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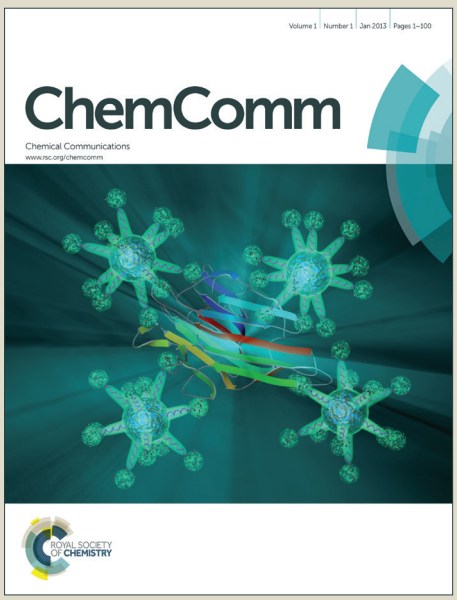

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ARTICLE

Cyclization and Annulation Reactions of Nitrogen-Substituted Cyclopropanes and Cyclobutanes

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Cyclization and annulation reactions initiated by ring-opening of small rings, especially cyclopropanes and cyclobutanes are now well-established in synthetic chemistry. Nevertheless, the potential of aminocyclopropanes and cyclobutanes, an important subclass for the synthesis of nitrogen-rich building blocks, has remained unexploited for a long time, despite important pioneering results. In the last decade, the situation has changed dramatically and new catalytic methods have emerged both for cyclization and annulation reactions. The purpose of this feature article is to present recent progress in this area, including our own work using donor-acceptor substituted cyclopropanes and cyclobutanes.

1. Introduction

Cyclic compounds incorporating nitrogen functionalities are omnipresent in pharmaceuticals and bioactive natural products. Many synthetic compounds are based on flat aromatic ring systems, whereas natural products are richer in saturated nitrogen-substituted hetero- and carbocycles. This is probably due to the synthetic challenges associated with the stereoselective synthesis of saturated (poly)cyclic systems, which artificially limits the chemical space of compounds routinely examined in the pharmaceutical industry. Indeed, a broader availability of chemical libraries with more varied three-dimensional structures has been identified as one of the most urgent needs in medicinal chemistry.[1] This goal can be achieved only with the development of new efficient methods for the stereoselective synthesis of (poly)cyclic saturated compounds. In this context, nitrogen-substituted five- and six-membered rings are frequently encountered in bioactive compounds, both natural and synthetic (Figure 1). Consequently, efficient methods to access such ring systems would be highly valuable for the discovery of new bioactive molecules with enhanced properties.

In principle, a saturated carbo- or heterocycle can be generated either by a cyclization (one bond formed) or an annulation reaction (two or more bonds formed). The former may be easier to control, whereas the latter is more convergent and better suited for a fast entry into molecular complexity. In this context, ring expansion of cyclopropanes or cyclobutanes is a particularly attractive strategy, as the ring strain present in these molecules (around 27 and 26 kcal/mol respectively) allows the generation of reactive intermediates under mild conditions.[2] Nevertheless, unsubstituted cyclopropanes and cyclobutanes are still relatively inert, and their reactivity needs to be further increased by the introduction of substituents on the ring. For example, heterolytic bond cleavage becomes easier in the presence of either electron-donating or electron-withdrawing groups, which increase the polarisation of the bonds.

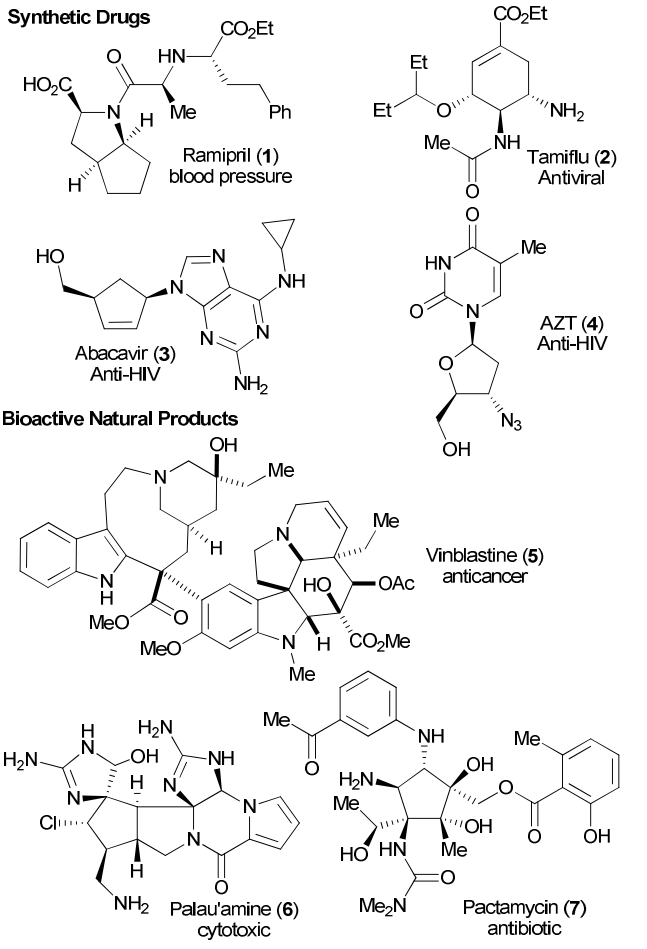
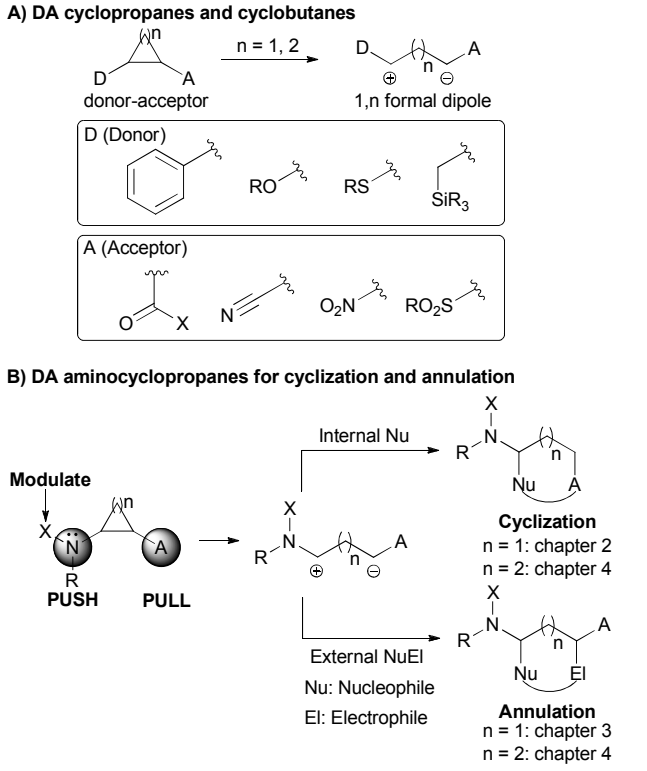


Figure 1. Important synthetic and natural bioactive compounds containing nitrogen-substituted five- and six-membered rings.

The generation of reactive intermediates is especially facile in the case of the 1,2-donor-acceptor substituted ring systems (DA cyclopropanes and cyclobutanes), which have been extensively studied in cyclization and annulation reactions (Scheme 1, **A**).[3] In the context of the synthesis of nitrogen-substituted ring systems, the use of aminocyclopropanes and aminocyclobutanes appears especially attractive, as the nitrogen atom is at the same time an important steering element to promote ring-opening and a desired functionality in the product (Scheme 1, **B**). Surprisingly, although many isolated examples were known, the potential of nitrogen-substituted DA systems was not systematically exploited in the synthesis of ring systems until very recently. Most studies on this class of compounds were focussed on their high structural rigidity, which led to their widespread used in medicinal chemistry, especially as peptide mimetics.[4] In contrast, the chemistry of DA systems bearing carbon or oxygen donor groups has been highly successful.[3] This is probably because modulating electronic density on nitrogen to find the right balance between stability and reactivity is especially challenging. The purpose of this feature article is to present pioneering work and recent progress in this area. The review will begin with cyclization reactions of aminocyclopropanes (chapter 2) and will continue with their annulation reactions (chapter 3). Finally, the much less developed chemistry of aminocyclobutanes will be presented in chapter 4.

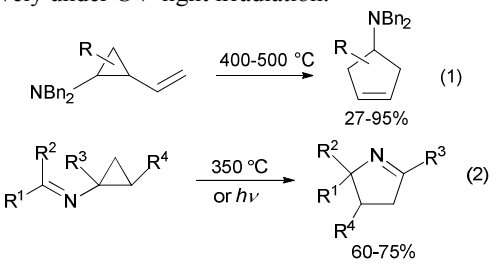


Scheme 1. DA small rings (**A**) and DA amino-substituted small rings in cyclization and annulation reactions (**B**).

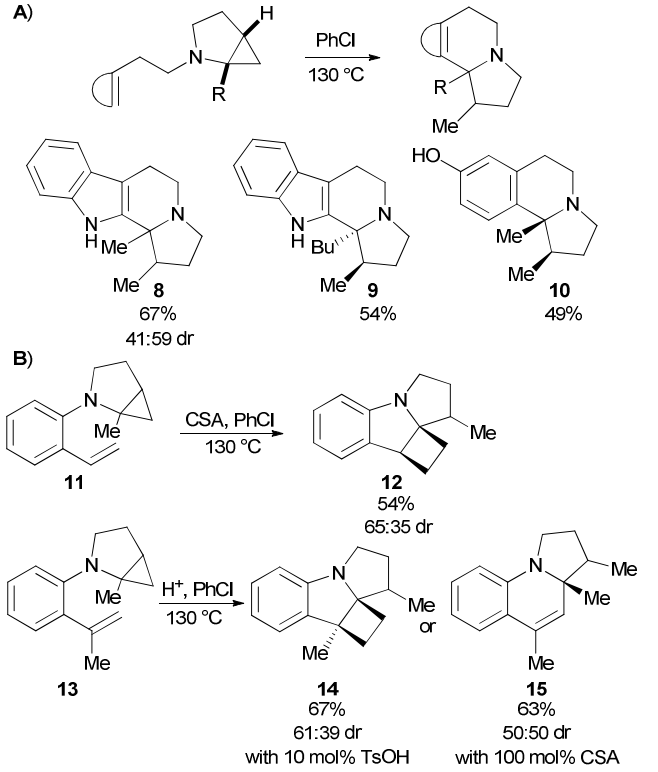
2. Cyclization Reactions of Aminocyclopropanes

