Ring Opening of Donor–Acceptor Cyclopropanes with N-Nucleophiles

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Abstract  
Ring opening of donor–acceptor cyclopropanes with various  
N-nucleophiles provides a simple approach to 1,3-functionalized com- 
ounds that are useful building blocks in organic synthesis, especially in  
assembling various N-heterocycles, including natural products. In this  
review, ring-opening reactions of donor–acceptor cyclopropanes with  
amines, amides, hydrazines, N-heterocycles, nitriles, and the azide ion  
are summarized.

1 Introduction

This review is focused on ring-opening reactions of do- 
nor–acceptor (DA) cyclopropanes with N-nucleophiles. The term ‘donor–acceptor substituted cyclopropanes’ was intro- 
duced by Reissig in 1980. Not only was the term convenient for describing the vicinal relationship between the donor and acceptor substituents in the small ring, but, crucially, it also pointed to the ability of such cyclopropanes to react similarly to three-membered 1,3-dipoles, with their carbocationic centers stabilized by an electron-donating group (EDG) and their carbanionic center stabilized by an electron-withdrawing group (EWG) (Scheme 1). Seebach introduced the term ‘reactivity umpolung’ that can be ascribed to this type of reactivity.

Key words  
donor–acceptor cyclopropanes, nucleophilic ring opening,  
N-nucleophiles, N-heterocycles, amines, azides, nitriles
During this period of time, the work published by the groups of Danishefsky, Reissig, Seebach, Stevens, Wenkert, and others led to new developments in a number of processes involving DA and acceptor-substituted cyclopropanes, exemplified by rearrangements in the small ring, yielding enlarged cycles or products of ring opening, as well as nucleophilic ring opening.3–9

Since the 1990s, the chemistry of such cyclopropanes has experienced a drastic increase in diversity due to the works of Charette, France, Ila and Junjappa, Johnson, Kerr, Pagenkopf, Tang, Tomilov, Wang, Waser, Werz, Yadav, and others.10–28 Currently, it is represented by dozens of types of reactions, including formal (3+n)-cycloaddition and annulation of DA cyclopropanes to various unsaturated compounds, different types of dimerization and complex cascade processes. These reactions contribute to efficient regio- and stereoselective approaches to densely functionalized acyclic and carbo- and heterocyclic compounds as well as complex polycyclic molecules, including natural products.

Nucleophilic ring opening of DA cyclopropanes is among the simplest and most efficient synthetic approaches to 1,3-functionalized compounds, either as an individual process or as one of the steps in cascade reactions. In the literature, an analogy is often drawn between this process and nucleophilic Michael addition (meanwhile, nucleophilic ring opening of activated cyclopropanes is often viewed as homologous to the Michael reaction) (Scheme 2).4,29 Alternatively, the stereochemical outcome of the nucleophilic ring opening of DA cyclopropanes, in most cases leading to the inversion of configuration for the reactive center in the three-membered ring, allows one to compare this reaction to bimolecular nucleophilic substitution (SN2).

The first examples of ring-opening reactions for activated cyclopropanes with C-, O-, and Hal-nucleophiles were described by Bone and Perkin at the end of the 19th century.28 However, thorough and systematic research into the reactions of activated cyclopropanes with N-nucleophiles only dates back to the mid-1960s and the works of Stewart.30,31 Nevertheless, at present, this is a well-developed area that has the widest reported representation in nucleophilic ring opening of activated cyclopropanes. These reactions have piqued the interest of researchers due to the possibility of their involvement in the synthesis of acyclic as well as cyclic derivatives of γ-aminobutyric acid (GABA), along with other diverse N-heterocyclic compounds (Scheme 3). High stereoselectivity characterizing three-membered ring opening by N-nucleophiles assures that those reactions can provide for the construction of enantio-merically pure forms, including those belonging to synthetic and natural biologically active compounds.

Since acceptor-substituted cyclopropanes are simpler in many ways, this has facilitated extensive studies of these compounds, with many of the discovered mechanisms and techniques later extrapolated to DA cyclopropanes. For this reason, an overview of their reactions with N-nucleophiles is also included in this review.

Among the ring-opening reactions of DA cyclopropanes initiated by N-nucleophiles, a crucial place is occupied by those involving amines and yielding acyclic functionalized amines (both as final products and as stable intermediates undergoing further transformations into various N-heterocyclic compounds). Hence, we have attempted to provide a thorough description of these reactions in our review. Besides nucleophilic ring opening with amines, the reactions of DA cyclopropanes with other N-nucleophiles (such as nitriles, azides, N-heteroaromatic compounds) are also taken into consideration.

On the other hand, formal (3+n)-cycloadditions of DA cyclopropanes to give N-containing unsaturated compounds can be mechanistically described as stepwise processes initiated by N-nucleophilic ring opening (Scheme 3). However, usually it is impossible to isolate the corresponding intermediates that readily form the resulting heterocycles. These reactions, which have been reported in a large series of papers [formal (3+2)-cycloadditions to imines,52–54 diazenes,36–39 N-aryls,40–42 heterocumulenes,43–45 nitriles,46–51 as well as (3+3)-cycloadditions54–57], form an independent branch in DA cyclopropane chemistry that is considered to be beyond the scope of this review.

Cyclopropylimine–pyrroline thermal rearrangement, discovered by Cloke,58 is another example of a related process (Scheme 3). Following this discovery, Stevens revealed the feasibility of employing significantly milder reaction conditions under acid catalysis.3 However, mechanistically, these reactions proceed as nucleophilic ring opening of a protonated iminocyclopropane with a counterion (usually, a halide) rather than as a true rearrangement. Therefore, re-
actions of carbonyl-substituted cyclopropanes (aldehydes or ketones) with amines, yielding pyrrolines, which can generally proceed via two independent pathways, including: 1. nucleophilic ring opening with the amine, followed by 1,5-cyclization, and 2. initial formation of imine, followed by Cloke–Stevens rearrangement (Scheme 3). It is not possible to differentiate between these two mechanisms in all cases. Therefore, in this review we attempted to examine the reactions of DA cyclopropanes with amines for those cases where there is clear evidence in favor of nucleophilic ring opening or where there is no mechanistic speculation. Meanwhile, isomerization of cyclopropylimines \(^{13,59,60}\) is beyond the scope of this review. 

2 Ring Opening with Amines

Nucleophilic ring opening of activated cyclopropanes with amines originated as a separate area of three-membered carbocycle chemistry in the mid-20th century, owing to the works of Stewart and Danishefsky et al. \(^{4,30,31,61}\) In these papers, they covered the outcomes of involving cyclopropanes 1,1-diacivated by EWG (namely, carboxylic ester, carbonitrile, and carboxamide groups) in reactions with primary and secondary amines under thermal activation.

Notably, Stewart and Westberg demonstrated that upon the action of secondary amines on the derivatives of cyclopropane-1,1-dicarboxylic acids \(1a\)–\(e\) cleavage occurs in the three-membered ring of 1 to yield \( \beta \)-aminoethylmalonates \(2a\)–\(g\) (Scheme 4). \(^{30}\) While diester \(1a\) required lengthy heating with an excess of the amine, analogous reaction of distyryl \(1b\) proceeded upon cooling. The reactions of the less nucleophilic primary amines with esters \(1a,c\) resulted in amidation of the initial compounds, preserving the three-membered ring.

In reactions with secondary amines, vinlylcyclopropane \(3a\) behaved similarly, yielding ring-opening products \(4a,b\) (Scheme 5). \(^{31}\) Notably, no products of conjugated 1,5-addition of the amines to vinlylcyclopropane were detected. Monoamidation of products \(4a,b\) proceeded as a side process. The reactions of \(3a\) with primary amines also proceeded with nucleophilic ring opening of the three-membered ring and subsequent intra- and intermolecular amidation of ester groups, yielding \( \gamma \)-lactams \(5a,b\) and \(6\), respectively. A significant percentage of nucleophilic ring-opening products for dimethyl ester \(3b\) with primary and secondary amines underwent decarboxylation under the studied conditions. Consequently, the reaction of \(3b\) with piperidine yielded a mixture of mono- and diesters \(7\) and \(8\) with \( \gamma \)-lactam \(9\) as the only product in the reaction with benzylamine.

The influence that alkyl substituents in the three-membered ring have upon the reactivity of cycloproanediesters was studied by Danishefsky and Rovnyak. \(^{61}\) In the case of 2-...
alkylcyclopropane-1,1-diesters, low chemoselectivity is observed for ring opening by amines: they attack both the C2 and C3 sites in the small ring. In particular, the reaction of DA cyclopropane 10 with pyrrolidine yielded a mixture of four products 11–14 (14.5:10:1.5:1) with the total yield amounting to 40% (Scheme 6). Upon the introduction of a second alkyl substituent to the C2 site of a DA cyclopropane, as exemplified by 15, the amine attacked this site exclusively. Meanwhile, the reaction rate dropped critically, which prevented complete conversion of 15 into 16. The diester of tetramethylcyclopropane-1,1-dicarboxylic acid proved to be inert under the studied conditions.

