Ring Opening of Donor–Acceptor Cyclopropanes with $N$-Nucleophiles

Ekaterina M. Budynina*  
Konstantin L. Ivanov  
Ivan D. Sorokin  
Mikhail Ya. Melnikov

Lomonosov Moscow State University,  
Department of Chemistry, Leninskie gory 1-3, Moscow 119991,  
Russian Federation  
ekatbud@kinet.chem.msu.ru

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Abstract Ring opening of donor–acceptor cyclopropanes with various $N$-nucleophiles provides a simple approach to 1,3-functionalized compounds 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 donor–acceptor (DA) cyclopropanes with $N$-nucleophiles. The term ‘donor–acceptor substituted cyclopropanes’ was introduced 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.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.20 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 nitro-les, 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,32–35 diazenes,36–39 N-aryl40–42 heterocumulenes,43–45 nitriles,46–53 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.1 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, 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 isomerized 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-diactivated 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 β-aminoethylmalonates 2a–g (Scheme 4).30 While diester 1a required lengthy heating with an excess of the amine, analogous reaction of dinitrile 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, vinylcyclopropane 3a behaved similarly, yielding ring-opening products 4a,b (Scheme 5).31 Notably, no products of conjugated 1,5-addition of the amines to vinylcyclopropane 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 γ-lactams 5a–d 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 γ-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 cyclopropane diesters was studied by Danishefsky and Rovnyak.61 In the case of 2-
alkylcyclopropane-1,1-diester, 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 tetramethycyclopropane-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 allows nucleophilic ring opening by amines.60 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[ε]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=C 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).

O’Bannon and Dailey researched a similar reaction for DA cyclopropane 23,68 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-
membered ring opening. A specific example of structural activation for electrophilic cyclopropanes was described in the works of Cook,\textsuperscript{70,71} wherein the reactions of tricyclo[2.2.1.0\textsubscript{2,6}]heptan-3-one with cyclic secondary amines were investigated (Scheme 11). Full conversion of 25 into amino ketones 26\texttextit{a-d} was already detected after 2 hours, even though additional thermal and catalytic activation took place.\textsuperscript{71}

Sprio-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,\textsuperscript{72} 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-I 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.\textsuperscript{71} 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).\textsuperscript{74} 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 CH\textsubscript{2}Cl\textsubscript{2}, yielding amines 36. From the relative configurations of stereocenters in products 36 it was concluded that the cleavage of the three-
Ring opening of 1,1-dinitrocyclopropane with amines

Ring opening of spiro-activated DA cyclopropane with amines

Ring opening of spiro-cyclopropanes with morpholine

Ring opening of 1,1-dinitrocyclopropane with amines

Ring opening of spiro-activated DA cyclopropane with amines

Ring opening of spiro-cyclopropanes with morpholine

External activation of electrophilic and DA cyclopropanes by the means of Lewis acids often allows for small ring opening to take place under milder conditions, improving the efficiency of the process. Schneider\textsuperscript{76} used diethylaluminum chloride to activate alkyl-, allyl-, and aryl-substituted di-tert-butyl cyclopropane-1,1-dicarboxylates 39 and 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 ammonia. When using tetrasubstituted cyclopropanes 39, trans-diastereoselectivity was observed exclusively.

It is proposed that an ambiphilic amine–Et\textsubscript{2}AlCl complex acts as the reactive species (Scheme 18). The amine, acting as a nucleophile, attacks the electrophilic center of the three-membered ring, whereas electrophilic aluminum induces ring opening in the cyclopropane, owing to coordination with the ester group.\textsuperscript{76}
A catalytic variant of the nucleophilic ring opening of cyclopropane-1,1-diester 43 was examined by the Kerr group, based on bicyclic derivatives of aniline, indolines (Table 1).\textsuperscript{77,78} Cyclopropanes 43, possessing either a tertiary or a quaternary reactive site, can be introduced into the reaction. The product \(\beta\)-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 flinderole C, confirmed to exhibit anti-malaria properties (Scheme 19).

