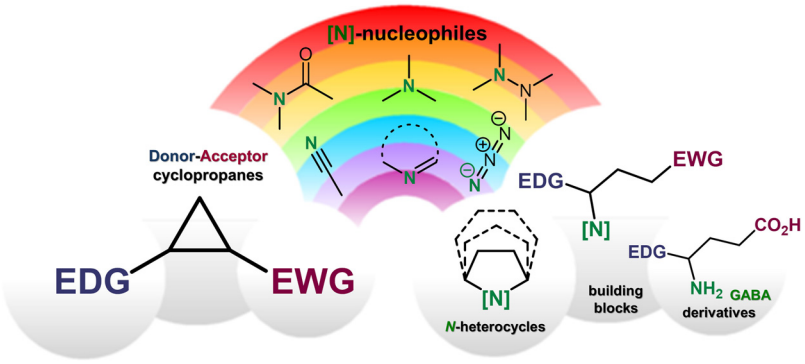
Synthesis E. M. Budynina et al. Short Review

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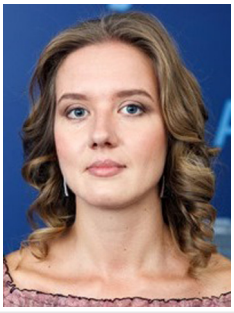
Abstract Ring opening of donor–acceptor cyclopropanes with various *N*-nucleophiles provides a simple approach to 1,3-functionalized compounds that are useful building blocks in organic synthesis, especially in assembling various *N*-heterocycles, including natural products. In this review, ring-opening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

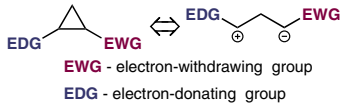
Key words donor–acceptor cyclopropanes, nucleophilic ring opening, *N*-nucleophiles, *N*-heterocycles, amines, azides, nitriles



Ekaterina M. Budynina studied chemistry at Lomonosov Moscow State University (MSU) and received her Diploma in 2001 and Ph.D. in 2003. Since 2013, she has been a leading research scientist at Department of Chemistry MSU, focusing on the reactivity of activated cyclopropanes towards various nucleophilic agents, as well as in reactions of (3+n)-cycloaddition, annulation, and cyclodimerization.

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.[1] 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.[2]

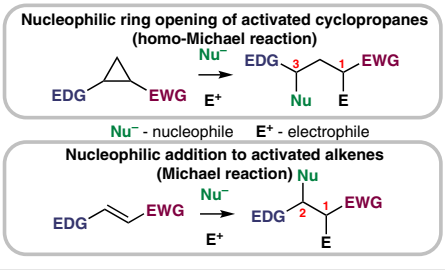


Scheme 1 Donor–acceptor cyclopropanes

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 (S_N2).



Scheme 2 Nucleophilic ring opening of activated cyclopropanes vs. nucleophilic addition to activated alkenes

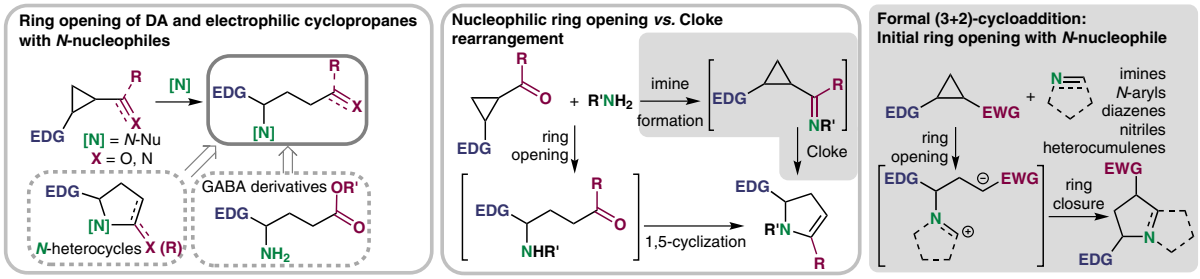
The first examples of ring-opening reactions for activated cyclopropanes with *C*-, *O*-, and *Hal*-nucleophiles were described by Bone and Perkin at the end of the 19th century.[29] However, thorough and systematic research into the reactions of activated cyclopropanes with *N*-nucleophiles only dates 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 enantiomerically 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,[32–35] diazenes,[36–39] *N*-aryls,[40–42] heterocumulenes,[43–45] nitriles,[46–53] as well as (3+3)-cycloadditions[54–57]], 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-



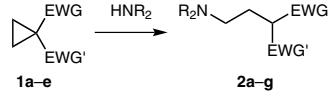
Scheme 3 Scope of the review; reactions in grey are beyond the scope of this review

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[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-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.

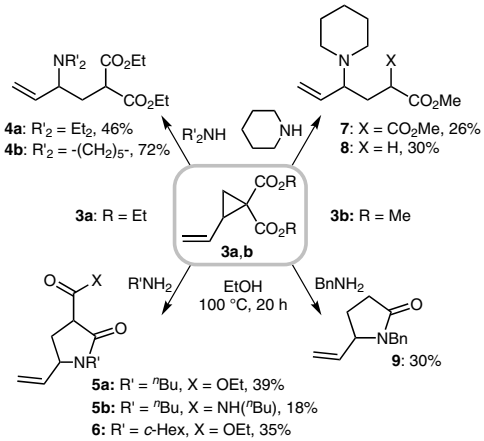


1a–e **2a–g**

1a, 2a: EWG, EWG' = CO_2Et, R_2 = Et_2, 40%
1a, 2b: EWG, EWG' = CO_2Et, R_2 = -$(CH_2)_5$-, 73%
1b, 2c: EWG, EWG' = CN, R_2 = Et_2, 30%
1b, 2d: EWG, EWG' = CN, R_2 = -$(CH_2)_5$-, 36%
1c, 2e: EWG = CN, EWG' = CO_2Et, R_2 = -$(CH_2)_5$-, 43%
1d, 2f: EWG = CN, EWG' = $CONH_2$, R_2 = -$(CH_2)_5$-, 49%
1e, 2g: EWG = $CONH_2$, EWG' = $CONH_2$, R_2 = -$(CH_2)_5$-, 45%

Scheme 4 Reactions of electrophilic cyclopropanes with secondary amines

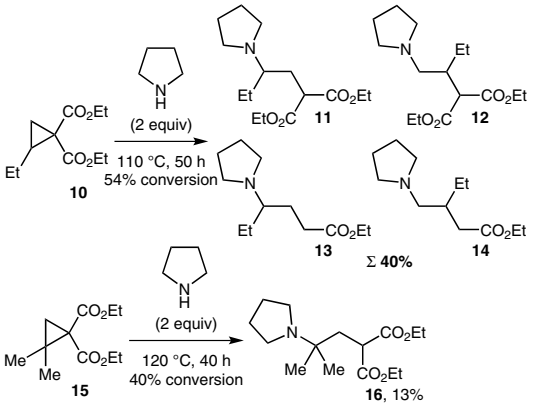
In reactions with secondary amines, vinylcyclopropane **3a** behaved similarly, yielding ring-opening products **4a**,**b** (Scheme 5).[31] Notably, no products of conjugated 1,5-addition of the amines to vinylcyclopropane were detected. Monoamidation of products **4a**,**b** proceeded as a side process. 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**,**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 γ-lactam **9** as the only product in the reaction with benzylamine.



Scheme 5 Reactions of vinyl-substituted DA cyclopropanes with primary and secondary amines

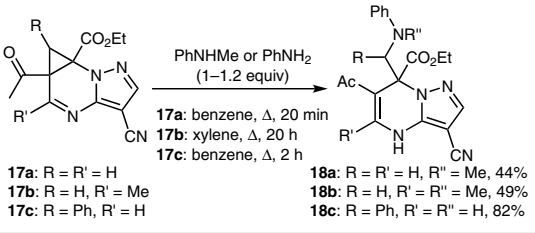
The influence that alkyl substituents in the three-membered ring have upon the reactivity of cyclopropanediesters was studied by Danishefsky and Rovnyak.[61] In the case of 2-

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.



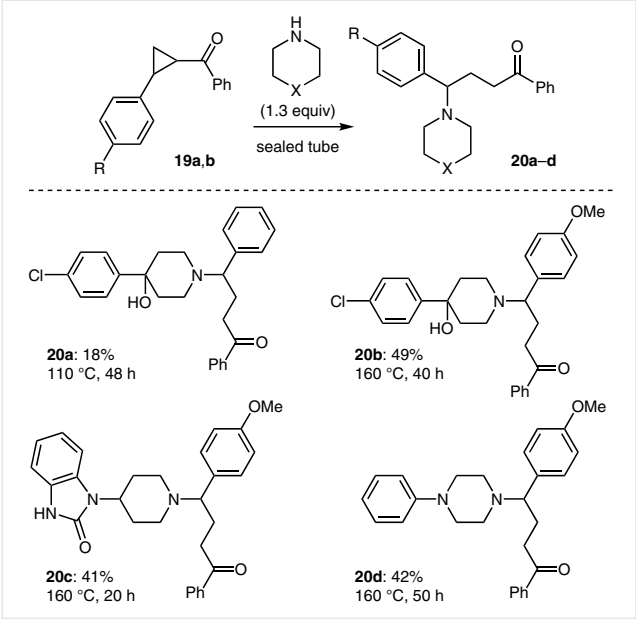
Scheme 6 Chemoselectivity in reactions of alkyl-substituted DA cyclopropanes with pyrrolidine

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 H_2C–CAc 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(CO_2Et) 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]



Scheme 7 Main direction in the ring opening of cyclopropa[*e*]pyrazolo[1,5-*a*]pyrimidines with *N*-methylaniline

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.[66] 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).

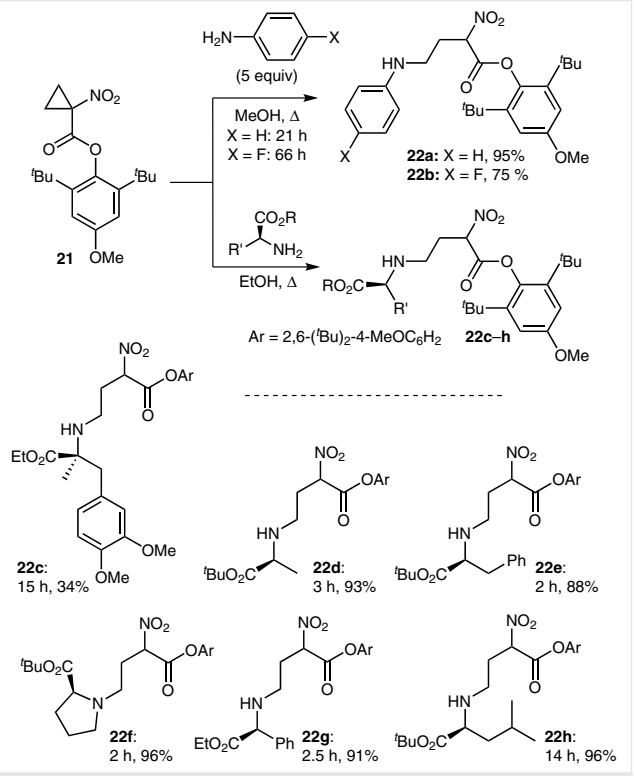


Scheme 8 Ring opening of ketocyclopropanes with secondary amines

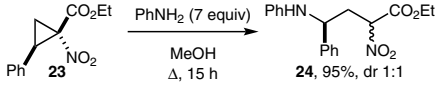
The activation of a three-membered ring by a strong EWG (e.g., the NO_2 group) allows the nucleophilic ring opening of activated cyclopropanes to be performed by weaker *N*-nucleophiles, namely, aniline derivatives. While researching approaches to the derivatives of α-amino acids, Seebach et al. showed 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-

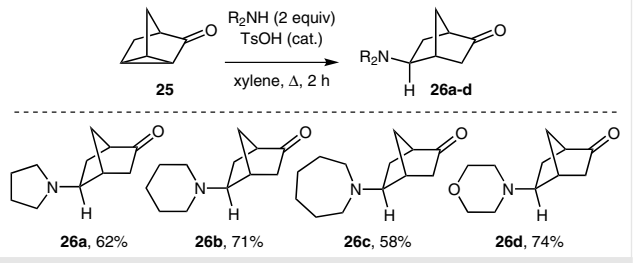


Scheme 9 Ring opening of electrophilic 1-nitrocyclopropane-1-carboxylate with anilines and amino acids



Scheme 10 Ring opening of DA 1-nitrocyclopropane-1-carboxylate with aniline

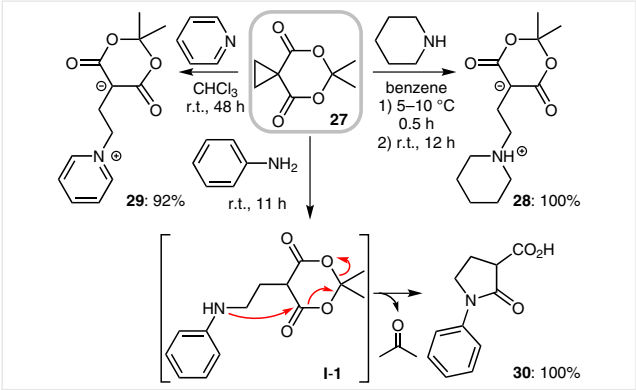
membered ring opening. A specific example of structural activation for electrophilic cyclopropanes was described in the works of Cook,[70,71] wherein the reactions of tricyclo[2.2.1.0^{2,6}]heptan-3-one **25** with cyclic secondary amines were investigated (Scheme 11). Full conversion of **25** into amino ketones **26a–d** was already detected after 2 hours,



Scheme 11 Ring opening of strained tricyclo[2.2.1.0^{2,6}]heptan-3-one with secondary amines

even though additional thermal and catalytic activation took place.[71]

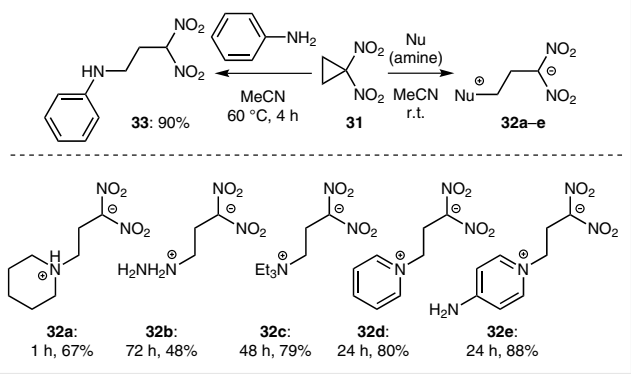
Spiro-activation of cyclopropanes proved to be a more universal technique for additional structural activation of these compounds. This term was introduced in the mid-1970s by Danishefsky, who employed electrophilic cyclopropane **27** in his research,[72] basing the initial structure upon Meldrum's 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 **I-1** with subsequent nucleophilic attack of the amino group upon the carbonyl group, accompanied by the elimination of acetone.