Sato and Uchimaru showed that activating a cyclopropane with only one EWG that is stronger than an ester group along with one EDG also permits three-membered ring opening by amines. Thus, full conversion of DA cyclopropanes 19a,b on reaction with cyclic secondary amines was observed under lengthy thermal activation yielding γ-amino ketones 20a–d in moderate yields (Scheme 8).

The chemoselectivity of the three-membered ring opening in cyclopropa[e]pyrazolo[1,5-a]pyrimidines 17 was examined by Kurihara in a series of papers.62–65 The reaction between 17a,b and N-methylaniline primarily proceeded via nucleophilic attack on the carbon center in the methylene group of 17 with cleavage in the H₂C–C₃ bond, yielding products 18a,b (Scheme 7).63 However, the reaction was characterized by low chemoselectivity, yielding a mixture of products, with those formed upon nucleophilic attack on the quaternary C(CO₂Et) atom among them. Meanwhile, a phenyl substituent on the methylene group led to a drastic increase in selectivity since ring opening of 17c exclusively gave 18c with 82% yield.65

The activation of a three-membered ring by a strong EWG (e.g., the NO₂ group) allows the nucleophilic ring opening of activated cyclopropanes to be performed by weaker N-nucleophiles, namely, aniline derivatives. While researching approaches to the derivatives of α-amino acids, Seebach et al. showed that reflux of 1-nitrocyclopropane-1-carboxylate 21 in methanol with excess aniline for an extended period led to acyclic amino derivatives 22a,b in high yields (Scheme 9).67 Lowering the nucleophilicity of aniline by introducing an EWG into the aromatic ring led to a significant increase in reaction time (from 21 to 66 hours) and a decrease in the yield of the target product 22b. The nucleophilic ring opening of 21 with diethylamine and esters of amino acids was performed under similar conditions (Scheme 9).68

O’Bannon and Dailey researched a similar reaction for DA cyclopropane 23,69 proving this compound to be more reactive towards aniline in comparison with 21. Full conversion of 23 into acyclic product 24 occurred in 15 hours under identical conditions (Scheme 10).

Introducing fragments of electrophilic and DA cyclopropanes into molecules with structural elements that facilitate additional strain can increase the probability of three-
A specific example of structural activation for electrophilic cyclopropanes was described in the works of Cook, wherein the reactions of tricyclo[2.2.1.0²⁶]heptan-3-one 25 with cyclic secondary amines were investigated (Scheme 11). Full conversion of 25 into amino ketones 26a–d was already detected after 2 hours, even though additional thermal and catalytic activation took place.²¹

Spiro-activation of cyclopropanes proved to be a more universal technique for additional structural activation of these compounds. This term was introduced in the mid-1970s by Danishefsky, who employed electrophilic cyclopropane 27 in his research, basing the initial structure upon Meldrum’s acid (27 was subsequently named ‘Danishefsky’s cyclopropane’). Specifically, it was demonstrated that cyclopropane 27 participated in reactions with primary, secondary, and tertiary amines under mild conditions at room temperature, yielding ring-opening products 28–30 (Scheme 12). In the cases when the amines were substantially stronger bases (e.g., piperidine) the products were betaines (e.g., 28). When aniline, which exhibits weaker basicity, was employed then the resulting product was lactam 30, which was formed upon the nucleophilic ring opening of 27 into acyclic amine 1-1 with subsequent nucleophilic attack of the amino group upon the carbonyl group, accompanied by the elimination of acetone.

1,1-Dinitrocyclopropane 31 exhibited analogous reactivity towards amines with various structures.²¹ Its reactions with primary, secondary, and tertiary amines were performed under very mild conditions and usually resulted in betaines 32 (Scheme 13). The reaction of 31 with weakly basic aniline proved to be the exception, yielding amine 33.

Schobert et al. investigated the reactivity of unusual spiro-activated DA cyclopropanes of type 35 towards primary and secondary amines (Scheme 14). Compounds 35 originate from allyl esters of tetronic acids (tetronates) 34 that undergo successive Claisen rearrangement and Conia-ene cyclization upon heating, yielding 35. The ring opening of 35 by primary and secondary amines proceeded under mild conditions or upon reflux in CH₂Cl₂, yielding amines 36. From the relative configurations of stereocenters in products 36 it was concluded that the cleavage of the three-membered ring in 35 proceeds in accordance with an S₂-
proving the efficiency of the process. Schneider\textsuperscript{76} used di-
ethyaluminum chloride to activate alkyl-, allyl-, and aryl-
substituted di-tert-butyl cyclopropane-1,1-dicarboxylates \textbf{39} and \textbf{41}; the tert-butyl substituents reduce the possibility of amidation (Scheme 16 and Scheme 17). This method was
efficient for primary and secondary amines as well as am-
monia. When using tetrasubstituted cyclopropanes \textbf{39},
trans-diastereoselectivity was observed exclusively.

External activation of electrophilic and DA cyclopro-
panes by the means of Lewis acids often allows for small
ring opening to take place under milder conditions, im-
like mechanism, wherein the configuration at the reactive
center of \textbf{35} is inverted.

Yates et al. demonstrated that even one activating EWG
in spirocyclopropanes \textbf{37a–e} facilitated their ring opening
by morpholine yielding cyclohexanone derivatives \textbf{38a–c}
(Scheme 15).\textsuperscript{25} Notably, an exocyclic double bond signif-
ically increased the reactivity of cyclopropanes \textbf{37a,b} in
comparison with cyclopropanes \textbf{37c,d}, containing an endo-
cyclic double bond, and their saturated counterpart \textbf{37e}.

External activation of electrophilic and DA cyclopro-
panes by the means of Lewis acids often allows for small
ring opening to take place under milder conditions, im-
proving the efficiency of the process. Schneider\textsuperscript{76} used di-
ethyaluminum chloride to activate alkyl-, allyl-, and aryl-
substituted di-tert-butyl cyclopropane-1,1-dicarboxylates \textbf{39} and \textbf{41}; the tert-butyl substituents reduce the possibility of amidation (Scheme 16 and Scheme 17). This method was
efficient for primary and secondary amines as well as am-
monia. When using tetrasubstituted cyclopropanes \textbf{39},
trans-diastereoselectivity was observed exclusively.
Scheme 18 Ring opening of alkyl-, alkenyl- and aryl-substituted DA cyclopropanes with amine–Et₂AlCl complex

A catalytic variant of the nucleophilic ring opening of cyclopropane-1,1-diesters 43 was examined by the Kerr group, based on bicyclic derivatives of aniline, indolines (Table 1).77,78 Cyclopropanes 43, possessing either a tertiary or a quaternary reactive site, can be introduced into the reaction. The product β-aminoethylmalonates 44a–p can be converted into pyrrolinoindoles 45a–p upon reaction with manganese(III) acetate as a result of a domino process that involves oxidation and radical 1,5-cyclization. Product 45o was utilized in the synthesis of 47, which contained the main structural fragment of bis-indole alkaloid flinderol C, confirmed to exhibit anti-malaria properties (Scheme 19).

Tomilov et al. successfully reacted 1- and 2-pyrazolines with cyclopropane-1,1-diesters 43a,b,n in the presence of Lewis acids (Table 2).79 Notably, the reactions of both 1- and 2-pyrazolines were performed under mild conditions yielding the products of nucleophilic ring opening 48 as well as formal (3+2)-cycloaddition products 49. It was established that the efficiency and chemoselectivity of the process can be directed by the correct choice of Lewis acid. The best results were achieved when employing Sc(OTf)₃ and GaCl₃; interestingly, the GaCl₃ gave exclusive nucleophilic ring opening yielding 48. The authors79 interpreted the fact that both the products of nucleophilic ring opening 48 as well as the products of (3+2)-cycloaddition 49 were formed in the

Table 1 Catalytic Reaction of Cyclopropane-1,1-diesters with Indolines and Transformation of the Ring-Opening Products into Pyrrolinoindoles