Tomilov et al. successfully reacted 1- and 2-pyrazolines with cyclopropane-1,1-diester 43a,b,n in the presence of Lewis acids (Table 2).\textsuperscript{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 GaCl\(_3\); interestingly, the GaCl\(_3\) gave exclusive nucleophilic ring opening yielding 48. The authors\textsuperscript{79} 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

![Scheme 18 Ring opening of alkyl-, alkenyl- and aryl-substituted DA cyclopropanes with amine–Et\(_2\)AlCl complex](image)

**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>(t_1) (h)</th>
<th>Yield (%) of 44 (method)</th>
<th>(t_2) (h)</th>
<th>Yield (%) of 45</th>
</tr>
</thead>
<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-BrC(_6)H(_4)</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-ClC(_6)H(_4)</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>62 (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>(CH(_2))(_2)NPhth</td>
<td>H</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>l</td>
<td>C≡CEt</td>
<td>Me</td>
<td>H</td>
<td>2</td>
<td>80 (A)</td>
<td>1.5</td>
<td>65</td>
</tr>
<tr>
<td>k</td>
<td>C≡CPh</td>
<td>Me</td>
<td>H</td>
<td>3</td>
<td>79 (A)</td>
<td>1.5</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>(CH(_2))(_2)OTBS</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>CH(_3)CN</td>
<td>3</td>
<td>63* (B)</td>
<td>3</td>
<td>63</td>
</tr>
</tbody>
</table>

* dr (%) = 1:1.
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\(^8^0\) 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.\(^6^7,6^9\) For instance, it was established that the ring in 1-nitro-2-phenylcyclopropane-1-carboxylate 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, \(\alpha\)-nitro-\(\gamma\)-aminobutanoylates 51 were obtained in good yields. Furthermore, upon the introduction of optically active cyclopropanes (\(R\))- and (\(S\))-50a as well as (\(S\))-50e it was discovered that the process exhibited enantioselectivity, resulting in a total \(S\)\(,\)\(2\) 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 52.\(^8^1\) 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).\(^8^2,8^3\) 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 stereoconfiguration at C2 of the initial cyclopropane (Scheme 25). The product, \(\alpha\)-nitro-\(\gamma\)-aminobutanoic acid (\(R\))-51p, was employed in the synthesis of lact-
### Table 2  Reaction of Cyclopropane-1,1-diesters with Pyrazolines: Nucleophilic Ring Opening vs. (3+2)-Cycloaddition

<table>
<thead>
<tr>
<th>Pyrazoline</th>
<th>LA (mol%)</th>
<th>T (°C)</th>
<th>t</th>
<th>Yield (%) (dr)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>48, 49</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>Sc(OTf)$_3$ (5) / GaCl$_3$ (100)</td>
<td>20</td>
<td>12 h</td>
<td>61 (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) / GaCl$_3$ (100)</td>
<td>20</td>
<td>12 h</td>
<td>85 (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>80°</td>
<td>12 h</td>
<td>–</td>
</tr>
<tr>
<td><strong>43a: R = H</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>i</td>
<td>Sc(OTf)$_3$ (5) / GaCl$_3$ (100)</td>
<td>20</td>
<td>9 h</td>
<td>66 (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>
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<tr>
<td><strong>43b: R = Ph</strong></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

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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-pyrrolidinone.

An early example of such a domino process, described by Stewart and Pagenkopf in 1969, involved vinylcyclopropane-1,1-diesters 3a,b and aliphatic amines (Scheme 5). Subsequently, similar processes were mostly carried out for spiro-activated cyclopropanes, synthetically derived from Meldrum’s acid. For example, Danishefsky noted that lactam 30 was formed in the reaction of cyclopropane 27 with aniline in a quantitative yield (Scheme 12). The Bernabé group synthesized 2-oxopyrrolidinocarboxylic acids 67 by the reaction of spiro-activated cyclopropanes 66 with NH₄OH in dioxane (Scheme 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-carbamoylcylopropanecarboxylic acids instead.

