Selective Carbon-Carbon Bond Cleavage of Cyclopropylamine Derivatives

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ABSTRACT: This review summarizes synthetic developments reported from 1987 to 2019 that exploit C-C single bond cleavage of cyclopropylamine-based systems. The synthetic and mechanistic aspects of key methodologies are highlighted, and examples where aminocyclopropanes are exploited as key intermediates in multistep synthesis are also discussed. The review encompasses cases where aminocyclopropanes participate in polar reactions, pericyclic processes, radical-based reactions and C-C bond activations.

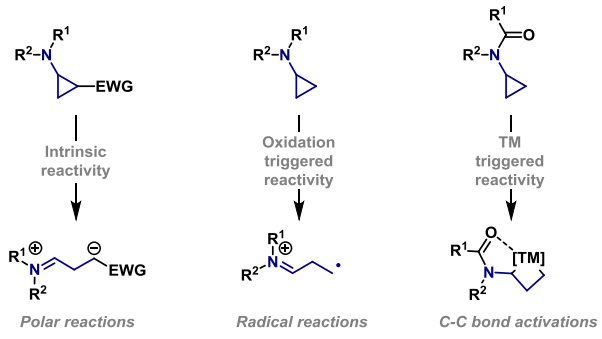
CONTENTS

1. INTRODUCTION

The strain embodied within cyclopropanes provides a powerful driving force for ring-opening reactions, and this has been exploited extensively as a design tactic in organic synthesis.[1-3] This review encompasses key developments reported from 1987 to 2019 in the specific field of cyclopropylamine-based ring-opening reactions. An in-depth overview of earlier investigations in this area has been published.[4]

Cyclopropylamines are an especially interesting class of readily available cyclopropane. Specific substitution patterns can be accessed via a range of methods, including Curtius rearrangement of cyclopropyl carboxylic acids,[5,6] (2+1) cycloadditions between carbenoids and N-alkenyl systems,[7,8] and variants of the Kulinkovich reaction.[9,10] The N-substituent of aminocyclopropanes avails a range of powerful mechanistic options for promoting ring cleavage (Scheme 1). For example, the N-lone pair provides a "push", which means that cyclopropane rings are often relatively electron rich and can behave as competent nucleophiles in certain cases. Incorporation of this feature into donor-acceptor (DA) based systems results in a highly labile cyclopropane C-C bond, and this provides many opportunities in reaction design. In addition to these polar reaction pathways, oxidation to N-centered radicals can be used to trigger β-scission en route to reactive carbon-centered radicals. Finally, the inherent strain of the cyclopropane ring enables metal-catalyzed C-C bond activation processes; here, the N-unit can be modified to facilitate and control such processes.

Scheme 1. Selected Reactivity Modes Available to Aminocyclopropane Derivatives.

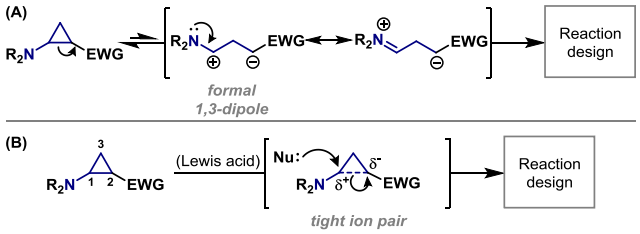


The aim of this review is to summarize the different approaches available for achieving selective C-C bond cleavage of cyclopropylamine derivatives. Some conventional and well-established methods, such as cyclopropane hydrogenation, are not discussed here, as these methods have been reviewed previously.[4,11] Reactions of cyclopropanes possessing other classes of N-based substituent (e.g. nitro-cyclopropanes) are also not covered here.

2. Methodologies Employing Donor-Acceptor Cyclopropylamine Derivatives

Cyclopropylamines equipped with electron-withdrawing groups (EWG) at the β-position function as an important subclass of donor-acceptor (DA) cyclopropanes.[12,13] For cyclopropylamine-based systems, the nitrogen acts as an electron-donating group, such that the vicinal C-C bond is strongly polarized and prone to cleavage under a range of conditions to give a 1,3-dipole (Scheme 2A). Alternatively, these strongly polarized systems can undergo direct S_N2-like ring opening, a process that is often proposed to proceed via a tight ion pair (Scheme 2B). In this scenario, α-stereochemistry present in the starting material can be transferred to the product. Usually, the C1-C2 bond between the donor- and acceptor-bearing sites of the cyclopropane unit is broken; several exceptions, where unexpected cleavage is observed, are also covered below.

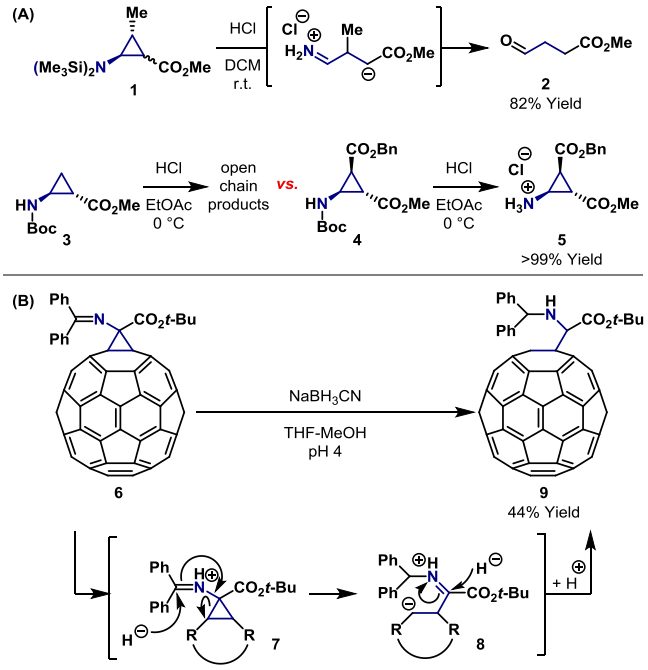
Scheme 2. Cleavage of the C-C Bond in Donor-Acceptor Cyclopropylamine Derivatives



2.1. Acid and Base Promoted Reactivity

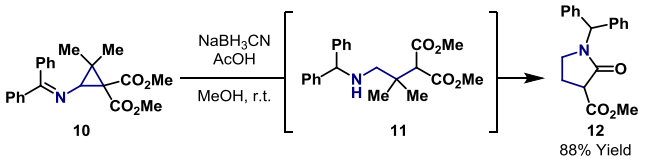
There are numerous reports where DA cyclopropylamines undergo C-C bond cleavage under acidic conditions[14-21] or even just by solvolysis in polar protic solvents[22]; often these processes provide ketones or aldehydes after hydrolysis of the resulting iminium ion (cf. Scheme 2A). For example, Reißig and co-workers[23] showed that aldehyde **2** is formed upon acid-promoted deprotection of **1**. Similarly, the Reiser group observed open chain products upon HCl-promoted deprotection of NHBoc cyclopropylamine **3**. Interestingly, under the same conditions, cyclopropylamine **4**, which contains two electron withdrawing ester groups, did not undergo ring cleavage and instead cyclopropane **5** was isolated in quantitative yield (Scheme 3A).[16] Alternatively, the iminium ion that forms upon ring cleavage can be reduced to an amine in the presence of a hydride source.[24-28] This is exemplified by Keller, Pyne and co-workers' reduction of methano[60]fullerene derivative **6**. Here, initial reduction of iminium ion **7** is followed by ring opening to give new iminium ion **8**. This then undergoes reduction and protonation to give **9** (Scheme 3B).[24,25]

Scheme 3. (A) Acid-Promoted C-C Bond Cleavage and (B) Reductive Ring Opening of DA Cylopropylamines



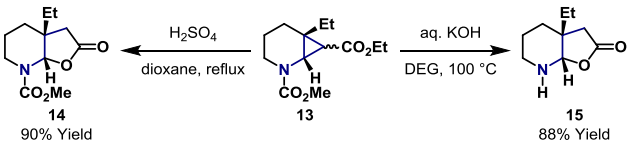
Reductive ring openings of the type shown in Scheme 3B can be exploited for the design of tandem processes. For example, De Kimpe and Mangelinckx[29] showed that exposure of **10** to $NaBH_3CN$ in AcOH results in sequential imine reduction, cyclopropane cleavage and iminium ion reduction to provide amino ester **11**. This cyclized in situ to generate γ-lactam **12** in 88% yield (Scheme 4).

Scheme 4. Reductive Ring Opening of DA Cylopropylamine with Concomitant Cyclization



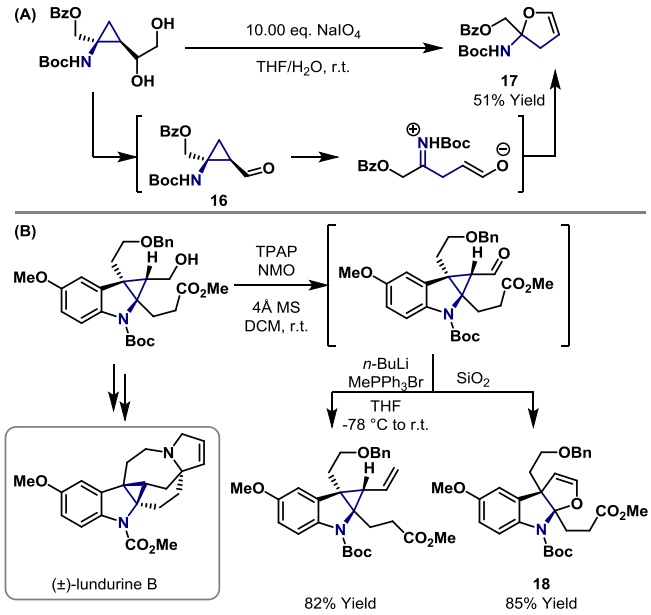
Early reports by Wenkert group[30,31] demonstrated that, under forcing conditions, both acidic and alkaline hydrolysis of ester-substituted aminocyclopropane **13** provides γ-lactones (**14** and **15**) in high yield (Scheme 5). Here, the iminium ion is intercepted by the pendant carboxylic acid or carboxylate. For **15**, the basic conditions also effected hydrolysis of the carbamate unit.

Scheme 5. Ring Opening-Lactonization Cascade



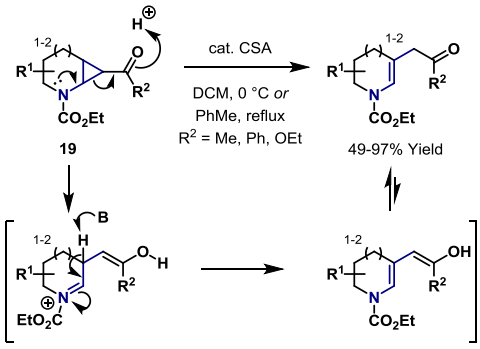
Another example of cyclization after ring-opening has been demonstrated by Rifé and Ortuño.[32] Aminocyclopropylaldehyde **16**, generated under oxidative conditions, is unstable and readily undergoes ring-opening to form a zwitterionic intermediate. In this case, cyclization occurs upon the attack of the pendant enolate to give dihydrofuran derivative **17** (Scheme 6A). This problem of aminocyclopropylaldehyde instability may be avoided by submitting it directly to subsequent reaction conditions. In the total synthesis of the indole alkaloid lundurine B by Nishida and co-workers[33] this was achieved by direct Wittig methylenation, thereby circumventing degradation to dihydrofuran **18** (Scheme 6B).

Scheme 6. Formation of Dihydrofurans from Aminocyclopropylaldehydes



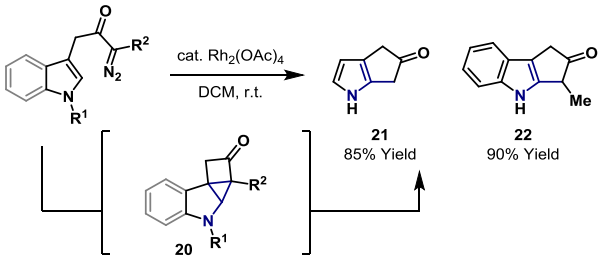
The Torii group[34] described a camphorsulfonic acid-promoted ring-opening of substrates **19** (Scheme 7). The reaction conditions were generally mild (DCM, 0 °C) for systems with a ketone at the β-position of the cyclopropylamine unit. However, when an ester was employed (R^2 = OEt) as the electron-withdrawing group, heating at reflux in toluene was required for complete reaction.

Scheme 7. Ring Opening to Enecarbamates



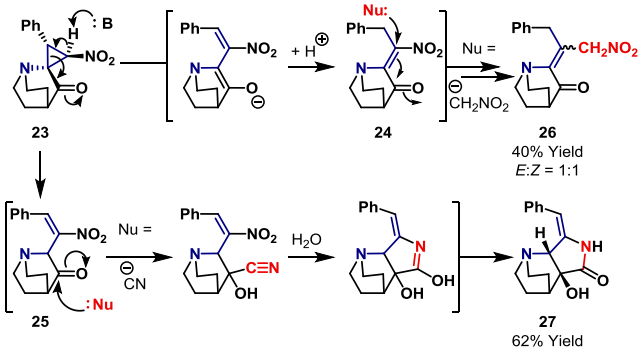
In certain cases, cleavage of the distal bond of the cyclopropylamine ring may occur instead. For example, Salim and Capretta[35] observed spontaneous ring-opening of indole and pyrrole derived cyclopropanation adducts **20** to give five-membered cyclic products, such as **21** and **22** (Scheme 8).

Scheme 8. Spontaneous Ring Opening of Cyclopropanation Adducts



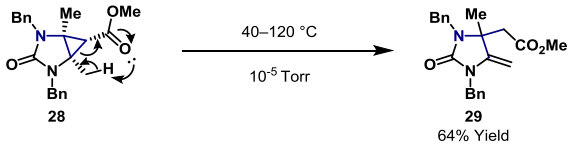
A nitro-substituted DA aminocyclopropane incorporated into the quinuclidinone core of **23** exhibited unusual reactivity, as demonstrated by Luthman and co-workers (Scheme 9).[36] Here, after ring opening to **24** or **25**, intra- or intermolecular substitution of the vinylic nitro group with various nucleophiles (amines, alkoxides, nitromethane, cyanide) gave products such as **26** and fused pyrrolidone **27**.

Scheme 9. Ring Opening of a Nitro-Substituted DA Aminocyclopropane



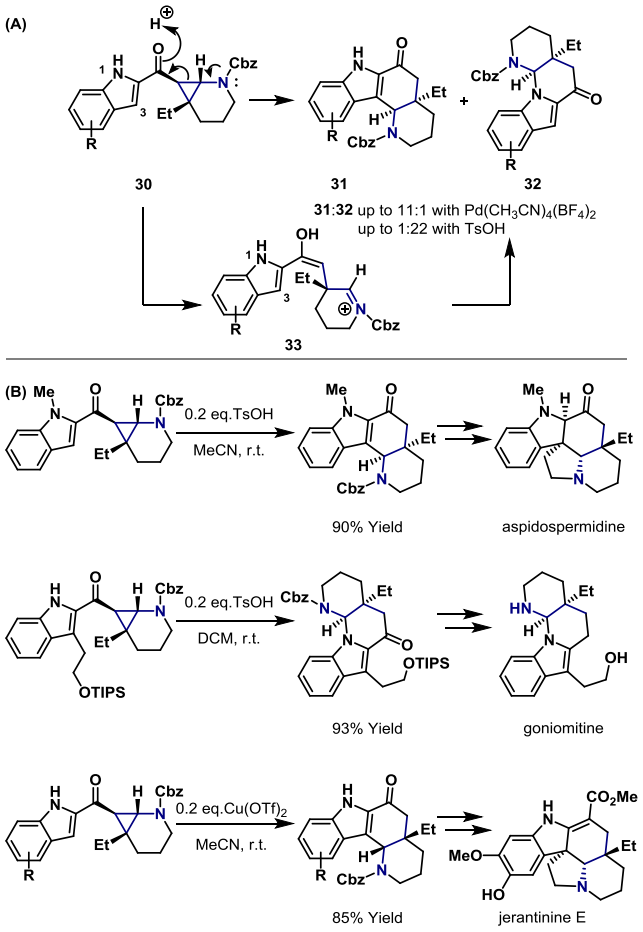
A key consideration for designing transformations that employ DA aminocyclopropanes is the stability of the starting material, which is "spring loaded" to react. Generally, the substrates are designed such that the lone pair of the nitrogen atom is delocalized, into, for example, a carbonyl group (i.e. as part of an amide, carbamate or urea). Unprotected DA cyclopropylamines are much more reactive because the nitrogen center is more efficient at stabilizing the developing positive charge during the ring-opening process (cf. Scheme 2). Indeed, DA cyclopropylamines formed by cyclopropanation of enamines were found to be so unstable that they underwent C-C bond cleavage during silica gel chromatography.[37,38] Some systems may be stable at lower temperature, but decompose upon heating. For example, under thermal conditions, **28** rearranged to **29** via a [1,5]-H shift (Scheme 10).[39]

Scheme 10. Thermal Decomposition of a DA Aminocyclopropane



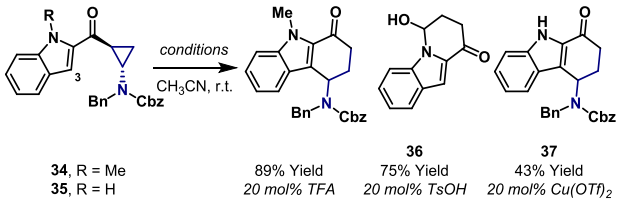
Protected DA cyclopropylamines have found use as versatile intermediates in the total syntheses of indole alkaloids. This aspect is nicely demonstrated by studies from the Waser group[40-42] where selective alkylation at different positions of tethered indoles could be achieved by fine tuning the reaction conditions or substrate. For example, cyclization via the C3 position of indole **30** was observed using soft Lewis acids (e.g. $Pd(NCCH_3)_4(BF_4)_2$) to give **31** as the major product (Scheme 11A). Conversely, Brønsted acids (e.g. TsOH) promoted cyclization via nitrogen to generate selectively **32**. It was suggested that milder Lewis acids could potentially exert an influence during the formation of the acyl iminium intermediate **33** and favor the reaction at the softer C3 position of the indole ring. Variants of these ring-opening transformations have been used in total syntheses of aspidospermidine, goniomitine and jerantinine E (Scheme 11B). Note how the regioselectivity of cyclization can be controlled by blocking the indole nitrogen with a methyl group, thereby enforcing cyclization to the C3-regioisomer for the synthesis of aspidospermidine. In the case of jerantinine E, copper(II) triflate was used as a soft Lewis acid, analogous to $Pd(NCCH_3)_4(BF_4)_2$ used in Scheme 11A.