<table>
<thead>
<tr>
<th>44, 45</th>
<th>R</th>
<th>R’</th>
<th>R”</th>
<th>t₁ (h)</th>
<th>Yield (%) of 44 (method)</th>
<th>t₂ (h)</th>
<th>Yield (%) of 45</th>
</tr>
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<tbody>
<tr>
<td>a</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>16</td>
<td>80 (A)</td>
<td>16</td>
<td>82</td>
</tr>
<tr>
<td>b</td>
<td>Ph</td>
<td>H</td>
<td>H</td>
<td>16</td>
<td>74 (A)</td>
<td>16</td>
<td>86</td>
</tr>
<tr>
<td>c</td>
<td>4-BrC₆H₄</td>
<td>H</td>
<td>H</td>
<td>16</td>
<td>71 (A)</td>
<td>16</td>
<td>84</td>
</tr>
<tr>
<td>d</td>
<td>4-ClC₆H₄</td>
<td>H</td>
<td>H</td>
<td>3</td>
<td>73 (A)</td>
<td>16</td>
<td>63</td>
</tr>
<tr>
<td>e</td>
<td>2-naphthyl</td>
<td>H</td>
<td>H</td>
<td>16</td>
<td>63 (A)</td>
<td>16</td>
<td>61</td>
</tr>
<tr>
<td>f</td>
<td>2-furyl</td>
<td>H</td>
<td>H</td>
<td>4</td>
<td>63 (A)</td>
<td>16</td>
<td>75</td>
</tr>
<tr>
<td>g</td>
<td>vinyl</td>
<td>H</td>
<td>H</td>
<td>16</td>
<td>72 (A)</td>
<td>16</td>
<td>91</td>
</tr>
<tr>
<td>h</td>
<td>i-Pr</td>
<td>H</td>
<td>H</td>
<td>24</td>
<td>24 (A)</td>
<td>6</td>
<td>60</td>
</tr>
<tr>
<td>i</td>
<td>Ph</td>
<td>H</td>
<td>(CH₂)₂NPhth</td>
<td>0.3</td>
<td>72* (A)</td>
<td>0.5</td>
<td>92</td>
</tr>
<tr>
<td>j</td>
<td>C≡CH</td>
<td>Me</td>
<td>H</td>
<td>2</td>
<td>77 (A)</td>
<td>1</td>
<td>65</td>
</tr>
<tr>
<td>k</td>
<td>C≡CET</td>
<td>Me</td>
<td>H</td>
<td>2</td>
<td>80 (A)</td>
<td>88 (B)</td>
<td>65</td>
</tr>
<tr>
<td>l</td>
<td>C≡CPh</td>
<td>Me</td>
<td>H</td>
<td>3</td>
<td>79 (A)</td>
<td>79 (B)</td>
<td>61</td>
</tr>
<tr>
<td>m</td>
<td>Ph</td>
<td>Me</td>
<td>H</td>
<td>2.5</td>
<td>85 (A)</td>
<td>76 (B)</td>
<td>83</td>
</tr>
<tr>
<td>n</td>
<td>vinyl</td>
<td>Me</td>
<td>H</td>
<td>3</td>
<td>50 (A)</td>
<td>44 (B)</td>
<td>40</td>
</tr>
<tr>
<td>o</td>
<td>C≡CH</td>
<td>Me</td>
<td>(CH₂)₂OTBS</td>
<td>1.5</td>
<td>80* (B)</td>
<td>3</td>
<td>80</td>
</tr>
<tr>
<td>p</td>
<td>C≡CH</td>
<td>Me</td>
<td>CH₃CN</td>
<td>3</td>
<td>63* (B)</td>
<td>3</td>
<td>63</td>
</tr>
</tbody>
</table>

* dr (%) = 1:1.
as well as (S)-50e it was discovered that the process exhibited enantioselectivity, resulting in a total S N2 inversion of configuration at C2 of the initial cyclopropane (Scheme 21).

Subsequently, the Charette group expanded this approach to include analogous cyano and keto esters. A similar stereo-outcome was observed employing optically active DA cyclopropanes (S)-52a-c; stereoinformation was fully preserved in 53, while inversion of configuration occurred at the C2 stereocenter of the initial cyclopropane (Scheme 22).

Mattson et al. activated 1-nitrocyclopropane-1-carboxylates 50 with difluoroborylphenylurea 54 in reactions with amines (Scheme 23). The activation pathway for cyclopropanes 50 involves coordination of urea 54 with the nitro group of the cyclopropane (Scheme 24). The presence of a difluoroboryl substituent at the ortho site in the aryl group increased the efficiency of the reaction by 20%, which was ascribed to an increase in the acidity of the hydrogen atoms in the amide group, owing to the coordination of boron with the oxygen atom in the carbonyl group in 54.

Nucleophilic ring opening of the optically active DA cyclopropane (S)-50g by p-(trifluoromethoxy)aniline proceeded with full preservation of stereoinformation along with inversion of stereoisomerization at C2 of the initial cyclopropane (Scheme 25). The product, α-nitro-γ-aminobutanoic acid (R)-51p, was employed in the synthesis of lactines.

reactions with both 1- and 2-pyrazolines by invoking a Lewis acid initiated isomerization of 1-pyrazoline into 2-pyrazoline, which became the reactant in both processes.

The Charette group demonstrated that additional catalytic activation of nitrocyclopropanecarboxylates 50 allowed substantial relaxation in the conditions of their cleavage with amines in comparison with the methods suggested by Seebach and Dailey. For instance, it was established that the ring in 1-nitrocyclopropane-1-carboxylates 50a was opened by aniline upon continuous heating at 90 °C, while the introduction of nickel(II) perchlorate hexahydrate as a catalyst allowed this reaction to complete at room temperature at an even higher rate (Scheme 20). The efficiency of the suggested technique was demonstrated by employing a series of 2-aryl- and 2-vinyl-substituted 1-nitrocyclopropane-1-carboxylates 50a-d together with derivatives of aniline and secondary cyclic amines as nucleophiles; consequently, α-nitro-γ-aminobutanoates 51 were obtained in good yields. Furthermore, upon the introduction of optically active cyclopropanes (R)- and (S)-50a

![Scheme 19](image-url)  
**Scheme 19** Synthesis of the core structure of bis-indole alkaloid flinderole C

![Scheme 20](image-url)  
**Scheme 20** Catalytic vs. thermal ring opening of nitrocyclopropanecarboxylates with primary and secondary amines

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**Table 2** Reaction of Cyclopropane-1,1-diesters with Pyrazolines: Nucleophilic Ring Opening vs. (3+2)-Cycloaddition

![Diagram of reaction](image)

<table>
<thead>
<tr>
<th>Pyrazoline</th>
<th>LA (mol%)</th>
<th>T (°C)</th>
<th>t</th>
<th>Yield (%) (dr)</th>
</tr>
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<tbody>
<tr>
<td>48, 49</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>43b:</strong> R = Ph</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>Sc(OTf)_3 (5)</td>
<td>20</td>
<td>12 h</td>
<td>61 (1:1)</td>
</tr>
<tr>
<td></td>
<td>GaCl_3 (100)</td>
<td>0–5</td>
<td>5 min</td>
<td>72 (1:1)</td>
</tr>
<tr>
<td>b</td>
<td>Sc(OTf)_3 (5)</td>
<td>20</td>
<td>12 h</td>
<td>31 (1:1)</td>
</tr>
<tr>
<td>c</td>
<td>Sc(OTf)_3 (5)</td>
<td>20</td>
<td>160 h</td>
<td>5</td>
</tr>
<tr>
<td>d</td>
<td>Sc(OTf)_3 (5)</td>
<td>20</td>
<td>24 h</td>
<td>–</td>
</tr>
<tr>
<td>e</td>
<td>GaCl_3 (100)</td>
<td>10</td>
<td>5 min</td>
<td>60 (1.5:1)</td>
</tr>
<tr>
<td>f</td>
<td>Sc(OTf)_3 (5)</td>
<td>20</td>
<td>12 h</td>
<td>85 (2:1)</td>
</tr>
<tr>
<td></td>
<td>GaCl_3 (100)</td>
<td>10</td>
<td>5 min</td>
<td>95 (2:1)</td>
</tr>
<tr>
<td>g</td>
<td>Sc(OTf)_3 (5)</td>
<td>20</td>
<td>3 h</td>
<td>96 (1.8:1)</td>
</tr>
<tr>
<td>h</td>
<td>Sc(OTf)_3 (10)</td>
<td>80a</td>
<td>12 h</td>
<td>–</td>
</tr>
<tr>
<td><strong>43n:</strong> R = 2-thienyl</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>i</td>
<td>Sc(OTf)_3 (5)</td>
<td>20</td>
<td>9 h</td>
<td>66 (1:1)</td>
</tr>
<tr>
<td></td>
<td>GaCl_3 (100)</td>
<td>5</td>
<td>15 min</td>
<td>72 (1:1)</td>
</tr>
<tr>
<td>j</td>
<td>Sc(OTf)_3 (5)</td>
<td>20</td>
<td>3 h</td>
<td>28 (1:1)</td>
</tr>
<tr>
<td><strong>43a:</strong> R = H</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>k</td>
<td>GaCl_3 (100)</td>
<td>20</td>
<td>3 h</td>
<td>79</td>
</tr>
</tbody>
</table>

*The reaction was carried out in 1,2-dichloroethane.
am 56, which can act as a reverse agonist of the CB-1 receptor.82

The Tang group has developed an asymmetric catalytically induced version for the nucleophilic ring opening of activated cyclopropanes with amines.84–86 Conditions analogous to those suggested in Charette’s method80 facilitated ring opening for cyclopropane-1,1-diesters 57a–n by secondary amines yielding 58a–w. Notably, the most convenient yield/enantiomeric excess relationship for products 58 was achieved upon employing tris-indaneoxazoline 59 as a ligand for asymmetric induction (Scheme 26).84 It is proposed that the presence of the third indaneoxazoline fragment in 59 is crucial to the control of the reaction rate and asymmetric induction.