Scheme 27 Transforms of optically active amines into N-heterocycles

Scheme 28 Three-component ring opening of 62 with amines and hydrazine

Scheme 29 Three-component ring opening of 1-acylcyclopropane-1-carboxamides with amines and malononitrile

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). It is proposed that 69 is formed via a mechanism that analogous to the one proposed by Danishefsky, wherein the intermediate amine 1-2 undergoes cyclization into lactam 69 with loss of acetone. The
The Schobert group identified a curious reaction between allyl tetronates 34a-d and primary amines under severe conditions (Scheme 32). The produced lactams 70a-f appear to be formed in a complex domino process, wherein, at first, esters 34 undergo Claisen rearrangement and Conia-ene cyclization to give spirocyclopropanes 1-3. Nucleophilic three-membered ring opening of 1-3 with amines yields intermediate 1-4, the subsequent lactamization of 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).

![Scheme 33 Alternative synthesis of lactams from allyloxycoumarins](image)

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 derivative of which antagonizes bradykinin (B1, B2) receptors. The synthesis was based upon the ring opening of vinylcy clopropane 72 by aniline with subsequent lactamization and oxidation to give vinylnpyrrolidone 73, which reacted with N-benzylglycine and underwent subsequent intramolecular (3+2)-cycloaddition yielding tetracyclic diamine 74, a precursor of (±)-martinellic acid (Scheme 34).

![Scheme 34 Total synthesis of (±)-martinellic acid](image)

Katamreddy, Carpenter et al. proposed a synthetic approach to potential agonists of GPR119, which can be used to treat type 2 diabetes (Scheme 35). In the first step, Danishefsky’s cyclopropane 27 was transformed into lactam 75 on treatment with a substituted aniline, which then yielded the target pyrrolizinone and indolizinone, was described in the works of Danishefsky et al. It was based on the intra-
molecular nucleophilic ring opening of cyclopropane-1,1-diesters with amines under the conditions of the Gabriel synthesis, with subsequent γ-lactamization. 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 95 (Scheme 39).100 The addition of various aldehydes to 95 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 1-6, which reacted with aldehydes, predominantly yielding cis-94 (Scheme 42). Switching the steps by generating E-hydrazones 1-7 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(Ts)₂]₂ as the catalyst. Their technique involved a cascade consisting of nucleophilic small ring opening initiated by an amine and yielding intermediates 1-8, followed by Conia-ene cyclization which, in turn, yielded products 95 (Scheme 44). This was confirmed by the isolation of acyclic intermediate 1-8 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 I-9 (Scheme 45).130 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).

Scheme 44 Cascade transformation of DA cyclopanes into piperidines via nucleophilic ring opening/Conia-ene reaction

Scheme 45 Synthesis of azetidines via nucleophilic ring opening/oxidative α-amination

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 Lhomme. 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).105,108 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 methylaniline 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).

Scheme 46 Synthesis of tetrahydroquinolines

Scheme 47 Nucleophilic ring opening/1,5-cyclization in reaction of 1-acylcyclopropane-1-carboxylates and 1-acylcyclopropane-1-carboxamides with amines

The devised approach to pyrrolines was then used in the total synthesis of isoreteneacrol, a pyrrolizidine alkaloid, in its racemic form (Scheme 48).105 Subsequently, the Lhomme group designed enantioselective approaches to the alkaloids (+)-laburnine, (+)-tashiromine, and (−)-isoreteneacrol 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 nitropyrorrines 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 105, 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, tetrahydropyridolones 110, on reaction with aliphatic and aromatic primary amines as well as ammonia, even at room temperature (Scheme 52).109

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 yielded amine 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 pyrrolines 110 was devised, starting from cyclohexane-1,3-dione (Scheme 54).111
Zhang and Zhang performed an analogous reaction employing ketamides 113 and primary aromatic or aliphatic amines (Scheme 55). Accordingly, a series of pyrrolino-diacylcyclopropanes were synthesized in high yields.