Scheme 11. DA Cyclopropylamine Ring Opening en Route to Indole Alkaloids



The generality of the processes outlined in Scheme 11 extends to simpler acyclic carbamates (Scheme 12).[43] C-C bond-forming cyclization with N-methyl indole **34** proceeded smoothly at the C3 position simply by using trifluoroacetic acid. However, under similar conditions, N-H indole **35** cyclized via nitrogen to afford the corresponding aminal which then hydrolysed to give **36**. When the Brønsted acid was replaced by $Cu(OTf)_2$ the regioselectivity switched to C-C bond formation at the C3 position of the indole to provide **37**.

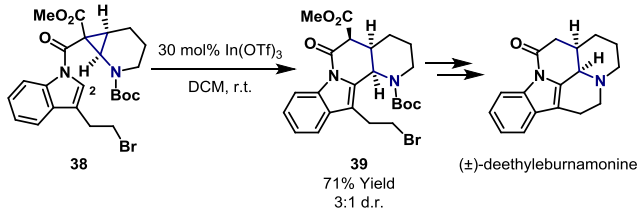
Scheme 12. Different Regioselectivity of Ring Opening Promoted Indole Cyclizations



Related cascade processes have been realized where the indole is linked via nitrogen. France and co-workers[44,45] showed that In(III)-catalyzed cyclopropane ring-opening of **38** can be used to trigger Friedel–Crafts-like alkylation at the C2 position of an indole (Scheme 13). This allowed the formation of hydropyrido[1,2-

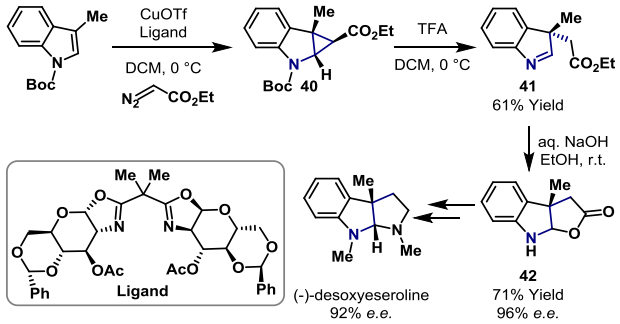
a]indole-based product **39**, a key intermediate in the total synthesis of (±)-deethyleburnamonine.

Scheme 13. DA Cyclopropylamine Ring Opening en Route to (±)-Deethyleburnamonine



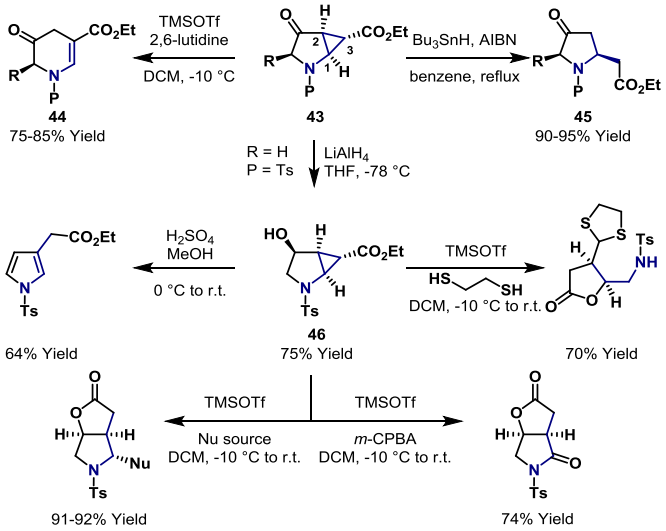
The cyclopropane unit can also be incorporated onto the core of the indole unit. Boysen and co-workers[46] demonstrated that acid-promoted cleavage of the N-Boc group of DA cyclopropane **40** led to ring opening to provide **41** (Scheme 14). This functioned as a key intermediate in the synthesis of (-)-desoxyeseroline. Substrate **40** could be accessed asymmetrically by enantioselective Cu-catalyzed cyclopropanation with ethyl diazoacetate and so this approach allowed the stereoselective installation of the challenging quaternary stereocenter of **42** (96% e.e.).

Scheme 14. DA Cyclopropylamine Ring Opening en Route to (-)-Desoxyeseroline



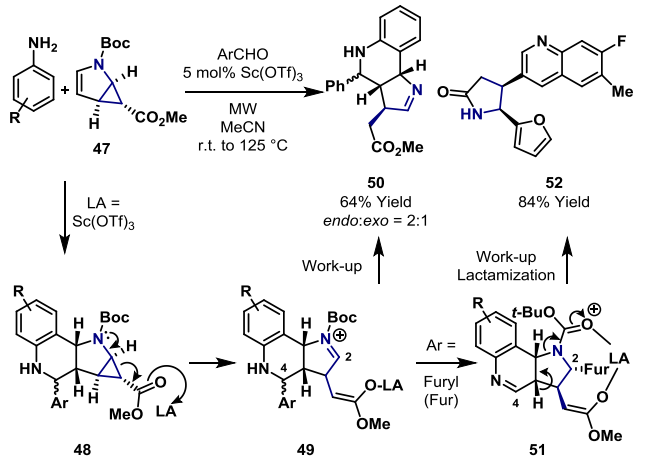
Gharpure and co-workers[47] have synthesized a wide range of heterocyclic compounds by employing donor-acceptor cyclopropanes **43** (Scheme 15). For example, treatment with a Lewis acid (TMSOTf) provided 6-ring products **44** via cleavage of the C1-C2 bond. Conversely, exposure of **43** to Bu_3SnH/AIBN led to 5-ring products **45** via cleavage of the C2-C3 bond. This process presumably occurs via the intermediacy of an O-stannyl ketyl radical[48] and demonstrates how the presence of additional functionality can be harnessed to override the inherent polar reactivity of the DA aminocyclopropane unit. Reduction of the ketone of **43** provided alcohol **46**, which could be induced to undergo a variety of transformations via C-C cleavage of the DA aminocyclopropane.

Scheme 15. Transformations of DA Cyclopropylamines



Reactive units equipped with DA aminocyclopropanes can be used to trigger complex multicomponent processes. In one such example, Reiser and Roy[49] showed that system **47** can be converted to imines (**50**) or lactams (**52**) upon exposure to an aniline and aldehyde using $Sc(OTf)_3$ as catalyst (Scheme 16). Both processes likely commence with (microwave irradiation-assisted) Povarov reaction at the enamide of **47**. This generates DA aminocyclopropane **48** where the N-lone pair is no longer cross-conjugated such that C-C cleavage of the cyclopropane becomes more facile (vs **47**). This process unveils 1,3-dipole **49**, which affords adduct **50** upon loss of the Boc group and work-up. When Ar = 2-furyl (or related heteroarenes), an alternate pathway predominated to provide **51**. Here, furyl migration from C4 to C2 is followed by aromatizing E1 elimination, Boc deprotection and lactamization to provide *cis*-4,5-disubstituted pyrrolidinone **52**. The scope of this latter process was fully explored.

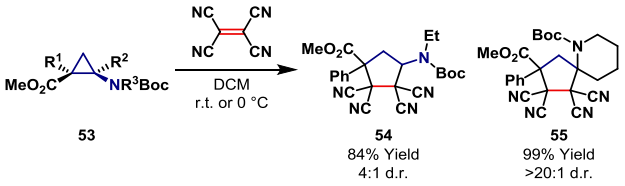
Scheme 16. Multicomponent Reactions with a DA Cyclopropylamine, Anilines and Aromatic Aldehydes



2.2. Cycloaddition Reactions

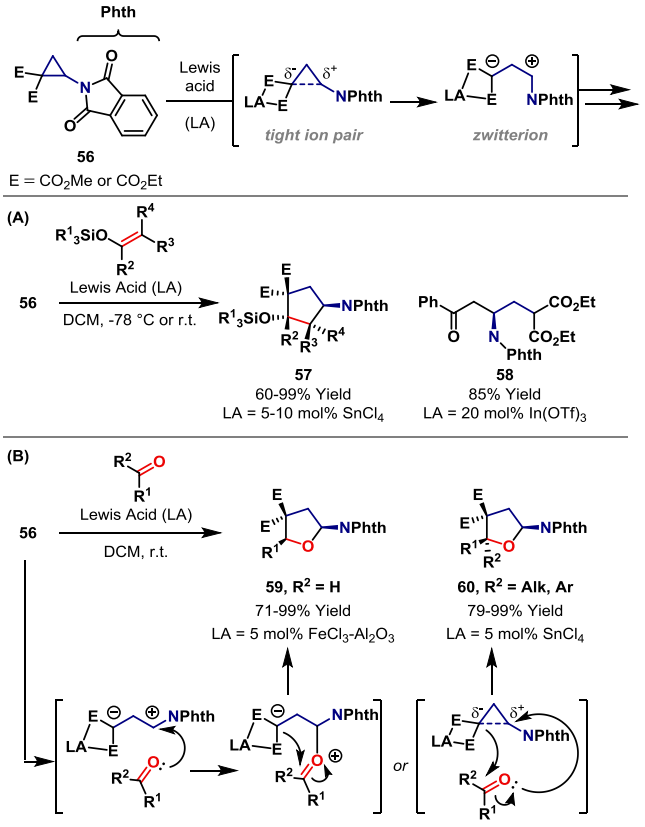
The dipole analysis presented in Scheme 2 suggests that DA aminocyclopropanes should have significant potential for the development of cycloaddition processes. Early examples of (3+2) cycloaddition processes were reported by Park and Beak (Scheme 17).[50] In this case, two cyclic products, **54** and **55**, were formed upon addition of tetracyanoethylene to DA aminocyclopropane **53**. However, the reaction exhibited limited alkene scope and cycloaddition was not observed with other electron-poor alkenes, such as fumaronitrile, dimethyl maleate, and acrylonitrile.

Scheme 17. Cycloaddition Between DA Cyclopropylamines and Tetracyanoethylene



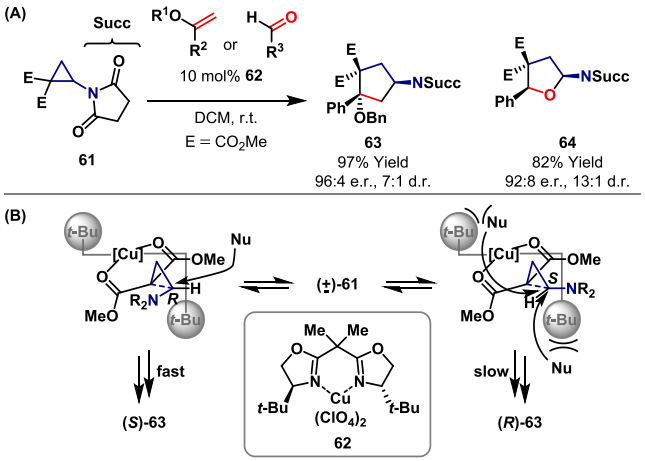
The Waser group has made substantial advances in the area of DA aminocyclopropane-based cycloaddition processes.[51-54] In 2011, the first catalytic (3+2) cycloaddition of aminocyclopropanes was reported.[55] In this work, it was established that enol ethers undergo $SnCl_4$ catalyzed cycloaddition with DA aminocyclopropanes **56** to provide amino-substituted cyclopentanes **57** (Scheme 18A). Critically, the processes were found to be stereospecific, such that the relative and absolute stereochemistry of the DA cyclopropane, and the relative stereochemistry of the enol ether are transferred to the product. This result was rationalized by invoking concerted nucleophilic attack of the enol ether onto a tight, configurationally stable ion pair (rather than onto a "free" zwitterion, see Scheme 2). The process is critically dependent on the choice of Lewis acid; for example, when $In(OTf)_3$ was used in place of $SnCl_4$ as the catalyst, no cycloaddition occurred and only acyclic β-amino ketone **58** was obtained. A related method developed by Doyle and co-workers[56] enables cycloadditions with enoldiazoacetates; here, stereospecificty was not assessed. Later, the Waser group extended the scope of the (3+2) process to encompass aldehydes or ketones as the "2 component", thereby affording 2-aminotetrahydrofurans **59-60** (Scheme 18B).[57,58] An Fe-based Lewis acid was most effective for aldehyde-based cycloadditions, and, in contrast to the work in Scheme 18A, these processes were not stereospecific, such that ring formation via a "free" zwitterion is the likely pathway. For ketone-based cycloadditions, $SnCl_4$ was optimal and stereospecificity with respect to the cyclopropane was again observed. Thus, careful choice of conditions allows entry into stereospecific or racemizing reaction manifolds.

Scheme 18. Cycloaddition Between DA Cyclopropylamines and Silyl Enol Ethers, Aldehydes or Ketones



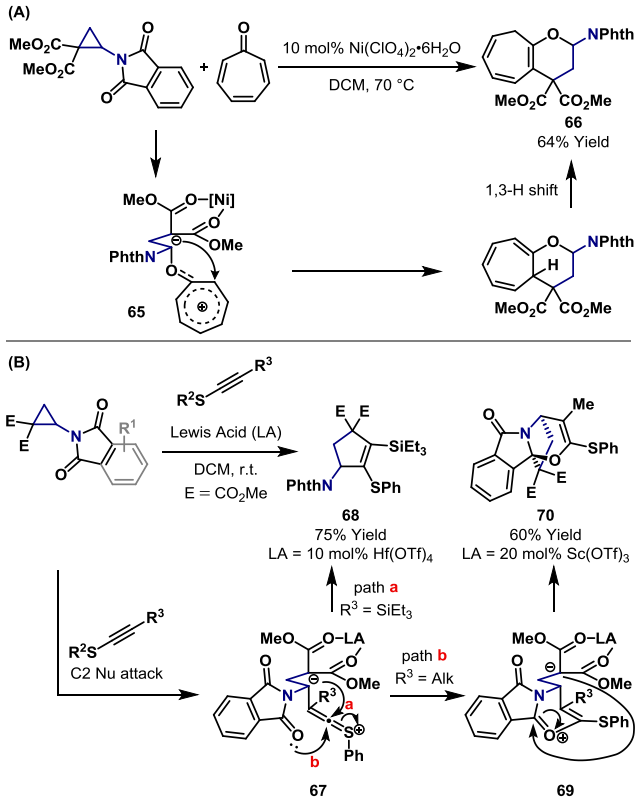
Dynamic kinetic asymmetric (3+2) cycloadditions of diester substituted aminocyclopropane **61** can be achieved using homochiral copper bisoxazoline complex **62** as catalyst (Scheme 19A).[59] The protocol is effective for enantioselective cycloadditions with either enol ethers or aldehydes to deliver enantioenriched amino-cyclopentanes **63** or tetrahydrofurans **64**, respectively. A mechanism involving Cu-catalyzed racemization of the starting cyclopropane in advance of enantiodetermining nucleophilic attack of the enol ether or aldehyde was proposed (Scheme 19B). A similar catalytic system has been used for ring-opening desymmetrization of a DA *meso*-diaminocyclopropane with indole nucleophiles.[60]

Scheme 19. Dynamic Kinetic Asymmetric (3+2) Cycloadditions of Aminocyclopropanes



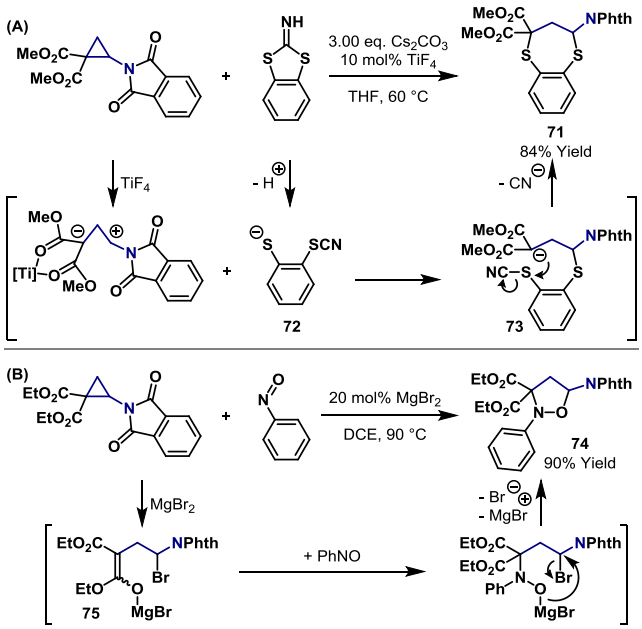
The use of tropone,[61,62] alkynyl triazenes[63] and thioalkynes[64] in Lewis acid catalyzed (3+2) annulations with DA aminocyclopropanes has also been demonstrated. Under $SnCl_4$ or Ni-catalyzed conditions, (8+3) cycloadditions with tropone provide bicyclic products **66**. The processes were postulated to proceed via tropylium-type zwitterionic intermediate **65** (Scheme 20A). In the case of cycloadditions with thioalkynes, interesting polycyclic structures **70** were observed alongside cycloadducts **68** (Scheme 20B). The latter arise via the expected cyclization of the C-anion of **67** onto the thioketene unit (path a) and this pathway predominates when silyl-substituted thioalkynes are used. Alternatively, attack of the phthalimide carbonyl of **67** can deliver oxonium intermediate **69** (path b), which then triggers 1,2-addition of the enolate leading to **70**.