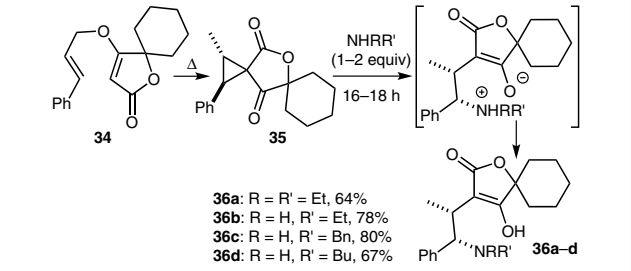
Scheme 12 Ring opening of Danishefsky's cyclopropane with amines

1,1-Dinitrocyclopropane **31** exhibited analogous reactivity towards amines with various structures.[73] 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).[74] Compounds **35** originate from allyl esters of tetronic acids (tetronates) **34** that undergo successive Claisen rearrangement and Coniaene cyclization upon heating, yielding **35**. The ring opening of **35** by primary and secondary amines proceeded under mild conditions or upon reflux in CH_2Cl_2, 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 S_N2-



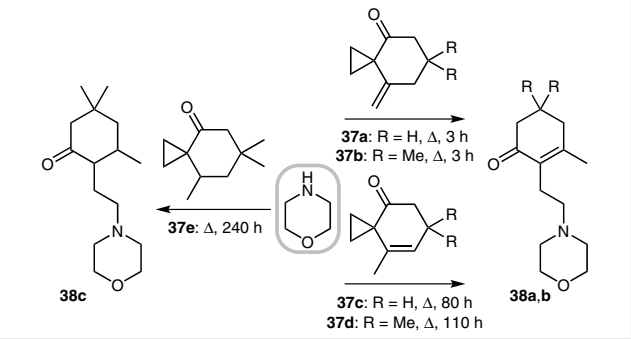
Scheme 13 Ring opening of 1,1-dinitrocyclopropane with amines



Scheme 14 Ring opening of spiro-activated DA cyclopropane with amines

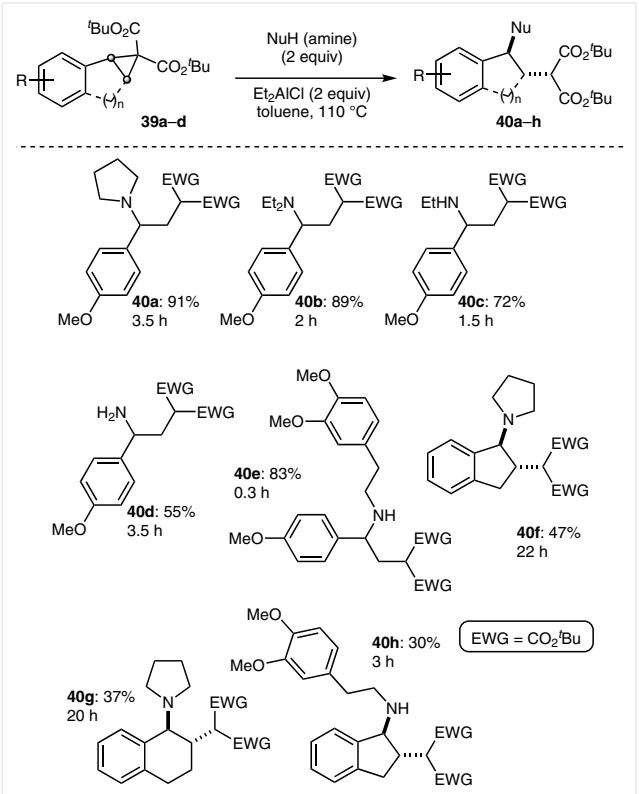
like mechanism, wherein the configuration at the reactive center of **35** is inverted.

Yates et al. demonstrated that even one activating EWG in spirocyclopropanes **37a–e** facilitated their ring opening by morpholine yielding cyclohexanone derivatives **38a–c** (Scheme 15).[75] Notably, an exocyclic double bond significantly increased the reactivity of cyclopropanes **37a**,**b** in comparison with cyclopropanes **37c**,**d**, containing an endocyclic double bond, and their saturated counterpart **37e**.

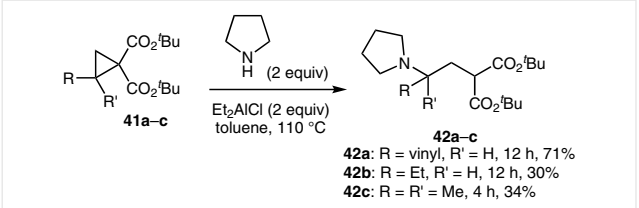


Scheme 15 Ring opening of spiro-cyclopropanes with morpholine

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[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.

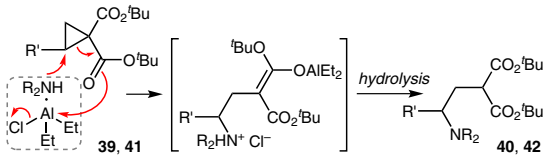


Scheme 16 Et_2AlCl-triggered ring opening of aryl-substituted DA cyclopropanes with amines



Scheme 17 Et_2AlCl-triggered ring opening of alkyl- and alkenyl-substituted DA cyclopropanes with pyrrolidine

It is proposed that an ambiphilic amine–Et_2AlCl 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.[76]

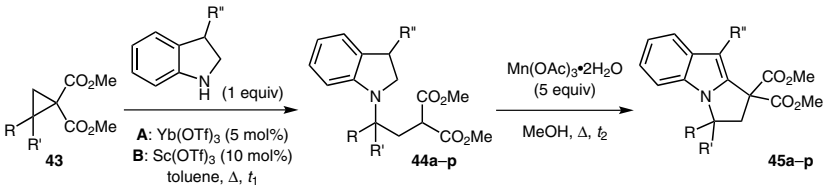


Scheme 18 Ring opening of alkyl-, alkenyl- and aryl-substituted DA cyclopropanes with amine–Et_2AlCl complex

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 flinderole C, confirmed to exhibit anti-malaria properties (Scheme 19).

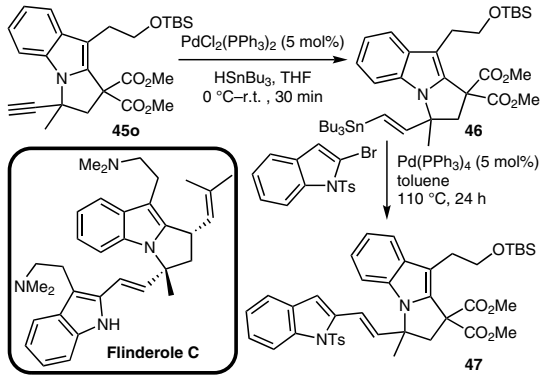
Tomilov et al. successfully reacted 1- and 2-pyrazolines with cyclopropane-1,1-diesters **43a**,**b**,**n** in the presence of Lewis acids (Table 2).[79] Notably, the reactions of both 1- and 2-pyrazolines were performed under mild conditions yielding the products of nucleophilic ring opening **48** 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 $GaCl_3$; interestingly, the $GaCl_3$ gave exclusive nucleophilic ring opening yielding **48**. The authors[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

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



44, 45	R	R′	R′′	t_1 (h)	Yield (%) of **44** (method)	t_2 (h)	Yield (%) of **45**
a	H	H	H	16	80 (A)	16	82
b	Ph	H	H	16	74 (A)	16	86
c	4-BrC_6H_4	H	H	16	71 (A)	16	84
d	4-ClC_6H_4	H	H	3	73 (A)	16	63
e	2-naphthyl	H	H	16	63 (A)	16	61
f	2-furyl	H	H	4	63 (A)	16	75
g	vinyl	H	H	16	72 (A)	16	91
h	*i*-Pr	H	H	24	24 (A)	6	60
i	Ph	H	$(CH_2)_2NPhth$	0.3	72[a] (A)	0.5	92
j	C≡CH	Me	H	2	77 (A) 88 (B)	1	65
k	C≡CEt	Me	H	2	80 (A) 72 (B)	1.5	65
l	C≡CPh	Me	H	3	79 (A) 79 (B)	1.5	61
m	Ph	Me	H	2.5	85 (A) 76 (B)	2	83
n	vinyl	Me	H	3	50 (A) 44 (B)	1	40
o	C≡CH	Me	$(CH_2)_2OTBS$	1.5	80[a] (B)	3	80
p	C≡CH	Me	CH_2CN	3	63[a] (B)	3	63

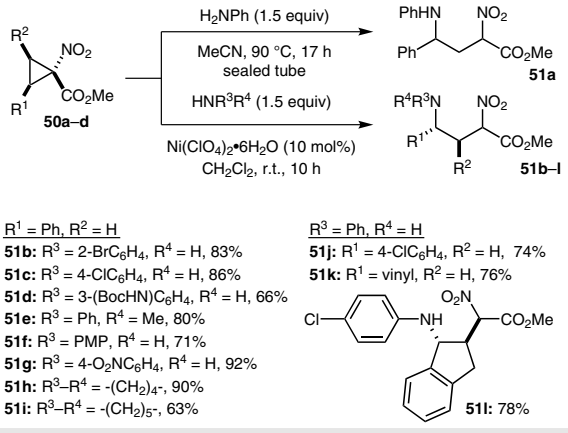
[a] dr (%) = 1:1.



Scheme 19 Synthesis of the core structure of bis-indole alkaloid flinderole C

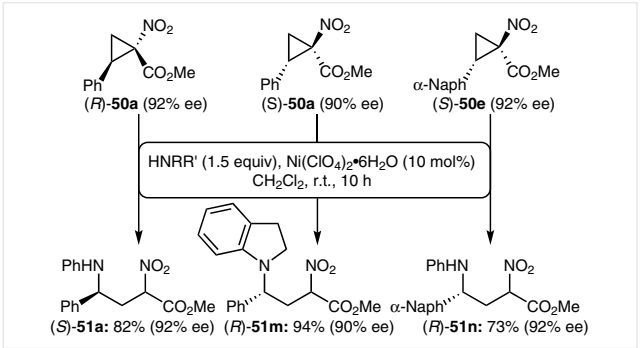
reactions with both 1- and 2-pyrazolines by invoking a Lewis acid initiated isomerization of 1-pyrazoline into 2-pyrazoline, which became the reactant in both processes.

The Charette group demonstrated[80] 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.[67,69] 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, α-nitro-γ-aminobutanoates **51** were obtained in good yields. Furthermore, upon the introduction of optically active cyclopropanes (*R*)- and (*S*)-**50a**



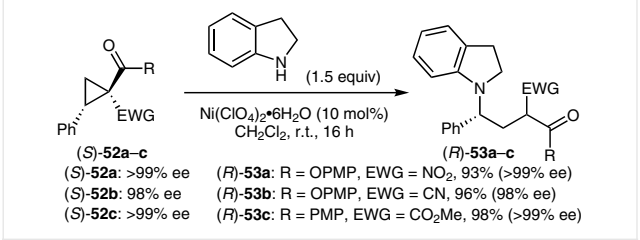
Scheme 20 Catalytic vs. thermal ring opening of nitrocyclopropanecarboxylates with primary and secondary amines

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).



Scheme 21 Enantioselective S_N2-like ring opening of 1-nitro-2-phenylcyclopropane-1-carboxylate with amines

Subsequently, the Charette group expanded this approach to include analogous cyano and keto esters **52**.[81] 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).

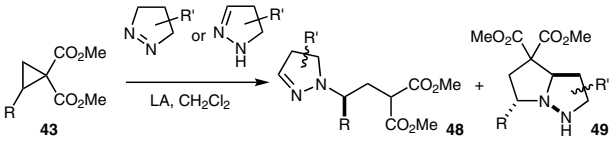


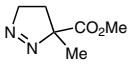
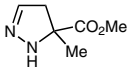
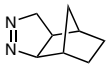
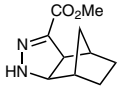
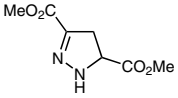
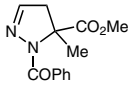
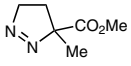
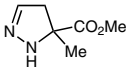
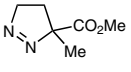
Scheme 22 Enantioselective S_N2-like ring opening of optically active DA cyclopropanes with indoline

Mattson et al. activated 1-nitrocyclopropane-1-carboxylates **50** with difluoroborylphenylurea **54** in reactions with amines (Scheme 23).[82,83] 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**.