2.1 Cyclizations with Non-Activated Aminocyclopropanes

In general, it is difficult to control the regioselective ring-opening of aminocyclopropanes bearing no acceptor substituent under mild conditions. It is therefore not surprising that studies involving such compounds are rare and often are based on rearrangement involving further π systems in the molecule. Two representative examples are the vinylcyclopropane to cyclopentene rearrangement (eqn 1)[5] and the synthesis of pyrrolines from imines derived from aminocyclopropanes (eqn 2).[6] The former needs usually to be performed at high temperature under flash vacuum pyrolysis conditions, except if electron-withdrawing substituents are introduced on the olefin.[5c] The latter can also be run at high temperatures or alternatively under UV-light irradiation.[6]



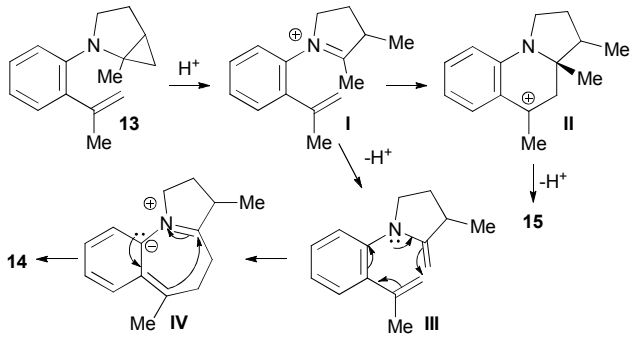
An interesting study has been performed by Six and co-workers, who demonstrated that ring-opening of bicyclic aminocyclopropanes was possible under milder thermal conditions.[7] They first reported in 2005 the intramolecular cyclization of aminocyclopropanes on electron-rich aromatic rings, such as indoles or phenols to give polycyclic compounds **8-10** in 49-67% yield (Scheme 2, **A**).[7b]



Scheme 2. Cyclization of bicyclic aminocyclopropanes on aromatic ring (**A**) and styrene derivatives (**B**).

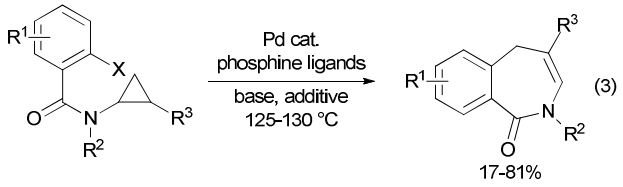
In 2013, they reported the acid-mediated rearrangement of aniline derivatives **11** and **13** (Scheme 2, **B**).[7c] The reaction of

terminal olefin **11** in presence of a stoichiometric amount of camphorsulfonic acid (CSA) gave exclusively aminocyclobutane **12** in 54% yield, whereas dihydroquinoline derivative **15** was obtained under the same conditions for geminally disubstituted olefin **13**. In this case, the corresponding aminocyclobutane **14** could be obtained if a catalytic amount of acid was used. Mechanistically, this type of reaction has been proposed to proceed via an iminium intermediate **I**, which would be generated upon acid-mediated ring opening (Scheme 3). Direct cyclization to give carbocation **II**, a reaction facilitated by the presence of the methyl group, would lead to formation of dihydroquinoline **15** after elimination. On the other hand, isomerization to enamine **III**, followed by two successive electrocyclic reactions via intermediate **IV** would give cyclobutane **14**.

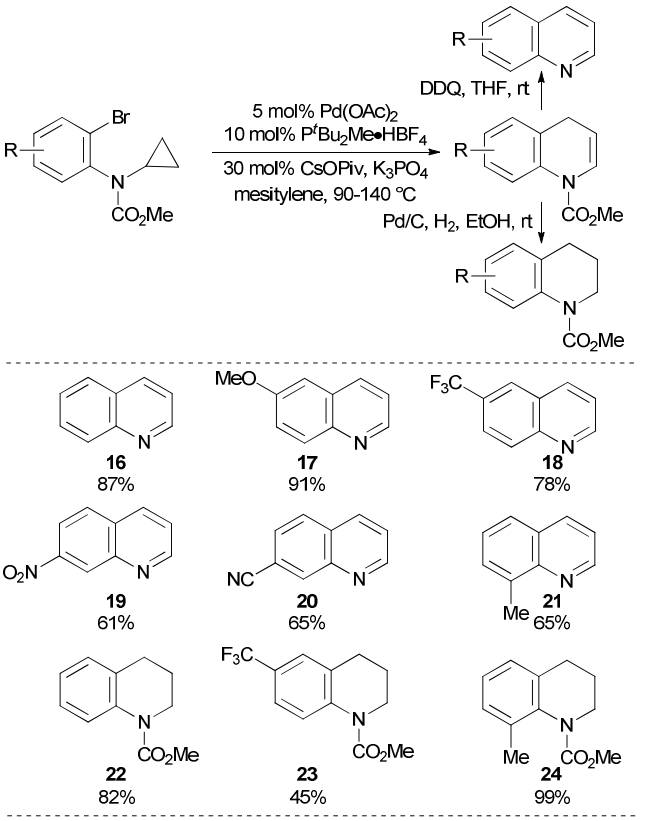


Scheme 3. Proposed mechanism for the cyclization of bicyclic aminocyclopropane **13**.

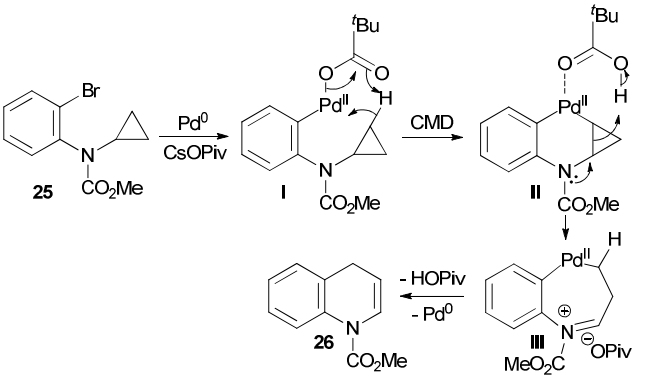
Transition metal catalysts have been broadly applied in the activation of strained rings, especially cyclopropanes. It is consequently surprising that no example involving aminocyclopropanes was known until 2012, when Rousseaux, Liegault and Fagnou reported the first palladium-catalyzed ring expansion of cyclopropyl anilines to give dehydroquinolines (Scheme 4).[8] The sensitive products could be either oxidized or reduced to the more stable quinolines **16**-**21** or tetrahydroquinolines **22**-**24** respectively. Mechanistically, the reaction has been proposed to be initiated by oxidative addition of palladium onto the C-Br bond of bromide **25** and anion exchange to give palladium(II) pivalate intermediate **I** (Scheme 5). The palladium center is now ideally positioned to promote C-H functionalization on the cyclopropane via a Concerted-Metalation-Deprotonation (CMD) mechanism. At this point, the strong electron-donating capacity of nitrogen promotes ring opening of **II**, eventually assisted by the pivalic acid. Finally, deprotonation and reductive elimination from **III** leads to the observed product **26**. In 2012, Grimaud, Al Kaïm and co-workers then reported an efficient access to the needed anilines and heterocyclic derivatives thereof using an Ugi multi-component reaction.[9] In the same work, they then extended the methodology to benzoic amide derivatives to access seven-membered rings (eqn 3).



Finally, the scope of benzamides for this transformation was studied more in detail by Charette and co-workers in 2013, who also further optimized the reaction conditions.[10]



Scheme 4. Pd-catalyzed cyclization of aminocyclopropanes.

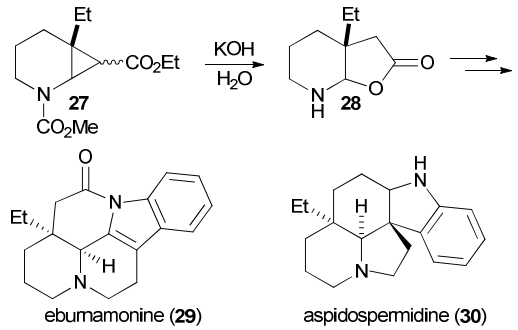


Scheme 5. Proposed mechanism for Pd-catalyzed cyclization of aminocyclopropanes.

2.2 Cyclizations with Donor-Acceptor Substituted Aminocyclopropanes

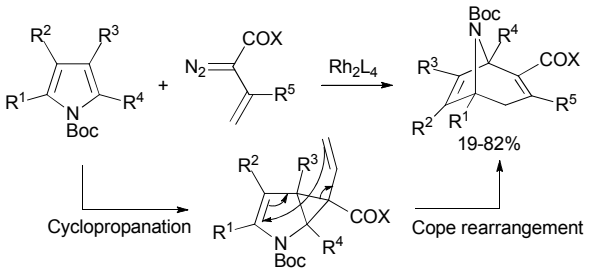
We have seen in the previous section that aminocyclopropanes lacking acceptor substituents are often difficult to activate, requiring harsh conditions or allowing only limited transformations. In contrast, the introduction of an acceptor substituent leads to very reactive DA cyclopropanes. Calculations by Schneider and Werz have indeed shown that

ring-opening is very facile for this class of compounds.[11] In fact, the reactivity is now so high that the aminocyclopropanes often open spontaneously. Pioneering work in this area was done by Wenkert and co-workers, who introduced DA aminocyclopropane **27** as a key building block for the synthesis of indole alkaloids, such as eburnamonine (**29**) and aspidospermidine (**30**) (Scheme 6).[12] In this work, ester-substituted aminocyclopropane **27** was usually immediately hydrolysed to give lactone **28**.



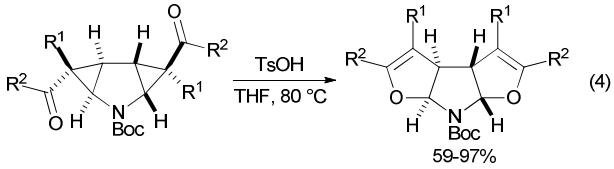
Scheme 6. DA cyclopropane **27** as building block for alkaloid synthesis.

Surprisingly, there were only few examples on further use of cyclization reactions of DA cyclopropanes after this seminal work. For example, Park and co-workers reported in 2012 that 2-amino furans could be obtained from diazo compounds and enamines in the presence of a copper catalyst, but the putative cyclopropane intermediate was not isolated.[13] An important exception is constituted by the special class of DA cyclopropanes obtained through the cyclopropanation of pyrroles and indoles. These cyclopropanes are usually highly reactive and cannot be isolated, as ring-opening occurs immediately. An interesting transformation was reported by Davies and co-workers in 1997 (Scheme 7).[14] In this case, pyrroles were reacted with vinyl-substituted donor-acceptor substituted diazo compounds in the presence of a rhodium catalyst. The formed DA aminocyclopropanes immediately rearranged to form tropane derivatives via a Cope rearrangement. The use of a chiral catalyst led to the formation of enantioenriched products with up to 51% ee. Alternatively, a chiral auxiliary on the ester group of the diazo compound could also be used. 5,5- and 6,4- bicyclic side products resulting from the rearrangement of zwitterionic intermediates were also observed during the reaction.