Scheme 20. Cycloaddition Between DA Cyclopropylamines and (A) Tropone or (B) Thioalkynes



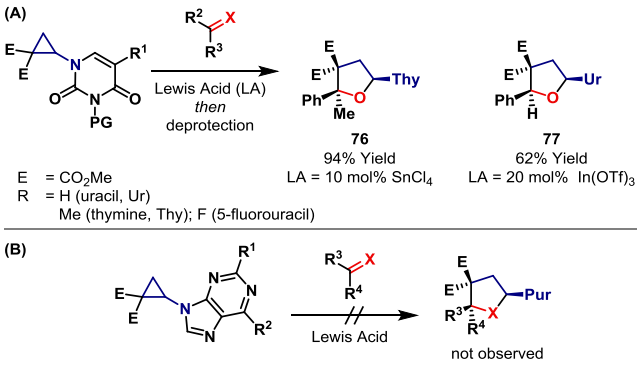
Benzodithioloimine,[65] thiochalcones[66] and nitrosobenzene[67] were also used as partners for the cycloaddition reaction. The construction of 7-membered rings (**71**) occurs in the case of benzodithioloimine (Scheme 21A). Anion **72**, formed upon deprotonation of benzodithioloimine, attacks LA-activated cyclopropane to give anionic intermediate **73**, which cyclizes with the loss of cyanide anion. When nitrosobenzene is employed, the formation of a 5-membered ring **74**, containing two different heteroatoms, occurs (Scheme 21B). The proposed mechanism for this transformation involves the formation of ring-opened brominated intermediate **75**. This is then followed by the addition of nitrosobenzene and intramolecular S_N2-type substitution.

Scheme 21. Cycloaddition Between DA Cyclopropylamines and (A) Benzodithioloimine or (B) Nitrosobenzene



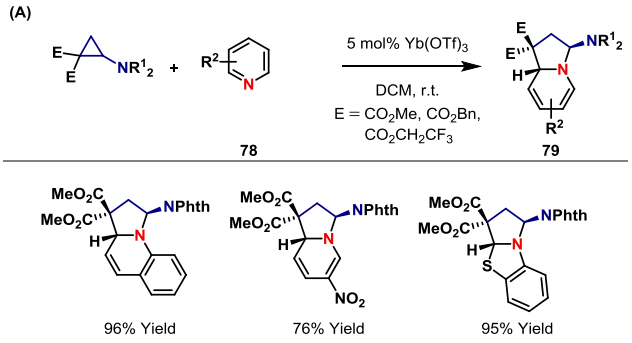
Nucleobase-substituted diester cyclopropanes containing thymine, uracil or 5-fluorouracil also undergo cycloaddition with aldehydes, ketones, and enol ethers to give cyclic products such as **76** and **77** (Scheme 22A).[68] However, when purine was used as nucleobase, no C-C-bond cleavage was observed (Scheme 22B).[69] The low reactivity was rationalised by the modified electronics of the cyclopropane ring.

Scheme 22. Cycloadditions Involving Nucleobase-Substituted Diester Cyclopropanes



In related processes, a range of nitrogen-based heterocycles **78**, such as quinolines, isoquinolines, and electron-deficient pyridines – were shown to participate in ytterbium(III) catalyzed (3+2) dearomatizing annulations with DA aminocyclopropanes (Scheme 23).[70] The method is notable because it allows the direct assembly of complex, functionalized heterobicyclic scaffolds **79**. A mechanism involving cleavage of the DA aminocyclopropane to its corresponding zwitterion was proposed (cf. Scheme 18).

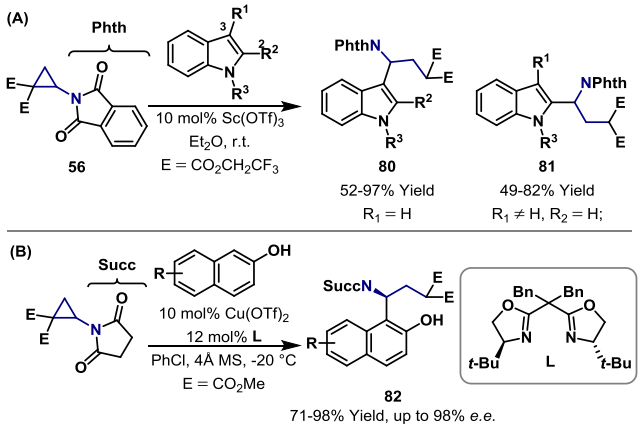
Scheme 23. Cycloaddition Between DA Cyclopropylamines and Nitrogen-Based Heterocycles



2.3. Ring Opening Mono- and Bis-functionalizations of DA Cyclopropylamines

Carbon-based nucleophiles can also be used for simpler ring openings of DA cyclopropylamines. For example, Waser and co-workers[71] reported a Lewis acid-catalyzed Friedel-Crafts reaction involving indoles (Scheme 24A). Here, alkylation occurred preferentially at the C3 position to provide **80**. Indoles that already possess C3-substitution undergo alkylation with DA aminocyclopropanes at the C2 position to give adducts **81**. The C-NPhth bond of products **80** is labile under the Lewis acidic conditions such that further reaction with another equivalent of indole can occur. To minimize this, extensive studies were undertaken to fine tune the structure of DA aminocyclopropane **56**, and this led to inclusion of the trifluoroethyl esters on the acceptor unit. It was shown that other electron-rich aromatics (e.g. anisole, pyrrole) undergo the same transformation, albeit with modest regioselectivities with respect to the arene.

Scheme 24. Friedel-Crafts Alkylations with DA Cyclopropylamines

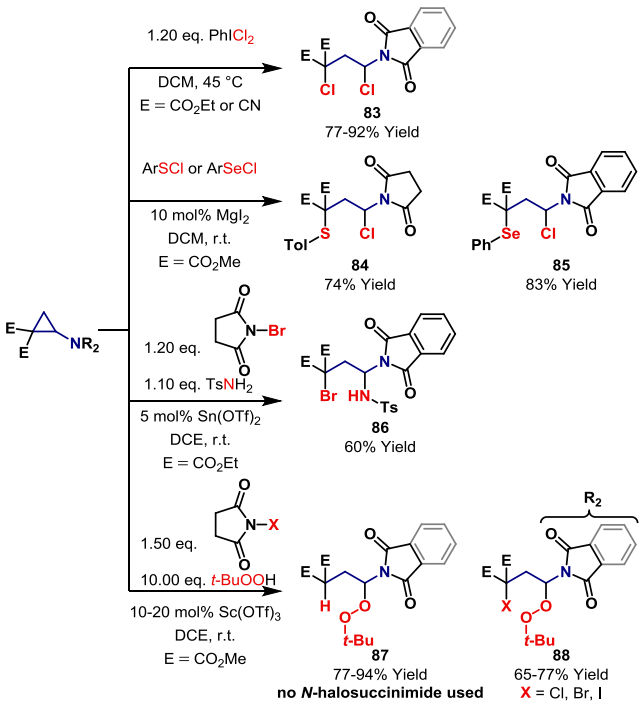


Enantioselective Friedel–Crafts alkylations of β-naphthols with DA aminocyclopropanes were reported later by the Guo group (Scheme

24B).[72] The reaction leads to the formation of a series of γ-aryl γ-aminobutyric acid derivatives **82** with high enantioselectivity and yields using $Cu(OTf)_2$ and bisoxazoline ligand **L**. In certain cases, competing O-alkylation of the naphthol was observed. The scope of the transformation includes other electron rich arenes such as anthracen-2-ol, 1,3,5-trimethoxybenzene and 1-methylindole.

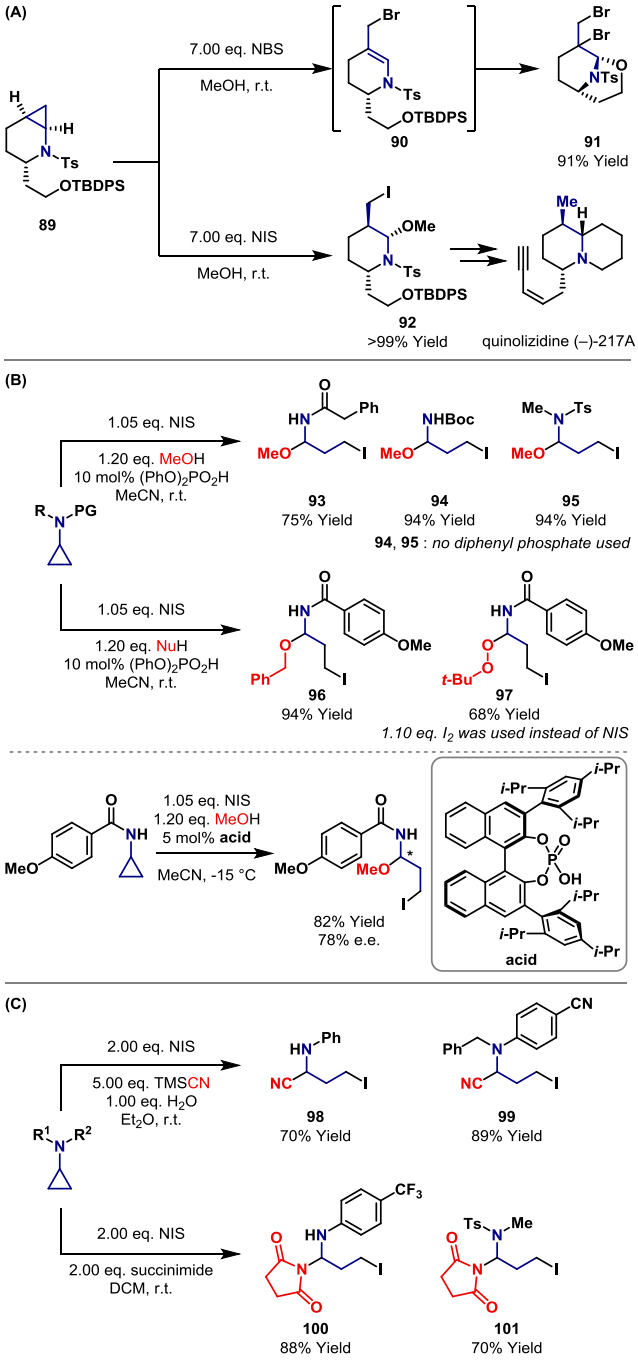
The processes in Scheme 24 involve mono-functionalization of the DA-aminocyclopropane; however, ring opening can also be used as the basis for promoting 1,3-bisfunctionalizations (Scheme 25). In 2014, the Werz group[73] reported that iodobenzene dichloride promotes 1,3-dichlorination of DA cyclopropanes under mild conditions. The method was effective on phthalimide- and succinimide-protected aminocyclopropanes and this enabled access to 1,3-dichlorinated derivatives **83**. A radical-based mechanism was invoked. Later, the approach was expanded to 1,3-bisfunctionalizations using strongly polarized sulfenyl and selenyl halides.[74] Interestingly, the use of magnesium iodide as the Lewis acid was found to be crucial for high yields. With DA aminocyclopropanes, ring-opening occurred with high regioselectivity such that the C-Cl bond formed α to nitrogen (e.g. **84** and **85**). As demonstrated by Studer and co-workers, 1,3-aminobrominations are possible and can be achieved simply be exposing the DA aminocyclopropane to NBS and $TsNH_2$ in the presence of $Sn(OTf)_2$.[75] Under these conditions, **86** was formed in 60% yield and this time halogenation occurred α to the ester groups, a result that likely reflects a polar rather than radical-based reaction pathway. Finally, Saha and co-workers[76] used alkyl hydroperoxides to convert DA aminocyclopropanes into peroxides **87** and **88**; for the latter, concomitant halogenation was promoted by the inclusion of an *N*-halosuccinimide.

Scheme 25. 1,3-Bisfunctionalizations of DA Cyclopropylamines



The use of less activated cyclopropylamines for analogous bis-difunctionalizations is much less explored. In 2011, halogenative ring-opening of **89** was reported (Scheme 26A).[77] With *N*-bromosuccinimide, the enamine intermediate **90** presumably undergoes a second bromination and ring closure to give bicyclic product **91**. However, with *N*-iodosuccinimide, unstable aminal **92** was obtained in quantitative yield and directly subjected to the next step en route to the enantiospecific total synthesis of quinolizidine alkaloid (-)-217A. Waser and Wang[78] have explored this transformation in detail (Scheme 26B). Stable N,O-acetals **93**-**95** could be accessed *via* oxidative ring-opening of protected electron-neutral cyclopropanes. The scope of this transformation has been expanded to other types of nucleophile, such as benzyl alcohol, giving **96**, and *tert*-butyl hydroperoxide, giving **97**. High levels of enantioselectivity were observed for this process by using a chiral phosphoric acid catalyst. This was followed by a report from Zheng and Wang, who demonstrated methods where cyanide and succinimide units were instead installed at the α-position of the ring-opened products (**98**-**101**) (Scheme 26C).[79]

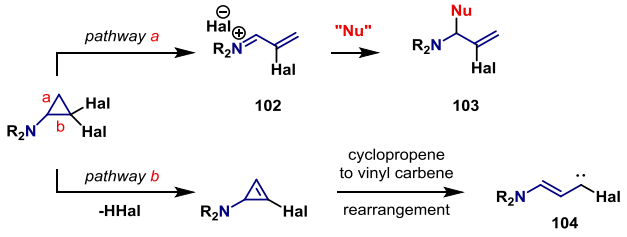
Scheme 26. 1,3-Bisfunctionalizations of Less Activated Cyclopropylamines



2.4. Reactions of DA aminocyclopropanes bearing dihalogenated acceptor units

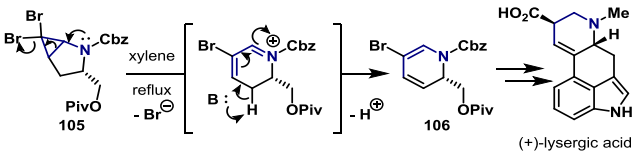
The ring opening of DA aminocyclopropanes bearing dihalogenated acceptor units is distinct from the processes described so far because two additional reaction pathways are available (Scheme 27). In *pathway a* ring-opening is promoted by the nitrogen lone pair; here, cleavage of bond a is followed by loss of a halide anion to give **102**. This iminium ion can be trapped by an exogenous nucleophile to provide vinyl halide products of type **103**. Alternatively, in *pathway b* initial elimination of HHal sets up a strained aminocyclopropene which can undergo rearrangement to vinyl carbene **104** and subsequent reaction.[80-82] In this sequence, bond b undergoes cleavage.

Scheme 27. General Reactivity of Dihalogenated Aminocyclopropanes



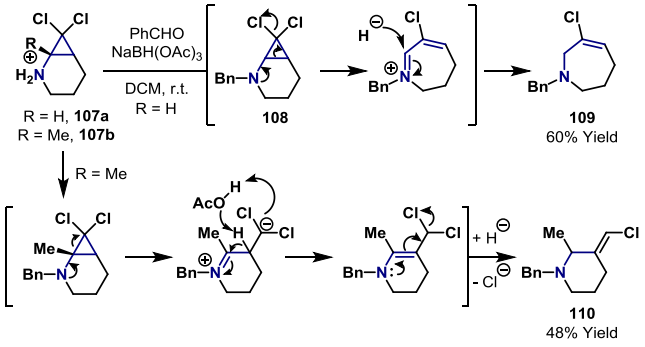
Dihalogen-substituted aminocyclopropanes have become valuable intermediates for ring expansion reactions.[83-90] For example, ring-opening of dibromocyclopropylamine derivative **105** proceed by *pathway a* to give dihydropyridine **106**. This was used as the key intermediate in a formal synthesis of (+)-lysergic acid (Scheme 28).[91]

Scheme 28. Dibrominated Cyclopropylamine Ring Opening en Route to (+)-Lysergic Acid



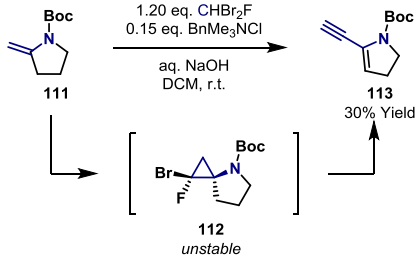
The facility with which dihalogenated DA aminocyclopropanes deviate into *pathway a* is strongly influenced by substituents. For example, exposure of **107a** (R = H) to reductive amination conditions effected initial N-benzylation to provide **108** (Scheme 29). This underwent spontaneous ring cleavage via *pathway a* to provide azepine **109**. However, when R = Me, a conventional DA aminocyclopropane pathway predominated (cf. Scheme 2) leading to 6-ring system **110**.[92]

Scheme 29. Regioselectivity of Ring Opening in Dihalogenated Aminocyclopropanes



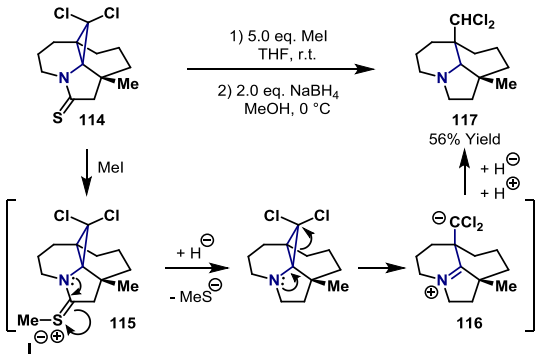
Under certain conditions, both halogen substituents may be eliminated to give a terminal alkyne.[93,94] For example, Laughlin and co-workers[94] observed that unstable fluorobromocyclopropyl derivative **112** is generated upon cyclopropanation of **111**. This decomposes through a ring opening-elimination sequence to give **113** (Scheme 30).

Scheme 30. Generation of a Terminal Alkyne from a Dihalogenated Aminocyclopropane



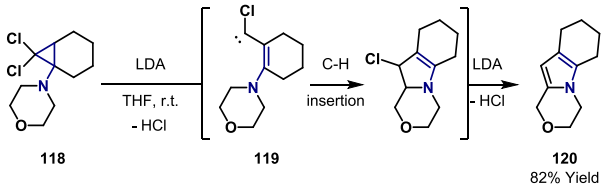
An unusual pathway for the ring cleavage of dihalogenated aminocyclopropanes was reported by Padwa and co-workers (Scheme 31).[95] Aminocyclopropane **115**, generated in situ from thioamide **114**, gives zwitterion **116**. Due to its structure, the resulting intermediate is unable to undergo the typical sequence of deprotonation and chloride expulsion. Instead, reduction with sodium borohydride leads to dichlorinated species **117**.