The yielded β-aminoethylmalonates 58 can then be readily transformed into optically active N-heterocyclic compounds, e.g., functionalized piperidines 60 or γ-lactams 61 (Scheme 27).

Kozhushkov and colleagues suggested a synthetic approach to β-aminoethyl-substituted pyrazoles 63, based on nucleophilic ring opening of diacetylcyclopropane 62 by primary and secondary amines under mild conditions assisted by hydrazine (Scheme 28).87,88
### 3 Ring Opening with Amines Accompanied by Secondary Processes Involving the N-Center

#### 3.1 Reactions of Cyclopropane-1,1-Diesters with Primary and Secondary Amines

##### 3.1.1 Synthesis of γ-Lactams

Secondary processes in reactions of activated cyclopropanes with amines can be facilitated by the presence of at least one additional electrophilic center, localized in the activating EWG of the initial cyclopropane. Thus, when primary amines are involved as reactants, the nucleophilic ring-opening reactions of cyclopropanes activated by ester groups can be accompanied by γ-lactamization of intermediate γ-amino esters into the derivatives of 2-pyrrolidinylamines.

An early example of such a domino process, described by Stewart and Pagenkopf in 1969, involved vinylicyclopropane-1,1-diester alkaloids 63,64 and malononitrile (Scheme 3).31 Subsequently, similar processes were mostly carried out for spiro-activated cyclopropanes, synthetically derived from Meldrum’s acid. For example, Danishefsky noted that lactam 50 was formed in the reaction of cyclopropane 27 with aniline in a quantitative yield (Scheme 12).72

The Bernabé group synthesized 2-oxopyrrolidinecarboxylic acids 67 by the reaction of spiro-activated cyclopropanes 66 with NH₄OH in dioxane (Scheme 30).30 It was shown that the electronic effects of the R substituent in the phenyl ring affected the pathway of this reaction: lactams 67 were only obtained when R is a donor group, while the presence of electron-neutral or acceptor aryl groups in 66 hindered ring opening of the cyclopropane leading to the corresponding 2-aryl-1-carbamoylcyclopropanecarboxylic acids instead.

Chen et al. devised a stereoselective approach to substituted γ-butyrolactams 69 based on nucleophilic ring opening of tetrasubstituted DA cyclopropanes 68 with anilines (Scheme 31).91,92 It is proposed that 69 is formed via a mechanism that analogous to the one proposed by Danishefsky,72 wherein the intermediate amine 1-2 undergoes cyclization into lactam 69 with loss of acetone. The
which initiates cleavage in the furanone fragment, ultimately leading to 70. Analogous reactivity towards amines is characteristic of allyloxycoumarins 71a,b, which yielded lactams 70g–k upon microwave activation (Scheme 33).

The cascade of nucleophilic ring opening with amines for spiro-activated cyclopropanes together with γ-lactamization was successfully employed in the synthesis of physiologically active compounds. Thus, the Snider group devised a total synthesis of (±)-martinellic acid, the derivatives of which antagonize bradykinin (B1, B2) receptors.94,95

The synthesis was based upon the ring opening of violyclopropane 72 by aniline with subsequent lactamization and oxidation to give violinpyrrolidone 73, which reacted with N-benzylglycine and underwent subsequent intramolecular (3+2)-cycloaddition yielding tetracyclic diamine 74, a precursor of (±)-martinellic acid (Scheme 34).95

Katamreddy, Carpenter et al. proposed a synthetic approach to potential agonists of GPR119, which can be used to treat type 2 diabetes (Scheme 35).96 In the first step, Danishefsky’s cyclopropane 27 was transformed into lactam 75 on treatment with a substituted aniline, which then yielded the target pyrrolinopyrimidines 79a,b after four additional steps.

The strategy of forming bicyclic γ-lactams, derivatives of pyrrolizinone and indolizinone, was described in the works of Danishefsky et al.97–99 It was based on the intra-

**Scheme 31** Tetrasubstituted cyclopropanes in a nucleophilic ring opening/γ-lactamization cascade

**Scheme 32** Domino- transformation of allyl tetranates into lactams via nucleophilic ring opening of DA cyclopropanes I–3 with amines

**Scheme 33** Alternative synthesis of lactams from allyloxycoumarins

**Scheme 34** Total synthesis of (±)-martinellic acid

**Scheme 35** Alternative synthesis of lactams from allyloxycoumarins
molecular nucleophilic ring opening of cyclopropane-1,1-diesters with amines under the conditions of the Gabriel synthesis, with subsequent γ-lactamation. Initially, cyclopropanes $80a,b$ ($n = 1, 2$) were used in this reaction giving five- and six-membered bicyclic amines, pyrrolizinone $81a$ and indolizinone $81b$ (Scheme 36).97

The devised method was employed in racemic syntheses of pyrrolizidine alkaloids (±)-isoretronecanol and (±)-trachelanthamidine (Scheme 37).98 Danishefsky suggested an analogous approach in the synthesis of pyrroloindoles $86$ and $89$, which can be viewed as structural analogues of mitomycin C (Scheme 38).99

### 3.1.2 Synthesis of Pyrroloisoxazolidines and -pyrazolidines

The strategy for the formation of heterobicycles (pyrroloisoxazolidines $91$ and -pyrazolidines $94$) was devised in the Kerr group.100,101 It was based on intramolecular nucleophilic ring opening of DA cyclopropanes with their nucleophilic N-center in a 1,5-relationship to the electrophilic C-center of the small ring.

For example, in the presence of Yb(OTf)$_3$ as a catalyst, alkoxyamine $90$ underwent intramolecular nucleophilic ring opening leading to intermediate isoxazolidine $I-5$ (Scheme 39).100 The addition of various aldehydes to $I-5$ triggered diastereoselective assembly of pyrroloisoxazoli-
A similar process was developed for hydrazine 93, which initially underwent intramolecular nucleophilic ring opening under catalysis by Yb(OTf)$_3$ to form intermediate pyrazoline I-6, which reacted with aldehydes, predominantly yielding cis-94 (Scheme 42). Switching the steps by generating E-hydrazones I-7 in situ followed by intramolecular formal (3+2)-cycloaddition furnished trans-94 in high yields (Scheme 43).

3.1.3 Synthesis of Piperidines

The Kerr group developed a new approach to substituted piperidines 95 via the reaction between cyclopropanes 43 and N-benzylpropargylamine with Zn[N(Tf)$_2$]$_2$ as the catalyst. Their technique involved a cascade consisting of nucleophilic small ring opening, initiated by an amine and yielding intermediates I-8, followed by Conia-ene cyclization which, in turn, yielded products 95 (Scheme 44). This was confirmed by the isolation of acyclic intermediate I-8 upon introducing scandium(III) triflate as a Lewis acid during optimization. It is notable that introducing optically active cyclopropanes 43 to the reaction led to piperidines 95 with complete inversion of configuration at the electrophilic center.
3.1.4 Synthesis of Azetidine and Quinoline Derivatives

Luo et al. designed an efficient approach to azetidines 96, based on a cascade of nucleophilic ring opening of cyclopropane-1,1-diesters 43 with aniline derivatives and intramolecular oxidative α-amination of the malonate fragment in intermediate 1-9 (Scheme 45).104 Cyclopropanes 43 containing electron-abundant aryl substituents give tetrahydroquinolines 97 via Lewis acid induced azetidine ring opening, leading to stabilized benzylic cations, followed by 1,6-cyclization via electrophilic aromatic substitution (Scheme 46).

3.2 Reactions of Ketocyclopropanes with Primary Amines: Synthesis of Pyrrole Derivatives

Similarly to cyclopropane-1,1-diesters, ketocyclopropanes can take part in domino reactions with primary amines, yielding pyrrole fragments. Systematic studies in this field were undertaken by a group of French chemists led by Lhommet. They designed efficient synthetic approaches to pyrrolines, starting from 1-acylcyclopropane-1-carboxylates and 1-acylcyclopropane-1-carboxamides.105–107 Under severe conditions, electrophilic cyclopropanes 98 reacted with primary aliphatic and aromatic amines giving pyrrolines 99a–k in good yields (Scheme 47).105 Experiments showed that imine 100, formed from cyclopropane 98a and benzylamine, did not yield pyrrole 99g upon heating; however, an analogous experiment carried out in the presence of methylamine yielded a mixture of pyrrolines 99a and 99g. This outcome pointed to the reaction proceeding via intermolecular nucleophilic ring opening of cyclopropane with the amine, followed by 1,5-cyclization (as opposed to Cloke–Stevens rearrangement).