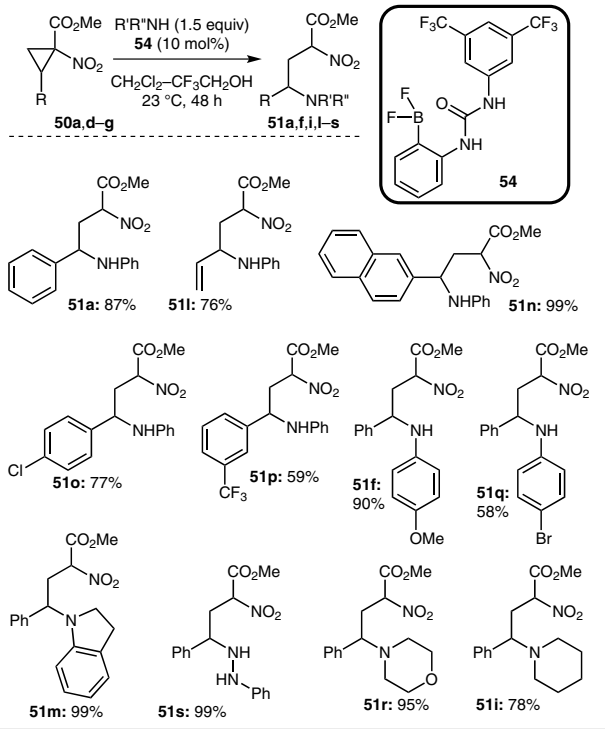
Nucleophilic ring opening of the optically active DA cyclopropane (*S*)-**50g** by *p*-(trifluoromethoxy)aniline proceeded with full preservation of stereoinformation along with inversion of stereoconfiguration at C2 of the initial cyclopropane (Scheme 25). The product, α-nitro-γ-aminobutanoic acid (*R*)-**51p**,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

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

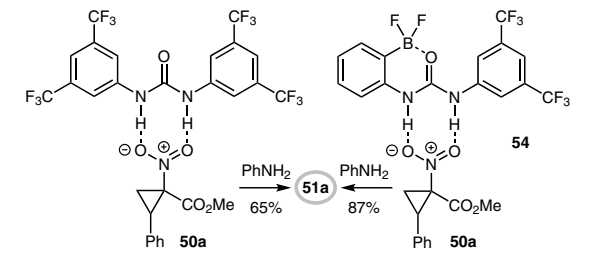


48, 49	Pyrazoline	LA (mol%)	*T* (°C)	*t*	Yield (%) (dr)	
					48	**49**
			43b: R = Ph			
a		$Sc(OTf)_3$ (5) $GaCl_3$ (100)	20 0–5	12 h 5 min	61 (1:1) 72 (1:1)	29 (1:1) –
b		$Sc(OTf)_3$ (5)	20	12 h	31 (1:1)	61 (1:1)
c		$Sc(OTf)_3$ (5)	20	160 h	5	63
d		$Sc(OTf)_3$ (5)	20	24 h	–	83
e		$GaCl_3$ (100)	10	5 min	60 (1.5:1)	–
f		$Sc(OTf)_3$ (5) $GaCl_3$ (100)	20 10	12 h 5 min	85 (2:1) 95 (2:1)	– –
g		$Sc(OTf)_3$ (5)	20	3 h	96 (1.8:1)	–
h		$Sc(OTf)_3$ (10)	80[a]	12 h	–	22 (1:1)
			43n: R = 2-thienyl			
i		$Sc(OTf)_3$ (5) $GaCl_3$ (100)	20 5	9 h 15 min	66 (1:1) 72 (1:1)	18 (1:1) –
j		$Sc(OTf)_3$ (5)	20	3 h	28 (1:1)	57 (1:1)
			43a: R = H			
k		$GaCl_3$ (100)	20	3 h	79	–

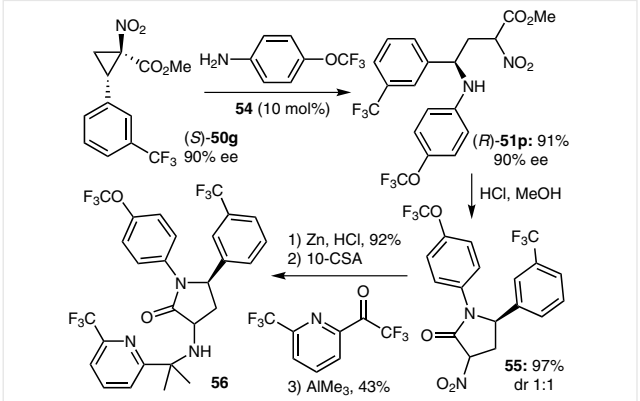
[a] The reaction was carried out in 1,2-dichloroethane.



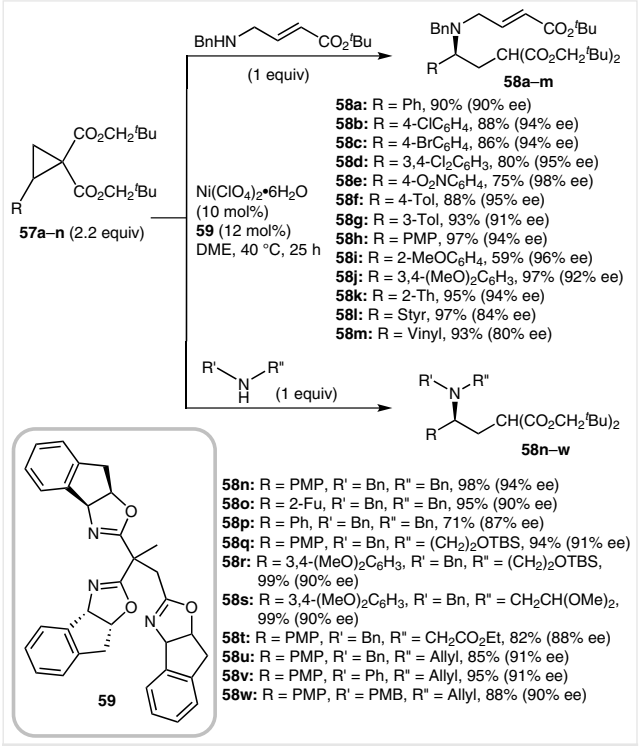
Scheme 23 Ring opening of 1-nitrocyclopropane-1-carboxylate with amines under catalysis by difluoroborylphenylurea



Scheme 24 Ring-opening efficiency for methyl 1-nitro-2-phenylcyclopropane-1-carboxylate in the presence of boronate and non-boronate ureas as a catalyst



Scheme 25 Total synthesis of the CB-1 receptor agonist



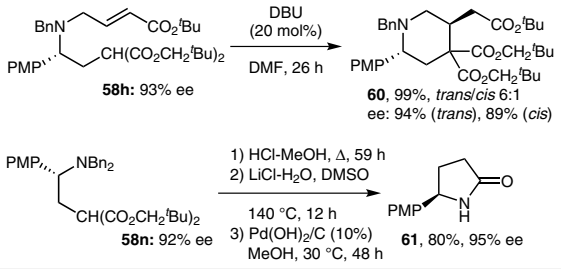
Scheme 26 Asymmetric catalytic ring opening of DA cyclopropanes with amines

am **56**, which can act as a reverse agonist of the CB-1 receptor.[82]

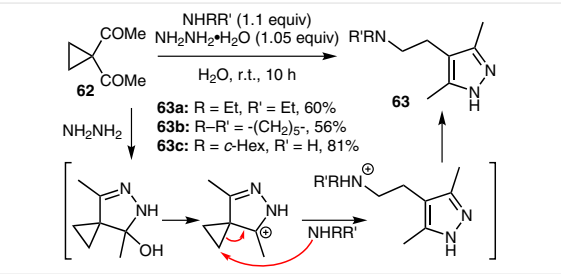
The Tang group has developed an asymmetric catalytically induced version for the nucleophilic ring opening of activated cyclopropanes with amines.[84–86] Conditions analogous to those suggested in Charette's method[80] facilitated ring opening for cyclopropane-1,1-diesters **57a–n** by secondary amines 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]

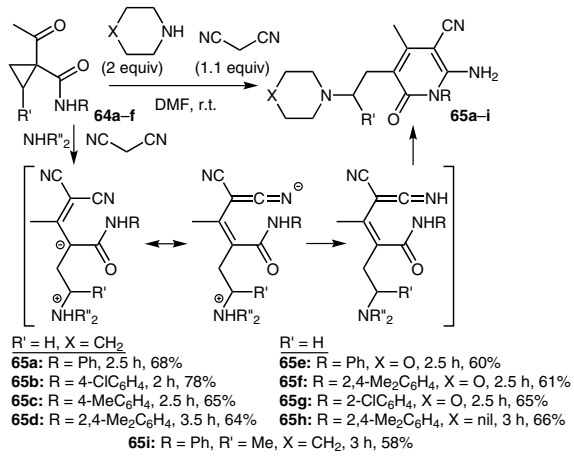


Scheme 27 Transformations of optically active amines into *N*-heterocycles



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

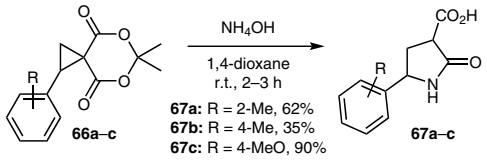
The Liang group developed a three-step domino process, involving 1-acylcyclopropane-1-carboxamides **64**, malononitrile, and secondary cyclic amines (Scheme 29).[89] This led to a method for the synthesis of β-aminoethyl-substituted pyridinones **65**. According to the hypothesized mechanism, the reaction was initiated by **64** and malononitrile undergoing Knoevenagel condensation with further nucleophilic small ring opening by the amine. Curiously, the secondary amine acts as both base and nucleophile.



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

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).[31] 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).[72]

The Bernabé group synthesized 2-oxopyrrolidinecarboxylic acids **67** by the reaction of spiro-activated cyclopropanes **66** with NH_4OH in dioxane (Scheme 30).[90] 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.



Scheme 30 Ring opening/γ-lactamization in the reaction of an aryl-substituted Danishefsky cyclopropane with ammonium hydroxide

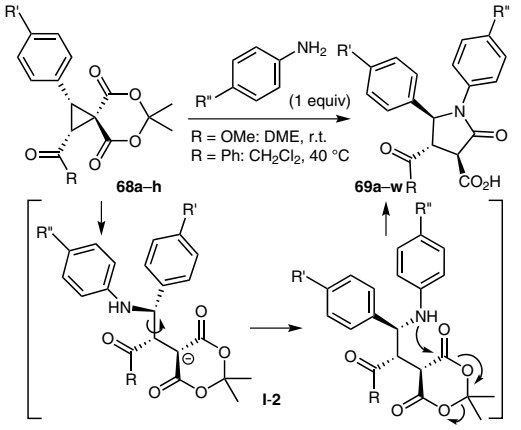
3 Ring Opening with Amines Accompanied by Secondary Processes Involving the *N*-Center

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-pyrrolidone.

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 **I-2** undergoes cyclization into lactam **69** with loss of acetone. The

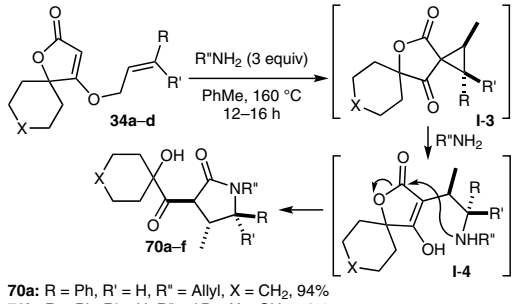


69a: R = OMe, R' = Me, R" = Me, 92%
69b: R = OMe, R' = H, R" = Me, 97%
69c: R = OMe, R' = Cl, R" = Me, 96%
69d: R = OMe, R' = NO_2, R" = Me, 74%
69e: R = OMe, R' = Me, R" = H, 97%
69f: R = OMe, R' = H, R" = H, 98%
69g: R = OMe, R' = Cl, R" = H, 97%
69h: R = OMe, R' = NO_2, R" = H, 70%
69i: R = Ph, R' = Me, R" = Me, 94%
69j: R = Ph, R' = H, R" = Me, 98%
69k: R = Ph, R' = Cl, R" = Me, 98%
69l: R = Ph, R' = NO_2, R" = Me, 76%
69m: R = Ph, R' = Me, R" = H, 97%
69n: R = Ph, R' = H, R" = H, 97%
69o: R = Ph, R' = Cl, R" = H, 98%
69p: R = Ph, R' = NO_2, R" = H, 77%
69q: R = Ph, R' = Me, R" = Cl, 96%
69r: R = Ph, R' = H, R" = Cl, 98%
69s: R = Ph, R' = Cl, R" = Cl, 97%
69t: R = Ph, R' = NO_2, R" = Cl, 68%
69u: R = Ph, R' = Me, R" = NO_2, 68%
69v: R = Ph, R' = H, R" = NO_2, 71%
69w: R = Ph, R' = Cl, R" = NO_2, 70%
69x: R = Ph, R' = NO_2, R" = NO_2, 0%

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

stereo-outcome of the reaction corresponds to an S_N2-like mechanism for nucleophilic ring opening of cyclopropane **68** by an amine.