Scheme 7. Synthesis of tropanes via the cyclopropanation of pyrroles.

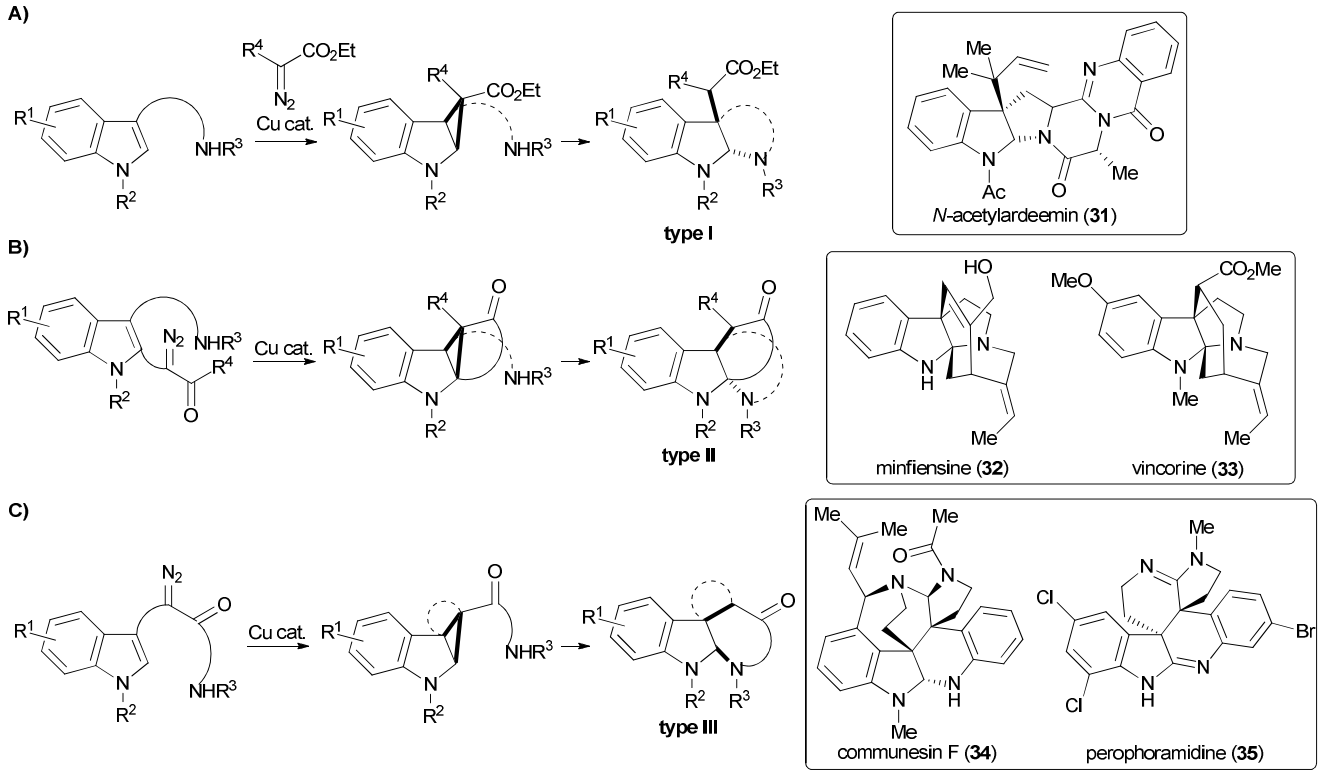
After having worked on related rearrangements of tetrahydrofuran derivatives,[15a-d] Werz and co-workers reported that stable bis-DA cyclopropanes derived from N-Boc pyrroles could also be rearranged to tricyclic annulated systems in good yields (eqn 4).[15e] A substituent in α position to the ketone was important to prevent ring-opening and rearomatization to a pyrrole.



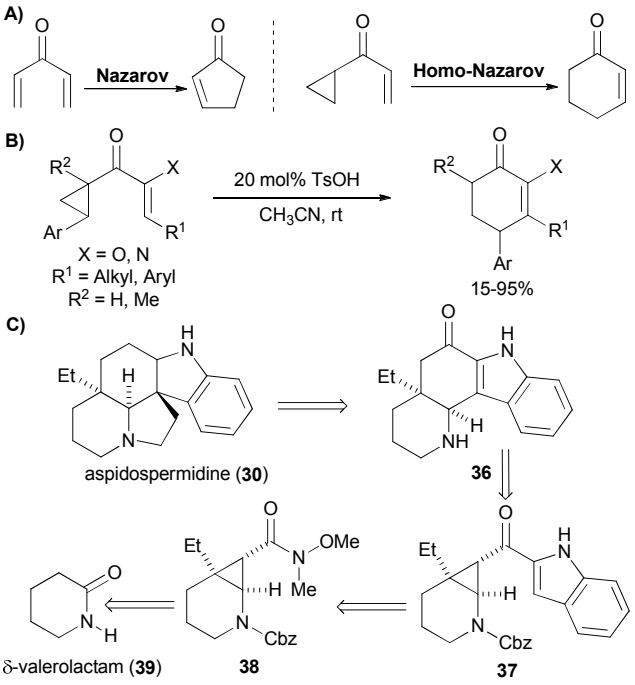
On the other hand, cyclopropanation-cyclization reaction sequences involving indoles have been studied intensively by Qin and co-workers.[16] They recognized that the highly reactive intermediate obtained from the cyclopropanation of indoles would be ideally suited for the fast elaboration of natural alkaloids. Over the years, they developed three different strategies for the construction of structurally diverse polycyclic cores of alkaloids (Scheme 8). In the type I sequence, an intermolecular cyclopropanation takes place, followed by intramolecular attack of a nitrogen nucleophile (Scheme 8, **A**). This strategy has been used for the synthesis of the alkaloid *N*-acetylardeemin (**31**).[16a-b] The two other strategies are based on intramolecular cyclopropanation. In the type II reaction, the diazo precursor is bound to the C2 position of indole (Scheme 8, **B**). After cyclopropanation and cyclization, C2-C3 bridged compounds are obtained. Using this approach, the total synthesis of minfiensine (**32**) and vincorine (**33**) was achieved.[16c-d] Finally, in the type III sequence, the diazo precursor is contained in the same chain as the nitrogen nucleophile. The obtained tetracyclic scaffolds were further elaborated to the natural products communesin F (**34**) and perophoramidine (**35**).[16e-f]

Our group became interested in the use of DA aminocyclopropanes in 2009, in the context of our work in the development of a homo-Nazarov reaction. In this transformation, one of the two olefins of a divinylketone is replaced by a cyclopropane leading to a homologous process of the well-known electrocyclic Nazarov reaction (Scheme 9, **A**). We anticipated that the formed cyclohexenones will be highly useful building blocks in organic synthesis. Nevertheless, our preliminary investigations showed that the cyclization of vinyl cyclopropyl ketones was most probably a stepwise process via carbocationic intermediates, and therefore best described as a formal homo-Nazarov process.[17] For the reaction to proceed under mild conditions it was necessary to use a DA cyclopropane, whereas an electron-rich aryl substituent was especially successful (Scheme 9, **B**).

At this point, we wondered if a DA aminocyclopropane could be used in the formal homo-Nazarov process. If yes, the reaction would become highly interesting for the synthesis of indole alkaloids, as the cyclization of aminocyclopropane **37** will lead after deprotection to the formation of tetracyclic indole derivative **36**, the intermediate use by Wenkert and Hudlicky in their total synthesis of aspidospermidine (**30**) (Scheme 9, **C**).[12b] The required aminocyclopropane **37** could be accessed from addition of an organometallic intermediate on Weinreb amide **38**, which could be obtained in a few steps from δ-valerolactam (**39**).



Scheme 8. Strategies based on DA cyclopropanes derived from indoles for the total synthesis of indole alkaloids

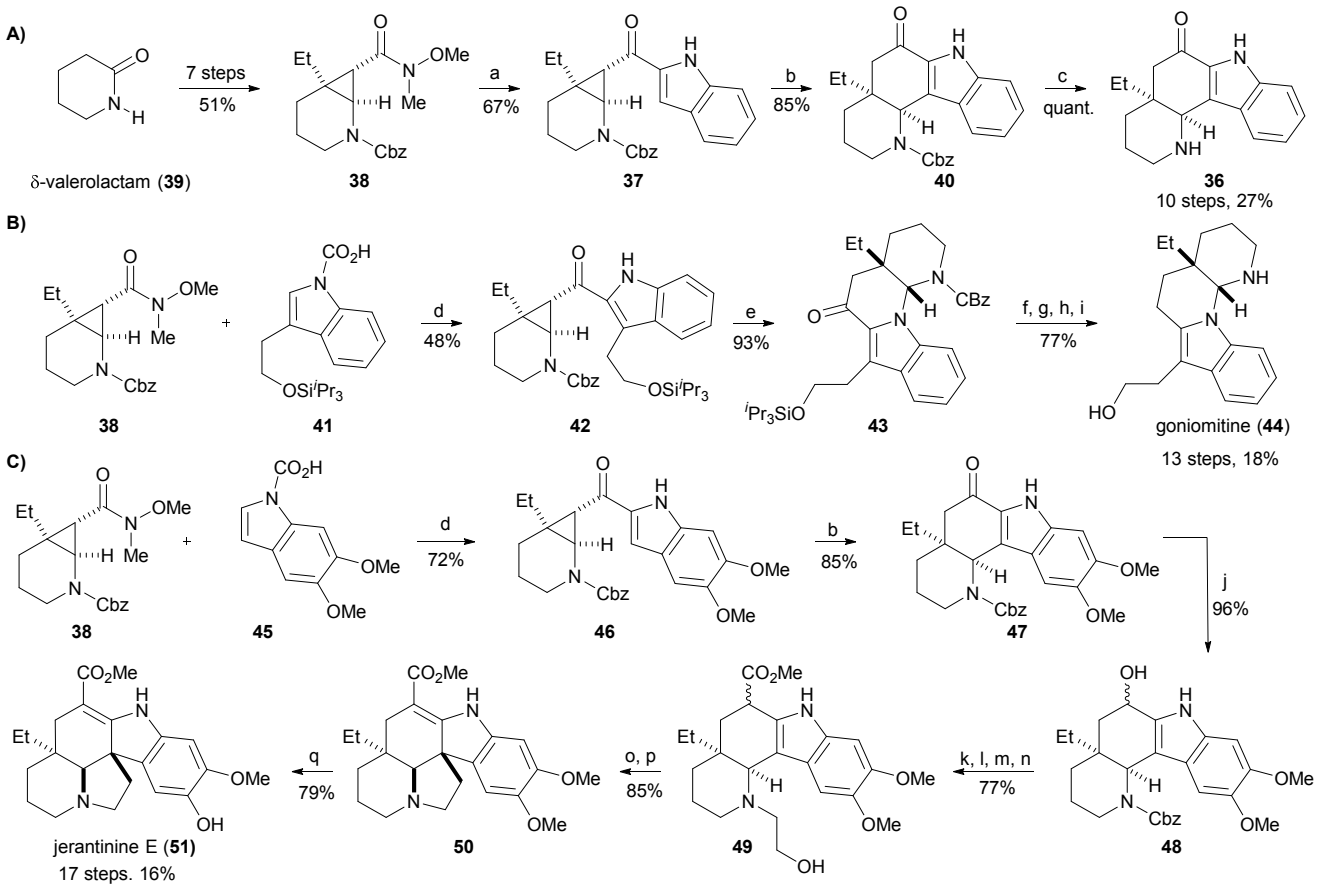


Scheme 9. Nazarov and homo-Nazarov reaction (**A**), first example of catalytic formal homo-Nazarov reaction (**B**) and retro-synthesis of aspidospermidine (**C**).