Scheme 31. Reductive Ring Opening of a Dichlorinated Cyclopropylamine



Examples, where dihalogenated DA aminocyclopropanes undergo cleavage via *pathway b* are relatively rare; however, this manifold is potentially valuable because of the high reactivity of the resulting carbene. For example, Banwell, Willis and co-workers[82] showed that exposure of **118** to LDA leads to heavily substituted pyrrole **120** (Scheme 32). A possible pathway involves initial elimination to a cyclopropene, which undergoes rearrangement to carbene **119** (cf. Scheme 27). This can insert into the activated C-H bond α to nitrogen prior to aromatizing elimination of HCl.

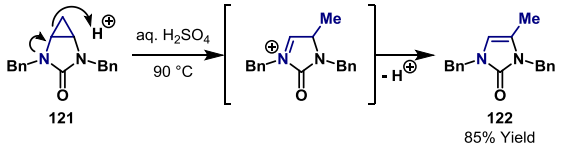
Scheme 32. Base-Promoted Transformation of a Dichlorocyclopropylamine to Afford a Substituted Pyrrole



3. Methodologies Based on Thermal Rearrangement

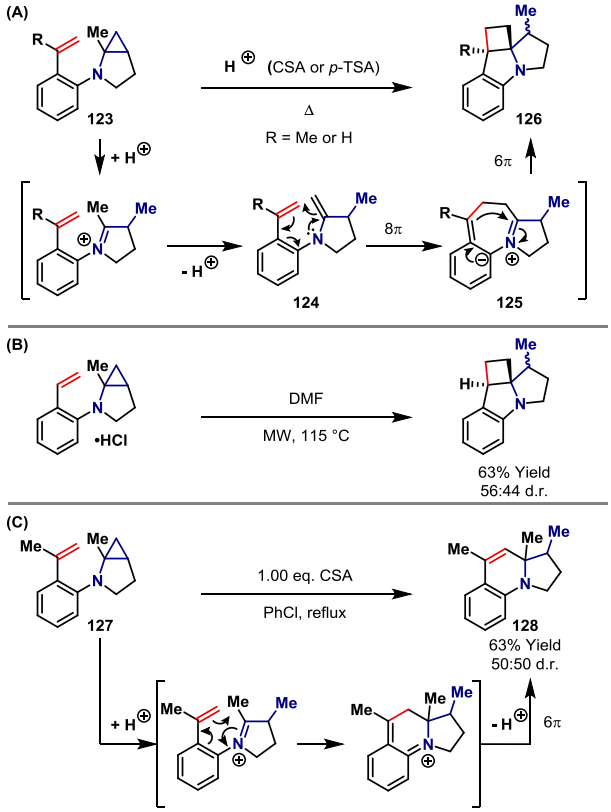
Simple cyclopropylamine systems undergo thermally promoted ring cleavage at high temperatures.[39,96,97] Often, this process can be promoted by employing acidic conditions. For example, adduct **122** formed when urea **121** was heated at 90 °C in aqueous sulfuric acid (Scheme 33).[39]

Scheme 33. Thermal Rearrangement of an Aminocyclopropane under Acidic Conditions



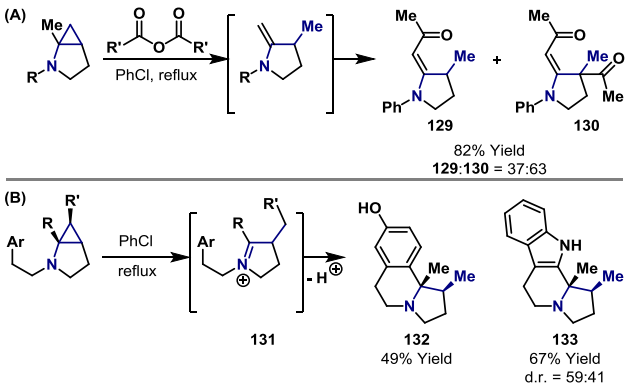
The iminium and/or enamine intermediates that are unveiled upon thermally promoted protonolytic cleavage can be harnessed in various transformations. Six and co-workers[98] demonstrated that cyclopropylamines **123** give cyclobuta[*b*]indoles **126** as a mixture of diastereomers when heated in the presence of acid (camphorsulfonic acid (CSA) or *p*-toluenesulfonic acid (*p*-TSA)) (Scheme 34A). Here, protonolytic generation of enamine **124** sets up an 8π-electrocyclization to give dipole **125**. This then undergoes 6π-electrocyclic ring closure to give cyclobutane **126**. The addition of an exogenous acid can be avoided if instead a protic salt of the starting material is used (Scheme 34B). When a stoichiometric amount of CSA was used for substrate **127**, a distinct outcome was observed where 6π–electrocyclization generated tricyclic product **128** (Scheme 34C). However, using 10 mol% *p*-TSA reverted the reaction outcome back to cyclobutane **126**.

Scheme 34. Transformations of 2-Azabicyclo[3.1.0]hexanes Derivatives Bearing Alkenes



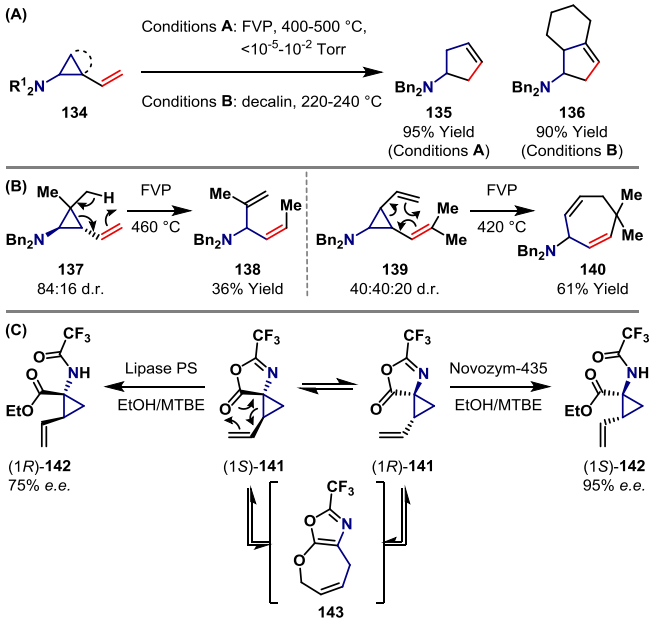
This simple ring cleavage method was exploited further by trapping the key enamine intermediate with carboxylic acid anhydrides; this gave a mixture of mono- and bis-acylated products, such as **129** and **130** (Scheme 35A).[99] Alternatively, the iminium intermediate can be harnessed in other ways. For example, iminium ions **131** were trapped out in Pictet-Spengler-like cyclizations to give tricyclic products, such as **132** and **133** (Scheme 35B).[100,101]

Scheme 35. Reaction of 2-Azabicyclo[3.1.0]hexanes with (A) Acid Anhydrides and (B) Tethered Aromatics



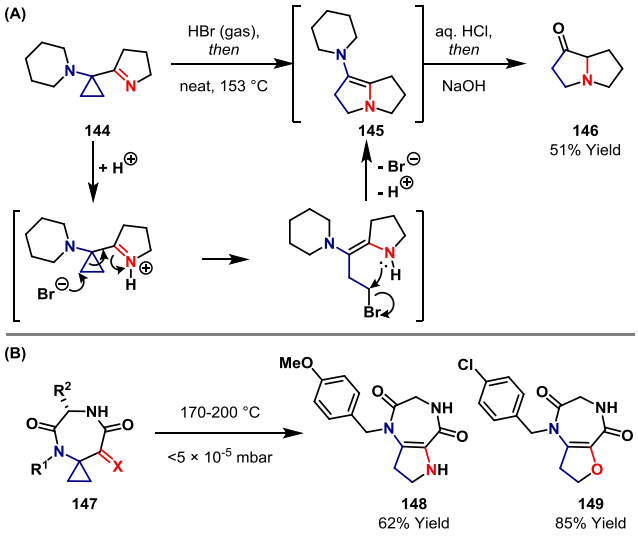
Vinylcyclopropylamines **134** can undergo thermally promoted [1,3]-sigmatropic shifts to give cyclopentene derivatives (e.g., **135** and **136**) (Scheme 36A). The de Meijere group[102,103] reported two sets of conditions for this transformation: Conditions A, using flash vacuum pyrolysis (FVP), are favored for *trans*-configured vinylcyclopropylamines, whereas milder Conditions B (heating in decalin) are favored for the *cis*-diastereomers. Interestingly, only trace amounts of the corresponding cyclopentenes were observed in the case of **137** and **139** (Scheme 36B). For **137**, an ene-type rearrangement gave linear product **138**, whereas a Cope rearrangement was invoked for the conversion of **139** to **140**. The reversibility of [3,3]-sigmatropic rearrangements of vinylcyclopropylamines has been exploited in enzymatic dynamic kinetic resolutions.[104] Here, either enantiomer of the target **142** can be accessed by enantioselective hydrolysis of the ester group in **141**. The isomerization of starting azlactone **141** proceeds by concerted [3,3]-sigmatropic oxadivinylcyclopropane rearrangement, which involves the formation of racemic dihydrooxepine intermediate **143**. Treatment with immobilised Lipase PS gave (1*R*)-**142** in 75% *e.e.*, while Novozym-435 (immobilised *Candida antarctica* Lipase B) gave (1*S*)-**142** in 95% *e.e.* (Scheme 36C)

Scheme 36. [3,3]-Sigmatropic Rearrangements of Vinylcyclopropylamines



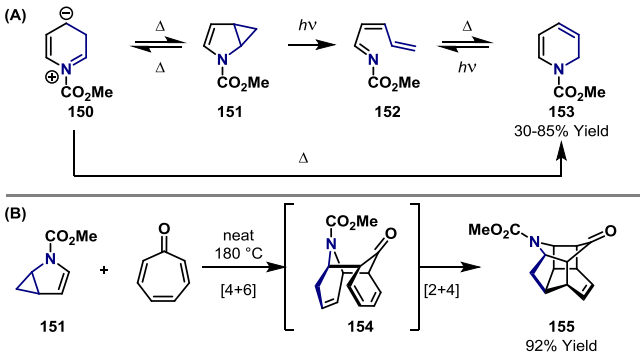
Aminocyclopropyl systems with other types of π-unsaturation adjacent to the cyclopropane unit also undergo rearrangement. In 1989, Wasserman and co-workers[105] reported that treatment of pyrroline **144** with gaseous hydrobromide and subsequent pyrolysis afforded enamine **145** via bromide-assisted ring-opening; this was isolated as unstable pyrrolizidinone **146** after workup (Scheme 37A). A similar process promoted by ammonium iodide was also reported.[106] Finally, de Meijere group[107] showed that products such as heterocycles **148** and **149** can be synthesized via Cloke–Wilson[108,109] rearrangement upon sublimation of substrates **147** (Scheme 37B).

Scheme 37. Rearrangement of Cyclopropanes with Various Tethered π-Unsaturates



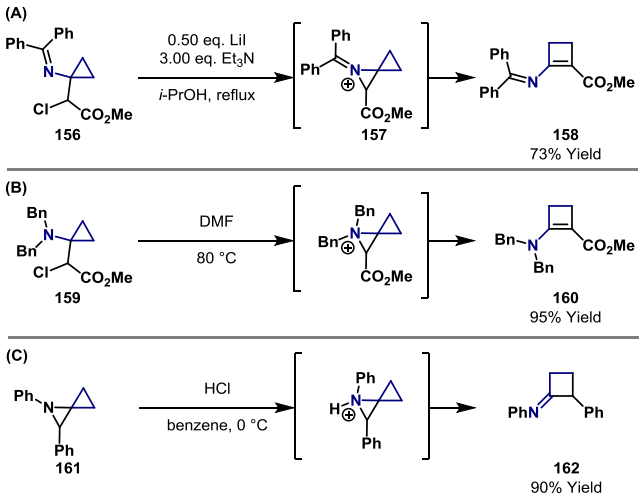
Cyclic substrates, which contain both the alkene and cyclopropylamine within their core, have also been studied. For example, Kumagai and co-workers[110] studied the photochemical rearrangement of azabicyclohexene **151**. In contrast to the known thermal rearrangement of **151**,[111] which proceeds via ylide intermediate **150**, it was found that azahexatriene **152** formed upon photolysis by [2+4] cycloreversion (Scheme 38A). Thermal electrocyclic ring closure of **152** then generated **153**. When **153** was photolyzed, conversion back to **152** was observed in addition to the formation of other products. An intricate cyclic product **155** was isolated by the Ugi group[112] upon cycloaddition of the aforementioned azabicyclohexene **151** and tropone. Here, *endo*-[4+6]-cycloaddition of ylide intermediate **150** to tropone gives **154**, which undergoes further intramolecular Diels-Alder reaction to give **155** (Scheme 38B).

Scheme 38. Rearrangements of Protected Azabicyclohexene



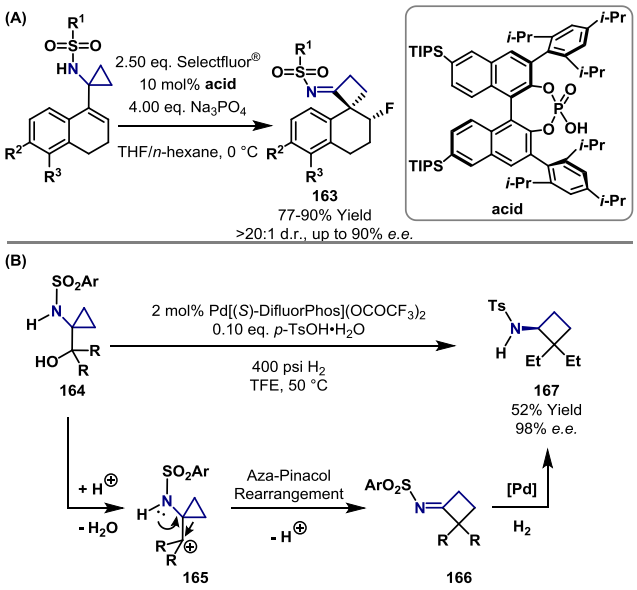
Other types of cyclopropylamine based rearrangement have also been reported. For example, cyclopropylimine **156** underwent intramolecular substitution to afford a spiro-fused cation **157**, which then rearranged to **158** (Scheme 39A).[113] This process was relatively slow (7 days), but amine analogue **159** rearranged much faster (48 h) to give cyclobutene **160** in 95% yield (Scheme 39B).[114] It should be noted, that earlier work by Crandall and Conover[115] had demonstrated that bicyclic aziridine **161** rearranges to cyclobutanimine **162** upon treatment with acid at low temperature (Scheme 39C)

Scheme 39. Rearrangements involving Spirobicyclic Intermediates



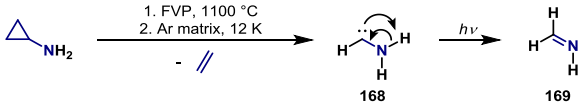
Recent methodologies for the synthesis of similar four-membered ring systems diverge from harsh thermal conditions. Bürgi, Alexakis and co-workers[116] developed an enantioselective aza-semipinacol rearrangement (Scheme 40A). This transformation uses a chiral phosphoric acid controlled enantioselective alkene fluorination to allow the rapid assembly of complex structures **163**. The Zhou group[117] has demonstrated that cyclobutanimines resulting from these types of rearrangement may be reduced enantioselectively to provide aminocyclobutanes, such as **167** (Scheme 40B). In this case, imine **166** is formed by aza-pinacol rearrangement of carbocation **165** which is derived from acid promoted ionization of β-hydroxycyclopropylamine **164**. Recently, a photochemical transformation involving similar sulfonyl-protected cyclopropylamine intermediates has been reported.[118]

Scheme 40. Enantioselective Synthesis of Aminocyclobutanes



In 2018, aminomethylene **168** was first characterized by matrix isolation IR and UV/Vis spectroscopy by Eckhardt and Schreiner (Scheme 41).[119] This simplest aminocarbene was obtained by flash vacuum pyrolysis of cyclopropylamine and subsequent trapping of the pyrolysate in an inert argon matrix at 12 K. The carbene quickly rearranges to methanimine **169** upon irradiation.

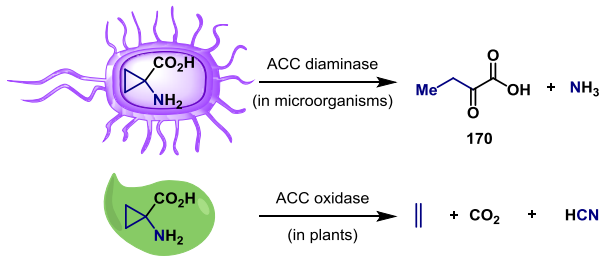
Scheme 41. Formation of Aminomethylene from Cyclopropylamine



4. Methodologies Employing Cyclopropylamine Derivatives with α-EWG Substituents

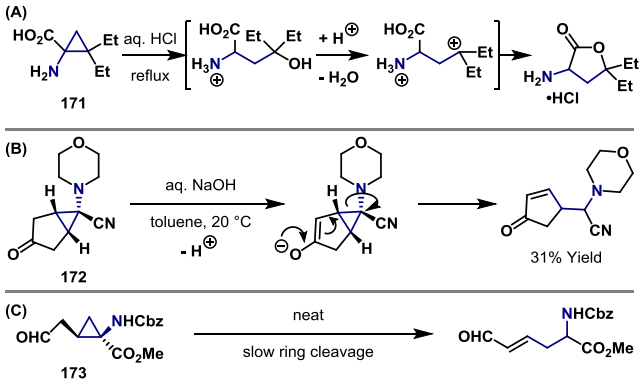
Among aminocyclopropanes that bear electron-withdrawing substituents at the α-position, 1-aminocyclopropane-1-carboxylic acid (ACC) is perhaps the most prominent. In microorganisms, this compound is degraded by ACC deaminase to α-ketobutyrate **170** and ammonia.[120-122] In plant cells, this acid produces ethylene upon aerobic oxidation (Scheme 42).[123] Ethylene is a phytohormone, which regulates key processes in plants, such as fruit ripening and seed germination. The accepted mechanism of ethylene formation involves the formation of an aminium radical cation, promoted by ACC oxidase enzyme.[124] The use of alternative systems, such as hypochlorite,[125] iron compounds,[126-130] and other metal complexes[131-133] has been demonstrated.