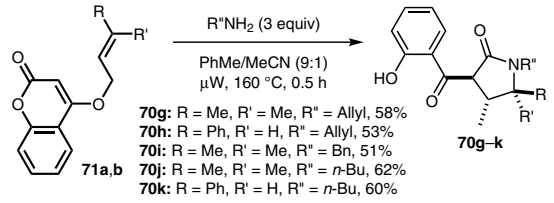
The Schobert group identified a curious reaction between allyl tetronates **34a–d** and primary amines under severe conditions (Scheme 32).[93] The produced lactams **70a–f** appear to be formed in a complex domino process, wherein, at first, esters **34** undergo Claisen rearrangement and Conia-ene cyclization to give spirocyclopropanes **I-3**. Nucleophilic three-membered ring opening of **I-3** with amines yields intermediate **I-4**, the subsequent lactamization of



70a: R = Ph, R' = H, R" = Allyl, X = CH_2, 94%
70b: R = Ph, R' = H, R" = *i*-Bu, X = CH_2, 72%
70c: R = Ph, R' = H, R" = *n*-Bu, X = CH_2, 84%
70d: R = Ph, R' = H, R" = Allyl, X = O, 71%
70e: R = *n*-Pr, R' = H, R" = *n*-Bu, X = CH_2, 65%
70f: R = Me, R' = Me, R" = EtO$(CH_2)_3$, X = CH_2, 89%

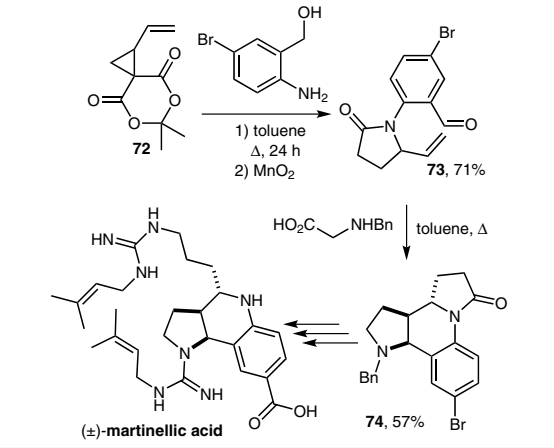
Scheme 32 Domino-transformation of allyl tetronates into lactams via nucleophilic ring opening of DA cyclopropanes **I-3** with amines

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

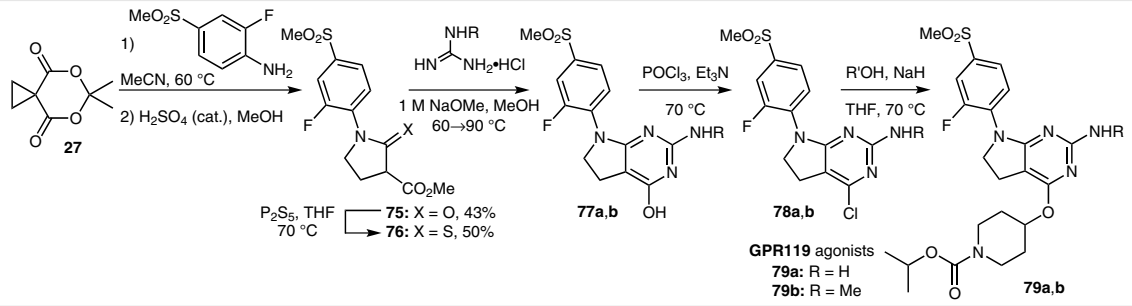
The cascade of nucleophilic ring opening with amines for spiro-activated cyclopropanes together with γ-lactamization was successfully employed in the synthesis of physiologically active compounds. Thus, the Snider group devised a total synthesis of (±)-martinellic acid, the derivatives of which antagonize bradykinin (B_1, B_2) receptors.[94,95] The synthesis was based upon the ring opening of vinylcyclopropane **72** by aniline with subsequent lactamization and oxidation to give vinylpyrrolidone **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]



Scheme 34 Total synthesis of (±)-martinellic acid

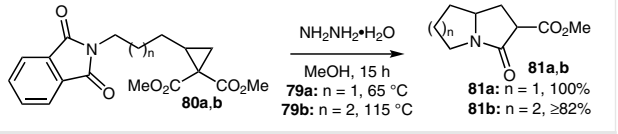
Katamreddy, Carpenter et al. proposed a synthetic approach to potential agonists of GPR119, which can be used to treat type 2 diabetes (Scheme 35).[96] In the first step, Danishefsky's cyclopropane **27** was transformed into lactam **75** on treatment with a substituted aniline, which then yielded the 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 35 Synthesis of potential agonists of GPR119 via ring opening of Danishefsky's cyclopropane with a substituted aniline

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]



Scheme 36 Synthesis of bicyclic γ-lactams via intramolecular ring opening of cyclopropanes

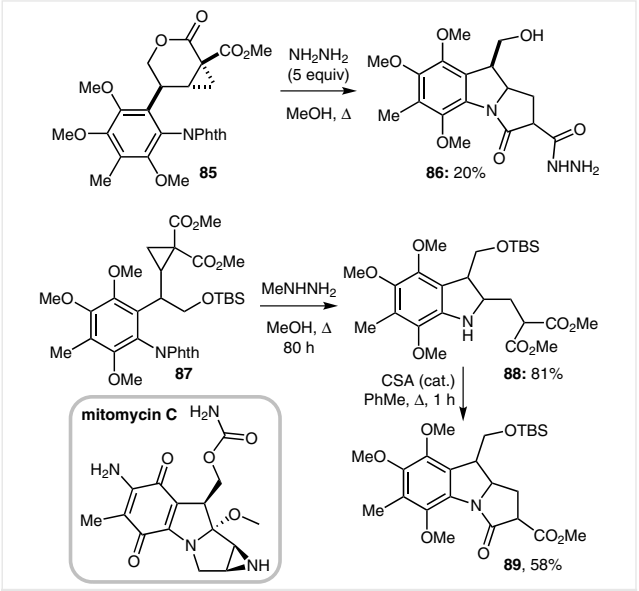
The devised method was employed in racemic syntheses of pyrrolizidine alkaloids (±)-isoretronecanol and (±)-trachelanthamidine (Scheme 37).[98]

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]

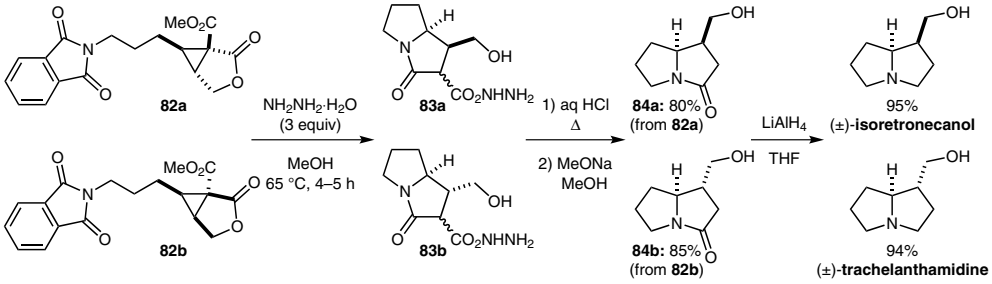
3.1.2 Synthesis of Pyrroloisoxazolidines and -pyrazolidines

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.

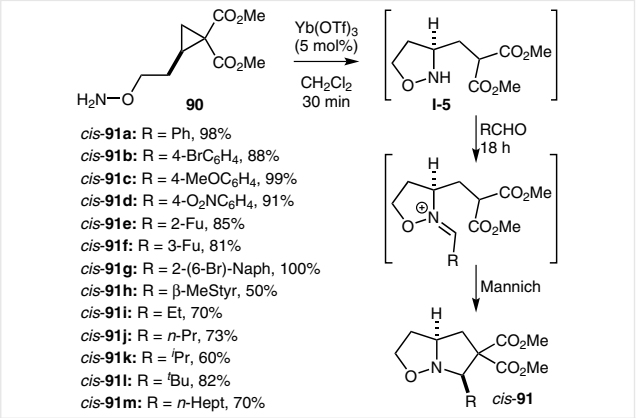
For example, in the presence of $Yb(OTf)_3$ as a catalyst, alkoxyamine **90** underwent intramolecular nucleophilic ring opening leading to intermediate isoxazolidine **I-5** (Scheme 39).[100] The addition of various aldehydes to **I-5** triggered diastereoselective assembly of pyrroloisoxazoli-



Scheme 38 Synthesis of structural analogues of mitomycin C



Scheme 37 Total synthesis of pyrrolizidine alkaloids (±)-isoretronecanol and (±)-trachelanthamidine

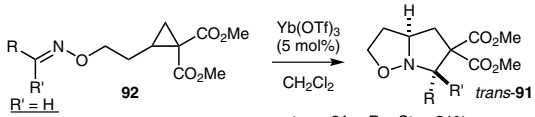


cis-**91a:** R = Ph, 98%
cis-**91b:** R = 4-BrC_6H_4, 88%
cis-**91c:** R = 4-$MeOC_6H_4$, 99%
cis-**91d:** R = 4-$O_2NC_6H_4$, 91%
cis-**91e:** R = 2-Fu, 85%
cis-**91f:** R = 3-Fu, 81%
cis-**91g:** R = 2-(6-Br)-Naph, 100%
cis-**91h:** R = β-MeStyr, 50%
cis-**91i:** R = Et, 70%
cis-**91j:** R = *n*-Pr, 73%
cis-**91k:** R = ^{i}Pr, 60%
cis-**91l:** R = ^{t}Bu, 82%
cis-**91m:** R = *n*-Hept, 70%

Scheme 39 Synthesis of *cis*-pyrroloisoxazolidines via initial intramolecular nucleophilic ring opening

dines **91**, exclusively as *cis*-isomers, via imine formation followed by Mannich-type cyclization.

Meanwhile, an approach to analogous *trans*-**91** was based on intramolecular formal (3+2)-cycloaddition within 2-[2-(iminooxy)ethyl]cyclopropane-1,1-dicarboxylates **92** (Scheme 40). Imines **92** were generated from amine **90** and various aldehydes, mostly as *E*-isomers. Therefore, the order of mixing for the reactants and the catalyst defined the stereo-outcome by switching the mechanism from intramolecular nucleophilic ring opening to intramolecular formal (3+2)-cycloaddition.

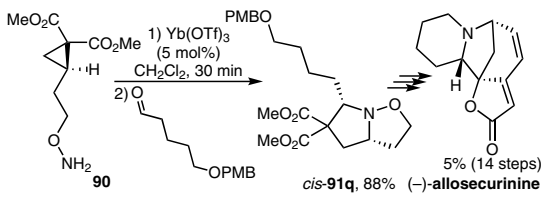


R' = H
trans-**91a:** R = Ph, 98%
trans-**91b:** R = 4-BrC_6H_4, 99%
trans-**91c:** R = 4-$MeOC_6H_4$, 99%
trans-**91d:** R = 4-$O_2NC_6H_4$, 99%
trans-**91n:** R = 2-Py, 97%
trans-**91g:** R = 2-(6-Br)-Naph, 99%

trans-**91o:** R = Styr, 81%
trans-**91h:** R = 2-Me-Styr, 85%
trans-**91k:** R = *i*-Pr, 82%
trans-**91l:** R = *t*-Bu, 75%
R' = CO_2Me
trans-**91p:** R = Ph, 98%

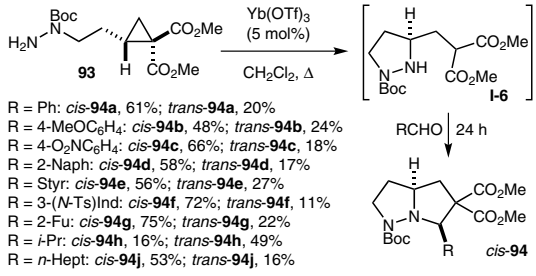
Scheme 40 Synthesis of *trans*-pyrroloisoxazolidines via intramolecular (3+2)-cycloaddition

This reaction was successfully employed in the total synthesis of alkaloid (–)-allosecurinine (Scheme 41).[102]



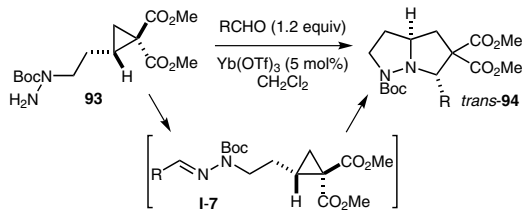
Scheme 41 The total synthesis of alkaloid (–)-allosecurinine

A similar process was developed for hydrazine **93**, which initially underwent intramolecular nucleophilic ring opening under catalysis by $Yb(OTf)_3$ to form intermediate pyrazolidine **I-6**, which reacted with aldehydes, predominantly yielding *cis*-**94** (Scheme 42).[101] 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).