In the forwards sense, Weinreb amide **38** could be obtained in seven steps and 51% overall yield from δ-valerolactam (**39**) using a slightly modified approach described by Grieco and Kaufman (Scheme 10, **A**).[18] Addition of bis-lithiated N-carboxy indole to **38** under tightly controlled conditions led to the formation of aminocyclopropane **37** in 67% yield. The copper-catalyzed cyclization of **37** occurred smoothly in 80% yield to give the tetracyclic indole derivative **40**, which was easily deprotected to give Wenkert intermediate **36**. At this point the formal total synthesis of aspidospermidine (**30**) was accomplished.[19]

During the optimization of the cyclization of aminocyclopropane **37**, we observed a fascinating dependence of the regioselectivity of the reaction in dependence of the reaction conditions (Scheme 11).[19,20] When the catalyst was switched from copper to a Brønsted acid, and the solvent changed from acetonitrile to dichloromethane, the N-cyclization product **52** could be isolated in 80% yield. It was finally possible to convert N-cyclization product **52** back to the C-cyclization product **40** using the copper catalyst, although the reaction was much slower. This indicated that **40** was formed under kinetic control. Indeed, product **40** was shown to be more stable by 6.6 kcal/mol by calculation.[20b]

The possibility to obtain the N-cyclization product was highly interesting, because the formed tetracylic system constitutes the core of another alkaloid natural product, goniomitine (**44**), which had been much less studied than aspidosperimidine (**30**).[21] In fact, the N-cyclization of aminocyclopropane **42**, obtained from the bis-lithiated intermediate derived from indole **41** onto Weinreb amide **38**, was obtained in 93% yield.

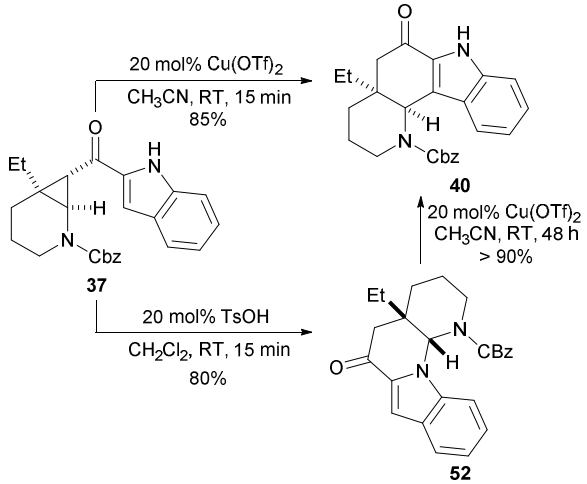


Scheme 10. Formal total synthesis of aspidospermidine (**30**) (**A**), total synthesis of goniomitine (**43**) (**B**) and total synthesis of jerantinine E (**51**) (**C**). Reaction conditions: a) N-carboxy indole, ^{t}BuLi, LiCl, THF, -78 °C; b) 20 mol% $Cu(OTf)_2$, CH_3CN; c) Pd/C, H_2, EtOH; d) ^{t}BuLi, LiCl, THF, -78 °C; e) 20 mol% TsOH, CH_2Cl_2; f) $NaBH_4$, MeOH; g) Ac_2O, pyridine; h) Pd/C, H_2, EtOH; i) TBAF, THF; j) $LiAlH_4$, THF; k) BF_3•OEt_2, Me_3SiCN, CH_2Cl_2; l) HCl, MeOH, then H_2O; m) Pd/C, H_2, EtOH; n) $BrCH_2CH_2OH$, Na_2CO_3, MeOH; o) MsCl, Et_3N, CH_2Cl_2; p) KO^{t}Bu, THF; q) $(NH_4)_2Ce(NO_3)_6$, H_2O, CH_3CN, then $Na_2S_2O_4$.

From that a short four-step sequence (reduction, acylation, hydrogenation and silyl deprotection) without any purification of the intermediate products gave goniomitine (**44**) in 18% overall yield for 13 steps.[19] Preliminary investigations seemed to indicate a sub-micromolar cytotoxicity, but more in depth investigations showed later no significant bioactivity.[22]

After the encouraging results obtained in the case of aspidospermidine (**30**) and goniomitine (**44**), we decided to examine the synthesis of another indole alkaloid, jerantinine E (**51**). This compound had been isolated from the Malayan plant *Tabernaemontana corymbosa* by Kam and co-workers in 2008 and displayed interesting cytotoxicity,[23] but it had never been accessed synthetically.

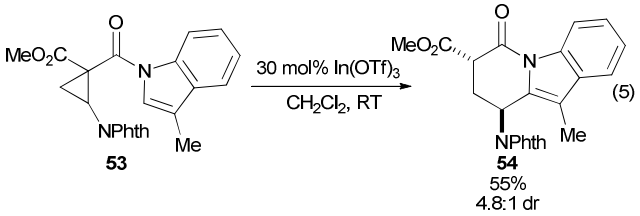
Using bis-methoxy indole derivative **45** instead of N-carboxy indole, the addition cyclization sequence worked also well to give tetracyclic intermediate **47**.[24] Reduction with lithium aluminium hydride gave then alcohol **48**. Several attempts to reduce alcohol **48** and then introduce the last ring of the molecule failed, as the very electron-rich indole derivatives were not stable. It was consequently decided to first introduce the ester group present in the natural product to diminish the electron-density of the intermediates. A carbocation was easily generated from alcohol **48** by addition of boron trifluoride etherate and intercepted by trimethylsilyl cyanide. Pinner methanolysis of the nitrile group then gave the corresponding methyl ester. At this point, the Cbz group was removed by hydrogenolysis and the tertiary amine alkylated to give more stable alcohol **49**.

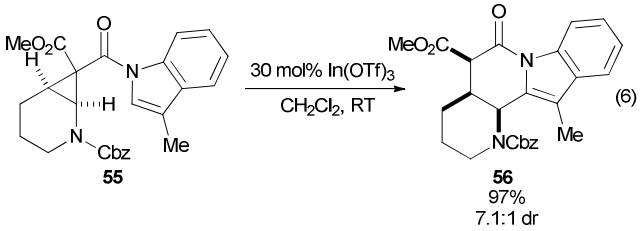


Scheme 11. Regioselective cyclization of aminocyclopropane **37**.

The fifth ring of jerantinine E (**51**) was then closed in 85% yield by mesylation of the alcohol followed by treatment with potassium *tert*-butoxide to give O-methylated jerantinine E (**50**). Finally, selective deprotection of the methoxy group in *para* position to the nitrogen under oxidative conditions followed by reductive work-up gave jerantinine E (**51**) in 16% yield over 17 steps. The availability of a multi-gram amount of jerantinine E (**51**) allowed us to study his cytotoxicity against both breast and lung cancer cell lines and to determine his mode of action as being an inhibitor of the polymerization of tubulin.[24]

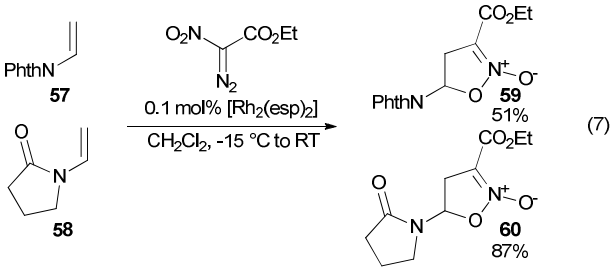
In addition to our own work, several examples of cyclization of DA aminocyclopropanes have appeared recently, often as isolated examples in studies involving other types of DA cyclopropanes. For example, France and co-workers studied the cyclization of DA cyclopropanes in which the electron-withdrawing group is bond to the nitrogen atom of indoles.[25] In this work, two examples of aminocyclopropanes were also reported (eqn 5 and 6). In the latter case, a tetracyclic system **56** was obtained, which set the basis for a total synthesis of the indole alkaloid deethyleburnamonine.[25b]





Werz and co-workers included two examples of aminocyclopropanes in their studies of the rearrangement of nitro-substituted DA cyclopropanes (eqn 7).[26] The cyclopropanes formed from enamides **57** and **58** were unstable and immediately rearranged to form the corresponding cyclic nitronates **59** and **60**. Finally, several rearrangement reactions of bicyclic aminocyclopropanes were also studied by Gharpure and co-workers.[27]

To summarize this first section, the potential of aminocyclopropanes in cyclization reactions has been long overlooked, despite interesting preliminary works by Wenkert and others. In the last decade however, important breakthroughs have been realized. Without acceptor substituents, the first C-C activation methods using palladium catalysis have now appeared. In the field of DA cyclopropanes, the Qin group has shown the utility of cyclopropanes derived from indoles in a series of impressive total syntheses of indole alkaloids. Finally, our own work on the formal homo-Nazarov reaction has opened a new route towards the synthesis of *aspidosperma* and *gonioma* alkaloids. Many more applications can be expected in the future.

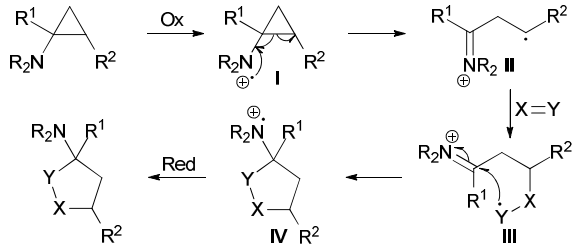


3. Annulation Reactions of Aminocyclopropanes

In annulation reactions, several bonds are formed in a single process. They allow consequently a more convergent synthesis and a faster increase of molecular complexity. On the other hand, controlling the regio- and stereoselectivity of the reaction is highly challenging. Although annulation reactions have been extensively used in the case of DA cyclopropanes bearing carbon or oxygen donor-groups,[3,28] the use of aminocyclopropanes was limited to a few rare examples prior to the work of our group.