The devised approach to pyrrolines was then used in the total synthesis of isoretroenealin, a pyrrolizidine alkaloid, in its racemic form (Scheme 48).105 Subsequently, the Lhommet group designed enantioselective approaches to the alkaloids (+)-laburnine, (+)-tashiromine, and (-)-isoretroenealin based on the transformation of acylcyclopropanes into pyrrolines.106
An analogous method was proposed for the synthesis of 4,5-dihydro-1H-pyrole-3-carboxylates 103a–s from DA cyclopropanes 102 containing alkyl, aryl, and alkenyl substituents as an EDG (Scheme 49).107

The Charette group expanded the scope of this reaction to include 1-acyl-1-nitrocyclopropanes and 1-acylcyclopropane-1-carbonitriles 104, which react with primary amines under milder conditions, yielding nitropyroles 105a–n or cyanopyrrolines 105o–s (Scheme 50).108 Interestingly, aniline derivatives produced pyrrolines 105 in significantly higher yields than aliphatic amines. It is proposed that the reaction started with nucleophilic small ring opening in 104 by the amine, leading to intermediate amino ketone 110, which then undergoes cyclization to form 105 as a result of intramolecular nucleophilic attack of the amino group upon the carbonyl center. Pyrrolines 105 were readily oxidized to give pyrroles 106a–c on treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).

Cao et al. devised an analogous two-step approach to 2-fluoromethyl-substituted pyrrole-3-carboxylates 108 (Scheme 51).109

Nambu et al. demonstrated that spiro-activated cyclopropane-1,1-diketones 109 formed bicyclic pyrrolines, tetrahydroidindolones 110, on reaction with aliphatic and aromatic primary amines as well as ammonia, even at room temperature (Scheme 52).110

There are two possible mechanisms for such reactions: 1. nucleophilic ring opening of the cyclopropane with the amine, followed by a subsequent nucleophilic attack of the amino group upon the carbonyl group, and 2. the formation of an imine with a subsequent Cloke–Stevens rearrangement. However, it was noted that imine formation was not detected in the reaction even when catalytic amounts of trifluoroacetic acid were introduced into the system. This indicates that it is more likely the mechanism involves nucleophilic ring opening of cyclopropanes 109 by amines.

Cyclopropane 109b acted as a model compound, showing the possibility of applying the devised technique in the synthesis of indole derivatives of type 112 (Scheme 53).110

Furthermore, a one-pot approach to pyrroline 110 was devised, starting from cyclohexane-1,3-dione (Scheme 54).111
and Scheme 57). The introduction of Ni(ClO₄)₂·6H₂O as a catalyst, analogously to Charette’s technique for the ring opening of 1-nitrocyclopropane-1-carboxylates 50 (Scheme 20), provided the optimal conditions for this reaction. The use of the catalyst resulted, in most cases, in significantly milder heating conditions and also a reduction in the time for the reaction to go to completion; the pyrrolinocarboxylates 116a–n, q–s and acylpyrrolines 116o, p were obtained in good yields.

Scheme 53 Transformation of a cyclopropane into an indole

Zhang and Zhang performed an analogous reaction employing ketamides 113 and primary aromatic or aliphatic amines (Scheme 55). Accordingly, a series of pyrrolinoquinolones 114 were synthesized in high yields.

Scheme 54 One-pot approach to pyrroline 110o from cyclohexane-1,3-dione

The France group suggested a catalytic variant of the reaction technique for the synthesis of pyrrolines 118 based on the kinetically controlled separation in the reaction of 1,1-dicyclocopropanes 117 with aniline derivatives (Scheme 58). The optimal catalytic system Sc(OTf)₃–119 provided the best yield-to-enantioselectivity relationship. The scope

Scheme 55 Synthesis of pyrrolinoquinolones from spiro[2.5]octanes

The Liu and Feng group designed an asymmetric catalytic technique for the synthesis of pyrrolines 118 based on the best yield-to-enantioselectivity relationship. The scope

Scheme 56 Catalytic conversion of cyclopropanes into pyrrolines
of the method was demonstrated on a representative series that included the reaction 1,1-diacyl-2-aryl-, 2-alkyl-, and 2-alkenylcyclopropanes 117a–w with primary aryl- and aliphatic amines under the optimized conditions to produce pyrrolopyridinones 118a–l in good yields and with enantioselectivities of up to 97% ee. The possibility of this process proceeding via a Cloke–Stevens rearrangement was excluded as no imines were detected in the process.

The Zhang group also suggested an approach to functionalized pyrroles 124, based on the following cascade: 1. nucleophilic ring opening of 1-acylcyclopropane-1-carboxylates 123a–o and 1-acylcyclopropane-1-carboxylates 123p–q with primary amines, 2. cyclization of the intermediate ketamine 1-13 to give pyrrole 1-14, and 3. oxidation of 1-14 to give pyrrole 124 (Scheme 62 and Scheme 63). Curiously, iron(III) chloride, employed here in catalytic quantities, played a dual role, acting both as a Lewis acid (additionally activating the cyclopropane towards ring opening) and as a one-electron oxidizer, regenerated during the course of the reaction.

An original method for the synthesis of 3,3′-bipyroles 126 from the Werz group118,119 was based on the reaction between tricyclic compounds 125, the structure of which included fragments of two cyclopropanes as well as tetrahydrofuran, and primary amines (Scheme 64). In some cases, diketopyrroles 127 were obtained as secondary prod-

The presence of a second amino group at the ortho site in the aniline ring, employed as the nucleophile, induced a more complicated domino process. In this case, the formation of the pyrroline ring was an intermediate stage, whereas, the ultimate products were benzimidazole derivatives 120 (Scheme 59).

Therefore, the interactions between ketocyclopropanes and primary amines can involve a more complex pattern than a two-step process, such as the ‘nucleophilic small ring opening–1,5-cyclization’ sequence. This depends upon the functional groups in the initial molecules and the conditions chosen for the reaction. The Zhang group synthesized pyrrolopyridinones 122 from electrophilic cyclopropanes 121 containing both an amide group and a fragment of an α,β-unsaturated ketone in their structure (Scheme 60). This functionalization of the small ring allows ring opening with primary amines to give γ-aminoketamides 1-11 that undergo 1,5-cyclization to give 2-vinylpyrroline-3-carboxamides 1-12. The latter, in turn, undergo intramolecular conjugated aza-addition to yield pyrrolopyridinones 122 (Scheme 61).
Synthesis of diketopyrroles under the action of primary amines

Scheme 64: Transformation of dicyclopropanes into pyrroles

Scheme 65: Proposed mechanisms for formation of bipyrroles via Cloke–Stevens rearrangement and diketopyrroles via nucleophilic ring opening

Yang, Zhang et al. devised an effective synthetic approach to optically active 2-(polyoxylalkyl)pyroles 129 containing two stereogenic centers. The synthesis of 129 was based upon the reaction of cyclopropa[b]pyranones 128 with primary aromatic and aliphatic amines in the presence of InBr₃ as a catalyst (Scheme 66). The reaction is proposed to proceed via imine 119, further rearrangement of which leads to pyrrole 127 (Scheme 67).

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and primary amines as reactants. The reaction was carried out at reflux in CH₂Cl₂ with catalytic amounts of zinc triflate (Scheme 68). In contrast to the mechanism in Scheme 67, the mechanism for the transformation of 130 into 131 involves the formation of amine 1-19 and its cyclization, yielding bicyclic pyrroline 1-21, which, in turn, yields pyrrole 131 upon pyran ring opening (Scheme 69).

**Scheme 67** Proposed mechanism for the transformation of cyclopropylpyranones into 2-(polyoxyalkyl)pyrroles via imine rearrangement

In 2016 Chusov and colleagues reported a ruthenium(III)-catalyzed reaction of ketocyclopropanes 132 with anilines in the presence of CO as a reductant, providing a direct method to access pyrrolidines 133 in high yields (Scheme 70).

**Scheme 68** Cascade transformation of ketocyclopropanes into 3-(polyoxyalkyl)pyrroles

**Scheme 69** Proposed mechanism for the transformation of ketocyclopropanes into 3-(polyoxyalkyl)pyrroles via nucleophilic ring opening

3.3 Reactions of Cyclopropane-1,1-dicarbonitriles with Primary Amines: Synthesis of Pyrrole Derivatives

Yamagata et al. compared the reactivities of cyclopropane-1,1-dicarbonitrile (1b) and 1-cyanocyclopropane-1-carboxylate 1c towards aniline derivatives (Scheme 71). It was shown that 1b underwent ring opening upon treatment with amines under milder conditions than 1c. Poorly nucleophilic nitroanilines were inert towards 1b,c under studied conditions.