R = Ph: *cis*-**94a**, 61%; *trans*-**94a**, 20%
R = 4-$MeOC_6H_4$: *cis*-**94b**, 48%; *trans*-**94b**, 24%
R = 4-$O_2NC_6H_4$: *cis*-**94c**, 66%; *trans*-**94c**, 18%
R = 2-Naph: *cis*-**94d**, 58%; *trans*-**94d**, 17%
R = Styr: *cis*-**94e**, 56%; *trans*-**94e**, 27%
R = 3-(*N*-Ts)Ind: *cis*-**94f**, 72%; *trans*-**94f**, 11%
R = 2-Fu: *cis*-**94g**, 75%; *trans*-**94g**, 22%
R = *i*-Pr: *cis*-**94h**, 16%; *trans*-**94h**, 49%
R = *n*-Hept: *cis*-**94j**, 53%; *trans*-**94j**, 16%

Scheme 42 Predominant formation of *cis*-pyrrolopyrazolidines via initial intramolecular nucleophilic ring opening

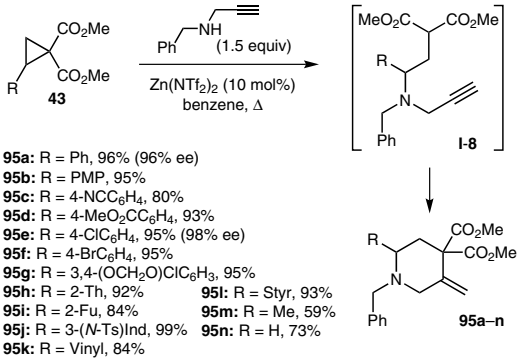


trans-**94a:** R = Ph, 85%
trans-**94b:** R = 4-$MeOC_6H_4$, 83%
trans-**94c:** R = 4-$O_2NC_6H_4$, 90% (>99% ee)
trans-**94d:** R = 2-Naph, 80% (*cis*-**94d:** 17%)
trans-**94e:** R = Styr, 83%
trans-**94f:** R = 3-(*N*-Ts)Ind, 60% (*cis*-**94f:** 22%)
trans-**94g:** R = 2-Fu, 89%
trans-**94h:** R = *i*-Pr, 85%
trans-**94i:** R = *t*-Bu, 70% (>99% ee)
trans-**94j:** R = *n*-Hept, 48% (*cis*-**94j:** 14%)

Scheme 43 Synthesis of *trans*-pyrrolopyrazolidines via intramolecular (3+2)-cycloaddition

3.1.3 Synthesis of Piperidines

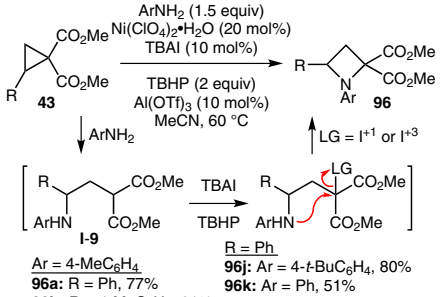
The Kerr group developed a new approach to substituted piperidines **95** via the reaction between cyclopropanes **43** and *N*-benzylpropargylamine with $Zn(NTf_2)_2$ as the catalyst.[103] Their technique involved a cascade consisting of nucleophilic small ring opening, initiated by an amine and yielding 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.



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

3.1.4 Synthesis of Azetidine and Quinoline Derivatives

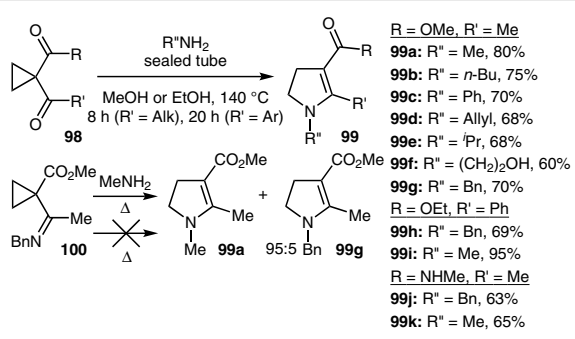
Luo et al. designed an efficient approach to azetidines **96**, based on a cascade of nucleophilic ring opening of cyclopropane-1,1-diesters **43** with aniline derivatives and intramolecular oxidative α-amination of the malonate fragment in intermediate **I-9** (Scheme 45).[104] Cyclopropanes **43** 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).



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

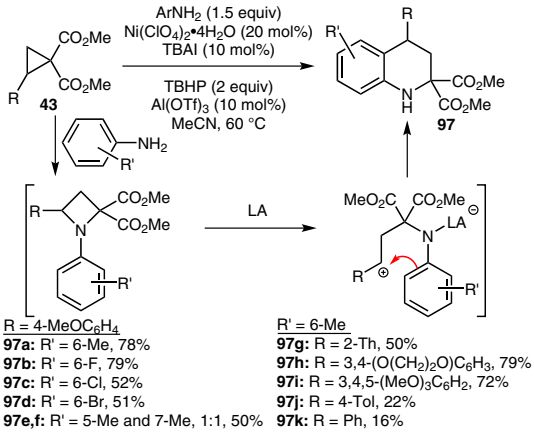
3.2 Reactions of Ketocyclopropanes with Primary Amines: Synthesis of Pyrrole Derivatives

Similarly to cyclopropane-1,1-diesters, ketocyclopropanes can take part in domino reactions with primary amines, yielding pyrroline 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 pyrroline **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).

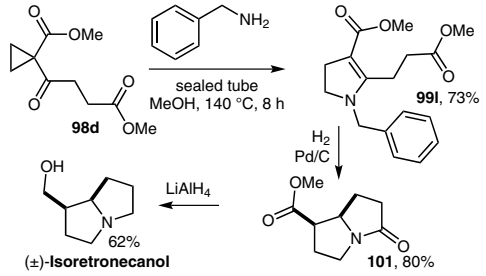


Scheme 47 Nucleophilic ring opening/1,5-cyclization in reaction of 1-acylcyclopropane-1-carboxylates and 1-acylcyclopropane-1-carboxamides with amines

The devised approach to pyrrolines was then used in the total synthesis of isoretronecanol, a pyrrolizidine alkaloid, in its racemic form (Scheme 48).[105] Subsequently, the Lhommet group designed enantioselective approaches to the alkaloids (+)-laburnine, (+)-tashiromine, and (–)-isoretronecanol based on the transformation of acylcyclopropanes into pyrrolines.[106]

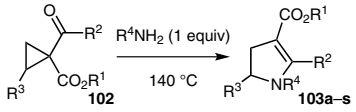


Scheme 46 Synthesis of tetrahydroquinolines



Scheme 48 Total synthesis of alkaloid (±)-isoretronecanol

An analogous method was proposed for the synthesis of 4,5-dihydro-1*H*-pyrrole-3-carboxylates **103a–s** from DA cyclopropanes **102** containing alkyl, aryl, and alkenyl substituents as an EDG (Scheme 49).[107]



R¹ = Me, R² = Me, R³ = Vinyl
103a: R⁴ = Bn, 8 h, 60%
103b: R⁴ = Me, 8 h, 50%
103c: R⁴ = *c*-Pr, 8 h, 45%
103d: R⁴ = Ph, 20 h, 58%
103e: R⁴ = 4-FC$_6$H$_4$, 20 h, 41%
R¹ = Et, R² = Ph, R³ = Vinyl
103f: R⁴ = Bn, 8 h, 72%
103g: R⁴ = Me, 8 h, 70%
103h: R⁴ = *c*-Pr, 8 h, 57%
103i: R⁴ = Ph, 20 h, 60%
103j: R⁴ = 4-FC$_6$H$_4$, 20 h, 44%

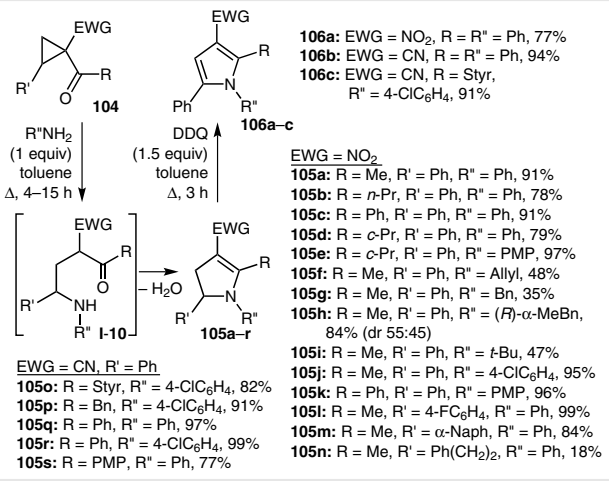
R¹ = Et, R² = Ph, R⁴ = Me
103k: R³ = Ph, 8 h, 72%
R¹ = Me, R² = Me, R⁴ = Me
103l: R³ = Ph, 8 h, 69%
103m: R³ = Et, 24 h, 58%
103n: R³ = *n*-Hept, 16 h, 35%
103o: R³ = (CH$_2$)$_3$CH=CH$_2$, 20 h, 45%
103p: R³ = (CH$_2$)$_9$CH=CH$_2$, 24 h, 50%
103q: R³ = (CH$_2$)CH=CMe$_2$, 15 h, 25%
103r: R³ = CH$_2$CH(Me)(CH$_2$)CH=CMe$_2$, 20 h, 45%
103s: R³ = (CH$_2$)$_4$Ph, 15 h, 40%

Scheme 49 Synthesis of 4,5-dihydro-1*H*-pyrrole-3-carboxylates

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 nitropyrrolines **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 **I-10**, 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, tetrahydroindolones **110**, on reaction with aliphatic and aromatic primary amines as well as ammonia, even at room temperature (Scheme 52).[110]

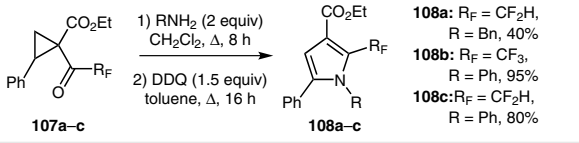


106a: EWG = NO$_2$, R = R" = Ph, 77%
106b: EWG = CN, R = R" = Ph, 94%
106c: EWG = CN, R = Styr, R" = 4-ClC$_6$H$_4$, 91%

EWG = NO$_2$
105a: R = Me, R' = Ph, R" = Ph, 91%
105b: R = *n*-Pr, R' = Ph, R" = Ph, 78%
105c: R = Ph, R' = Ph, R" = Ph, 91%
105d: R = *c*-Pr, R' = Ph, R" = Ph, 79%
105e: R = *c*-Pr, R' = Ph, R" = PMP, 97%
105f: R = Me, R' = Ph, R" = Allyl, 48%
105g: R = Me, R' = Ph, R" = Bn, 35%
105h: R = Me, R' = Ph, R" = (*R*)-α-MeBn, 84% (dr 55:45)
105i: R = Me, R' = Ph, R" = *t*-Bu, 47%
105j: R = Me, R' = Ph, R" = 4-ClC$_6$H$_4$, 95%
105k: R = Ph, R' = Ph, R" = PMP, 96%
105l: R = Me, R' = 4-FC$_6$H$_4$, R" = Ph, 99%
105m: R = Me, R' = α-Naph, R" = Ph, 84%
105n: R = Me, R' = Ph(CH$_2$)$_2$, R" = Ph, 18%

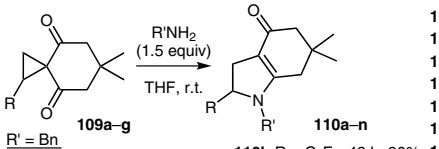
EWG = CN, R' = Ph
105o: R = Styr, R" = 4-ClC$_6$H$_4$, 82%
105p: R = Bn, R" = 4-ClC$_6$H$_4$, 91%
105q: R = Ph, R" = Ph, 97%
105r: R = Ph, R" = 4-ClC$_6$H$_4$, 99%
105s: R = PMP, R" = Ph, 77%

Scheme 50 Sequential synthesis of pyrrolidines and pyrroles



108a: R$_F$ = CF$_2$H, R = Bn, 40%
108b: R$_F$ = CF$_3$, R = Ph, 95%
108c: R$_F$ = CF$_2$H, R = Ph, 80%

Scheme 51 Synthesis of 2-fluoromethyl-substituted pyrrole-3-carboxylates



R = Ph
110a: R' = Bn, 3 h, 97%
110b: R' = PMB, 3 h, 92%
110c: R' = Allyl, 5 h, 98%
110d: R' = *n*-Bu, 2.5 h, 95%
110e: R' = ^{t}Bu, 60, 85%
110f: R' = Ph, 2 h, 76%
110g: R' = PMP, 1 h, 86%
110h: R' = H, 2 h, 31%

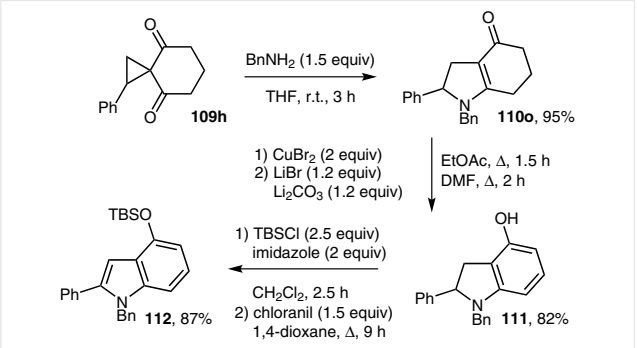
R' = Bn
110i: R = 4-Tol, 2.5 h, 86%
110j: R = 4-ClC$_6$H$_4$, 4.5 h, 97%
110k: R = 2-ClC$_6$H$_4$, 20 h, 97%
110l: R = C$_6$F$_5$, 48 h, 90%
110m: R = ^{n}Bu, 8 h (reflux), 96%
110n: R = H, 36 h, 92%

Scheme 52 Transformation of cyclopropanes into tetrahydroindolones

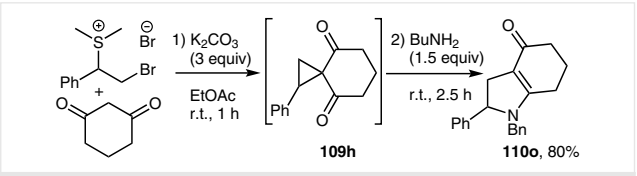
There are two possible mechanisms for such reactions: 1. nucleophilic ring opening of the cyclopropane with the amine, followed by a subsequent nucleophilic attack of the yielded amine upon the carbonyl group, and 2. the formation of an imine with a subsequent Cloke–Stevens rearrangement. However, it 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 **109h** 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]

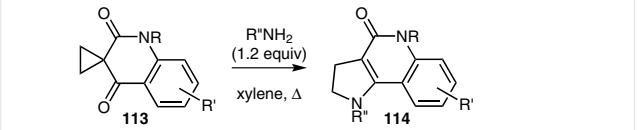


Scheme 53 Transformation of a cyclopropane into an indole



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

Zhang and Zhang performed an analogous reaction employing ketamides **113** and primary aromatic or aliphatic amines (Scheme 55).[112] Accordingly, a series of pyrrolinoquinolones **114** were synthesized in high yields.