The France group suggested a catalytic variant of the reaction between 1-acylcyclopropane-1-carboxylates or 1,1-diacylcyclopropanes 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 pyrrolinecarboxylates 116a–q, s and acylypyrrolines 116o, p were obtained in good yields.

The Liu and Feng group designed an asymmetric catalytic technique for the synthesis of pyrrolines 118 based on the kinetically controlled separation in the reaction of 1,1-diacylcyclopropanes 117 with aniline derivatives (Scheme 58). The optimal catalytic system Sc(OTf)₃–Ni(ClO₄)₂·6H₂O provided the optimal conditions for this reaction. The scope of the reaction was broad and included a variety of substrates, providing high yields and enantioselectivities.

The Liu and Feng group designed an asymmetric catalytic technique for the synthesis of pyrrolines 118 based on the kinetically controlled separation in the reaction of 1,1-diacylcyclopropanes 117 with aniline derivatives (Scheme 58). The optimal catalytic system Sc(OTf)₃–Ni(ClO₄)₂·6H₂O provided the optimal conditions for this reaction. The scope of the reaction was broad and included a variety of substrates, providing high yields and enantioselectivities.
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 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 pathway 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 electrocyclic cyclopropanes 121 containing both an amide group and a fragment of an α,β-unaturated ketone in their structure (Scheme 60). This functionalization of the small ring allows ring opening with primary amines to give γ-aminoketamides I–11 that undergo 1,5-cyclization to give 2-vinylpyrrolopyridinones I–12. The latter, in turn, undergo intramolecular conjugatedaza-addition to yield pyrrolopyridinones 122 (Scheme 61).

The Zhang group also suggested an approach to functionalized pyrroles 124, based on the following cascade: 1. nucleophilic ring opening of 1-acylcyclopropane-1-carboxamides 123a–o and 1-acylcyclopropane-1-carboxylates 123p,q with primary amines, 2. cyclization of the intermediate ketamine I–13 to give pyrrole I–14, and 3. oxidation of I–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′-bipyrrroles 126 from the Werz group 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-
products in these reactions. A mechanism has been proposed for the formation of bipyroles 126 that involves the generation of diimines I-15 with subsequent Cloke–Stevens rearrangement (A, Scheme 65). However, this process does not explain the formation of pyrroles 127, and an alternative mechanistic explanation is suggested, involving nucleophilic small ring opening with the amine and the resulting tetrahydrofuran I-17 rearranging to form pyrrolidine I-18 that is transformed into pyrrole 127 (B, Scheme 65).

Yang, Zhang et al. devised an effective synthetic approach to optically active 2-(polyoxalkyl)pyrroles 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 I-19, further rearrangement of which leads to pyrrole 129 (Scheme 67). The reaction is performed at 40 °C, 2 h.

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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 direct method to access pyrrolidines \( 133 \) in high yields (Scheme 70).\(^{122}\)

![Scheme 70 Direct formation of pyrrolidines by ruthenium(III)-catalyzed reaction of ketocyclopropanes with anilines and CO](image)

### 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).\(^{123}\) It was shown that \( 1b \) underwent ring opening upon treatment with anilines under milder conditions than \( 1c \). Poorly nucleophilic nitroanilines were inert towards \( 1b,c \) under studied conditions.