**Scheme 70** Direct formation of pyrrolidines by ruthenium(III)-catalyzed reaction of ketocyclopropanes with anilines and CO

An unusual result was produced by Fu and Yan in the reaction of 2,3-dicyanocyclopropane-1,1-dicarbonitriles 136 with imines 137; instead of the expected (3+2)-cycladdition products the reaction gave pyrroles 138 (Scheme 72).

In order to explain the formation of iminopyrroles 138, a mechanism is proposed (Scheme 73) that involves nucleophilic ring opening of cyclopropane 136 with aniline, the product of hydrolysis of imine 137 to give I-22. The latter undergoes 1,5-cyclization by nucleophilic addition of the amine to the cyano group to give pyrroline I-23. Oxidative aromatization of I-23 into pyrrole I-24 is followed by formation of imine 138 upon the reaction of I-24 and the aldehyde.
Amines

4 Ring Opening with Tertiary Aliphatic Amines

Reactions of activated cyclopropanes with tertiary aliphatic amines are peculiar in that they involve an amine initiating ring opening of the three-membered ring to yield a nucleophilic intermediate that reacts with suitable electrophiles. Subsequent substitution by a different nucleophile returns the amine to the reaction mixture, allowing for its use as a catalyst.

An interesting example by Du and Wang utilized DA cyclopropane 139 (which contains an acrylate fragment among its EWG) which reacts with benzaldehydes in the presence of DABCO to yield isomeric lactones 140 and 141 (Scheme 75). A mechanism is proposed that involves initial tertiary amine opening of the cyclopropane ring to give enolate I-25, which then condenses with the aldehyde forming I-26 (Scheme 76). Intermediate I-26 undergoes nucleophilic substitution in which the amine is substituted by DABCO. The three-component reaction of cyclopropanes 136 with amines and aldehydes also resulted in the formation of pyrroles 138 (Scheme 74), which provides indirect support for the suggested mechanism.

Scheme 74

Three-component reaction of 2,3-diarylcyclopropane-1,1-dicarbonitriles with 4-methylaniline and aldehydes

Scheme 75

Formation of lactones via nucleophilic ring opening of a cyclopropane with DABCO

Scheme 76

Proposed mechanism for the transformation of a cyclopropane into a lactone
the carboxylic oxygen, followed by the elimination of alcohol and formation of the lactones 140 and 141.

The Liang group demonstrated that 1-acylcyclopropane-1-carboxamides 142 also reacted with DABCO. Furthermore, in the absence of electrophiles, the reaction resulted in stable betaines 143, wherein additional stabilization of the anionic center was provided by a hydrogen bond formed between the hydrogen atom in the amide group and the oxygen center in the enolate (Scheme 77). Upon addition of electrophilic reactants (e.g., alkyl halides E-Hal), C-alkylation of enolates 143 occurred, with salts 1-27 formed as intermediates. Treatment of 1-27 with NaOH for 30 minutes yielded 3-acyl-2-pyrrolidones 144, whereas 2-pyrrolidones 145 were formed after 12 hours (Scheme 78).

The scope of this reaction was expanded to include electrophilic alkenes, showing that the introduction of a tertiary amine in catalytic amounts did not lead to a loss in efficiency (Scheme 79). Additionally, it was found that, in the absence of any other electrophiles, 1-acylcyclopropane-1-carboxamide 142 acted in this capacity. Therefore, two molecules of 142a-c formed the resulting lactams 147a-c (Scheme 80).

5 Ring Opening with Amides

Zhang and Schmalz designed a gold(I)-catalyzed reaction between alkynyl-substituted cyclopropane 148 and 2-pyrrolidone, affording furan derivative 149 (Scheme 81). Two possible mechanisms are proposed for this process, differing in the exact order of the three-membered ring opening and the formation of the furan fragment. In one of those mechanisms, upon the coordination of a cationic gold(1) species, further reaction is initiated by nucleophilic attack of pyrrolidine on the activated three-membered ring, resulting in the formation of the furan ring.
A similar palladium(II)-catalyzed process by Shi et al. allowed the synthesis of pyrrole derivatives, this is exemplified by the reaction of 1-alkynylcyclopropyl oxime \( \text{150} \) to give pyrrole \( \text{151} \) (Scheme 82).\(^{130}\)

Flitsch and Wernsmann performed the ring opening of cyclopropyltriphenylphosphonium tetrafluoroborate \( \text{152} \) with imide anions, followed by formation of a five-membered N-heterocycle \( \text{153a-c} \) via an aza-Wittig reaction (Scheme 83).\(^{131}\) This reaction was used in the total synthesis of pyrrolizidine alkaloid (\( \text{2} \))-isoretrocanol. Under similar conditions, reaction of \( \text{152} \) with monothioimidies yielded a mixture of aza-Wittig cyclization products \( \text{153a,b} \) and \( \text{154a,b} \) via a nucleophilic attack on both C=S and C=O groups, as well as acyclic products of primary nucleophilic ring opening \( \text{155a,b} \) (Scheme 84).

For ring opening with phthalimide, see Scheme 111.

### 6 Ring Opening with Hydrazines

In the mid-2000s, Cao et al. described the synthesis of pyrazoles \( \text{157} \) based on the reaction between cyclopropanes \( \text{156} \) and hydrazine in 1,2-dimethoxyethane at reflux (Scheme 85).\(^{132,133}\) It is proposed that cyclopropylhydrazone \( \text{1-28} \) is formed in the first step, which undergoes intramolecular nucleophilic ring opening under the conditions to give dihydropyrazole \( \text{I-29} \); elimination of malonodinitrile from \( \text{I-29} \) gives the final pyrazole \( \text{157} \).

In 2016, Wang et al. showed that a similar reaction took place upon mixing cyano esters \( \text{158} \) and aryldrazines in the presence of \( \text{H}_2\text{SO}_4 \), yielding \( \text{N-aryl-substituted pyrazoles} \ (\text{159}) \) (Scheme 86).\(^{134}\)

\[ \begin{align*} 
\text{Ar}^* = \text{Ph} \quad \text{Ar} = \text{Ph} \\
\text{Ar}^* = \text{Ph} \quad \text{Ar} = \text{4-ClC}_6\text{H}_4, 82\% \\
\text{Ar}^* = \text{Ph} \quad \text{Ar} = \text{2-ClC}_6\text{H}_4, 79\% \\
\text{Ar}^* = \text{Ph} \quad \text{Ar} = \text{3-ClC}_6\text{H}_4, 75\% \\
\text{Ar}^* = \text{Ph} \quad \text{Ar} = \text{4-Tol}, 81\% \\
\text{Ar}^* = \text{Ph} \quad \text{Ar} = \text{4-BrC}_6\text{H}_4, 84\% \\
\text{Ar}^* = \text{Ph} \quad \text{Ar} = \text{4-CIC}_6\text{H}_4, 87\% \\
\text{Ar}^* = \text{Ph} \quad \text{Ar} = \text{4-BrC}_6\text{H}_4, 85\% \\
\text{Ar}^* = \text{Ph} \quad \text{Ar} = \text{4-CIC}_6\text{H}_4, 85\% \\
\end{align*} \]

\[ \begin{align*} 
\text{Ar}^* = \text{Ph} \quad \text{Ar} = \text{PMP}, 89\% \\
\text{Ar}^* = \text{Ph} \quad \text{Ar} = \text{4-ClC}_6\text{H}_4, 90\% \\
\text{Ar}^* = \text{Ph} \quad \text{Ar} = \text{4-Tol}, 95\% \\
\end{align*} \]
In 2017, Srinivasan et al. demonstrated a similar process involving 2-aryl-3-arylcyclopropane-1,1-diesters 160 and arylhydrazines under milder conditions that did not result in elimination of the malonyl fragment (Scheme 87). Hence, pyrazolines 161 were produced in high yields. At the same time, the reaction of 160a with an unsubstituted hydrazine immediately yielded pyrazole 157a. This reaction is proposed to occur via intermediate formation of pyrazoline 161a with following elimination of the malonyl fragment.

For intramolecular nucleophilic ring opening of DA cyclopropanes with hydrazine, see Scheme 40.

7 Ring Opening with N-Heteroaromatic Compounds

7.1 Ring Opening with Pyridines

An early example of the ring opening of activated cyclopropanes by pyridines was reported by King in 1948. In this reaction, pyridine reacted with 3,5-cyclo-cholestan-6-one 162 in the presence of p-TsOH and upon prolonged heating the mixture yielded salt 163 (Scheme 88).