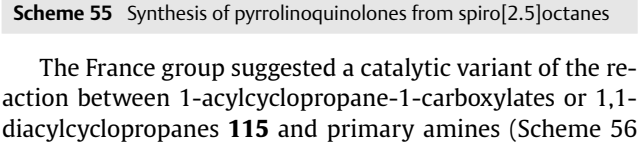


R = 4-ClC$_6$H$_4$
114a: R' = H, R" = PMP, 85%
114b: R' = H, R" = Bn, 88%
114c: R' = H, R" = 4-ClC$_6$H$_4$CH$_2$, 80%
114d: R' = H, R" = Ph, 72%
114e: R' = 4-Tol, R" = Bn, 86%

R' = H
114f: R = 4-F$_3$CC$_6$H$_4$, R" = Bn, 74%
114g: R = 4-EtO$_2$CC$_6$H$_4$, R" = Bn, 86%
114h: R = 4-Tol, R" = Bn, 86%
114i: R = 4-EtO$_2$CC$_6$H$_4$, R" = *c*-Hex, 79%

Scheme 55 Synthesis of pyrrolinoquinolones from spiro[2.5]octanes

The France group suggested a catalytic variant of the reaction between 1-acylcyclopropane-1-carboxylates or 1,1-diacylcyclopropanes **115** and primary amines (Scheme 56 and Scheme 57).[113] The introduction of Ni(ClO$_4$)$_2$·6H$_2$O as a catalyst, analogously to Charette's technique for the ring opening of 1-nitrocyclopropane-1-carboxylates **50** (Scheme 20),[80] 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–n,q–s** and acylpyrrolines **116o,p** were obtained in good yields.

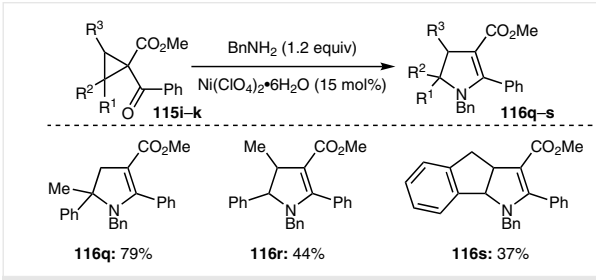


R^2 = MeO, R^4 = Bn
116j:[c] R^1 = Ph, R^3 = Ph, 85%
116k:[b] R^1 = Ph, R^3 = 4-FC$_6$H$_4$, 88%
116l:[c] R^1 = Ph, R^3 = 4-O$_2$NC$_6$H$_4$, 31%
116m:[b] R^1 = Et, R^3 = PMP, 85%
116n:[b] R^1 = 2-Th, R^3 = PMP, 83%

R^1 = Ph, R^2 = MeO, R^3 = PMP
116a:[a] R^4 = Et, 63%
116b:[a] R^4 = ^{i}Pr, 81%
116c:[b] R^4 = MeO(CH$_2$)$_2$, 83%
116d:[a] R^4 = (EtO)$_3$Si(CH$_2$)$_3$, 42%
116e:[a] R^4 = 3-Ind(CH$_2$)$_2$, 84%
116f:[b] R^4 = CH$_2$CH=CH$_2$, 96%
116g:[a] R^4 = CH≡CCH$_2$, 30%
116h:[c] R^4 = Ph, 74%
116i:[a] R^4 = (*S*)-Ph(Me)CH, 90%
R^2 = Me, R^4 = Bn
116o:[b] R^1 = Me, R^3 = Ph, 78%
116p:[b] R^1 = Ph, R^3 = Ph, 51%

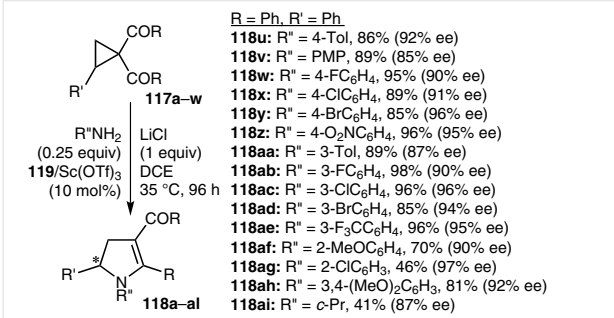
[a] DCE, reflux. [b] CH$_2$Cl$_2$, reflux. [c] Toluene, reflux.

Scheme 56 Catalytic conversion of cyclopropanes into pyrrolines



Scheme 57 Reaction of tetrasubstituted cyclopropanes with benzylamine

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).[114] The optimal catalytic system Sc(OTf)$_3$–**119** provided the best yield-to-enantioselectivity relationship. The scope



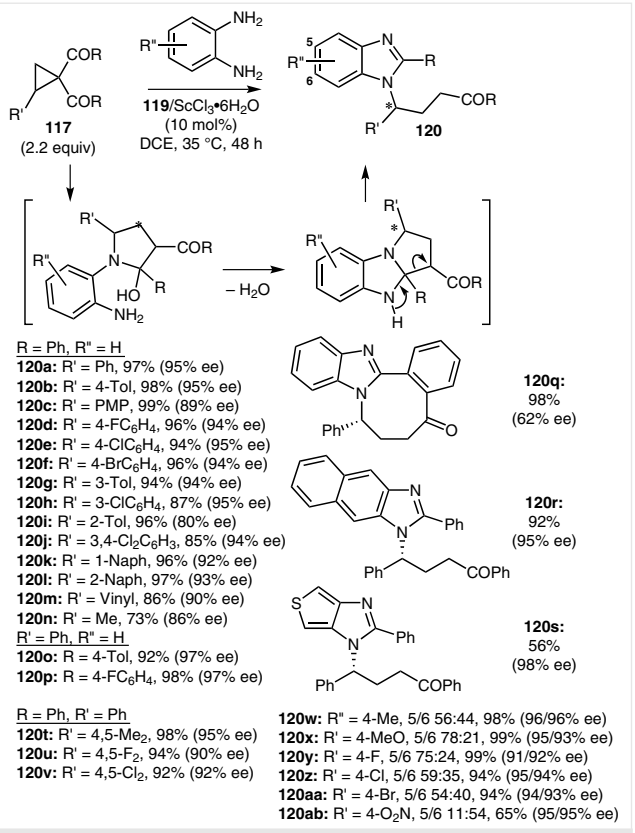
R = Ph, R' = Ph
118u: R" = 4-Tol, 86% (92% ee)
118v: R" = PMP, 89% (85% ee)
118w: R" = 4-FC$_6$H$_4$, 95% (90% ee)
118x: R" = 4-ClC$_6$H$_4$, 89% (91% ee)
118y: R" = 4-BrC$_6$H$_4$, 85% (96% ee)
118z: R" = 4-O$_2$NC$_6$H$_4$, 96% (95% ee)
118aa: R" = 3-Tol, 89% (87% ee)
118ab: R" = 3-FC$_6$H$_4$, 98% (90% ee)
118ac: R" = 3-ClC$_6$H$_4$, 96% (96% ee)
118ad: R" = 3-BrC$_6$H$_4$, 85% (94% ee)
118ae: R" = 3-F$_3$CC$_6$H$_4$, 96% (95% ee)
118af: R" = 2-MeOC$_6$H$_4$, 70% (90% ee)
118ag: R" = 2-ClC$_6$H$_3$, 46% (97% ee)
118ah: R" = 3,4-(MeO)$_2$C$_6$H$_3$, 81% (92% ee)
118ai: R" = *c*-Pr, 41% (87% ee)

R = Ph, R" = Ph
118a: R' = Ph, 82% (91% ee)
118b: R' = 4-Tol, 95% (91% ee)
118c: R' = PMP, 96% (92% ee)
118d: R' = 4-FC$_6$H$_4$, 94% (95% ee)
118e: R' = 4-ClC$_6$H$_4$, 86% (92% ee)
118f: R' = 4-BrC$_6$H$_4$, 88% (95% ee)
118g: R' = 3-Tol, 96% (92% ee)
118h: R' = 3-MeOC$_6$H$_4$, 81% (94% ee)
118i: R' = 3-ClC$_6$H$_4$, 67% (95% ee)
118j: R' = 3-BrC$_6$H$_4$, 71% (95% ee)
118k: R' = 2-Tol, 92% (94% ee)
118l: R' = 2-MeOC$_6$H$_4$, 95% (92% ee)
118m: R' = 2,4-Cl$_2$C$_6$H$_3$, 55% (90% ee)
118n: R' = 3,4-Cl$_2$C$_6$H$_3$, 66% (96% ee)
118o: R' = 2,3-(MeO)$_2$C$_6$H$_3$, 76% (90% ee)
118p: R' = 3,4-(MeO)$_2$C$_6$H$_3$, 98% (92% ee)
118q: R' = 1-Naph, 98% (96% ee)
118r: R' = 2-Naph, 97% (94% ee)
118s: R' = Vinyl, 43% (91% ee)
118t: R' = Me, 16% (66% ee)

R' = Ph, R" = Ph
118aj: R = 4-Tol, 63% (96% ee)
118ak: R = 4-FC$_6$H$_4$, 93% (94% ee)
118al: R = Me, 59% (73% ee)

Scheme 58 Asymmetric catalytic synthesis of 3-acyl-4,5-dihydro-1*H*-pyrroles

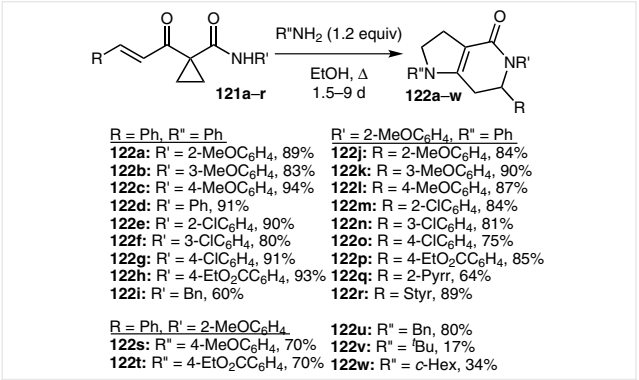
of the method was demonstrated on a representative series that included the reaction 1,1-diacyl-2-aryl-, 2-alkyl-, and 2-alkenylcyclopropanes **117a–w** with primary aryl- and alkylamines under the optimized conditions to produce pyrrolines **118a–al** in good yields and with enantioselectivities of 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.



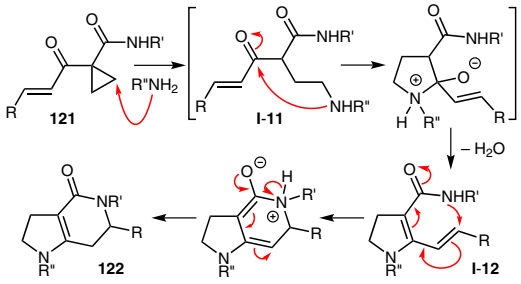
Scheme 59 Domino transformation of 1,1-diacylcyclopropanes to give benzimidazoles

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 pyrrolidine ring was an intermediate stage, whereas, the ultimate products were benzimidazole derivatives **120** (Scheme 59).[115]

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 of 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).[116] 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-vinylpyrrolidine-3-carboxamides **I-12**. The latter, in turn, undergo intramolecular conjugated aza-addition to yield pyrrolopyridinones **122** (Scheme 61).