![Scheme 71 Reactivities of cyclopropane-1,1-dicarbonitrile and methyl 1-cyanocyclopropane-1-carboxylate towards anilines](image)

An unusual result\(^{124,125}\) was produced by Fu and Yan in the reaction of 2,3-diallylcyclopropane-1,1-dicarbonitriles \( 136 \) with imines \( 137 \); instead of the expected \((3+2)\)-cycloaddition products the reaction gave pyrroles \( 138 \) (Scheme 72).\(^{124}\)

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 pyrrole \( I-23 \). 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.
trophiles. 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 1-25, which then condenses with the aldehyde forming 1-26 (Scheme 76). Intermediate 1-26 undergoes nucleophilic substitution in which the amine is substituted by...
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.27 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).128 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).129

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(I) species, further reaction is initiated by nucleophilic attack of pyrrolidone on the activated three-membered ring, resulting in the formation of the furan ring.

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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 150 to give pyrrole 151 (Scheme 82).\textsuperscript{130}

Filtsch and Wermsmann performed the ring opening of cyclopropyltriphenylphosphonium tetrafluoroborate 152 with imide anions, followed by formation of a five-membered N-heterocycle 153a-c via an aza-Wittig reaction (Scheme 83).\textsuperscript{131} This reaction was used in the total synthesis of pyrrolizidine alkaloid (±)-isoretronecanol. Under similar conditions, reaction of 152 with monothioimides yielded a mixture of aza-Wittig cyclization products 153a,b and 154a,b via a nucleophilic attack on both C=S and C=O groups, as well as acyclic products of primary nucleophilic ring opening 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 157 based on the reaction between cyclopropanes 156 and hydrazine in 1,2-dimethoxyethane at reflux (Scheme 85).\textsuperscript{132,133} It is proposed that cyclopropylhydrazone 1-28 is formed in the first step, which undergoes intramolecular nucleophilic ring opening under the conditions to give dihydropyrazole I-29; elimination of malonodinitrile from I-29 gives the final pyrazole 157.

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

\begin{itemize}
  \item \textit{© Georg Thieme Verlag Stuttgart · New York — Synthesis 2017, 49, 3035–3068}
\end{itemize}
In 2017, Srinivasan et al. demonstrated a similar process involving 2-aryl-3-arylcyclopropane-1,1-diester \(160\) and arenylhydrazines under milder conditions that did not result in elimination of the malonyl fragment (Scheme 87).\(^{135}\) Hence, pyrazolines \(161\) were produced in high yields. At the same time, the reaction of \(160\) with an unsubstituted hydrazine immediately yielded pyrazole \(157\). This reaction is proposed to occur via intermediate formation of pyrazoline \(161\) 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.\(^{136}\) 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 \(32\) (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.\(^{137–145}\) 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).\(^{139}\)

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.\(^{146}\) 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 cyclopropyltrifluorophenylphosphonium 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.\(^{17,147}\) 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 \(CH_2Cl_2\) or toluene together with the choice of the solvent polarity. Employing largely non-polar \(CH_2Cl_2\) or toluene together with \(p\)-TsOH as the catalyst gave the products of the N-nucleophilic ring open-

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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 (homo-Nazarov cyclization) (Scheme 92). Total synthesis of (±)-goniomitine was achieved employing Lewis acids as the catalyst yielding the products 166, whereas employing MeCN and 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 protein kinase C-β inhibitor JTT-010 was synthesized in a total of 167 steps yielding 168, whereas employing MeCN and soft Lewis acids as the catalyst yielded the products 169 of C3-nucleophilic ring opening (homo-Nazarov cyclization) (Scheme 91). 

**Scheme 92**  Total synthesis of (±)-goniomitine

**Scheme 93**  Conversion of cyclopropanecarboxylates into polyheterocycles via nucleophilic ring opening/nucleophilic substitution

**Scheme 94**  Total synthesis of the protein kinase C-β inhibitor JTT-010

**Scheme 95**  Ring opening of cyclopropane-1,1-diesters with di- and triazoles

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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 cyclopropyliphenylphosphonium tetrafluoroborate 152 with pyrazoles in basic medium with a subsequent Wittig reaction between intermediate phosphorus ylide 1-30 and an aliphatic or aromatic aldehyde.150 This technique allowed the exclusive synthesis of pyrazole-substituted alkylidene- 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).
Catalytic amounts of Pd(dba)$_3$-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. was based on the reaction between cyclopropylated 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.

