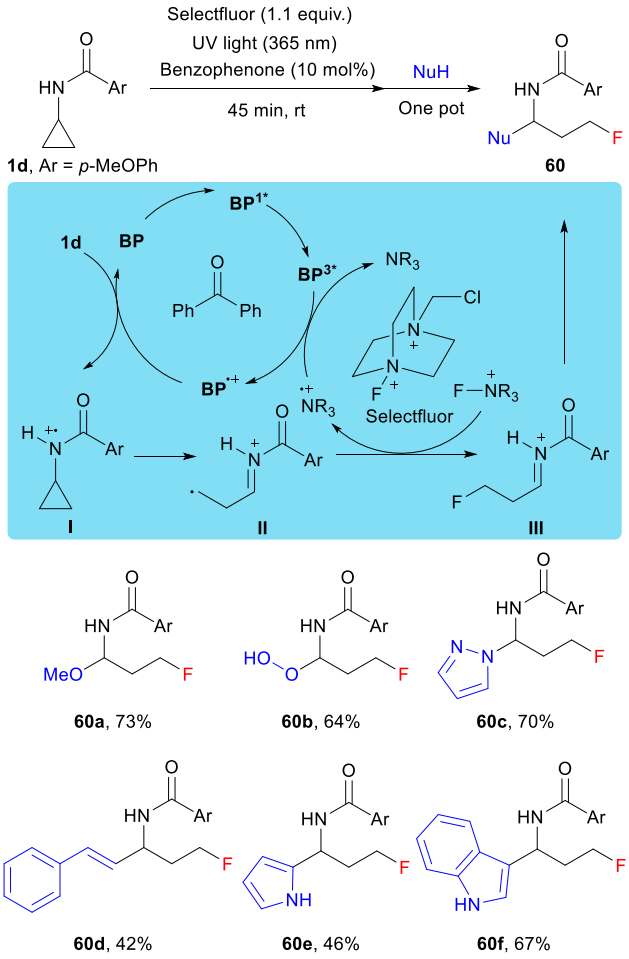
Scheme 23 Synthesis of thiochromans via biscationic synthons **55**.

The Zheng group also reported a similar ring-opening iodination of cyclopropyl anilines in 2019, with the imine trapped by a cyanide or a succinimide.[72] The Chang group described an iodine-mediated annulation reaction of N-cyclopropyl enamines for the synthesis of 1,4-dihydropyridines.[73] However, in these two examples a 2-electron, S_N2-like mechanism was proposed rather than a radical pathway, as the formation of a N-I bond was not observed by *in situ* NMR studies. However, this experiment cannot exclude a fast generation of the radical from the N-I bond, and the formed neutral nitrogen-centered radical is reported to undergo ring-opening faster than the corresponding nitrogen-centered radical cation.[74, 75]

3.2 Fluorination

Although the HLF reaction is an efficient approach for generating N-centered radicals, its application in the ring-opening reactions of aminocyclopropanes has been limited to iodination/bromination. Fluorination was not successful using this method. This can be explained by the high bond dissociation energy of a N-F bond which makes its homolytic cleavage a challenge, even if it can be formed.[76]