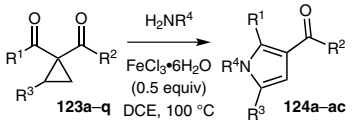
Scheme 60 Cascade transformation of electrophilic cyclopropanes to give pyrrolopyridinones



Scheme 61 Proposed mechanism for the transformation of electrophilic cyclopropanes into pyrrolopyridinones

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 pyrroline **I-14**, and 3. oxidation of **I-14** to give pyrrole **124** (Scheme 62 and Scheme 63).[117] 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′-bipyrroles **126** from the Werz group[118,119] was based on the reaction between tricyclic compounds **125**, the structure of which included fragments of two ketocyclopropanes as well as tetrahydrofuran, and primary amines (Scheme 64).[118] In some cases, diketopyrroles **127** were obtained as secondary prod-



R^1 = Me, R^2 = NH-n-XC_6H_4

124a: n-X = 4-Me, R^3 = H, R^4 = 4-ClC_6H_4, 68%
124b: n-X = 2-Cl, R^3 = H, R^4 = 2-ClC_6H_4, 61%
124c: n-X = 3-Cl, R^3 = H, R^4 = 3-ClC_6H_4, 66%
124d: n-X = 4-Cl, R^3 = H, R^4 = 4-ClC_6H_4, 68%
124e: n-X = 4-Me, R^3 = H, R^4 = 4-Tol, 63%
124f: n-X = 4-MeO, R^3 = H, R^4 = 4-$MeOC_6H_4$, 65%
124g: n-X = 4-Cl, R^3 = H, R^4 = 4-Bn, 61%
124h: n-X = 4-Me, R^3 = H, R^4 = 4-MeBn, 64%
124i: n-X = 4-Me, R^3 = H, R^4 = *c*-Hex, 21%
124j: n-X = 4-Me, R^3 = H, R^4 = ^{n}Bu, 31%
124k: n-X = 4-Cl, R^3 = Me, R^4 = 4-ClC_6H_4, 70%

R^1 = Ph, R^2 = NH-n-XC_6H_4

124l: n-X = 4-Cl, R^3 = H, R^4 = 4-ClC_6H_4, 85%
124m: n-X = 4-MeO, R^3 = H, R^4 = 4-$MeOC_6H_4$, 80%
124n: n-X = 4-Cl, R^3 = H, R^4 = Bn, 81%
124o: n-X = 4-Cl, R^3 = Me, R^4 = 4-ClC_6H_4, 78%

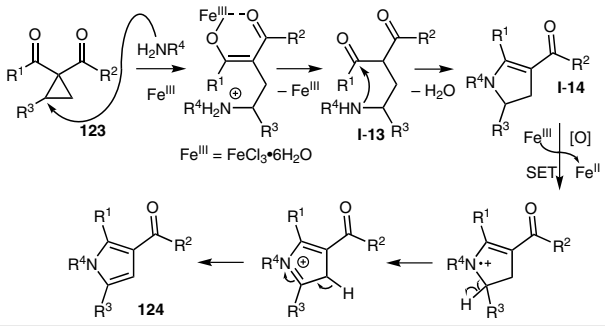
R^1 = Me, R^2 = OEt, R^3 = H

124p: R^4 = 4-ClC_6H_4, 72%
124q: R^4 = 3-ClC_6H_4, 68%
124r: R^4 = 2-ClC_6H_4, 56%
124s: R^4 = 4-Tol, 72%
124t: R^4 = 3-Tol, 77%
124u: R^4 = 2-Tol, 62%
124v: R^4 = Ph, 73%

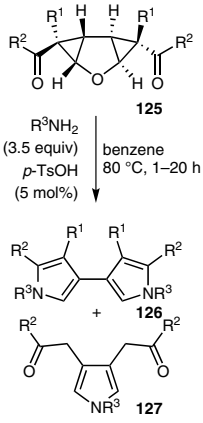
R^1 = PMP, R^2 = OEt, R^3 = H

124w: R^4 = 4-ClC_6H_4, 71%
124x: R^4 = 3-ClC_6H_4, 68%
124y: R^4 = 2-ClC_6H_4, 51%
124z: R^4 = 4-Tol, 78%
124aa: R^4 = 3-Tol, 67%
124ab: R^4 = 2-Tol, 58%
124ac: R^4 = Ph, 74%

Scheme 62 Cascade transformation of 1-acylcyclopropane-1-carboxamides and -carboxylates into pyrroles



Scheme 63 Proposed mechanism for the transformation of 1-acylcyclopropane-1-carboxamides and -carboxylates into pyrroles



R^1 = H

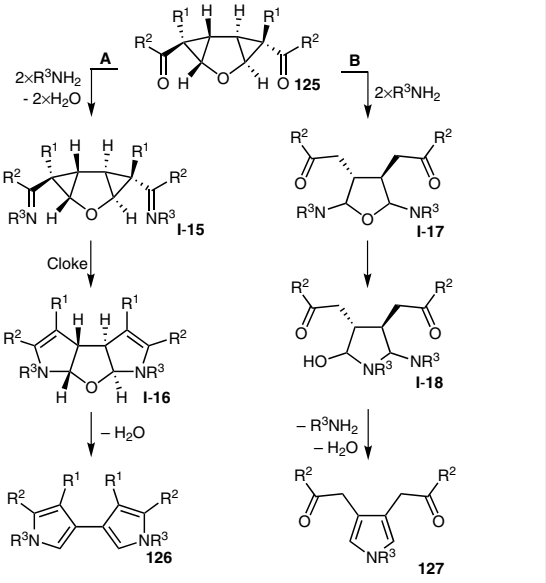
R^2 = Me, R^3 = Ph: **126a**, 81%
R^2 = Me, R^3 = 4-$F_3CC_6H_4$: **126b**, 45%
R^2 = Me, R^3 = Ts: **126c**, 26%; **127c**, 35%
R^2 = Me, R^3 = 4-NCC_6H_4: **127d**, 36%
R^2 = ^{n}Pr, R^3 = Ph: **126e**, 70%; **127e**, 23%
R^2 = ^{n}Pr, R^3 = 4-HOC_6H_4: **126f**, 79%
R^2 = ^{n}Pr, R^3 = 4-$F_3CC_6H_4$: **126g**, 33%; **127g**, 60%
R^2 = ^{n}Pr, R^3 = Ts: **126h**, 23%; **127h**, 59%
R^2 = ^{i}Pr, R^3 = Ph: **126i**, 41%; **127i**, 48%
R^2 = ^{i}Pr, R^3 = Ts: **126j**, 8%; **127j**, 69%
R^2 = Ph, R^3 = Ph: **126k**, 33%; **127k**, 53%
R^2 = Ph, R^3 = 4-$F_3CC_6H_4$: **126l**, 21%; **127l**, 69%

R^1 = Me

R^2 = 2-Fu, R^3 = PMP: **126m**, 76%
R^2 = 2-Fu, R^3 = Ph: **126n**, 76%
R^2 = 2-Th, R^3 = PMP: **126o**, 61%
R^2 = 2-(*N*-Me)Pyrr, R^3 = PMP: **126p**, 41%
R^2 = Me, R^3 = PMP: **126q**, 28%
R^2 = Me, R^3 = Ts: **126r**, 35%

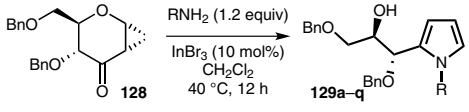
Scheme 64 Transformation of dicyclopropanes into bipyrroles and diketopyrroles under the action of primary amines

ucts in these reactions. A mechanism has been proposed for the formation of bipyrroles **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).



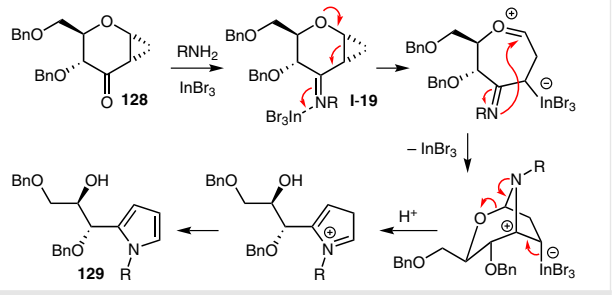
Scheme 65 Proposed mechanisms for formation of bipyrroles via Cloke–Stevens rearrangement and diketopyrroles via nucleophilic ring opening

Yang, Zhang et al. devised an effective synthetic approach to optically active 2-(polyoxyalkyl)pyrroles **129** containing two stereogenic centers.[120] The synthesis of **129** was based upon the reaction of cyclopropa[*b*]pyranones **128** with primary aromatic and aliphatic amines in the presence of $InBr_3$ 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).[120]



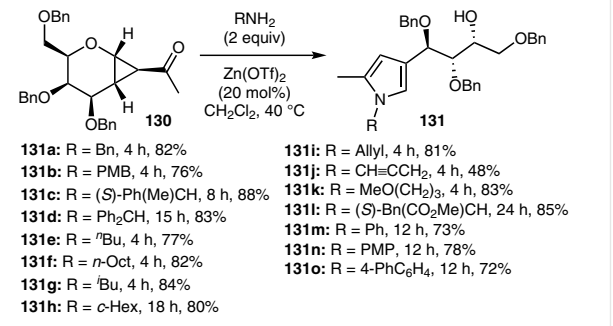
129a: 4-ClC_6H_4, 80%
129b: Ph, 64%[3]
129c: 4-MeC_6H_4, 84%
129d: 4-FC_6H_4, 77%
129e: 4-$F_3CC_6H_4$, 55%
129f: 4-$MeOC_6H_4$, 89%
129g: 4-PhC_6H_4, 70%
129h: 4-$Ph_3CC_6H_4$, 87%
129i: 4-(*N*-morpholino)C_6H_4,92%
129j: 2-Naph, 54%
129k: 2-$MeOC_6H_4$, 60%
129l: 3,4-$(MeO)_2OC_6H_4$, 90%
129m: Bn, 93%
129n: (*R*)-α-MeBn, 86%
129o: 4-$MeOC_6H_4(CH_2)_2$, 73%
129p: *c*-Hex, 84%
129q: ^{n}Pr, 89%

Scheme 66 Cascade transformation of cyclopropa[*b*]pyranones into 2-(polyoxyalkyl)pyrroles

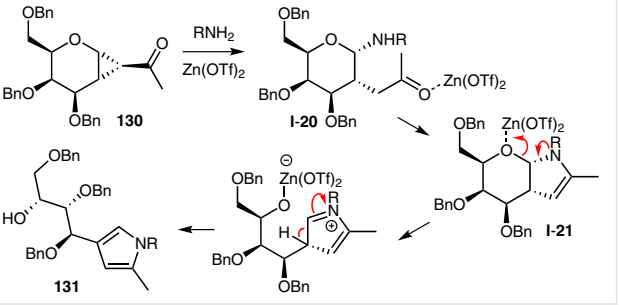


Scheme 67 Proposed mechanism for the transformation of cyclopropa[*b*]pyranones into 2-(polyoxyalkyl)pyrroles via imine rearrangement

Shao et al. developed a method for the synthesis for 3-(polyoxyalkyl)pyrroles **131** with three stereogenic centers involving ketocyclopropanes **130** (derivatives of galactose) and primary amines as reactants.[121] The reaction was carried out at reflux in CH_2Cl_2 with catalytic amounts of zinc triflate (Scheme 68). In contrast to the mechanism in Scheme 67 where the formation of an intermediate imine **I-19** is proposed (Scheme 67), the mechanism for the transformation of **130** into **131** involves the formation of amine **I-20** and its cyclization, yielding bicyclic pyrroline **I-21**, which, in turn, yields pyrrole **131** upon pyran ring opening (Scheme 69).

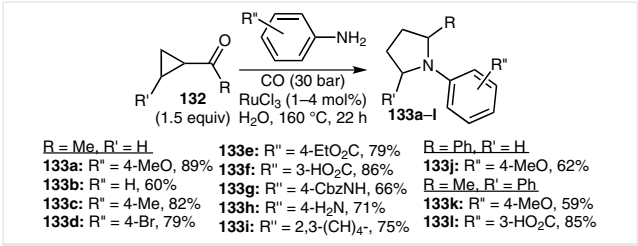


Scheme 68 Cascade transformation of ketocyclopropanes into 3-(polyoxyalkyl)pyrroles



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

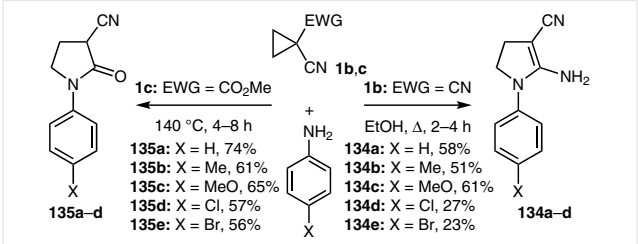
In 2016 Chusov and colleagues reported a ruthenium(III)-catalyzed reaction of ketocyclopropanes **132** with anilines in the presence of CO as a reductant, providing direct method to access pyrrolidines **133** in high yields (Scheme 70).[122]



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

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

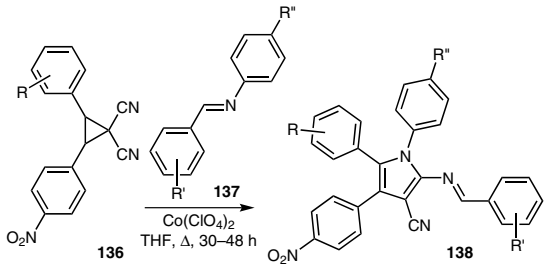
Yamagata et al. compared the reactivities of cyclopropane-1,1-dicarbonitrile (**1b**) and 1-cyanocyclopropane-1-carboxylate **1c** towards aniline derivatives (Scheme 71).[123] It was shown that **1b** underwent ring opening upon treatment with anilines under milder conditions than **1c**. Poorly nucleophilic 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

An unusual result[124,125] was produced by Fu and Yan in the reaction of 2,3-diarylcyclopropane-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 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.