Scheme 42. Transformation of 1-Aminocyclopropane-1-carboxylic Acid in Plants and Microorganisms



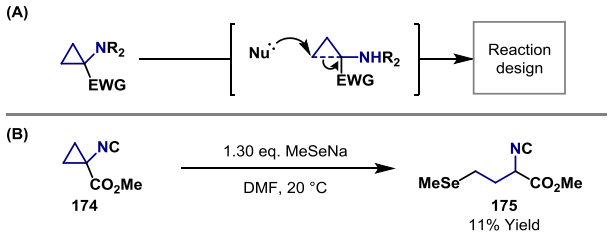
Cyclopropylamines with α-EWGs (e.g., **171-173**) may undergo cleavage under typical acidic[134,135] and basic[136,137] conditions (Scheme 43A and 43B). Sometimes such compounds are sufficiently unstable that they undergo spontaneous slow conversion to ring-opened products (Scheme 43C).[138]

Scheme 43. Bond Cleavage in Cyclopropylamine Derivatives with α-EWG Substituents



Nucleophilic ring-opening reactions, driven by the ability of the EWG to stabilize an adjacent carbanion, are also feasible (Scheme 44A). This transformation has been exemplified using halides[139,140] and methylselenide[141] as incoming nucleophiles. For example, Krief and Trabelsi[141] isolated ring-opened product **175** in low yield upon exposure of **174** to MeSeNa (Scheme 44B).

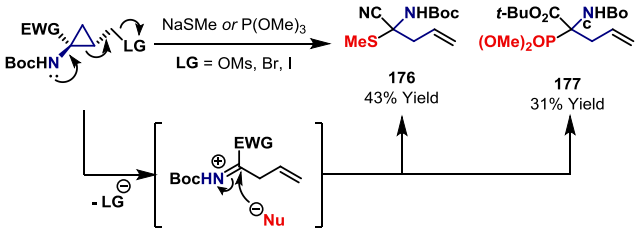
Scheme 44. S_N2-type Nucleophilic Ring-Opening of Aminocyclopropanes with α-EWG Substituents



If the substrate contains an appropriately positioned leaving group, then S_N1 reactions can be achieved. In Scheme 45, the substrate is designed such that the nucleophile attacks the most hindered carbon-center of the cyclopropane, thereby generating

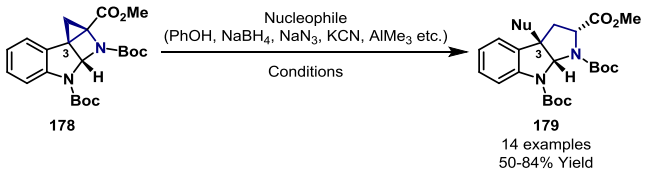
tetrasubstituted centers.[142-144] Using this approach, ring opened products **176** and **177** were isolated with sodium thiomethoxide or trimethyl phosphite as the nucleophile. The yields of these transformations are typically low, in part, because of competitive S_N2-type processes.

Scheme 45. Transformations of Aminocyclopropanes with α-EWG substituents



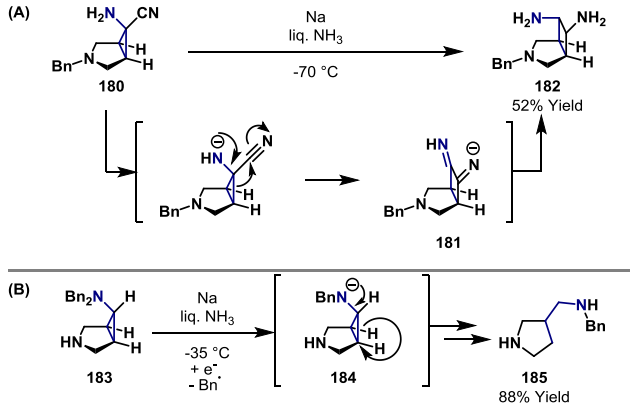
Certain cyclopropylamine derivatives with electron-withdrawing substituents at the α-position undergo ring expansion. Rainier and co-workers[96] employed the ring cleavage of cyclopropylazetoindolines **178** as a way to construct the C3 stereocenter of pyrroloindolines **179** (Scheme 46). A wide range of nucleophiles are suitable for this transformation and generally good yields were obtained.

Scheme 46. Ring Expansion of Cyclopropylazetoindolines



During studies on attempted reductive decyanation, Vilsmaier and co-workers[145] found that cyclopropylamine **180** instead undergoes rearrangement. Deprotonation promotes 1,2-shift to give diimine **181**, which is further reduced to **182** (Scheme 47A). The formation of ring-cleaved product **185** was observed when **183** was treated with sodium in ammonia (Scheme 47B). This result can be rationalized from **184** via a sequence of ring-opening, protonation and reduction.

Scheme 47. Rearrangements of Bicyclic Cyclopropylamines

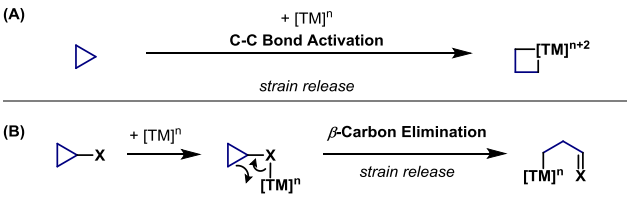


5. Ring Opening Assisted by Transition Metal Complexes

The cleavage of non-activated cyclopropane rings by transition metal complexes has been known for more than 60 years.[146] Surprisingly, the integration of this process into the design of metal-catalyzed methodologies has gained traction only more recently. Prior to this, efforts had focused on the use of more activated cyclopropane-based rings, such as vinyl cyclopropanes and alkylidene cyclopropanes.[147-153] More recent methodologies have enabled the routine exploitation of aminocyclopropane-based substrates in reaction design.

Two predominant pathways for the metal-catalyzed cleavage of C-C bonds of "simple" cyclopropanes exist. The first approach is a direct oxidative addition of a transition metal into C-C bond of cyclopropane, also known as "C-C bond activation" (Scheme 48A). The second pathway relies on β-carbon elimination to release the strain of the cyclopropane ring; in such cases, the metal's oxidation state remains unchanged (Scheme 48B).

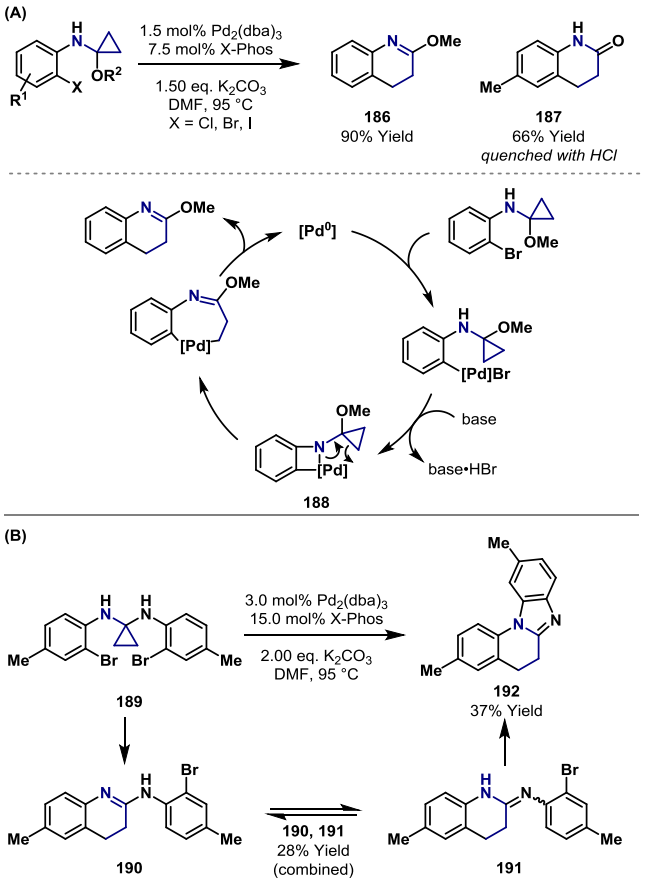
Scheme 48. Cleavage of Cyclopropanes by (A) C–C Activation and (B) β-Carbon Elimination



In 2008, Tsuritani and co-workers[154] reported Pd-catalyzed methodology for the synthesis of dihydroquinolines **186** and dihydroquinolinones **187** (Scheme 49A). Here, initial Ar-Br oxidative addition leads to aza-palladabenzocyclobutane **188**.[155,156] This undergoes β-carbon elimination prior to C-C reductive elimination, which releases the target. The electron-rich biphenyl-based ligand, X-Phos, was required for high yields. The reactivity of 1,1-dianilinocyclopropane **189** was also explored (Scheme 49B). In this case, three products were isolated: the expected quinolinone

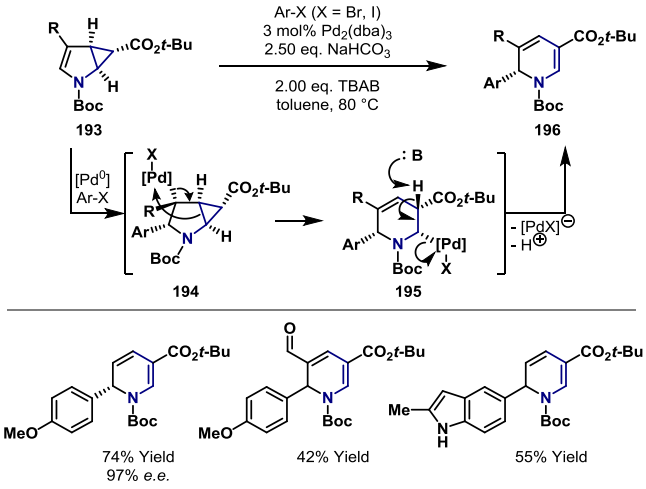
190, its isomerized form **191**, and substituted benzimidazole **192**. The latter likely forms by intramolecular *N*-arylation of **191**.[157]

Scheme 49. Pd-Catalyzed Synthesis of Dihydroquinolines from Cyclopropylamines



β-Carbon elimination is a general method for achieving ring cleavage of cyclopropylamines; however, the position of the Pd-center relative to nitrogen can be switched. For example, the Reiser group[158] reported palladium-catalyzed couplings between aryl halides and cyclopropanated pyrroles **193** (Scheme 50). Here, following carbopalladation of the N-vinyl carbamate unit, Heck-type intermediate **194** undergoes β-carbon elimination to provide **195**. At this stage, *syn*-β-hydride elimination cannot occur and, instead, base-promoted *anti*-elimination provides dihydropyridine **196**. A full scope study was undertaken, including derivatizations of the targets.

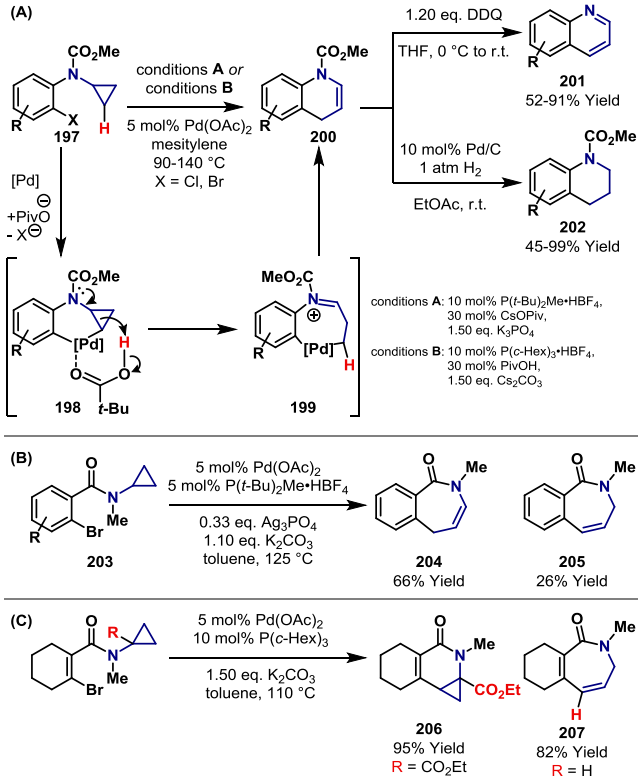
Scheme 50. Pd-Catalyzed Ring Expansions of Cyclopropanated Pyrroles



Alternate modes of ring cleavage can also be achieved under Pd-catalyzed conditions. For example, Rousseaux, Liégault and Fagnou[159] described a Pd(0)-catalyzed transformation of halophenyl cyclopropyl carbamates **197** (Scheme 51A). Here, it was proposed that the carboxylate additive (CsOPiv) facilitates concerted-metallation-deprotonation (CMD) of the cyclopropane C-H bond. This delivers intermediate **198**, where the resulting carboxylic acid ligand can protonolytically cleave the aminocyclopropane unit to provide **199**. Reductive elimination/proton loss generates targets **200**, which were either oxidized to quinolines **201** or reduced to tetrahydroquinolines **202** in a one-pot fashion.

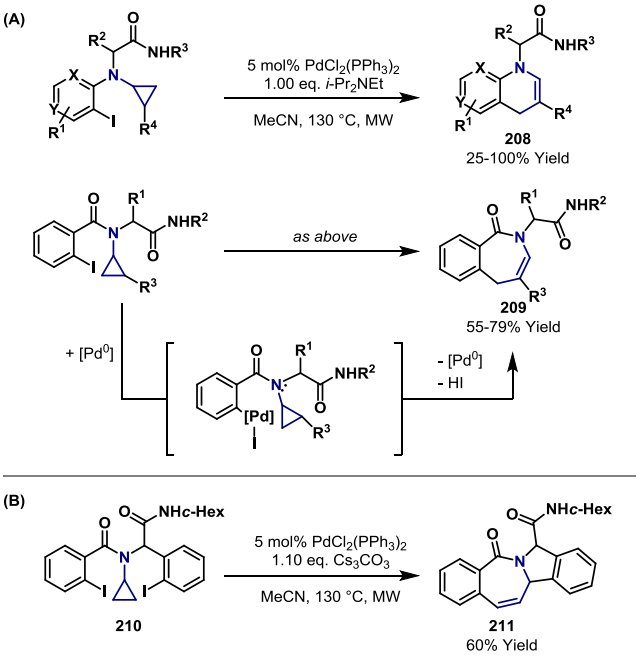
In conceptually related studies, the Charette group[160] explored ring-openings of cyclopropyl benzamides **203** (Scheme 51B). This provides a direct entry to benzazepines, albeit in low regioselectivity with respect to the alkene (cf. **204** vs **205**). Subsequently, studies initiated by oxidative addition of vinyl bromides were reported.[161] Interestingly, this provided cyclopropyl fused azacycles (e.g. **206**) and subsequent ring opening was not a predominant pathway when the cyclopropylamine was substituted with an electron-withdrawing group at the α-position. However, an electron-neutral cyclopropylamine delivered the corresponding ring-opened product **207** under the reaction conditions. (Scheme 51C).

Scheme 51. Pd-Catalyzed Ring Expansions of Cyclopropyl Benzamides



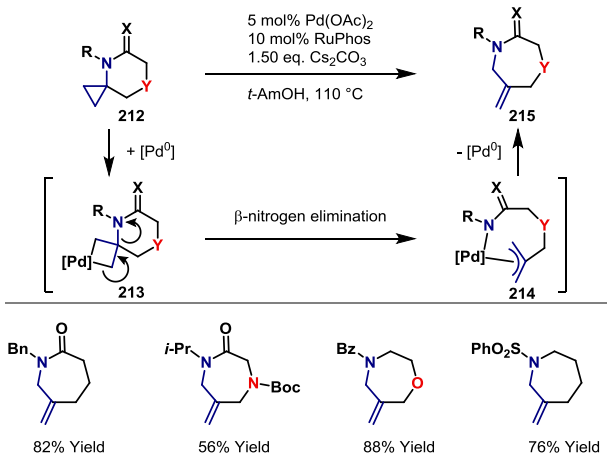
El Kaïm, Grimaud and co-workers[162] extended the scope of palladium-catalysed ring opening to give dihydropyridine derivatives **208** and benzazepinones **209** (Scheme 52A). Although leading to similar six- and seven-membered cyclic products (cf. Scheme 51A-C), this process does not proceed via a concerted-metallation–deprotonation mechanism. In these cases, the aminocyclopropane unit may attack the aryl-Pd(II) intermediate directly. Using substrate **210**, a cyclopropane ring opening–Heck cascade was demonstrated, leading to tetracyclic product **211** (Scheme 52B).

Scheme 52. Pd-Catalyzed Formation of Dihydropyridine Derivatives and Benzoazepinones



Uncommon regioselectivity for Pd-catalyzed aminocyclopropane C-C bond cleavage was observed by Rene and co-workers[163] in the context of spiro-fused cyclopropanes **212** (Scheme 53). In this case, experimental and DFT studies supported Pd-insertion into the less hindered distal bond of the cyclopropylamine unit to give palladacyclobutane **213**. Collapse of this by β-nitrogen elimination generates π-allyl intermediate **214**, which undergoes C-N bond forming reductive elimination to provide the targets. The methodology provides access to interesting 7-membered N-heterocycles **215**, including examples containing multiple heteroatoms.