Lacking an external source of hydrogen ions, activated cyclopropanes undergo ring opening to form betaines. As discussed in Section 2, Danishefsky's cyclopropane 27 and 1,1-dinitrocyclopropane 31 reacted with pyridines at room temperature to yield the corresponding betaines 29 and 32d (Schemes 12 and 13).

7.2 Ring Opening with Indoles

Typical reactions of DA cyclopropanes with indole derivatives are represented by the C2 and C3 alkylation of indoles by cyclopropanes as well as by (3+2)-cycloaddition of cyclopropanes to the C2-C3 bond in indoles. In these cases, the chemoselectivity mainly depends upon the sites where substituents are located in the indole. However, reaction of 3-methyl-1H-indole (N-unsubstituted skatole) with a cyclopropane-1,1-dicarboxylate 1a under harsh conditions resulted in N-alkylation proceeding along with formal (3+2)-cycloaddition and leading to product 164 (Scheme 89).

The Rainier group developed a synthesis for the highly strained DA cyclopropane 165, which underwent ring opening upon treatment with a large series of nucleophiles under very mild conditions. Specifically, it was shown that ring opening of 165 with an indole catalyzed by a base yielded product 166, and this reaction went to completion in 5 minutes at 0 °C (Scheme 90).

For the nucleophilic ring opening of cyclopropyltri-phenylphosphonium tetrafluoroborate 152 with indole, see Scheme 98.

An intramolecular variant of ring opening for DA cyclopropanes 167 upon an N-attack by an indole fragment was devised in the Waser group. The pathway taken by the reaction was defined by the choice of the catalyst together with the choice of the solvent polarity. Employing largely non-polar CH2Cl2 or toluene together with p-TsOH as the catalyst gave the products of the N-nucleophilic ring open-
The Inaba group demonstrated that the presence of a leaving group at C2 of the indole facilitated fusion of a newly formed pyrrolidine ring via a cascade of nucleophilic ring opening/nucleophilic substitution (Scheme 91). N-Nucleophilic ring opening was used in the total synthesis of alkaloid goniomitine (Scheme 92).

The synthesis of (±)-goniomitine was accomplished via nucleophilic ring opening (homo-Nazarov cyclization) (Scheme 93). The total synthesis of the protein kinase C-β inhibitor JTT-010 (Scheme 94) using soft Lewis acids as the catalyst yielded the products 169 of C3-nucleophilic ring opening (homo-Nazarov cyclization) (Scheme 91). N-Nucleophilic ring opening was used in the total synthesis of alkaloid goniomitine (Scheme 92).

The total synthesis of (±)-goniomitine is shown in Scheme 92. The synthesis involved the use of soft Lewis acids as the catalyst to yield the products 169 of C3-nucleophilic ring opening (homo-Nazarov cyclization) (Scheme 91). The total synthesis of the protein kinase C-β inhibitor JTT-010 (Scheme 94) using soft Lewis acids as the catalyst yielded the products 169 of C3-nucleophilic ring opening (homo-Nazarov cyclization) (Scheme 91).
opening of cyclopropanes 1 or 170, followed by nucleophilic substitution and leading to 171–173 (Scheme 93). Analogous processes were carried out for imidazoles and benzimidazoles. Based upon this reaction, they devised a synthesis of the protein kinase C-β inhibitor JTT-010 (Scheme 94).

7.3 Ring Opening with Di- and Triazoles

Five-membered heterocycles with several nitrogen atoms (di- and triazoles) can be successfully employed as nucleophiles in the processes of ring opening for activated cyclopropanes.

Kotsuki et al. achieved the ring opening of cyclopropane-1,1-diesters 1a, 15a,b, 43b by treatment with di- and triazoles catalyzed by a Lewis acid combined with microwave-induced activation.149 Monoadducts 174 were the primary products in this reaction; however, in most cases diadducts 175 were formed in comparable amounts (Scheme 95). Furthermore, in the reactions of 1,2,4-triazole and purine, regioisomeric monoadducts 174 were formed.

Under similar conditions, Danishefsky’s cyclopropane 27 reacted with excess pyrazole via nucleophilic ring opening and subsequent amidation by the second equivalent of pyrazole yielding 176 (Scheme 96).

Chung and co-workers designed a process relying on the ring opening of cycloproplytriphenylphosphonium tetrafluoroborate 152 with pyrazoles in basic medium with a subsequent Wittig reaction between intermediate phosphorus ylide I-30 and an aliphatic or aromatic aldehyde.150 This technique allowed the exclusive synthesis of pyrazole-substituted alkylidine- and benzylidenebutanoates 177 as the E-isomer (Scheme 97). Analogous reactions were performed for a series of N-nucleophiles, generated in a basic medium from morpholine, indole, and sulfonamide, as well as for the azide ion (Scheme 98).

Niu, Guo et al. reported the synthesis of acyclic derivatives of nucleosides based on the nucleophilic ring opening of 2-vinylcyclopropane-1,1-dicarboxylates 3a–e with purines.151 The regioselectivity in this process was governed by the choice of the catalyst. Activation by Lewis acids resulted in 1,3-addition; MgI₂ as the catalyst gave N7-adducts 178a–I while AlCl₃ gave N9 adducts 179a–k (Scheme 99).

Scheme 97  Ring opening of a cycloproplytriphenylphosphonium tetrafluoroborate with pyrazoles followed by Wittig reaction

Scheme 98  Ring opening of a cycloproplytriphenylphosphonium tetrafluoroborate with various N-nucleophiles

Scheme 99  Lewis acid triggered ring opening of 2-vinylcyclopropane-1,1-dicarboxylates with purines
Catalytic amounts of \( \text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3 \) directed the reaction towards conjugated 1,5-addition, yielding N9-adducts 180a–k (Scheme 100). Reduction of 179 and 180 allowed the production of structural analogues of acyclic nucleosides (e.g., penciclovir and famciclovir) which have potential for anti-HIV activity.

7.4 Ring Opening with Pyrimidines

Another approach to structural analogues of nucleosides by Shao et al.\textsuperscript{152} was based on the reaction between cyclopropanated lyxose 181 and pyrimidines and yielded nucleosides 182a,b (Scheme 101). This reaction was carried out under mild conditions when cyclopropane 181 underwent additional acidic activation.

Activated cyclopropanes are able to take part in the Ritter reaction with nitriles as alkylating agents, yielding functionalized amides. This reaction can be initiated either by strong or weak Lewis acids, depending on the activity of the initial cyclopropane. Palumbo, Wenkert et al. utilized a reagent consisting of trimethylsilyl chloride, silver tetrafluoroborate, and acetonitrile for the ring opening for DA cyclopropanes under mild conditions.\textsuperscript{153} The efficiency of this reagent was demonstrated in the ring opening of cyclopropane 19a, forming acyclic amide 183a (Scheme 102). The Vankar group identified a similar ring opening of ketocyclopropanes 19a,c leading to amides 183a–d in the presence of concentrated sulfuric acid.\textsuperscript{154}

Schobert et al.\textsuperscript{74} found that spiro-activated DA cyclopropanes 35 react with nitriles in a reaction catalyzed by ytterbium(III) triflate, a Lewis acid of average strength (Scheme 103).

The proposed mechanism involves the coordination of the Lewis acid with the EWG in 35 as well as opening the three-membered ring to give intermediate I-31. Subsequent attack of the nitrile upon the flat carbenionic center in I-32 along the path with lower steric hindrance produces (\( R^*\),\( R^*\))-acetamides 184a–c.

In 2013, the Jiang group developed a new, efficient synthetic approach to the derivatives of indolizinone 187, based on the domino reaction between ketocyclopropanes

(\( R^*\),\( R^*\))-acetamides 184a–c.
**Table 3** Ring Opening of Ketocyclopropanes with Benzonitriles Yielding Indolizinone Derivatives