3.1 Annulations with Non-Activated Aminocyclopropanes

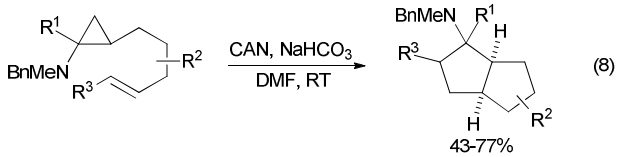
Only very few examples of annulations have been reported for aminocyclopropanes bearing no electron-withdrawing substituent. This is not surprising when considering that the harsh conditions required for ring-opening makes a selective annulation reaction especially challenging. An interesting approach was developed based on the oxidative activation of electron-rich cyclopropylamines (Scheme 12).[29] Electron-rich amines are easily oxidized to the corresponding radical cation **I**, which initiated ring-opening to generate a 1,3 radical iminium intermediate **II**. Reaction with a radical acceptor, for example a π system leads to **III**, which then cyclizes to give the new ammonium radical **IV**. Finally, reduction gives the cyclopentylamine resulting from a formal cycloaddition under mild conditions.

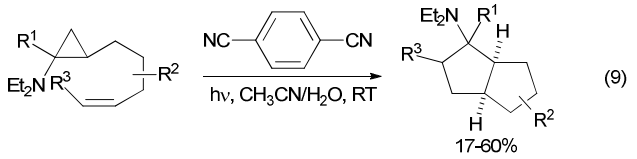


Scheme 12. Activation of electron-rich cyclopropylamines via oxidation.

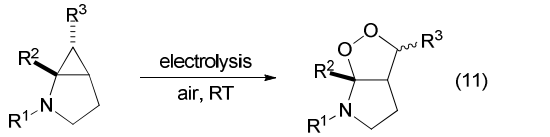
This strategy was first successfully implemented for intramolecular reactions. Iwata an co-workers used cerium ammonium nitrate (CAN) as oxidant in the generation of 5,5-bicyclic compounds in 1998 (eqn 8).[29a] In the same year, Cha and co-workers reported the use of photochemical conditions with dicyanobenzene as sensitizer to perform this transformation (eqn 9).[29b] In 2001, they examined the use of bicyclic aminocyclopropanes (eqn 10).[29c] In this case, oxidation of the amine occurred readily in air, but the annulation product was not formed. Instead, the radical intermediate was intercepted by oxygen to form a hydroperoxide, which was

easily reduced with triethylphosphite to the corresponding alcohol.



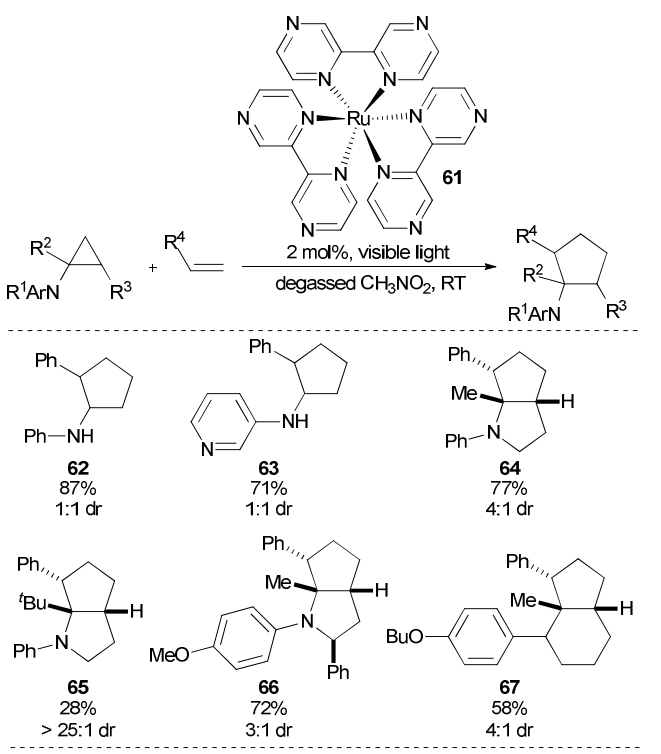


A first example of intermolecular reaction was reported by Six, Buriez and co-workers in 2007.[29d,e] When studying the cyclic voltammetry of bicyclic aminocyclopropanes obtained via a Kulinkovich cyclopropanation, they observed the formation of an endoperoxide under aerobic conditions (eqn 11). This product resulted from the formal cycloaddition of the aminocyclopropane and molecular oxygen. Although the obtained peroxides could be characterized, they decomposed rapidly via ring-opening and dehydration.

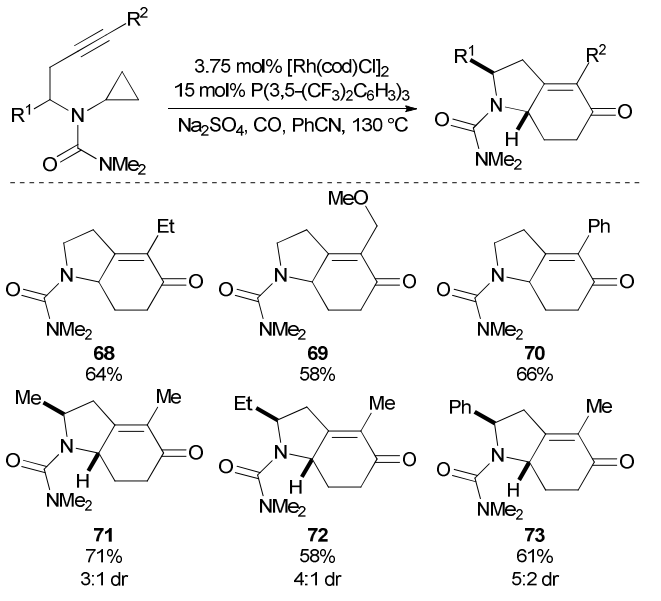


An important breakthrough was reported in 2012 by Zheng and co-workers who used ruthenium photocatalyst **61** to promote the intermolecular annulation of electron-rich aminocyclopropanes and styrene derivatives (Scheme 13).[29f] The reaction proceeded in good yield and regioselectivity for both simple and bicyclic aminocyclopropanes, but a 1:1 mixture of diastereoisomers was obtained in the case of simple aminocyclopropanes (products **62** and **63**). In the case of bicyclic cyclopropanes, 5,5-bicyclic products could be obtained with moderate diastereoselectivity (products **64**-**67**). Only in the case of a bulky *tert*-butyl group an excellent diastereoselectivity was observed, but at the cost of the conversion.

A second option to activate aminocyclopropanes under mild conditions would be the use of transition metals. Surprisingly, the first example of such transformation only appeared in 2013: Bower and co-workers reported the carbonylative annulation of aminocyclopropanes and alkynes for the synthesis of cyclohexenones (Scheme 14).[30] The reaction worked well for both alpha unbranched (products **68**-**70**) and branched (products **71**-**73**) aminocyclopropanes. Nevertheless, relatively high temperatures were still required for the reaction to proceed. The first step of the reaction is most probably an oxidative addition of the rhodium(I) catalyst onto the C-C bond of the cyclopropane. The urea directing group was essential to direct the reaction onto the more substituted C-C bond. Subsequent steps are most probably alkyne and CO insertion, followed by reductive elimination.



Scheme 13. Photoredox catalysis for the intermolecular [3+2] annulation of aminocyclopropanes and styrene derivatives.

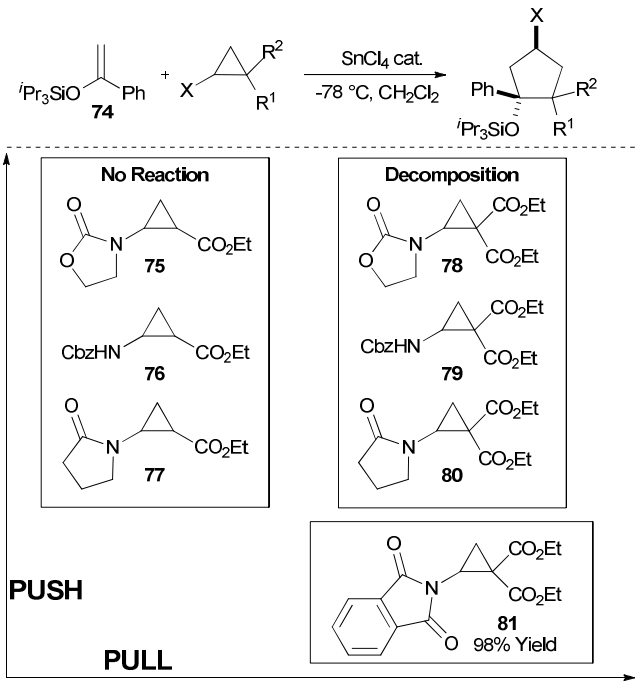


Scheme 14. Carbonylative annulation of aminocyclopropanes and alkynes for the synthesis of cyclohexenones.

3.2 Annulations with Donor-Acceptor Substituted Aminocyclopropanes

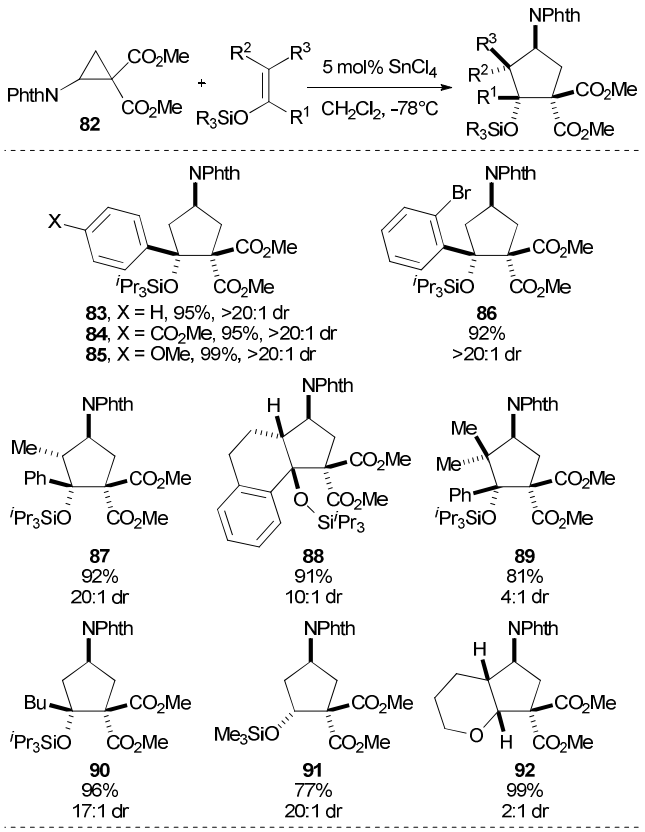
After our own work on the use of DA aminocyclopropanes for the synthesis of indole alkaloids, we wondered if more convergent annulation methods could be developed. To our

surprise, no annulation reaction of DA aminocyclopropanes had been reported up to 2011. We decided to start our investigation by the electronic modulation of the donor and acceptor parts of the cyclopropanes for the annulation reaction with enol ether **74** (Scheme 15).[31] The ring opening of ester-substituted aminocyclopropanes **75-77**, which have been used as structural elements in peptidomimetics,[4] could not be obtained under mild reaction conditions with any Lewis acid tested. We then attempted to increase the "pull" in the system by introducing a second ester group and examined diester aminocyclopropanes **78-80**. These substrates were not stable and decomposed directly after cyclopropanation. However, when the electron-density was diminished on the nitrogen atom using a phthalimide group, a perfect fit was obtained between reactivity and selectivity. Many Lewis acids could initiate the ring-opening of cyclopropane **81**, but tin tetrachloride at low temperature was the only one to give a quantitative yield of the desired product as a single diastereoisomer. Other catalysts led to either partial or complete ring-opening of the five-membered ring product via a retro-aldol reaction.