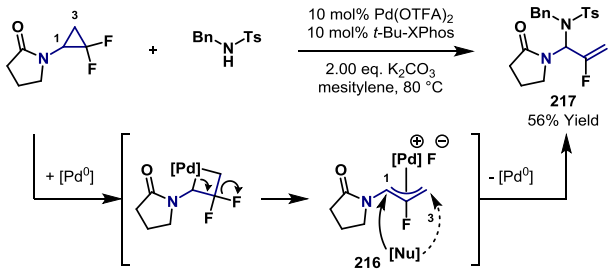
Scheme 53. Pd-Catalyzed Cleavage of the Distal Bond in a Cyclopropylamine-based Systems



An isolated example of Pd-catalyzed C-C bond cleavage of a difluorocyclopropylamine derivative was reported by the Fu group (Scheme 54).[164] The proposed mechanism starts with insertion of

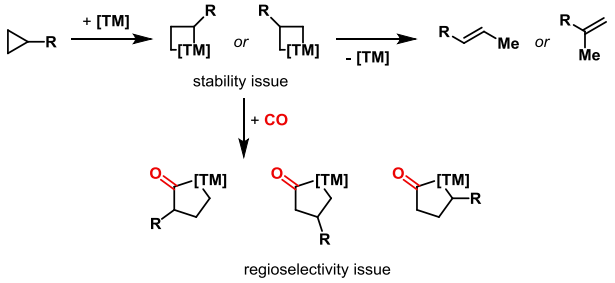
palladium into the lengthened C1-C3 bond of cyclopropane.[165] Then, β-fluorine elimination from the palladacyclobutane gives π-allyl complex **216**, which is susceptible to attack by an external nucleophile. In this case, the preferred site of nucleophilic attack was at C1, generating branched product **217**. Interestingly, for other classes of difluorinated cyclopropane, the process led to alternate regioselectivity, where the nucleophile attacked at C3.

Scheme 54. Pd-Catalyzed Cleavage of the C-C Bond of a Difluorocyclopropylamine



The intrinsic ring strain of cyclopropanes facilitates metal insertion into their C-C bond. However, the instability of the resulting metallacyclobutanes, which are prone to β-elimination, limits their use in reaction design. For the Pd-catalyzed insertion processes described above, the systems are designed such that a β-heteroatom elimination step is integral to the overall transformation. However, in simpler systems, β-hydride elimination usually dominates leading to simple alkene degradation products (Scheme 55). An alternate strategy for making productive use of cyclopropane derived metallacyclobutanes is to insert CO into them, as this process is fast with respect to β-hydride elimination. In 1968, Wilkinson and co-workers[166] showed, through stoichiometric studies, that rhodacyclopentanones can be generated by exposure of cyclopropane to $[Rh(CO)_2Cl]_2$. For substituted cyclopropanes, the regioselectivity of this process is uncertain, and can, in principle, lead to multiple regioisomers of the rhodacyclopentanone. McQuillin and Powell[167] examined this aspect in stoichiometric studies, which revealed substrate dependent regioselectivity for certain systems.

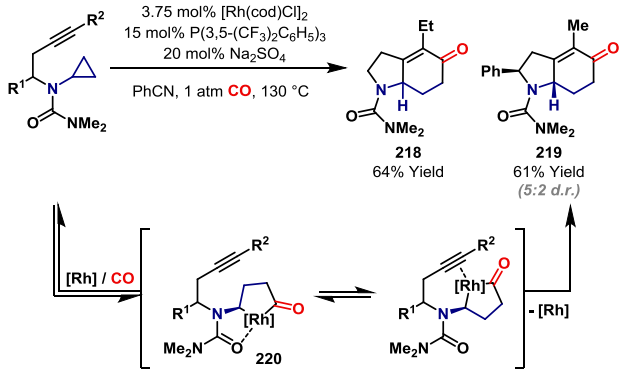
Scheme 55. Metal-Catalyzed C-C Bond Activation of Cyclopropanes



An alternative strategy for achieving regiocontrol during the formation of metallacyclopentanones is to use a nitrogen-based directing group. Rhodium-catalyzed carbonylation of simple cyclopropylamines to give γ-lactams was reported by Iqbal in 1971,[168] but further developments in this area occurred much later. Of particular relevance to this review are studies from the Bower group, who have developed the field of directing-group promoted C-C bond activation of cyclopropylamines.[153,169,170]

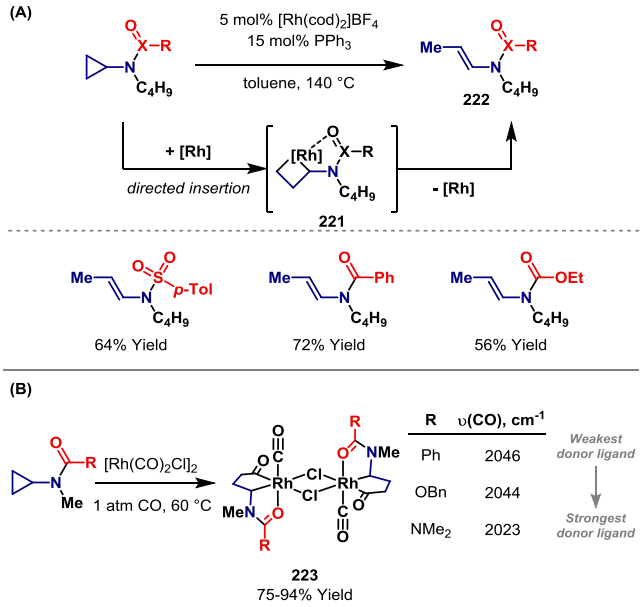
Early efforts focused on the development of a (3+1+2) cycloaddition process for the preparation of bicyclic products, such as **218** and **219** (Scheme 56).[171] These studies were inspired by seminal work from Narasaka and Koga,[172] where a tethered alkyne unit was used to direct insertion of Rh into the C-C bond of cyclopropanes. In contrast, the process in Scheme 56 uses a urea directing group to enhance the rate and control the regioselectivity of rhodacyclopentanone (**220**) formation. Directing group dissociation, alkyne insertion and C-C reductive elimination then leads to the targets.

Scheme 56. Rh-Catalyzed Carbonylative (3+1+2) Cycloadditions of Aminocyclopropanes and Alkynes



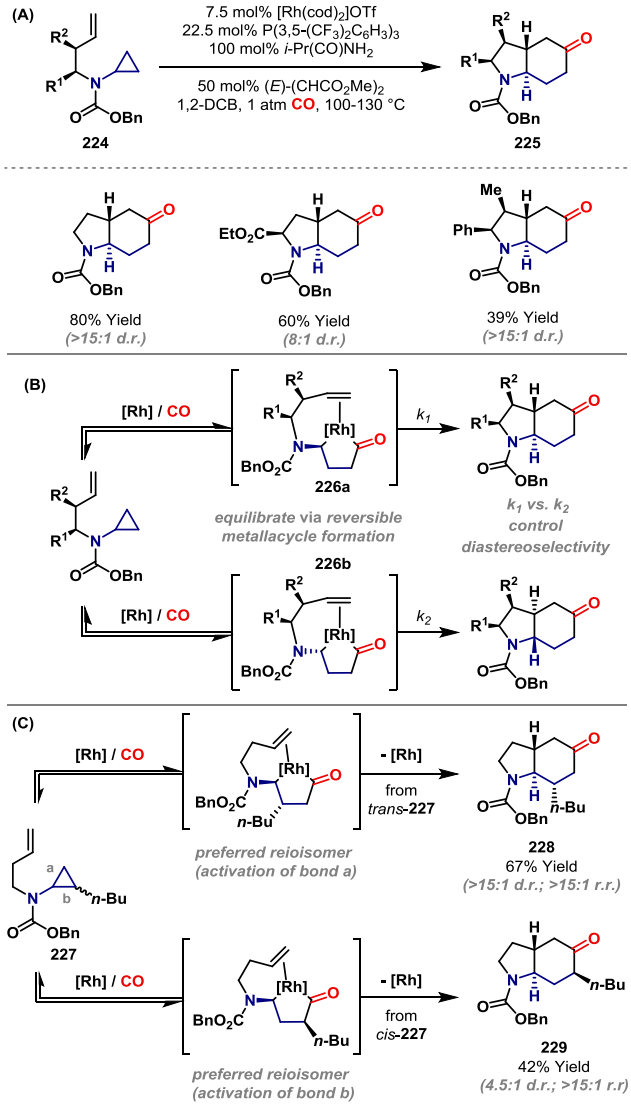
The process in Scheme 56 was underpinned by detailed studies on the directed C-C bond activation step. Different directing groups (e.g. sulfonamides, amides and carbamates) were evaluated for the ability to direct the formation of rhodacyclobutane **221** and provide N-alkenyl products **222** (via β-hydride elimination and C-H reductive elimination) (Scheme 57A). These studies were supported by the analysis of CO stretching frequencies of the corresponding rhodacyclopentanone complexes **223** – this revealed that urea directing groups are stronger donors than carbamates or amides (Scheme 57B). For the process in Scheme 56, a urea is required to outcompete the alkyne for coordination to Rh(I) prior to C-C oxidative addition of the cyclopropane. Subsequent studies showed that, under specific conditions and for certain substrates, replacement of $[Rh(cod)Cl]_2$ with $[Rh(cod)_2]OTf$ leads to higher yields and shorter reaction times.[173]

Scheme 57. Mechanistic Studies on the Directed C-C Bond Activation of Protected Aminocyclopropanes



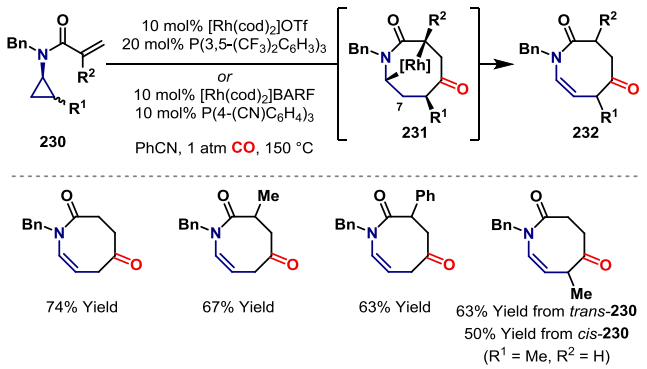
Alkenes coordinate less strongly to Rh(I) than alkynes, and so for alkene-based (3+1+2) cycloadditions, less strongly coordinating carbamate directing groups can be used.[174] This enables efficient Cbz-directed cycloadditions of **224** to provide interesting *trans*-fused heterocycles **225** (Scheme 58A). High yields required the addition of *i*-Pr(CO)NH_2 and dimethyl fumarate; the Lewis basicity of the former may assist with stabilization of the Rh-catalyst. An interesting feature of these processes is the high diastereoselectivity that is achieved with respect to the new stereocenter adjacent to nitrogen. Stoichiometric studies support a mechanism wherein *non-selective and reversible* generation of diastereomeric rhodacyclopentanones **226a** and **226b** precedes diastereo-determining alkene insertion (Scheme 58B). Geometry dependent regioselectivity was observed for 1,2-disubstituted aminocyclopropanes: cycloaddition of *trans*-**227** provided **228**, whereas cycloaddition of *cis*-**227** generated **229** (Scheme 58C). As confirmed by stoichiometric studies, these product regioselectivies reflect the inherent regiochemical preference of directed rhodacyclopentanone formation.

Scheme 58. Rh-Catalyzed Carbonylative (3 + 1 + 2) Cycloadditions of Aminocyclopropanes and Alkenes



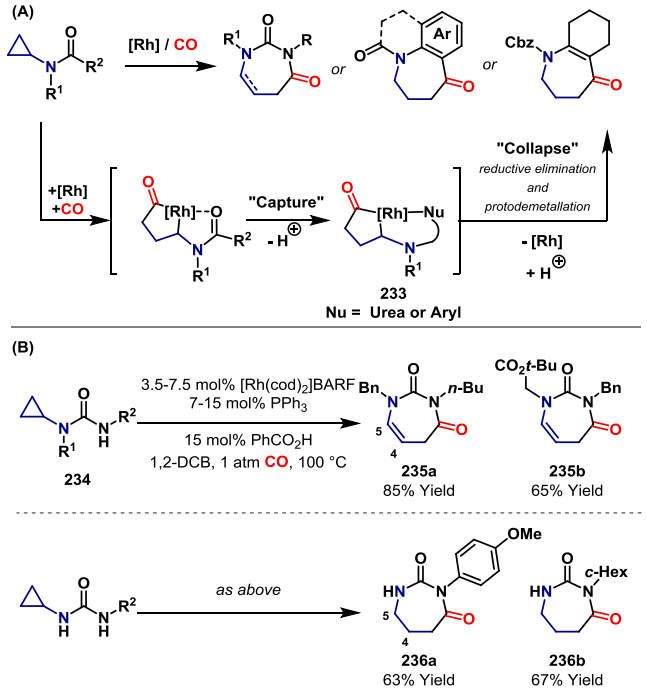
Acrylamide-based systems **230** undergo a distinct reaction pathway leading to challenging 8-membered rings **232** (Scheme 59).[175] Here, insertion of the alkene into the rhodacyclopentanone generates metallabicycle **231**, which suffers β-hydride elimination (via C7) and C-H reductive elimination to provide the targets. This pathway is supported by deuterium labelling studies. An unusual aspect is that both *trans*- and *cis*-1,2-disubstituted cyclopropanes (e.g. *trans*-**230** and *cis*-**230**, where R_1 = Me, R_2 = H) delivered the same regioisomer of the product (**232**) – a rationalization was advanced that invokes the aforementioned β-hydride elimination event as the first irreversible step in the reaction pathway.

Scheme 59. Rh-Catalyzed Carbonylative (7 + 1) Cycloadditions of Aminocyclopropanes and Alkenes



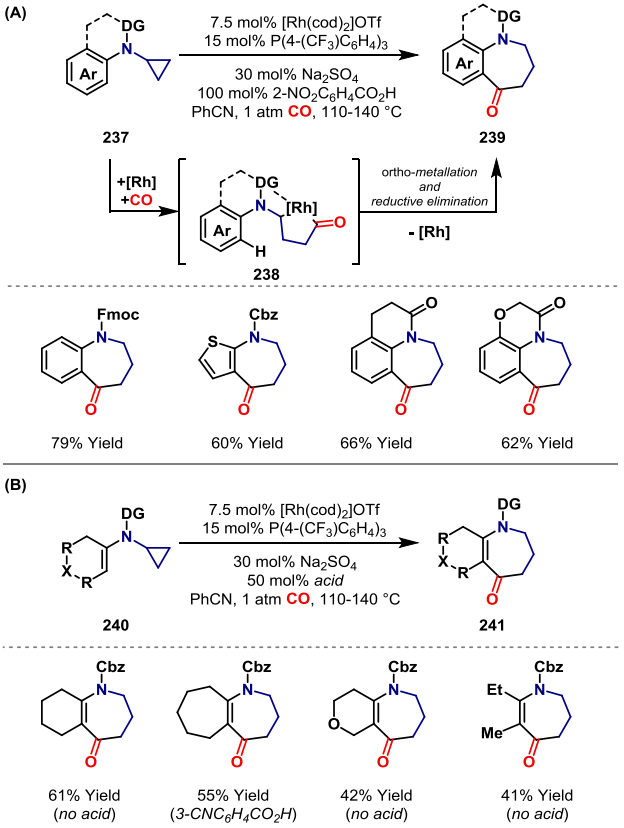
Rhodacyclopentanones generated by directed carbonylative C-C bond activation of aminocyclopropanes are sufficiently electrophilic at the Rh-center to engage conventional tethered protic nucleophiles (Scheme 60). This "capture" event generates intermediate **233** which undergoes C-N or C-C bond forming reductive elimination and protodemetallation ("collapse") to provide the challenging ring sizes (7- or 8-membered). Here, the relief of cyclopropane ring strain and the templating effect of the metallabicyclic intermediate (**233**) address the thermodynamic and entropic barriers that are typical of medium ring closures. In a prototype study, this approach was used to access 1,3-diazepanes from NH ureas **234**.[176] C4-5 unsaturated systems **235** were generated selectively for systems with substituents at R^1. Conversely, saturated products **236** formed preferentially when R^1=H.

Scheme 60. Rh-Catalyzed Carbonylative Formation of 1,3-Diazepanes from Urea-Protected Cyclopropylamines



The "capture—collapse" strategy extends to carbon-based nucleophiles. N-Aryl aminocyclopropanes **237** undergo efficient carbonylative ring expansion to provide pharmaceutically privileged benzazepines **239** (Scheme 61A).[177] Here the key rhodacyclopentanone intermediate (**238**) is used to effect *ortho*-metallation of the aryl unit in advance of the "collapse" sequence. Mechanistic studies suggest that all steps up to C-C reductive elimination are reversible. A relatively nucleophilic arene is required for metallation at the stage of **238**, suggesting that this process proceeds via an electrophilic aromatic substitution type mechanism. Based on this, investigations into other C-based nucleophiles were undertaken, and these studies showed that N-vinyl units (**240**) are also competent (Scheme 61B). This then allows access to non-benzofused azepines **241** in a direct manner.