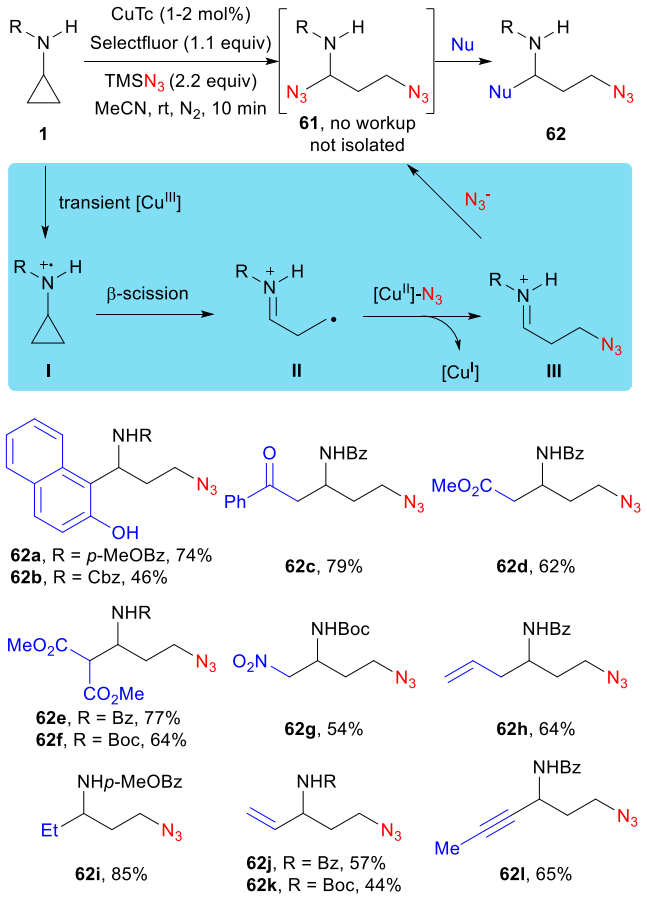
In 2020, our group realized a ring-opening fluorination using photoredox catalysis, with Selectfluor acting both as an oxidant and a fluorine source (Scheme 24).[33] During the screening of photoredox catalysts for the model reaction with *para*-methoxy benzoyl protecting group, [Ir(dF-CF_3ppy)$_2$(dtbbpy)]PF_6 (**2c**), Mes-Acr-Me$^+$ (**2f**) and benzophenone (**BP**) have been found similarly efficient, giving a fluorinated hemiaminal in 74-76% yield. A possible mechanism was proposed: A triplet state benzophenone **BP^{3*}** is formed after excitation and inter-system crossing, which can be further oxidized to a benzophenone radical cation **BP$^{\bullet+}$** by the Selectfluor-derived radical cation. The highly oxidative **BP$^{\bullet+}$** then takes one electron from **1d** to regenerate the ground state benzophenone **BP** and radical cation **I**, which undergoes β-scission, fluorination and nucleophilic attack with water to give a fluorinated hemiaminal. A series of 3-fluorinated amines **60a-f** can be accessed by substituting the hydroxy group in a one-pot manner with other nucleophiles, including alcohol, hydrogen peroxide, nitrogen-containing heterocycles, styryltrifluoroborate or electron-rich aromatic compounds. However, the substrate scope of this reaction was limited to *N*-cyclopropyl amides, as extension to *N*-cyclopropyl carbamates or sulfonamides was not successful.



Scheme 24 Benzophenone-catalyzed ring-opening fluorination of **1d**.

3.3 Azidation

The azido group can be seen as a masked amino group, as it can be easily reduced under different conditions to give the amine. Continuing our efforts in the ring-opening 1,3-difunctionalization of aminocyclopropanes, we developed in 2021 a copper-catalyzed diazidation-nucleophilic substitution cascade reaction for the preparation of 1,3-diamines (Scheme 25).[34] With the addition of $TMSN_3$ under similar photoredox conditions as developed in our fluorination project, a mixture of azidation and fluorination products was isolated and the chemoselectivity could not be further improved. After intensive screening of catalysts, we found that copper thiophene-2-carboxylate (CuTc) can catalyse efficiently the azidation of aminocyclopropanes **1** with different protecting groups (acyl, sulfonyl or carbamate), giving the diazides **61** in high yields within 10 minutes. The α-amino azide can then be replaced with various nucleophiles, such as 2-naphthol, enol ethers, malonate, nitromethane, allyltrimethylsilane, organozinc, organoboron or organomagnesium reagents to give products **62a-l** in 44-85% yield.

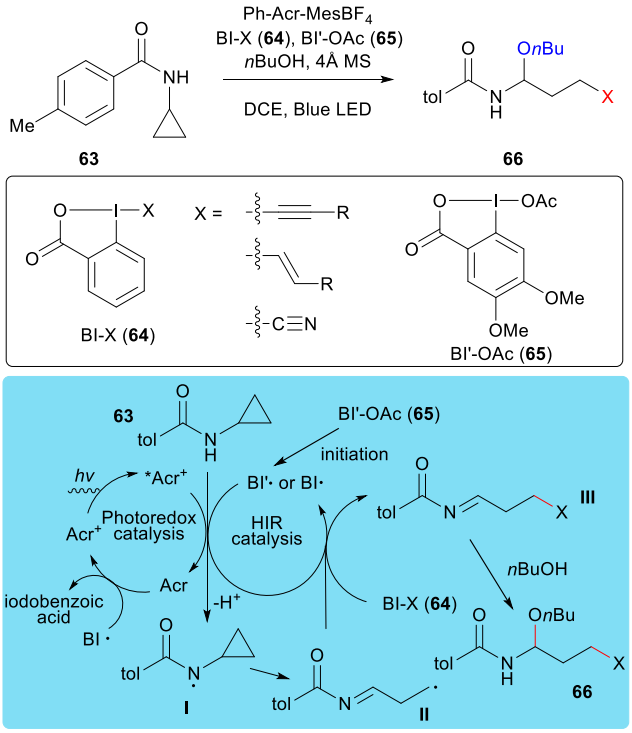


Scheme 25 Diazidation-nucleophilic substitution of aminocyclopropanes **1** for the synthesis of diamines **62**.