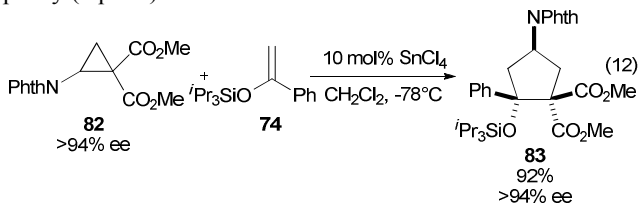
Scheme 15. Modulating the reactivity of DA cyclopropanes in the [3+2] annulation with enol ether **74**.

The scope of enol ethers in the [3+2] annulation was broad (Scheme 16). Silyl enol ethers bearing benzene rings with electron-rich and electron-poor substituents in para or ortho positions gave cyclopentylamines **83-86** as a single diastereoisomer in 92-99% yield. The reaction was stereospecific in relation to the geometry of the silyl enol ether, as product **87** was obtained as a single isomer starting from the *Z* enol ether. Bicyclic compound **88** or highly substituted cyclopentylamine **89** bearing an all-carbon quaternary center could also be obtained in good yields, although the diastereoselectivity was lower. An alkyl substituent on the enol ether was also well tolerated (product **90**). Less-substituted cyclopentylamine **91** was obtained in 77% yield starting from the silyl enol ether derived from acetaldehyde. Finally, alkyl enol ethers could also be used in the reaction, as demonstrated by the formation of bicyclic compound **92**.

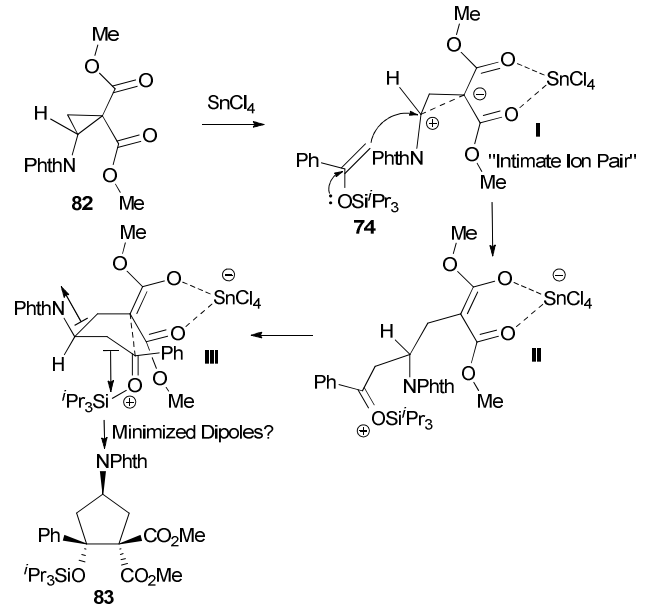


Scheme 16. Scope of the [3+2] annulation reaction of enol ethers with aminocyclopropane **82**.

When using enantioenriched aminocyclopropane **82**, cyclopentylamine **83** was obtained with the same enantiomeric purity (eqn 12).

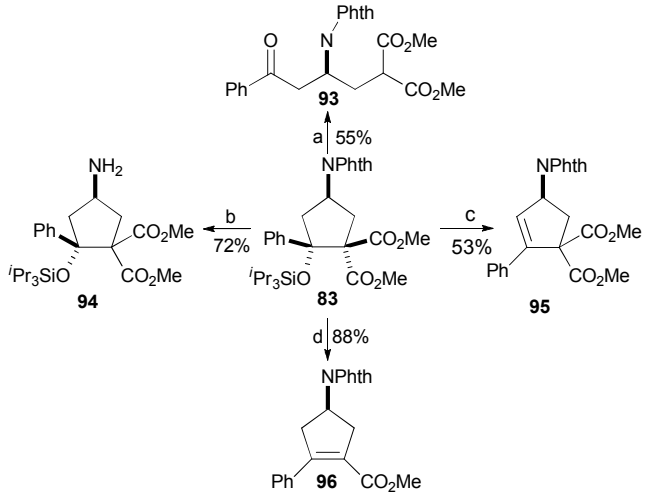


This result indicated that the reaction did not proceed via a ring-opened iminium zwitterionic intermediate. The most probable mechanism involves an "intimate ion-pair" **I**, as proposed by Johnson and co-workers in the case of other types of DA cyclopropanes (Scheme 17).[28e-f] In this case, the polarized C-C bond of cyclopropane **82** is elongated, but not fully broken, allowing an S_N2-like attack of enol ether **74**. Bond rotation in the obtained zwitterion **II** is then necessary to allow the final C-C bond formation on intermediate **III** to give cyclopentylamine **83** with high enantiopurity. The high diastereoselectivity observed could be rationalized by a minimization of the dipoles in zwitterion **III**, although this explanation remains highly speculative at this stage.



Scheme 17. Speculative mechanism for the [3+2] annulation reaction.

Finally, the transformation of cyclopentylamine **83** into other useful building blocks was examined (Scheme 18). In presence of indium triflate as catalyst, a retro-aldol reaction was observed to give ketone **93**. If enantioenriched cyclopentylamine **83** was used, no erosion of the enantiopurity was observed. Interestingly, ketone **93** could also be obtained in one-step from aminocyclopropane **82** using indium triflate as catalyst, but in this case a partial loss of the enantiopurity was obtained. Next, the phthalimide protecting group could be removed in 72% yield using 1,2-ethylenediamine in refluxing isopropanol to give free amine **94**.



Scheme 18. Transformations on cyclopentylamine **83**. Reaction conditions: a) 20 mol% $In(OTf)_3$, CH_2Cl_2, RT; b) 1,2-ethylenediamine, isopropanol, 82 °C; c) TMSOTf, CH_2Cl_2, RT; d) NaCl, H_2O/DMSO, 170 °C.

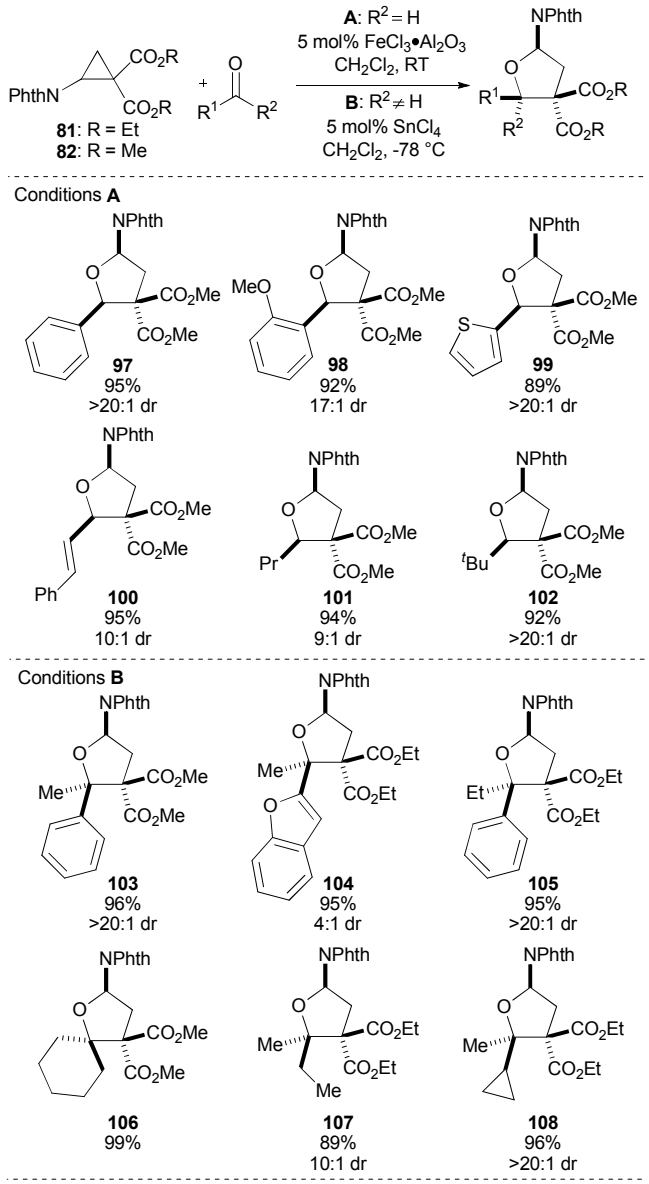
In presence of one equivalent of trimethylsilyl triflate, elimination of silanol to form olefin **95** was observed. Finally, under Krapcho decarboxylation conditions, conjugated olefin **96** was obtained after loss of carbon dioxide and silanol.

As a next objective, we wondered if the [3+2] annulation reaction of aminocyclopropanes could be extended to carbonyls as partners. The resulting tetrahydrofurylamines are important heterocycles, as they are at the core of DNA and RNA. In the case of aldehydes, re-optimization of the Lewis acid was necessary. Best results were obtained with iron trichloride as catalyst at room temperature (Scheme 19).[32] The iron catalyst was used adsorbed on alumina to enhance its stability and ease of use and prevent the formation of traces of acid. The reaction worked well with aromatic aldehydes to give the *cis*-substituted tetrahydrofurylamines **97-99** in 89-95% yield and a diastereoselectivity higher than 17:1. Cinnamaldehyde also worked well to give product **100** with slightly lower diastereoselectivity. Both linear and branched aliphatic aldehydes could also be used in the annulation process (products **101** and **102**). When the reaction was done using enantioenriched aminocyclopropanes, racemic products were obtained.