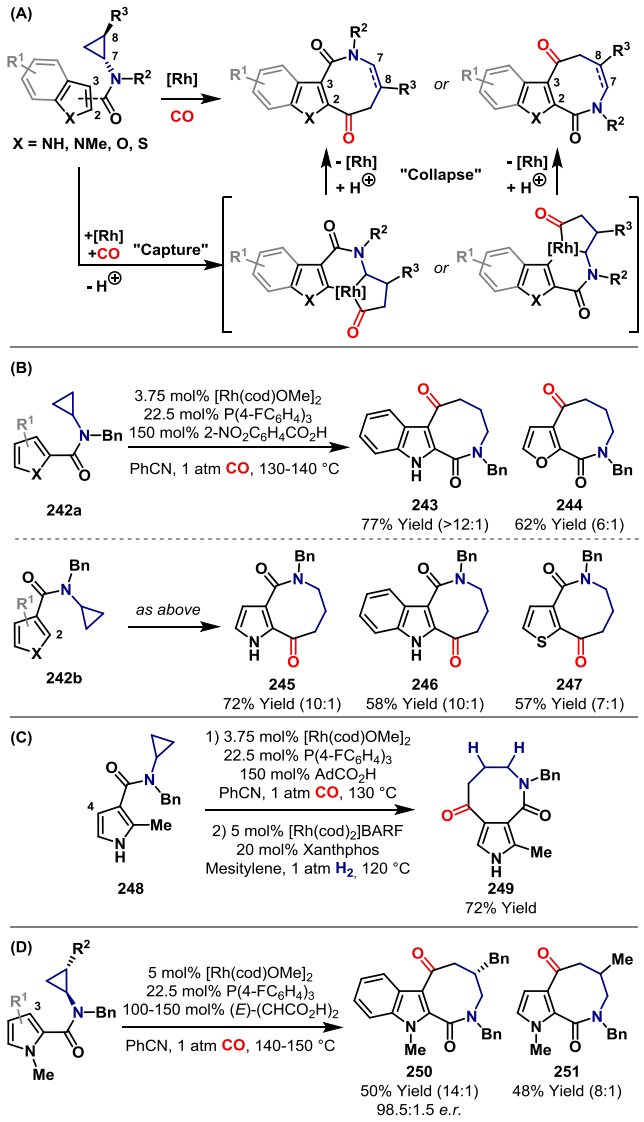
Scheme 61. Rh-Catalyzed Carbonylative Formation of Azepines from (A) Cyclopropylamines and (B) N-Vinyl Carbamates



The process described above are limited to the provision of 7-membered rings; however, if the substrate is redesigned so as the directing group and nucleophile are part of the same unit, access to more challenging 8-membered rings is also possible (Scheme 62A).[178] Using this strategy, a variety of electron rich heteroarenes **242** underwent carbonylative heterocyclization via either C3 or C2 to provide challenging 8-membered heterocycles (e.g. **243-247**) (Scheme 62B). Extensive studies were undertaken to establish conditions that gave high selectivity for the C7-C8 saturated products over the corresponding unsaturated variants. Cyclization via C4 of pyrrole **248** was also demonstrated but this provided **249** a 4:3 ratio with its unsaturated variant (Scheme 62C); this was resolved by using a separate hydrogenation step to give **249**.

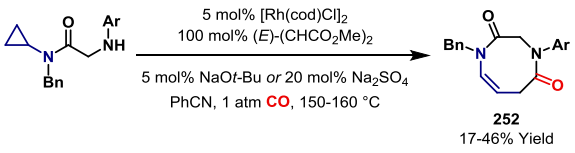
Processes involving substituted aminocyclopropanes provided access to adducts **250** and **251**; the former is derived from enantioenriched starting material (Scheme 62D).

Scheme 62. Directed Carbonylative C-C Bond Activation of Aminocyclopropanes to Generate Eight-Membered N-Heterocycles



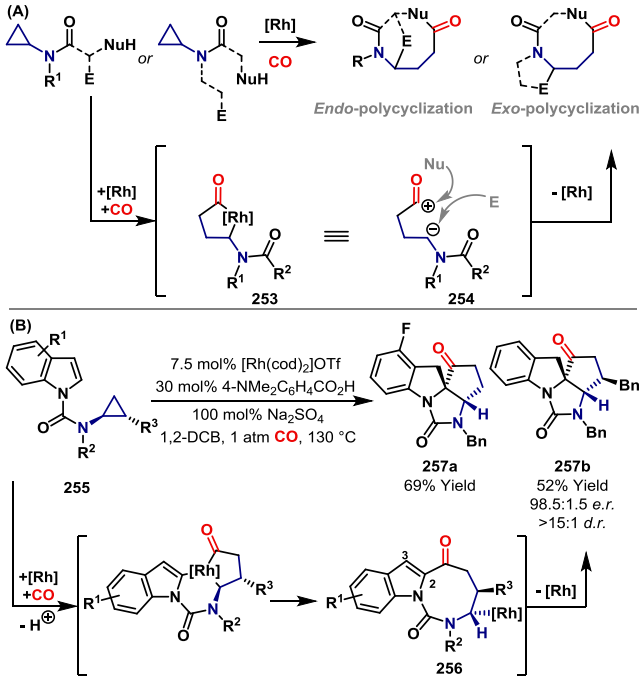
The methodology also extends to nitrogen-based nucleophiles to give 1,4-diazocane-2,5-diones **252** as demonstrated in Scheme 63.

Scheme 63. Generation of 1,4-Diazocanes by Rh-Catalyzed C-C Bond Activation of Aminocyclopropanes



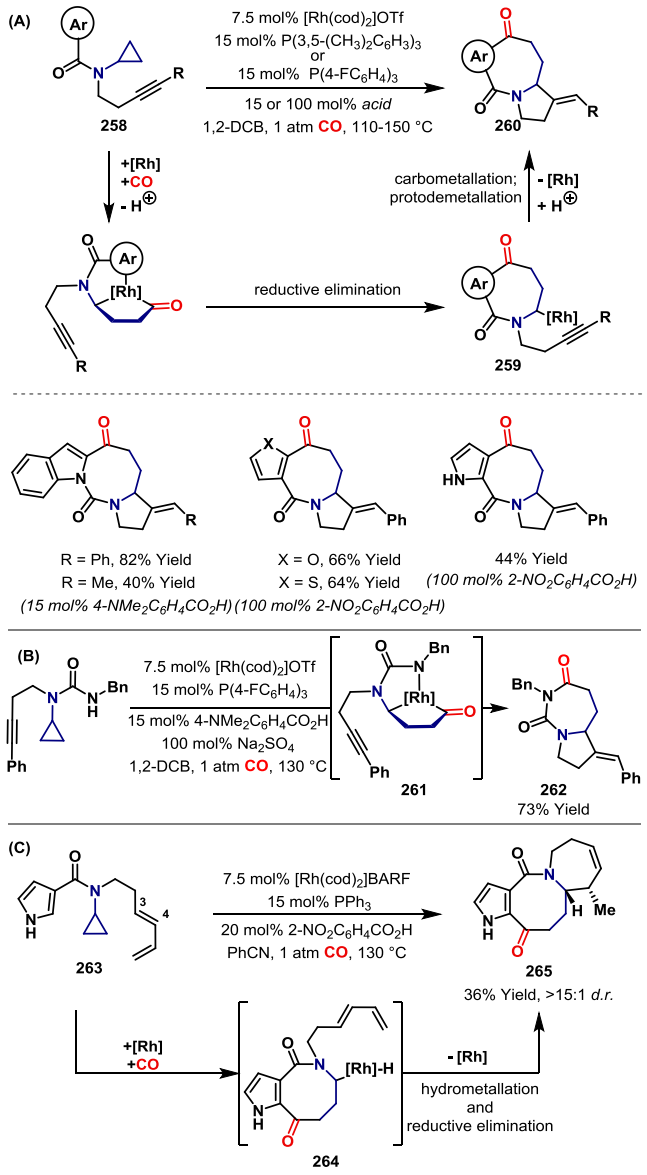
The "capture-collapse" strategy can be extended to the formation of multiple ring systems by delaying the final protodemetallation step (see Scheme 60A). In this approach, C-Nu bond forming reductive elimination is followed by carbometallation of a formally electrophilic component prior to protodemetallation (Scheme 64A).[179] This approach offers high flexibility and uses the rhodacyclopentanone **253** as a synthetic equivalent to ambiphilic synthon **254**. In one exemplar of this methodology, it was shown that indoles **255** are competent nucleophiles leading to intermediates **256**. From here, carbometallation of the indole C2-C3 π-system is followed by protodemetallation to give complex polycycles **257** (Scheme 64B). The mechanism of this process was probed experimentally and by DFT studies.

Scheme 64. Dearomatizing *Endo*-Polycyclizations of Indole Systems



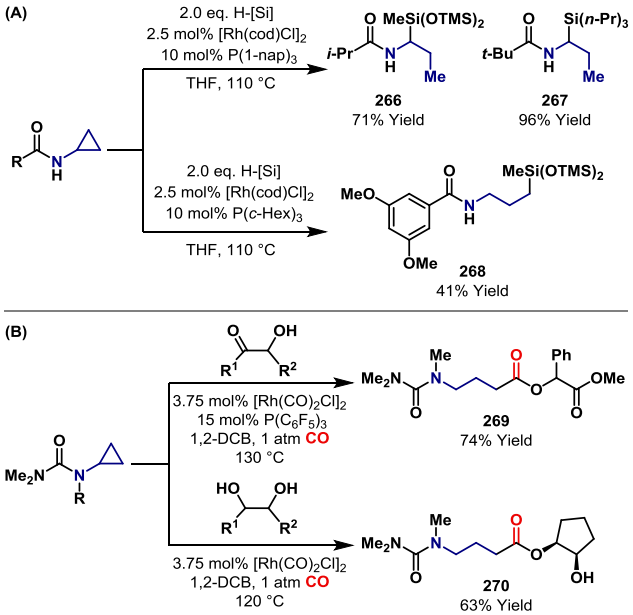
Exo-selective polycyclizations can also be achieved (Scheme 65A). For systems **258**, C-C reductive elimination generates **259** and this is followed by *syn*-stereospecific carbometallation of the alkyne prior to protodemetallation. A wide variety of electron rich arenes participate and this provided access to polycycles **260**. A related process accessed bicyclic 1,3-diazepane **262** - here the first ring forms by C-N reductive elimination from **261** (Scheme 65B). Other classes of electrophile can be used for the second cyclization. For the conversion of dienyl system **263** to polycycle **265**, a distinct mechanism was proposed involving protonation to Rh(III)-hydride **264** in advance of diene hydrometallation and C-C reductive elimination (Scheme 65C). This sequence accounts for the geometry switch observed at C3-C4.[180,181]

Scheme 65. Rh-Catalyzed *Exo*-Polycyclizations



Under certain conditions Rh-catalyzed directed C-C bond activation for aminocyclopropanes can be used for intermolecular processes. For example, the Yamaguchi group[182] reported regiodivergent Rh-catalyzed hydrosilylations of protected aminocyclopropanes under non-carbonylative conditions (Scheme 66A). Branched products (e.g. **266** and **267**) were favored when tri-1-naphthylphosphine (P(1-nap)$_3$) was used as ligand. Conversely, by using tricyclohexylphosphine, a more electron-rich and bulky ligand, regioselectivity was switched to give linear products such as **268**. Wang and co-workers[183] have shown that aminocyclopropane derived rhodacyclopentanones can be trapped by α-hydroxy carbonyl compounds or 1,2-diols to give esters, such as **269** and **270** (Scheme 66B); mechanistically, these processes are similar to the "capture-collapse" sequence shown in the Scheme 60A. It should be noted, that unsymmetrical diols gave poor regioselectivity and that the methodology is limited by the requirement for a non-labile urea directing group.

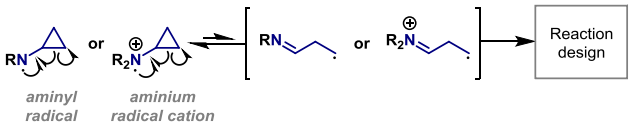
Scheme 66. Rh-Catalyzed Transformations of Aminocyclopropanes to Linear Products



6. Methodologies Based on Radical Intermediates

It has long been known that the formation of a radical at a position adjacent to a cyclopropyl ring leads to its rapid opening.[184-188] This process is often used as a "radical clock" for kinetic studies of radical reactions.[189] Within the context of aminocyclopropanes, fragmentation of an aminyl radical or aminium radical cation leads to the fast formation of more stable imine or iminium π-bonds (Scheme 67).

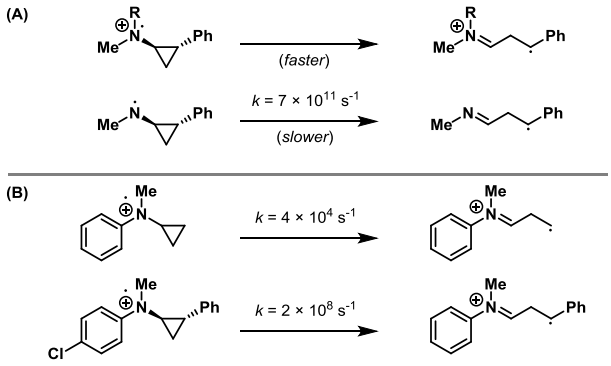
Scheme 67. Ring Opening of N-Centered Cyclopropylamine Radicals and Radical Cations



Radical clocks based on the cyclopropylamine systems have been used to detect aminium radical cations in enzymatic amine oxidations[190-201] and related chemical systems.[202-210] In general, reactions involving relatively stable aminyl radicals are much slower than those of their aminium cation radical counterparts (Scheme 68A).[211,212] However, for N-arylated cyclopropylamines, the opposite trend is observed because the rate for ring opening of the aminium cation radical is attenuated by its stabilization by the aromatic ring.[213] It was noted that the rate of reaction for such substrates increases with the incorporation of radical-stabilizing groups (e.g., phenyl) onto the cyclopropyl ring (Scheme 68B).[214]

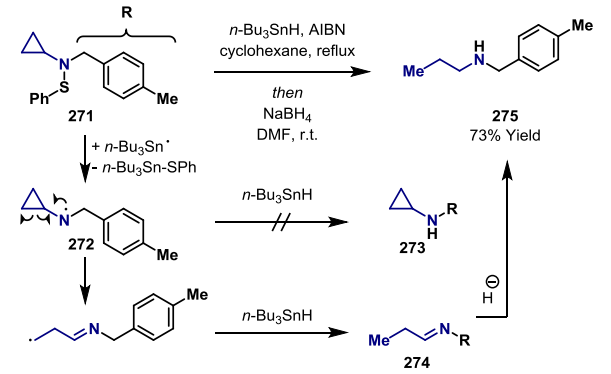
Accordingly, N-arylated cyclopropylamine substrates are not always reliable probes for confirming the presence of single electron transfer events. However, systems of this type have been used to probe the oxidative properties of triplet-state chromophoric dissolved organic matter.[215]

Scheme 68. Rates of Ring Opening for Some N-Centered Radical Intermediates



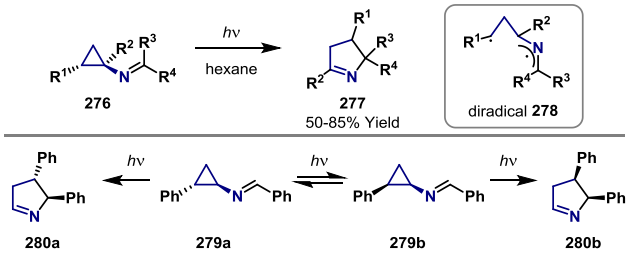
The susceptibility of aminocyclopropane based systems to undergo radical-based ring cleavage underpins a wide range of synthetic methodologies. Bowman and co-workers[216,217] have demonstrated how sulfenamides can be used as precursors to *N*-cyclopropylaminyl radicals (Scheme 69). Here, exposure of the substrate (e.g. **271**) to tributylstannyl radical effects homolytic cleavage of the weak N-S bond to provide **272**. Hydrogen atom abstraction then generates **274** which undergoes reduction to amine **275** ($NaBH_4$) prior to work-up. Only ring-opened products (**275**) were generated and competitive reduction to NH cyclopropanes (**273**)[218] was not observed. Similar transformations of N-sulfonyl aminocyclopropanes have been achieved during reductive S-N cleavage promoted by photoactivated neutral organic super electron donors.[219]

Scheme 69. Reductive Cleavage of Cyclopropyl Sulfenamides



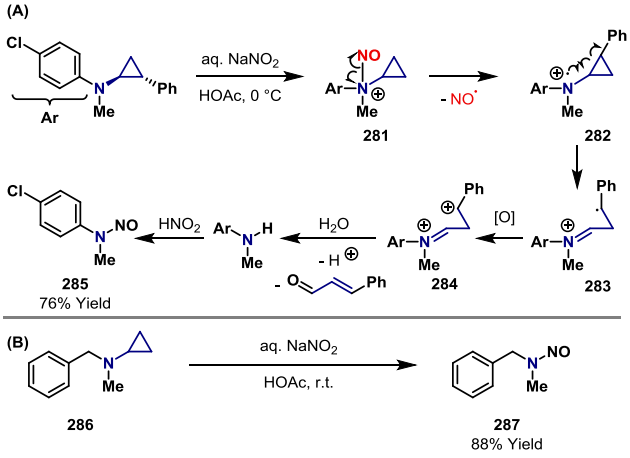
Another way to access *N*-centered radical-like reactivity is via photoexcitation of corresponding cyclopropylimines. Rodríguez, Campos and co-workers[220] reported the first photochemical rearrangements of *N*-cyclopropylimines **276** to 1-pyrrolines **277** (Scheme 70). This transformation builds up on a wider class of vinylcyclopropane rearrangements and the corresponding thermal rearrangements have also been reported.[221-224] Mechanistic and computational studies[225] revealed that there is no equilibrated excited-state intermediate (well-defined energy minimum) along the reaction pathway and that, on a model compound, the process proceeds via a "continuous diradical" **278**.[226] This diradical is accessed by relaxation of a singlet π-π* excited state that arises when **276** absorbs light. When substituted aminocyclopropanes are used, starting material epimerization (**279a** to **279b**) and rearrangement (**279** to **280**) have similar rates, such that the stereoselectivity of the processes decreases over the course of the reaction. This transformation has also been described for related *N*-cyclopropylimines bearing different substituent patterns.[29,227]

Scheme 70. Photochemical Rearrangement of N-Cyclopropylimines to 1-Pyrrolines



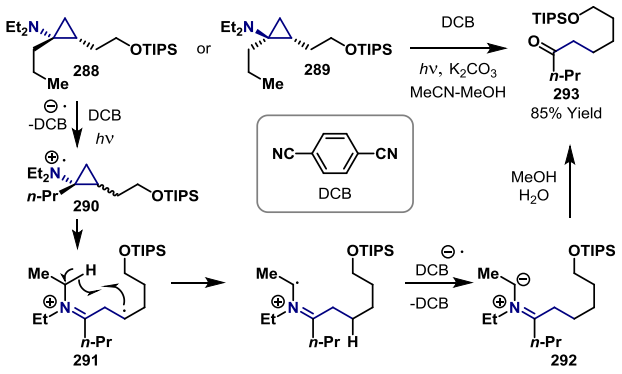
The generation of iminum cation radicals occurs during the nitrosation of *N*-cyclopropylanilines (Scheme 71A).[205] Here, the initially generated nitrosamine **281** undergoes N-N homolysis to provide **282**. Ring opening to iminium **283** is followed by oxidation of the benzylic radical to its corresponding carbocation **284** prior to E1 like elimination. After hydrolysis, this generates cinnamaldehyde and aniline, which undergoes nitrosation to provide **285**. Interestingly, an N-aryl unit is not required, and the conversion of N-benzyl analogue **286** to **287** was still efficient, albeit using a slightly higher reaction temperature (Scheme 71B).