We proposed a speculative mechanism for the diazidation: the reaction would be initiated by the oxidation of CuTc with Selectfluor to form a fleeting Cu(III) species, which then oxidizes aminocyclopropane **1** to give a radical cation **I**. Carbon radical **II** is then formed after β-scission. In a second step, the azide could be transferred from a Cu(II)-N_3 complex to **II**, regenerating a Cu(I) complex. A rebound-type mechanism with a Cu(III)-N_3 complex first oxidizing **1** and then transferring the azide to **II** can be considered, although we have no experimental support for it. Alternatively, the generation of a free azide radical that recombines with **II** can also be envisaged, though less likely. The azidation of **II** would lead to iminium **III**, which would be intercepted by an azide nucleophile to deliver the diazidation product **61**.

3.4 Alkynylation, alkenylation and cyanation using hypervalent iodine reagents.

The Chen group reported a ring-opening alkynylation reaction of cyclopropylamide **63** with hypervalent iodine reagents (HIR) **64** under mild photoredox catalysis conditions (Scheme 26).[77] They found that a catalytic amount of the cyclic iodine(III) reagent BI'-OAc (**65**) facilitated the single electron oxidation as well as the ring-opening alkynylation of cyclopropylamide **63**. By switching to other types of HIRs **64** such as BI-styrene or BI-CN, this reaction can be extended to alkenylation and cyanation without any modifications of the reaction conditions. The less stable imine intermediates were reacted with *n*-butanol to form N,O-acetals **66** and further nucleophilic substitution of the butoxy group has been realized with indole, 1-naphthol, thiophenol etc. as nucleophiles.



Scheme 26 Ring-opening alkynylation, alkenylation and cyanation of aminocyclopropanes by hypervalent iodine reagents.

4. Conclusion

Ring-opening reactions of aminocyclopropanes through a radical pathway have been extensively investigated over the last decade. Several different activation modes were exploited in order to generate a nitrogen-centered radical or radical cation species: single electron oxidation, homolytic cleavage of a weak N-X bond and direct excitation of imine substrates. The scope is not any more limited to *N*-alkyl or *N*-aryl substituted aminocyclopropanes, even deactivated substrates with *N*-acyl, *N*-sulfonyl or *N*-carbamate protecting groups can be now employed. Due to the inherent ring strain, ring opening processes initiated by nitrogen-centered radicals rapidly yield a carbon-centred radical. Depending on the radical trapping reagents, this radical can then be engaged in two types of reactions: formal (3+2) cycloaddition (with alkenes, alkynes or singlet oxygen) and 1,3-difunctionalization (with a radical trapping reagent and a nucleophile).

In the field of (3+2) annulation in particular, photoredox was used to perform the reaction under mild conditions. By introducing a site in the substrate for coordination of a chiral catalyst, asymmetric catalysis was also realized for the first time on the formal (3+2) cycloaddition of aminocyclopropanes with alkenes. Tethering an alkene to different positions of aminocyclopropanes was shown to have a strong impact on the outcome of the radical cyclization step:

attaching it to C2 position led to a bicyclic product, while 1-aminonorbonane were accessed when it was attached to the C1 position.

Recent progress in 1,3-difunctionalization includes iodination/bromination, fluorination, azidation as well as alkynylation, and these methodologies share one common feature: A one-pot procedure, which involved ring opening reaction with radical-trapping reagents and subsequent nucleophilic addition on the masked imines. The requirement for a sequential ring-opening and nucleophile addition is due to the incompatibility of many nucleophiles with highly oxidizing reaction conditions. In many cases, successful extension to aminocyclobutanes[33,34,70,78-80] or nitrogen-substituted bicyclo[1.1.1]-pentanes[81] has been realized for synthesizing building blocks by a (4+2) annulation or a 1,4-difunctionlization reaction.

Despite these recent breakthroughs, the activation of aminocyclopropanes based on the formation of radical intermediates is still in its infancy when compared to the more mature field of donor-acceptor systems. The reaction types need to be further extended, with higher order of formal cycloadditions or other ring-opening functionalizations (arylation, alkylation, borylation etc.) to be established. Instead of employing aminocyclopropanes as suicide substrates for oxidative enzymes, repurposing their promiscuous functions for developing ring-opening reactions of aminocyclopropanes could be a fascinating field of future research. Furthermore, exploiting the imine/enamine tautomerism of ring-opened imine intermediates can also be interesting, and may result in the development of ring-opening 1,2,3-trifunctionalization reactions of aminocyclopropanes.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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