In the case of ketones, the conditions developed for enol ethers (tin tetrachloride at low temperature) were best.[33] The reaction worked well for aromatic ketones (products **103-105**), a class of substrates which has been challenging in annulation reactions with other DA cyclopropanes.[28] The formation of the diastereoisomer with the largest substituent of the ketone in *cis* position to the phthalimide was favoured. Tetrahydrofurylamines **106-108** were obtained in good yield and diastereoselectivity by the reaction of aliphatic aldehydes. Product **107** was still obtained in a very good 10:1 dr when 2-butanone with only a small steric difference between the two substituents was used. At -78 °C, the reaction of ketones was enantiospecific, giving access to enantioenriched tetrahydrofurylamines. Interestingly, when the reaction temperature was raised, the *cis*-selectivity was eroded. At -10 °C, only the *trans* diastereoisomer was obtained, albeit in low yield (19%). Finally, the use of phthalimido-substituted DA cyclopropanes was not limited to annulation reactions. An efficient Friedel-Crafts alkylation of indoles and other electron-rich aromatic compounds was also developed in our group using this class of DA cyclopropanes.[34]

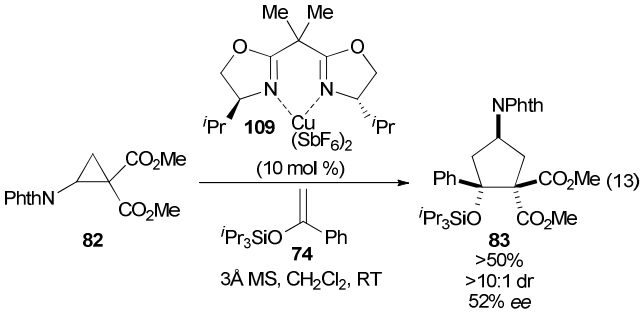
Up to now, the developed methods gave access to enantioenriched cyclopentyl- and tetrahydrofurylamines only if an asymmetric synthesis of the aminocyclopropanes was available. However, reported asymmetric cyclopropanation methods applied to vinyl phthalimide (**57**) gave only very low enantioselectivity. An alternative would be to use the easily available racemic aminocyclopropanes in a DYnamic Kinetic Asymmetric Transformation (DYKAT) to obtain enantioenriched products.[35] This type of transformations is highly challenging, as it requires controlling both the rate of racemization and the facial selectivity of the reaction. Several examples of DYKAT with DA cyclopropanes were known, but none of them involved aminocyclopropanes.[36] Only one example of DYKAT for the [3+2] annulation of DA cyclopropanes with cyclic enol ethers had been reported by

Tang and co-workers using a copper catalyst with elaborated bisoxazoline ligands.[36h]

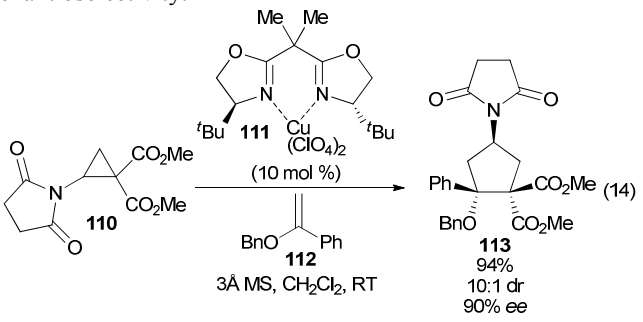


Scheme 19. [3+2] annulation of aminocyclopropanes with aldehydes and ketones.

We started our investigations by examining different chiral catalysts for the [3+2] annulation of aminocyclopropane **82** with silyl enol ether **74**. During these studies, an interesting lead result was obtained using copper-bisoxazoline complex **109**, which gave cyclopentylamine **83** in 52% ee and excellent diastereoselectivity (eqn 13).[37] Nevertheless, the enantioinduction was still too low, and the yield remained below 50%, as a retro-aldol reaction could not be avoided in product **83**.



After investigation of the protecting group on nitrogen, the structure of the enol ether and catalyst screening, conditions could finally be found to obtain the product in 94% yield and 90% *ee* (eqn 14). First, the yield could be improved to more than 90% by using alkyl enol ether **112** instead of silyl enol ether **74**, shutting down the retro-aldol side reaction. Second, the structure of the nitrogen protecting group has a strong influence on enantioinduction, and a better selectivity was obtained using succinimide-substituted aminocyclopropane **110**. Finally, the structure of the copper catalyst **111** was equally important for enantioinduction: Both a sterically hindered ligand bearing a *tert*-butyl group and the use of perchlorate as counteranion were essential for success. It is also worth mentioning that the reaction required strictly anhydrous conditions, as the copper aqua complex led to a lower enantioselectivity.



Using these conditions on preparative scale, cyclopentylamine **113** could be obtained in 97% yield and 92% enantioselectivity (Figure 2). Good enantioselectivity was also obtained for different alkyl groups on the oxygen (products **114** and **115**), but in the case of the electron-deficient trifluoroethyl group (product **115**), the diastereoselectivity was lost. Thiophene-substituted cyclopentylamine **116** was also obtained in good yield and enantioselectivity. The best enantioselectivity was observed for cyclopentylamine **117**, which has no substituent in alpha position to the oxygen. Interestingly, the reaction was not limited to enol ethers. Using the same reaction conditions, the [3+2] annulation also worked well with both aromatic (products **118-120**) and aliphatic (product **121**) aldehydes with enantioselectivities ranging from 83% to 92%.

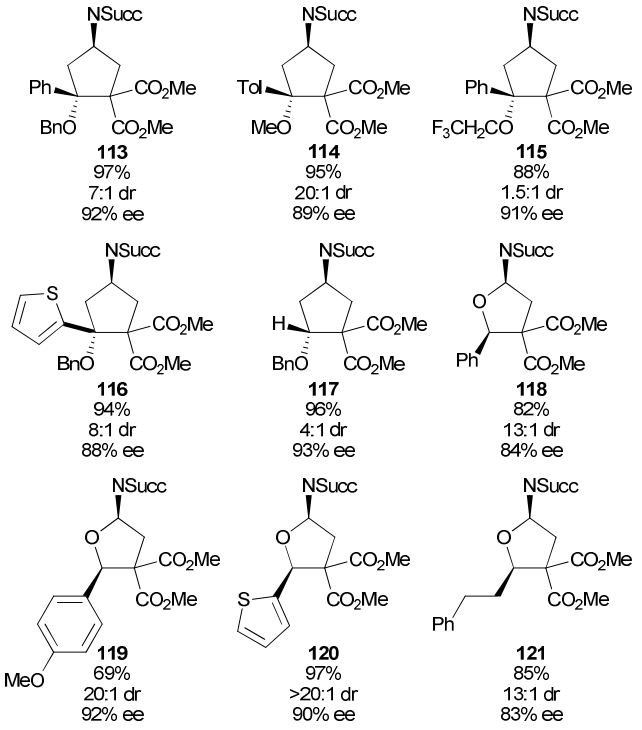
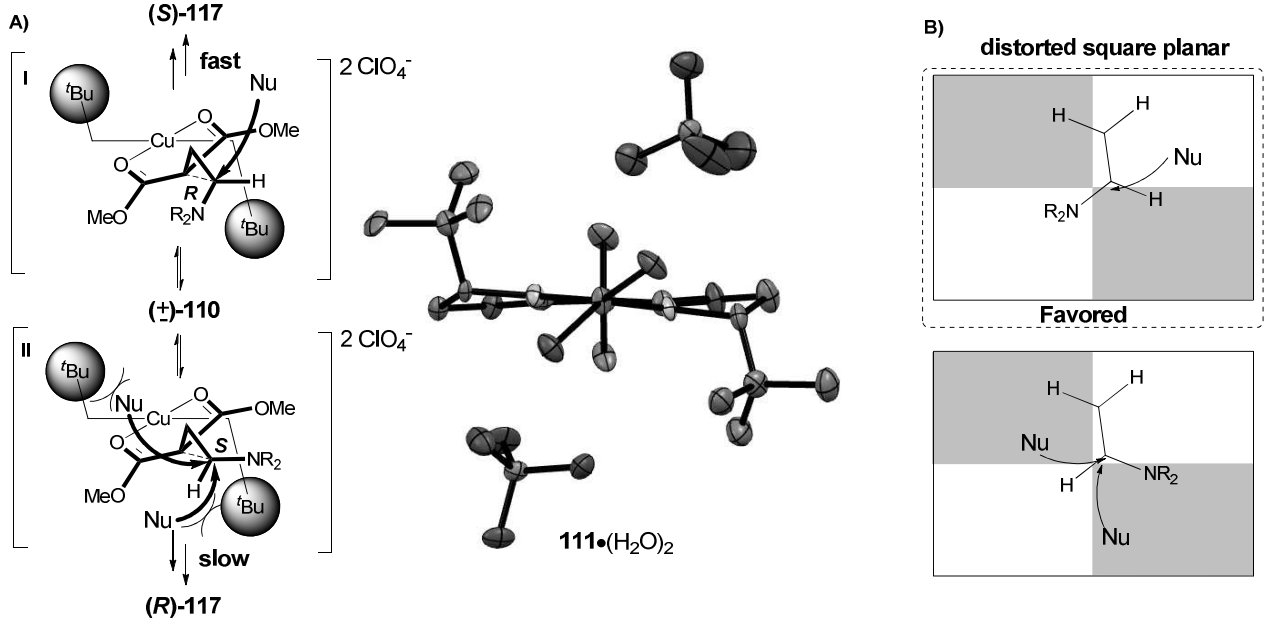


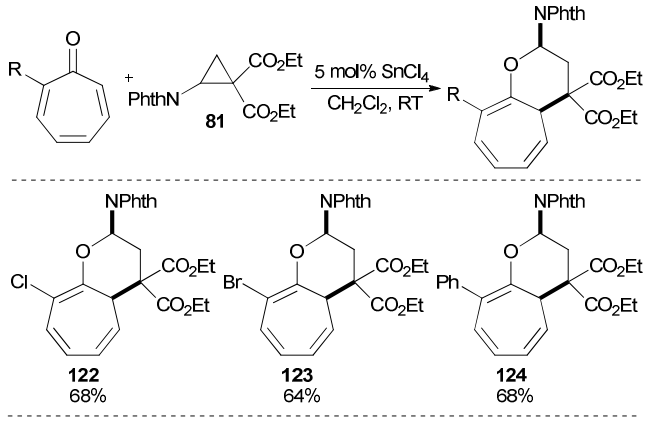
Figure 2. Scope of the asymmetric [3+2] annulation reaction. Conditions of eqn 14 were used.