Scheme 71. Nitrosation of N-Cyclopropylanilines



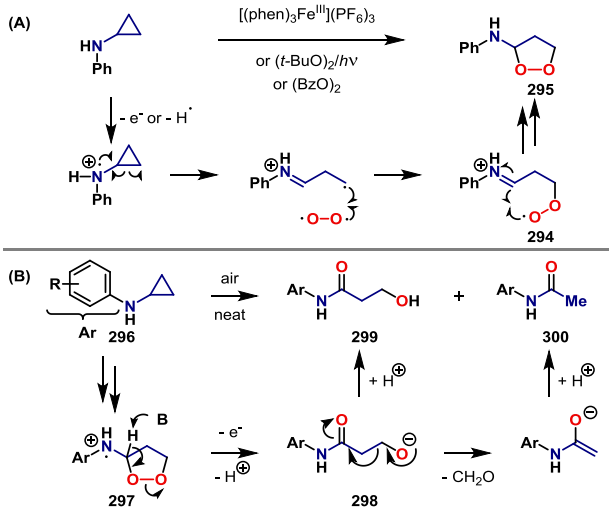
Other oxidants can also be used to promote the cleavage of aminocyclopropanes via aminium cation radicals. For example, 1,4-dicyanobenzene (DCB) photosensitized oxidation of tertiary aminocyclopropanes **288** or **289** was shown to afford ketone **293** (Scheme 72).[228] Here, initial oxidation to **290** triggers ring cleavage to 2° alkyl radical **291**. 1,5-Hydrogen atom abstraction and reduction generates **292**, which affords **293** by protonation and hydrolysis. A similar process was described by Joullié and Faler,[229] where air was invoked as the oxidant.

Scheme 72. DCB Photosensitized Oxidation of Tertiary Aminocyclopropanes



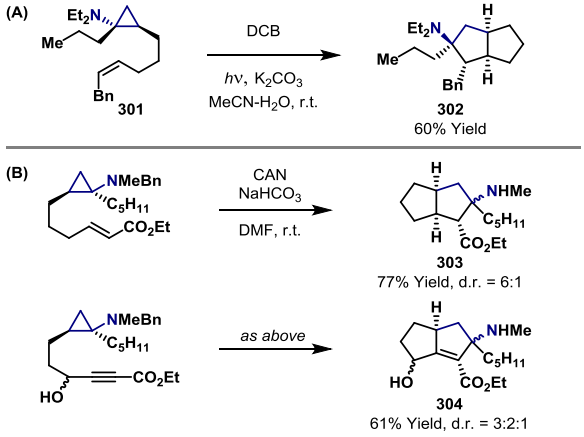
The cyclopropylaminium radical can also be trapped out with molecular oxygen to provide endoperoxides, such as **295**, under various conditions, as demonstrated by Wimalasena and co-workers (Scheme 73A).[230] Here, Fe(III) or peroxide promoted conditions were used for reaction initiation. Ring opening of the radical cation is followed by reaction with oxygen, which leads to cycloadduct **294**. Later, Six, Buriex and co-workers[231,232] showed that similar transformations are feasible under aerobic electrochemical conditions. The formation of endoperoxides has even been observed during purification of functionalized *N*-cyclopropylanilines on silica gel; the use of neutral alumina suppressed this pathway.[233] Indeed, *N*-cyclopropylanilines are readily prone to decomposition in air, as reported by Blackburn and co-workers (Scheme 73B).[234] In this work, simple aerobic oxidation of *N*-cyclopropylanilines **296** gave β-hydroxypropionamides **299** and dehomologated products **300**. A plausible pathway involves base-mediated decomposition of cyclic peroxide **297** to form alkoxide **298**. This undergoes either protonation (to **299**) or retro-aldol reaction (to **300**).

Scheme 73. Reaction of Cyclopropylaminium Radicals with Molecular Oxygen



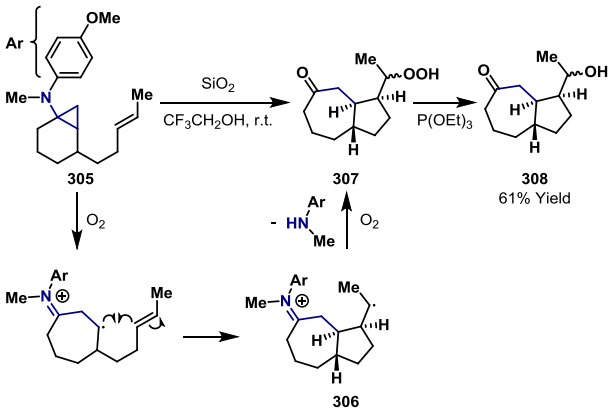
The radical based cycloadditions of aminocyclopropanes with oxygen described above are part of a wider range of related cycloaddition processes. Indeed, in addition to oxygen, the cation radical that forms on ring opening can be trapped by various pendant π-unsaturates (alkenes and alkynes) to give new ring systems. In 1998, the Cha and Iwata groups independently reported that bicyclic compounds can be produced from substituted cyclopropylamines.[235,236] Cha and co-workers showed that substrates **301**, bearing tethered olefins, give bicyclic products **302** by photosensitized chemical oxidation with DCB (Scheme 74A). A drawback of this methodology is that the tertiary amine functionality of the products is unstable to the reaction conditions, and this results in compromised yields due to product degradation. The Iwata group circumvented this problem by using an alternate initiating strategy where cerium ammonium nitrate (CAN) cleaves an *N*-benzyl unit (Scheme 74B). This gives a secondary amine (e.g. **303**) as the product, which is more resistant to subsequent oxidation. Under the same conditions, systems containing tether alkynes cyclize to provide bicyclic cyclopentenes (e.g. **304**).

Scheme 74. Reaction of Cyclopropylaminium Radicals and Pendant π-Unsaturates



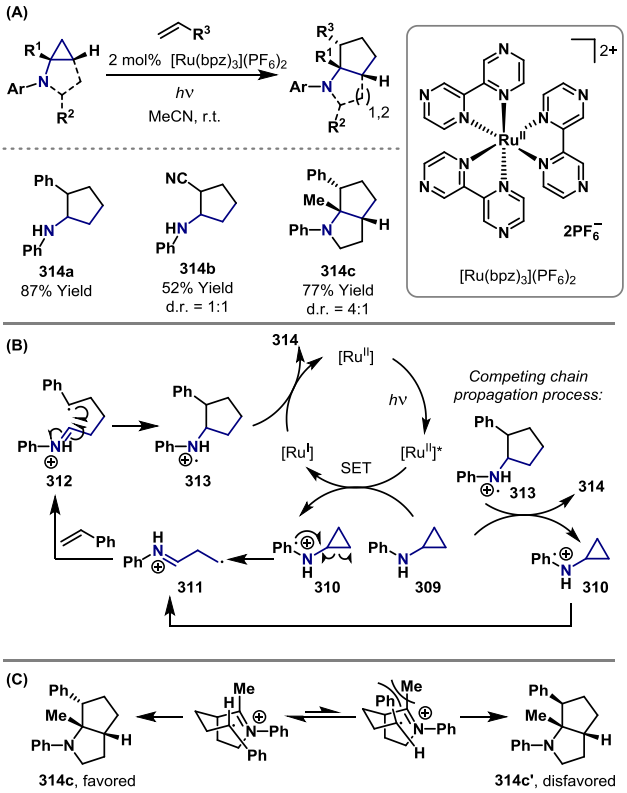
Cha and co-workers[237] showed that, under aerobic conditions, cycloadditions to N-aryl cyclopropylamines with alkenes can be "interrupted" to give peroxy compounds. For example, silica promoted aerobic cleavage of **305** triggered cyclization to radical **306**, which was trapped by oxygen to provide **307**. Reduction of the peroxide was achieved using $P(OEt)_3$[238] and this generated **308** in 61% yield (Scheme 75). The method represents a powerful approach to complex carbocycles with the aminocyclopropane unit functioning as both a radical precursor and masked ketone.

Scheme 75. Aerobic C-C Bond Cleavage of Substituted Cyclopropylaniline



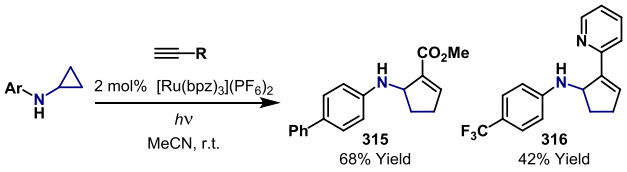
In 2012, the first intermolecular photocatalytic cycloaddition between cyclopropylamines and alkenes was reported by Zheng and co-workers (Scheme 76A).[239,240] A plausible mechanism starts with the oxidation of **309** to cyclopropylaminium radical **310** promoted by a photoexcited Ru(II) complex. The radical then undergoes ring-opening to give radical cation **311**, which undergoes Giese-like reaction with the olefin.[241] Intramolecular addition of the carbon centered radical **312** to the iminium ion is followed by reduction to **314** by the Ru(I) complex, which closes the photoredox cycle (Scheme 76B). Mechanistic studies[242] showed that, alongside the photoredox process, a competing chain process is operative, where starting material **309** is oxidized by radical cation **313**. The process offers good levels of diastereocontrol when the starting cyclopropylamine is bicyclic; for example, **309c** was obtained in 4:1 d.r. The selectivity was rationalized by considering the relative stability of the relevant envelope like transition states involved in the ring closing step (Scheme 76C).

Scheme 76. Photocatalytic Cycloadditions between Cyclopropylamines and Alkenes



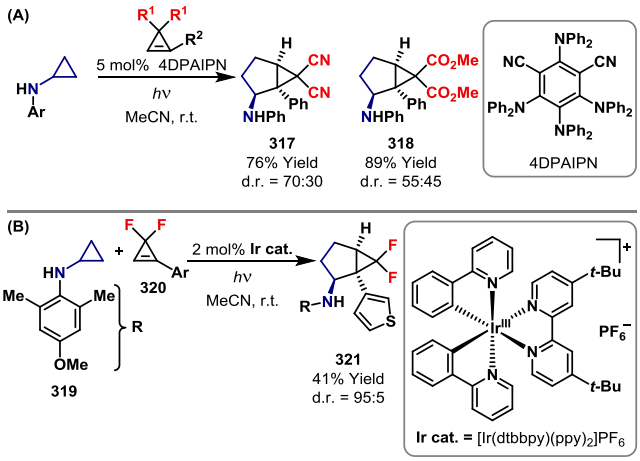
The processes described above were expanded to incorporate alkynes as a "2-component"; this provided versatile access to aminocyclopentenes, such as **315** and **316** (Scheme **77**).[243] Subsequently, diynes and enynes were also found to be competent reaction partners.[244]

Scheme 77. Photocatalytic Cycloadditions between Cyclopropylamines and Alkynes



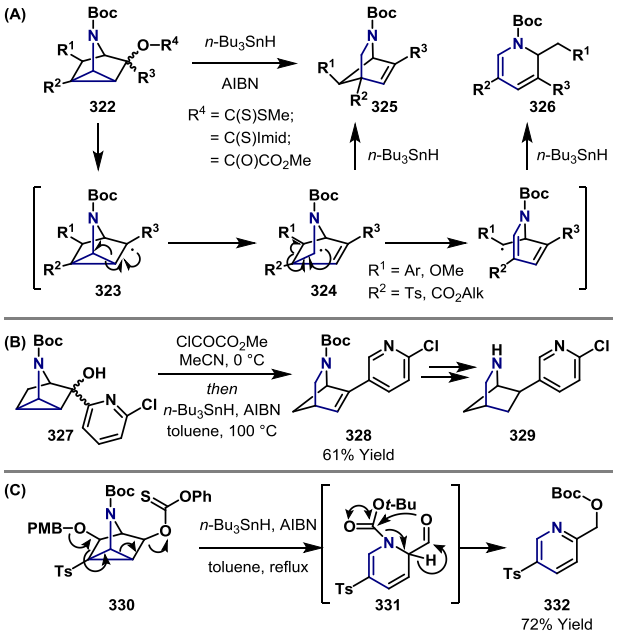
As a further expansion of this avenue, Waser and co-workers[245] reported the synthesis of bicyclo[3.1.0]hexanes (e.g. **317** and **318**) from cyclopropenes and cyclopropylanilines using either an organic or iridium-based photoredox catalyst (Scheme 78). 2,4,5,6-Tetrakis(diphenylamino)isophthalonitrile (4DPAIPN) was used as a general catalyst for this process, however, it gave moderate diastereoselectivity with most of substrates (Scheme 78A). The combination of the less oxidizing $[Ir(dtbbpy)(ppy)_2]PF_6$ photocatalyst, difluorocyclopropenes and an electron rich cyclopropylaniline **319** was found to be the best for achieving high levels of diastereoselectivity in this transformation (Scheme 78B). For example, under these conditions, cycloaddition of **319** with **320** provided **321** in 95:5 d.r.

Scheme 78. Synthesis of Bicyclo[3.1.0]hexanes from Cyclopropenes and Cyclopropylanilines



The processes described so far in this section have triggered ring cleavage of the amino cyclopropane by generating a radical at nitrogen. However, the ring strain inherent in this unit allows other types of ring cleavage process. Hodgson and co-workers have studied extensively the fate of Boc-protected bridged cyclopropylamines **322** when exposed to *n*-Bu_3SnH/AIBN (Scheme 79). Radical intermediates **323** can be accessed from the corresponding xanthate, thiocarbonylimidazolide or oxalyl ester. β-Scission of **323** to **324** is promoted by relief of ring strain and the resulting radical **324** can be trapped directly by *n*-Bu_3SnH to provide **325**. Alternatively, dihydropyridines **326** can be accessed via further rearrangement before the trapping event (Scheme 79A).[246] This methodology has been used to transform **327** to **328**, which is a precursor en route to epibatidine analogue **329** (Scheme 79B).[247,248] A related rearrangement strategy was developed for the synthesis of kainoid amino acids.[249] In certain cases, alternate pathways can predominate; for example, pyridine derivative **332** was generated from thiocarbonate **330** (Scheme 79C).[250] This process likely involves a non-radical-based rearrangement to give 1,2-dihydropyridine aldehyde **331** as an intermediate.

Scheme 79. Radical-Based Rearrangements of Bridged Cyclopropylamines



7. CONCLUSION AND OUTLOOK

This review outlines diverse processes based on the selective C-C bond cleavage of cyclopropylamine derivatives. The generation of reactive species from the cyclopropylamine precursor can be achieved by various approaches. This enables cyclopropylamines to be exploited as reactive units in various fields of synthetic chemistry, including catalysis promoted by Lewis acids, transition metals, and photoredox active species. Cycloaddition processes are a common methodological application for cyclopropylamine-based substrates, often providing quick access to complex N-heterocyclic structures. This area has gained considerable traction in recent years and new methodologies offer elegant and diverse transformations.

Possible avenues or future development include: (a) the exploitation of unstable cyclopropylamine derivatives in reaction design; (b) the further development of methodologies that are not dependent upon the presence of bespoke substituents on the cyclopropylamine ring; and (c) the greater integration of cyclopropylamines into enantiospecific or enantioselective transformations.

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Notes

The authors declare no competing financial interest.

Biographies

Olga O. Sokolova graduated from the Higher Chemical College (HCC RAS, MUCTR) in 2016, where she researched electrochemical and multicomponent reactions with Prof. Mikhail

N. Elinson at the Zelinsky Institute of Organic Chemistry (2011-16). She did a short project with Dr. Vladimir V. Burlakov (Nesmeyanov Institute of Organoelement Compounds) and she has also undertaken summer placements with Prof. John F. Bower and with Prof. Antonio M. Echavarren (Institut Català d'Investigació Química). She began her Ph.D. studies in 2016 under the supervision of John F. Bower, where she is developing new rhodium-catalyzed C−C activation-based methodologies.

John F. Bower obtained an M.Sci. in 2003 from the University of Bristol, where he remained to study for a Ph.D. (2007) under the guidance of Professor Timothy Gallagher. He then undertook postdoctoral appointments with Professor Michael Krische at the University of Texas at Austin (2007–2008) and Professor Timothy Donohoe at the University of Oxford (2008–2010). In 2010, he was awarded a Royal Society University Research Fellowship and commenced his independent career at the University of Bristol where he was promoted to Professor in 2017. In 2020, he was appointed to the Regius Chair of Chemistry at the University of Liverpool. His research has been recognized by a number of awards and fellowships, including the 2013 Royal Society of Chemistry Harrison−Meldola Memorial Prize, the 2015 Royal Society of Chemistry Hickinbottom Award, a 2016 Philip Leverhulme Prize, a 2014 ERC Starter Grant and a 2019 ERC Consolidator Grant.

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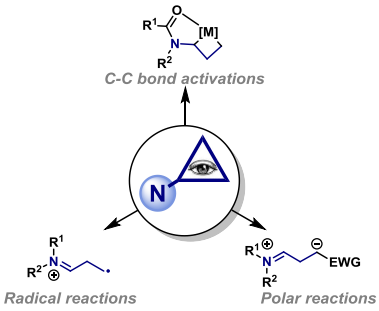
Table of Contents artwork


C-C bond activations
Radical reactions
Polar reactions
EWG