8 Ring Opening with Nitriles (Ritter Reaction)

Activated cyclopropanes are able to take part in the Ritter reaction with nitriles as alkylation 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. 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.

The proposed mechanism involves the coordination of the Lewis acid with the EWG in the presence of concentrated sulfuric acid. The Vankar group identified a similar ring opening of ketocyclopropanes 19a,c leading to amides 183a–d in the presence of concentrated sulfuric acid. The proposed mechanism involves the coordination of the Lewis acid with the EWG in the presence of concentrated sulfuric acid.

Shobert et al. 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 the presence of concentrated sulfuric acid. The Vankar group identified a similar ring opening of ketocyclopropanes 19a,c leading to amides 183a–d in the presence of concentrated sulfuric acid.
...benzonitriles 186\textsubscript{a–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\textsubscript{3} 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 66\textsubscript{c–e} readily underwent nucleophilic ring opening by the azide ion yielding 188\textsubscript{a–c} (Scheme 106).

#### Table 3  Ring Opening of Ketocyclopropanes with Benzonitriles Yielding Indolizinone Derivatives

<table>
<thead>
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<td>Yield (%)</td>
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<tr>
<td>Ph</td>
<td>84</td>
</tr>
<tr>
<td>4-FC\textsubscript{6}H\textsubscript{4}</td>
<td>90</td>
</tr>
<tr>
<td>4-ClC\textsubscript{6}H\textsubscript{4}</td>
<td>84</td>
</tr>
<tr>
<td>R', R'' = H, X = Cl</td>
<td>R</td>
</tr>
<tr>
<td>Ph</td>
<td>72</td>
</tr>
<tr>
<td>Yield (%)</td>
<td>57</td>
</tr>
</tbody>
</table>
Seebach et al. conducted a similar reaction, employing 1-nitrocyclopropane-1-carboxylate \(21\). 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 \(190\). The reaction between \(1a\) and sodium azide required prolonged heating in N-methyl-2-pyridil dine 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. 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.

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).

The Lee group devised an approach to optically active β-substituted γ-butyrolactones by nucleophilic ring opening of enantiomerically pure cyclopropane \(170\). 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).
Nucleophilic ring opening of the highly strained DA cyclopropane 165 by the azide ion yielded azidopyrrolidinolines 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. In order to elaborate under the same conditions proceeded with complete presen- 

The Kerr group developed a convenient synthetic approach to 4-azidobutanoates 202a–l, precursors of GABA and its derivatives.160 Their method was based on a domino process that involved nucleophilic ring opening of cyclopropanecarboxylic acids 201a–l with the azide ion, followed by decarboxylation (Scheme 114). Similar cyclopropane-1,1-diester did not react with sodium azide under these conditions.

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]D of 201a was compared that determined for optically active lactam 204 (Scheme 115).

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

2-((o-Alk-1-ynylphenyl)cyclopropane-1,1-dicarboxylate monomethyl esters 205 react with sodium azide via inter- 

Activated cyclopropane 207, wherein the amide fragment of the indolquinolinic system acts as an EWG, under- 

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

Scheme 116 Proposed mechanism for the transformation of 201 into 202

Scheme 117 Cascade transformation of DA cyclopropanes into tricyclic triazoles

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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 presence of a base, proceeded under mild conditions at 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 alkenyl-substituents as the EDG (R) and EWG, EWG’ = CO2Me,

EWG = CO2Et, EWG’ = NO2, R = Ph, 76%
EWG, EWG’ = CN, R = Ph, 43%
EWG, EWG’ = CO2Me, EWG = COMe, R = Ph, 80%
EWG = CO2Et, EWG = COPh2, R = Ph, 85%

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, amidazoles, 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.
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