The absolute configuration of cyclopentylamine **117** could be determined by X-ray crystallography, and the other compounds were assumed to have the same configuration. Although further studies will be needed to rationalize this result, a speculative model can be proposed based on the distorted square planar configuration of *tert*-butyl bisoxazoline copper complexes (Scheme 20).[38,39] Through the distortion of the symmetry, all trajectories of attack for the enol ether on the complex formed between catalyst **111** and the *S* enantiomer of cyclopropane **110** are blocked. Consequently, racemization can occur via ring-opening/closing to lead to the diastereoisomeric complex with *R* configuration of cyclopropane **110**, which reacts rapidly to give **117** with the observed stereochemistry. If correct, this model corresponds to a DYKAT of type I. Nevertheless, a DYKAT of type II involving attack on the fully ring-opened iminium intermediate cannot be excluded at this stage.

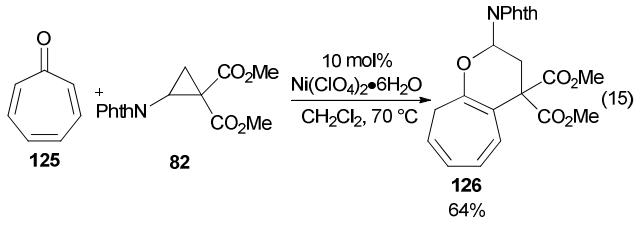
After publication of our work, other groups also reported other types of annulation reactions using DA aminocyclopropanes. In 2013, Sierra, Fernandez and Rivero reported the use of aminocyclopropane **81** in the tin-catalyzed [8+3] annulation with substituted tropones (Scheme 21).[40] Interestingly, the [3+2] annulation product with the ketone was not observed and a single diastereoisomer of the product was obtained. Both halogen (products **122** and **123**) or aromatic (product **124**) substituents were tolerated on the tropone. The same year Carretero, Adrio and co-workers also studied the [8+3] annulation of DA cyclopropanes with tropones, but using a nickel catalyst.[41] Although they focused mostly on carbon donor substituents, they reported a single example using aminocyclopropane **82** with tropone (**125**) (eqn 15). Interestingly, in this case another double bond isomer **126** of the annulation product was obtained in 64% yield.



Scheme 20. Speculative stereochemical model (**A**) and simplified quadrant cartoon (**B**) rationalizing the observed absolute configuration in the [3+2] annulation.



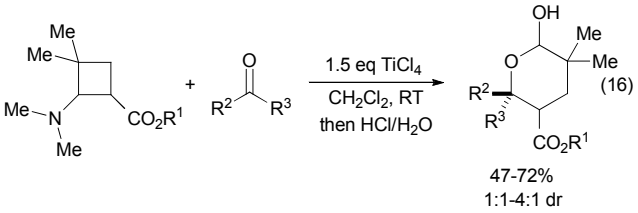
Scheme 21. [8+3] annulation reaction between aminocyclopropane **81** and tropones.



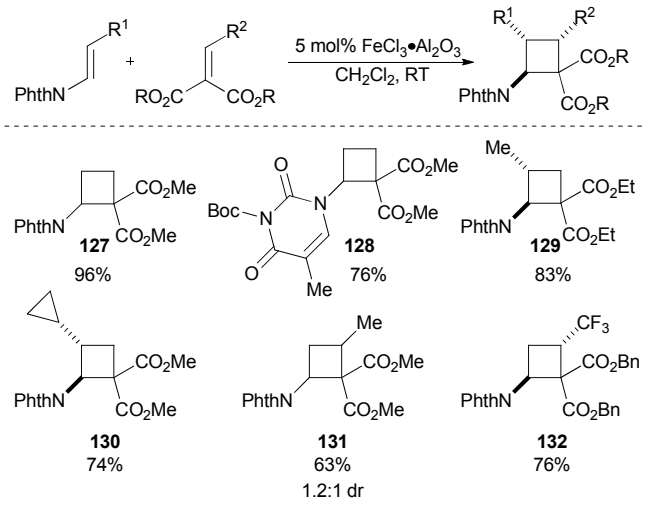
To conclude this second chapter, annulation reactions involving aminocyclopropanes with acceptor substituents have been long limited to [3+2] processes involving the oxidative activation of electron-rich aminocyclopropanes. Nevertheless, the first example of the use of a rhodium catalyst for an annulation reaction revealed the high potential of transition metal catalysts for such transformations, and further developments in this direction can be expected in the future. Surprisingly, there was no example of annulation reaction involving DA aminocyclopropanes prior to our own work. We found that with the right modulation of donor and acceptor groups, this class of cyclopropanes performed exceptionally well in metal-catalyzed [3+2] annulations with both enol ethers and carbonyl compounds to give cyclopentyl- and tetrahydrofurylamines with high yield and diastereoselectivity. The recent development of a DYKAT transformation of racemic aminocyclopropanes gave a practical access to enantioenriched building blocks. The first examples of other types of annulation using this new type of DA aminocyclopropanes presage well for future applications, including in the synthesis of bioactive compounds.

4. Reactions of Aminocyclobutanes

In comparison to aminocyclopropanes, the chemistry of aminocyclobutanes is much less developed. Nevertheless, important progress in the metal-catalyzed activation of cyclobutanes has been achieved recently.[42] In particular, the first examples of efficient annulation reactions involving DA cyclobutanes have been reported.[43] However, even if the ring opening of aminocyclobutanes has been known since a long time,[44] there was only one example of [4+2] annulation between DA aminocyclobutane and carbonyl compounds reported by Saigo and co-workers prior to 2013 (eqn 16).[43a] In this transformation, the obtained half aminals were unstable and directly hydrolysed. Consequently, the useful nitrogen functionality was lost.



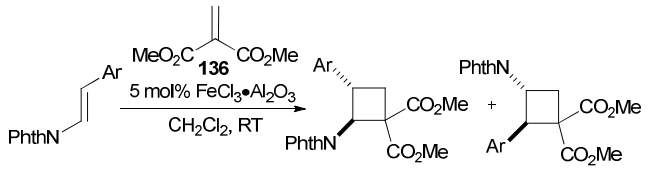
After our work on the use of DA aminocyclopropanes, we wondered if a similar strategy could be also applied in the case of DA aminocyclobutanes. Nevertheless, the reported methods for the synthesis of aminocyclobutanes were limited,[45] and none of them had been used in the case of diester-substituted aminocyclobutanes. The conditions reported for the synthesis of similar DA cyclobutanes bearing carbon or oxygen donor groups were not successful in the case of aminocyclobutanes.[43c,43h] Finally, we discovered that the iron catalyst we had used for the [3+2] annulation of aminocyclopropanes with aldehydes was also able to promote the [2+2] cycloaddition between enimide and alkylidene malonates to give the desired DA cyclobutanes in 63-96% yield (Scheme 22).[46] Phthalimide was again an excellent protecting and modulating group for the nitrogen, and the simplest DA cyclobutane **127** was obtained in 96% yield. Importantly, crude mixture of freshly synthesized methylidene malonate **136** could be used in the reaction, making the cumbersome purification of this very sensitive reagent not necessary. Thymine-derived DA aminocyclobutane **128** could also be obtained in 76% yield. *Trans*-substituted enimides gave cyclobutanes **129** and **130** in good yields, but *cis*-substituted enimides could not be used in the reaction. Substituted methylidene malonates gave products **131** and **132** in 63% and 76% yield respectively. The substituent had a strong influence on the diastereoselectivity, as a mixture was obtained with a methyl group (product **131**) but only the *trans* diastereoisomer was observed with a trifluoromethyl group (product **132**).



Scheme 22. [2+2] Cycloaddition of enamide and alkylidene malonates.

When enimide **133**-**135** bearing an aromatic group were used, the regiochemistry was dependent from the electronic nature of the substituent (Scheme 23). With a phenyl group, the usual 1,2-substituted aminocyclobutane diester **137** was observed. In contrast, in presence of a tolyl substituent, the 1,3 isomer **140** was also obtained, and this isomer was the only one observed in the case of an anisole substituent (product **142**). This result is

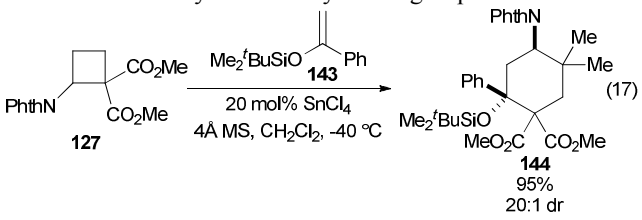
interesting, as it allows the "calibration" of the electronic properties of the phthalimide group in comparison with well-known benzene rings. This knowledge could be highly useful for the design of new reactions.



133: Ar = Ph	**137**	**138**	>20:1
134: Ar = 4-MePh	**139**	**140**	2.5:1
135: Ar = 4-MeOPh	**141**	**142**	>1:20

Scheme 23. [2+2] Cycloaddition with enamides bearing aromatic substituents.

With a new class of DA cyclobutanes in hand, we are now ready to test their performance in annulation reaction. In fact, the first preliminary result is highly promising: cyclohexylamine **144** was obtained in 95% yield and 20:1 dr by the tin-catalyzed [4+2] annulation between aminocyclobutane **127** and silyl enol ether **143** (eqn 17).[46] The scope of this reaction is currently under study in our group.



In conclusion, aminocyclobutanes in general and DA aminocyclobutanes in particular have been barely used in cyclization and annulation reactions so far. Nevertheless, the first preliminary results obtained in our group using phthalimide-substituted DA cyclobutanes are highly promising for further developments and for making these derivatives as useful as their three-membered ring counterparts.

5. Conclusions

The utility of strained rings, especially when substituted with donor and acceptor substituents, is now well-established in organic chemistry. Nevertheless, the potential of an important subclass, namely DA aminocyclopropanes and cyclobutanes, has remained unexploited for a long time in cyclization and annulation reactions, despite important pioneering results. In the last decade, impressive progress has been realized. Transition-metal and photoredox catalysis have emerged as new approaches to activate aminocyclopropanes under milder conditions. The use of DA aminocyclopropanes derived from indoles and the development of the formal homo-Nazarov reaction have led to new strategies for the synthesis of natural alkaloids. Finally, the discovery of phthalimido-substituted diester cyclopropanes and cyclobutanes as formal dipoles in [3+2] and [4+2] annulation reactions opened new perspectives in the synthesis of nitrogen-rich building blocks. With the first example of DYKAT reaction involving aminocyclopropanes, the access to enantio-enriched building blocks is now possible. It can truly be said now that DA nitrogen-substituted small rings are on the good way to join their carbon- and oxygen-substituted counterparts as very useful tools in synthetic chemistry.

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