<table>
<thead>
<tr>
<th>R&lt;sup&gt;1′&lt;/sup&gt;, R&lt;sup&gt;1′′&lt;/sup&gt; = H, X = H</th>
<th>R&lt;sup&gt;2&lt;/sup&gt; Yield (%)</th>
<th>Yield (%)</th>
<th>R&lt;sup&gt;2′&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2′′&lt;/sup&gt; Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>80</td>
<td>R</td>
<td>85</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
</tr>
<tr>
<td>4-FC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>85</td>
<td>3-FC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>70</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
</tr>
<tr>
<td>4-ClC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>84</td>
<td>3-ClC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>66</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
</tr>
<tr>
<td>4-Tol</td>
<td>72</td>
<td>1-naphthyl</td>
<td>55</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
</tr>
<tr>
<td>R&lt;sup&gt;2′&lt;/sup&gt;, R&lt;sup&gt;2′′&lt;/sup&gt; = H, X = Br</td>
<td>Bn</td>
<td>Bn</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>69</td>
<td>4-FC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>70</td>
<td>allyl</td>
</tr>
<tr>
<td></td>
<td>R&lt;sup&gt;2&lt;/sup&gt; = allyl</td>
<td>allyl</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td></td>
<td>R&lt;sup&gt;2′&lt;/sup&gt; = H</td>
<td>R&lt;sup&gt;2′′&lt;/sup&gt;</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Ph</td>
<td>84</td>
<td>Me</td>
<td>76</td>
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<tr>
<td></td>
<td>4-FC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>90</td>
<td>Me</td>
<td>71</td>
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<td></td>
<td>4-ClC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>84</td>
<td>allyl</td>
<td></td>
</tr>
<tr>
<td>R&lt;sup&gt;2′&lt;/sup&gt;, R&lt;sup&gt;2′′&lt;/sup&gt; = H, X = Cl</td>
<td>R&lt;sup&gt;2′&lt;/sup&gt;, R&lt;sup&gt;2′′&lt;/sup&gt; = allyl</td>
<td>Me</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>72</td>
<td></td>
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</tr>
</tbody>
</table>

**185a–h** and benzonitriles **186a–q** which contained (hetero)aromatic EDG (Table 3). The process occurs via a Ritter reaction, forming intermediate amide **I-33**, subsequent γ-lactamization yields **I-34** and this is followed by electrophilic aromatic substitution to give **187** (Scheme 104).

This approach was applied to the total synthesis of anticancer alkaloid (+)-crispine A (Scheme 105).

**9 Ring Opening with the Azide Ion**

In activated cyclopropanes, cleavage by the azide ion provides a convenient synthetic approach to organic azides characterized by 1,3-relationship between the N<sub>3</sub> group and the EWG. The first example of this type of reaction was reported by Bernabé in 1985. It was shown that, upon the action of sodium azide in a water/dioxane mixture, spiro-activated DA cyclopropanes **66c–e** readily underwent nucleophilic ring opening by the azide ion yielding **188a–c** (Scheme 106).
Seebach et al. conducted a similar reaction, employing 1-nitrocyclopropane-1-carboxylate 21.\(^{153}\) In this case, complete conversion of 21 into acyclic azide 189 required heating at 60 °C in DMF (Scheme 107).

Lindstrom and Crooks identified conditions that allowed transformation of the less reactive diester 1a into acyclic azidomalonate 190.\(^{156}\) The reaction between 1a and sodium azide required prolonged heating in N-methyl-2-pyrrolidone with triethylamine hydrochloride (Scheme 108). In the absence of Et₃N·HCl, 1a was not converted into 190. The reduction of azide 190 was accompanied by γ-lactamization, yielding pyrrolidone 191.

Aubé et al. showed that trimethylsilyl azide could be used as a source of the azide ion in the ring opening of activated cyclopropanes.\(^{157}\) Thus, during a complete synthesis of the alkaloid (+)-aspidospermidine, the ring in ketocyclopropane 192 was readily opened by an equimolar mixture of trimethylsilyl azide and tetrabutylammonium fluoride to yield azide 193 (Scheme 109). The ease with which nucleophilic ring opening of 192 occurred was explained in terms of the high stability exhibited by the intermediate enolate ion.\(^{157}\)

The reaction between dinitrocyclopropane 31 and sodium azide gave a stable γ-azidodinitropropane salt that only yielded the corresponding dinitroazidopropane 194 upon acidification (Scheme 110).\(^{73}\)

The Lee group devised an approach to optically active β-substituted γ-butyrolactones by nucleophilic ring opening of enantiomerically pure cyclopropane 170.\(^{158}\) The ring opening of 170 with the azide ion with no source of hydrogen ion present led to the formation of azidomethyl-substituted γ-butyrolactone (S)-195 in lower yields (conditions b) than in the presence of an acid (conditions a) (Scheme 111). An analogous pathway was observed for the ring opening of 170 with potassium phthalimide as a source of an N-nucleophile to afford (S)-196.

On this basis, the Lee group synthesized optically pure N-Boc-β-proline 199 (Scheme 112).\(^{159}\)
Nucleophilic ring opening of the highly strained DA cyclopropane 165 by the azide ion yielded azidopyrroloindo-line 200 under very mild conditions at room temperature (Scheme 113).146 Pyridinium p-toluenesulfonate (PPTS) was employed as a source of hydrogen ions in this reaction.

To interpret the collected data,160 a mechanism is suggested (Scheme 116) that involves intermediate formation of acyl azide I-36, which undergoes subsequent [3,3]-sigmatropic rearrangement to form ketene I-37. The hydrolysis of I-37, followed by decarboxylation of I-38, gives azido monoester 202. This mechanism is in good agreement with the obtained stereochemical result, explaining the inactivity of cyclopropane-1,1-diesters in this reaction.

Scheme 113
Ring opening of a highly strained DA cyclopropane with the azide ion

Scheme 114
Ring opening of cyclopropanecarboxylic acids with the azide ion

Scheme 115
Conversion of (S)-201a into pyrrolidone (S)-204

Scheme 116
Proposed mechanism for the transformation of 201 into 202

2-(o-Alk-1-ynylnaph)yclopropane-1,1-dicarboxylate monomethyl esters 205 react with sodium azide via intermediate γ-azidobutanoates I-39 which undergo intramolecular (3+2)-cycloaddition between the azido group and the C–C triple bond yielding tricyclic triazoles 206 (Scheme 117).161

Scheme 117
Cascade transformation of DA cyclopropanes into tricyclic triazoles

Activated cyclopropane 207, wherein the amidine fragment of the indolquinolinic system acts as an EWG, underwent diastereoselective ring opening upon treatment with NaN₃/NH₄Cl (1:1) mixture yielding azide 208 (Scheme 118).162 In contrast with a similar reaction that involved cyclopropanecarboxylic acids 201 (Scheme 115 and Scheme 116), for 207, ring opening proceeded with inversion of configuration at the stereocenter of the initial cyclopropane, which pointed to the mechanism of this process being S₂,2-like.

Treatment of the optically active cyclopropane (S)-201a under the same conditions proceeded with complete preservation of optical information, while the configuration of the stereocenter remained the same. In order to elaborate the absolute configuration of the stereocenter in 202a, the optical rotation [α]₀ of 202a was compared that determined for optically active lactam 204 (Scheme 115).

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The Zou group examined the nucleophilic ring opening of activated cyclopropanes annulated to glucopyranoside. Ring opening of unstable cyclopropanecarboxaldehyde 1-40, generated in situ from glycosides 209a,b in the presence of a base, proceeded under mild conditions at room temperature and resulted in azide 210a (Scheme 119). Similar ketocyclopropane 211 only reacted with sodium azide upon prolonged reflux in methanol yielding 210b. In both cases, ring opening proceeded stereoselectively, with the configuration of the reacting stereocenter being inverted.

Since 2015, our group has designed a preparatively convenient approach to polyfunctionalized alkyl azides 213 in order to use them as building blocks in the construction of various five-, six-, and seven-membered N-heterocycles. The method for the synthesis of 213 relied upon nucleophilic ring opening of DA cyclopropanes 212 activated with aryl-, hetaryl-, and alkynyl-substituents as the EDG (R) and ester, acyl, nitro, and cyano groups as EWG with the azide ion (Scheme 120). The experimental data showed that the reaction proceeded via an $S_n$2-like mechanism with reversal of configuration at the electrophilic center of cyclopropane 212. We localized $S_n$2-like transition states for a representative series of DA cyclopropanes by means of DFT calculations. The trend of variation in the calculated energy barriers corresponded to the changes in reactivity of the studied DA cyclopropanes.

10 Summary

Over the last few decades, a great amount of crucial new data has been collected on the ring opening of DA cyclopropanes with $N$-nucleophiles, owing to developments in synthetic methodologies as well as the design of novel types of DA cyclopropanes, nucleophiles, and catalysts (intended to allow milder reaction conditions and enantioselective synthesis). However, impressive progress in this area would not have been possible without significant contributions of many pioneering works, laying the foundation for the recent blossoming in this field. The reported reactions allow for the construction of a multitude of $N$-containing acyclic and cyclic compounds belonging to various classes: amines, amides, azides, azaheterocycles, and many others. Furthermore, stereospecificity that defines these processes facilitates convenient synthetic approaches to these compounds in optically active forms. Due to their manifold reactivities, the products of these reactions are characterized by their high synthetic potential and urgency as well, which provides researchers with powerful synthetic strategies to produce new compounds with high utility (including N-heterocycles, alkaloids, GABA and its derivatives) that are essential to biochemistry and pharmacology. Even though the present achievements are certainly convincing, still there are multiple opportunities for further progress, which hinges upon developments in even newer types of catalysts, search for unusual substrates, and original techniques combined with thorough insight into the mechanistic peculiarities of these processes.