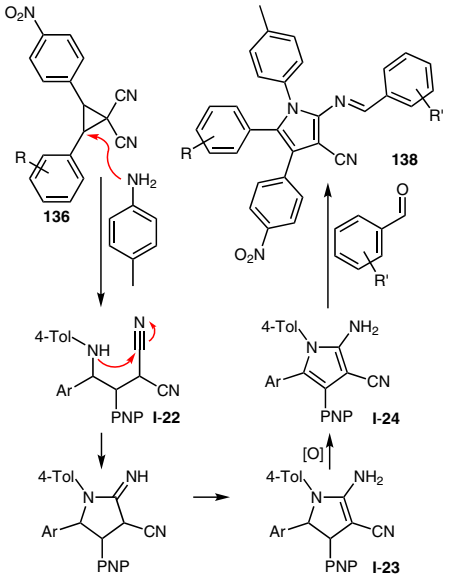


R' = 4-MeO, R" = Me
138a: R = H, 76%
138b: R = 4-Me, 80%
138c: R = 4-MeO, 82%
138d: R = 4-Et, 73%
138e: R = 4-(^{t}Bu), 71%
138f: R = 3-Cl, 78%
138g: R = 4-Br, 68%

R' = 3-Cl, R" = Me
138h: R = H, 70%
138i: R = 4-Me, 75%
138j: R = 4-MeO, 78%
138k: R = 4-(^{t}Bu), 65%
138l: R = 3-Cl, 68%

R' = 4-Br, R" = MeO
138m: R = 4-Me, 71%
138n: R = 4-MeO, 66%
138o: R = 3-Cl, 63%

Scheme 72 Cascade transformation of 2,3-diarylcyclopropane-1,1-dicarbonitriles into iminopyrroles

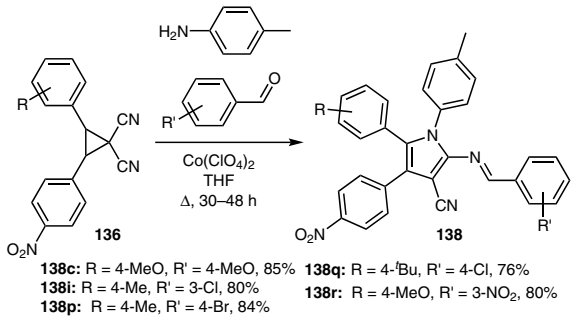


Scheme 73 Proposed mechanism for the transformation of 2,3-diarylcyclopropane-1,1-dicarbonitriles into iminopyrroles

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.

4 Ring Opening with Tertiary Aliphatic Amines

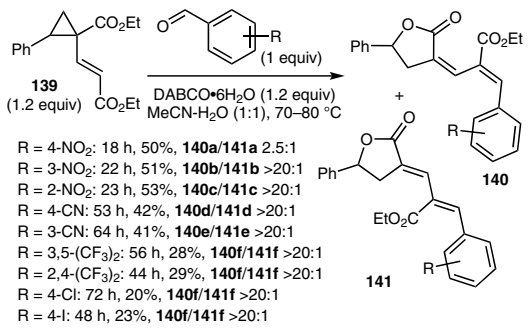
Reactions of activated cyclopropanes with tertiary aliphatic amines are peculiar in that they involve an amine initiating ring opening of the three-membered ring to yield a nucleophilic intermediate that reacts with suitable electrophiles. Subsequent substitution by a different nucleophile returns the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



138c: R = 4-MeO, R' = 4-MeO, 85%
138i: R = 4-Me, R' = 3-Cl, 80%
138p: R = 4-Me, R' = 4-Br, 84%
138q: R = 4-^{t}Bu, R' = 4-Cl, 76%
138r: R = 4-MeO, R' = 3-NO_2, 80%

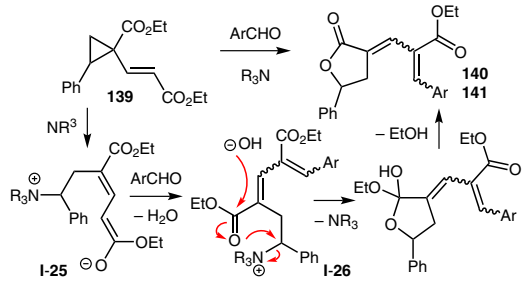
Scheme 74 Three-component reaction of 2,3-diarylcyclopropane-1,1-dicarbonitriles with 4-methylaniline and aldehydes

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).[126] 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



R = 4-NO_2: 18 h, 50%, **140a/141a** 2.5:1
R = 3-NO_2: 22 h, 51%, **140b/141b** >20:1
R = 2-NO_2: 23 h, 53%, **140c/141c** >20:1
R = 4-CN: 53 h, 42%, **140d/141d** >20:1
R = 3-CN: 64 h, 41%, **140e/141e** >20:1
R = 3,5-$(CF_3)_2$: 56 h, 28%, **140f/141f** >20:1
R = 2,4-$(CF_3)_2$: 44 h, 29%, **140f/141f** >20:1
R = 4-Cl: 72 h, 20%, **140f/141f** >20:1
R = 4-I: 48 h, 23%, **140f/141f** >20:1

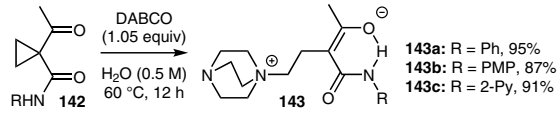
Scheme 75 Formation of lactones via nucleophilic ring opening of a cyclopropane with DABCO



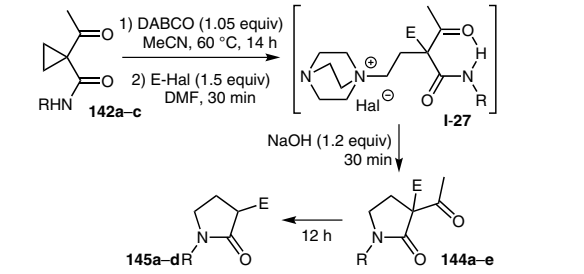
Scheme 76 Proposed mechanism for the transformation of a cyclopropane into a lactone

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.[127] 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 **I-27** formed as intermediates. Treatment of **I-27** with NaOH for 30 minutes yielded 3-acyl-2-pyrrolidones **144**, whereas 2-pyrrolidones **145** were formed after 12 hours (Scheme 78).



Scheme 77 Formation of stable betaines in reaction of 1-acylcyclopropane-1-carboxamides with DABCO



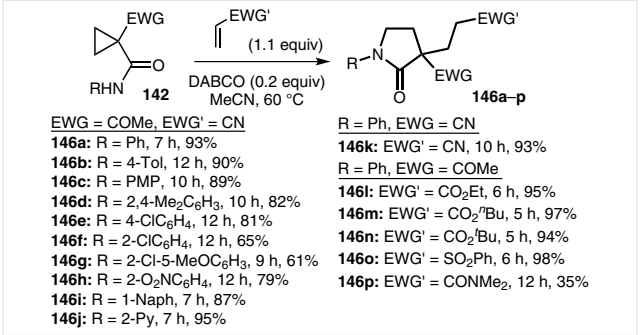
Scheme 78 DABCO-initiated reaction of 1-acylcyclopropane-1-carboxamides with electrophiles

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]

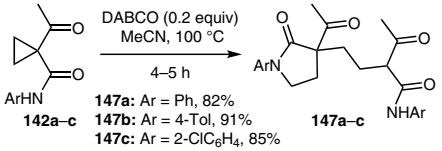
Additionally, it was found that, in the absence of any other electrophiles, 1-acylcyclopropane-1-carboxamide **142** acted in this capacity. Therefore, two molecules of **142a–c** formed the resulting lactams **147a–c** (Scheme 80).

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]

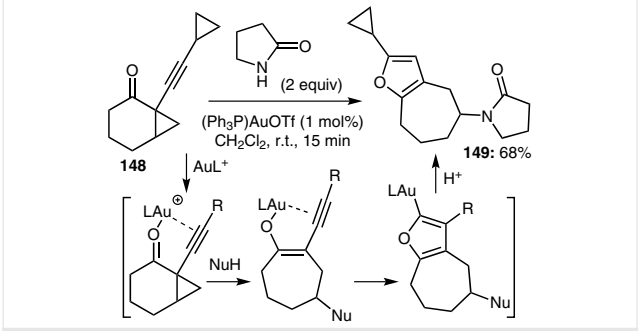


Scheme 79 DABCO-catalyzed reaction of 1-acyl- and 1-cyanocyclopropane-1-carboxamides with electrophilic alkenes

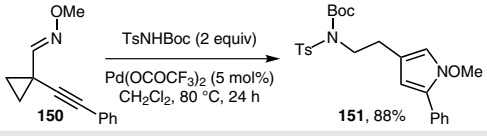


Scheme 80 1-Acylcyclopropane-1-carboxamides as electrophiles in a DABCO-catalyzed reaction

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.



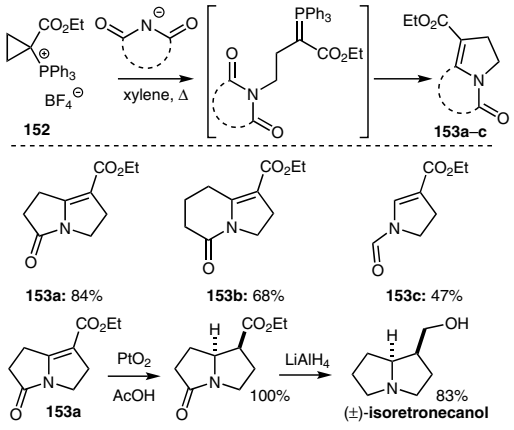
Scheme 81 Gold(I)-catalyzed transformation of an alkynyl-substituted cyclopropane into a furan derivative



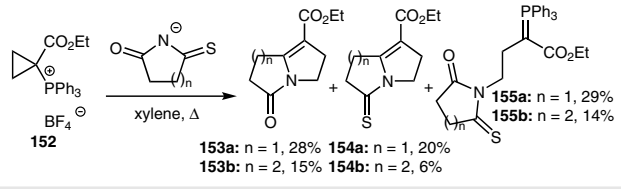
Scheme 82 Palladium(II)-catalyzed transformation of a 1-alkynylcyclopropyl oxime into a pyrrole derivative

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).[130]

Flitsch and Wernsmann 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).[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).



Scheme 83 Reaction of a cyclopropyltriphenylphosphonium tetrafluoroborate with imide anions and the total synthesis of (±)-isoretronecanol

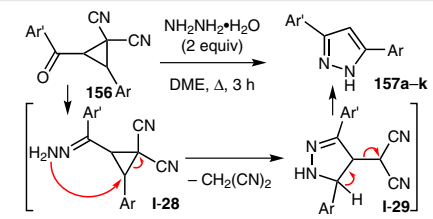


Scheme 84 Reaction of a cyclopropyltriphenylphosphonium tetrafluoroborate with monothioimides

For ring opening with phthalimide, see Scheme 111.

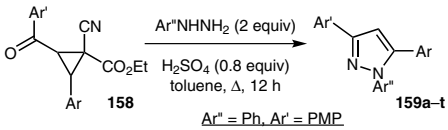
6 Ring Opening with Hydrazines

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).[132,133] It is proposed that cyclopropylhydrazone **I-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**.



Ar' = Ph
157a: Ar = Ph, 58%
157b: Ar = 4-FC6H4, 74%
157c: Ar = 4-BrC6H4, 69%
157d: Ar = 4-ClC6H4, 70%
157e: Ar = 2-ClC6H4, 75%
157f: Ar = 2,4-Cl2C6H3, 70%
157g: Ar = 4-MeC6H4, 69%
157h: Ar = 4-MeOC6H4, 55%
Ar = 4-F3CC6H4
157i: Ar = Ph, 90%
157j: Ar = 2-Fu, 80%
157k: Ar = 2-Th, 78%

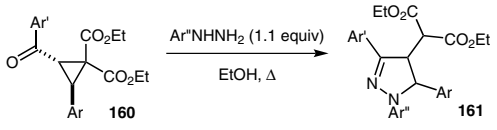
Scheme 85 Conversion of 2-acylcyclopropane-1,1-dicarbonitriles into pyrazoles on reaction with hydrazine



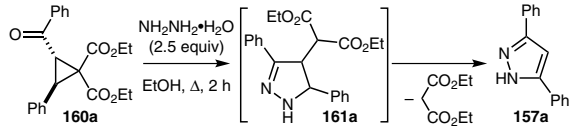
Ar" = Ph, Ar' = Ph
159a: Ar = 4-BrC6H4, 82%
159b: Ar = 2-ClC6H4, 79%
159c: Ar = 3-F-4PhOC6H3, 80%
159d: Ar = 3-ClC6H4, 75%
159e: Ar = 4-Tol, 81%
Ar" = Ph, Ar' = 4-ClC6H4
159f: Ar = 4-BrC6H4, 84%
159g: Ar = 4-ClC6H4, 87%
Ar" = Ph, Ar' = 4-BrC6H4
159h: Ar = 3-F-4PhOC6H3, 81%
159i: Ar = 4-IC6H4, 85%
Ar" = Ph, Ar' = PMP
159j: Ar = 4-ClC6H4, 83%
159k: Ar = 3-ClC6H4, 76%
159l: Ar = 2-ClC6H4, 78%
159m: Ar = 4-BrC6H4, 80%
159n: Ar = 3-BrC6H4, 73%
159o: Ar = 3-Tol, 72%
Ar" = 4-ClC6H4
159p: Ar = 3-ClC6H4, Ar' = PMP, 73%
159q: Ar = 4-BrC6H4, Ar' = 4-ClC6H4, 87%
159r: Ar = 4-BrC6H4, Ar' = PMP, 84%
Ar" = 4-Tol
159s: Ar = 2-ClC6H4, Ar' = Ph, 80%
159t: Ar = 4-BrC6H4, Ar' = 4-ClC6H4, 85%

Scheme 86 Conversion of cyano esters into *N*-arylpyrazoles in reaction with arylhydrazines

In 2016, Wang et al. showed that a similar reaction took place upon mixing cyano esters **158** and arylhydrazines in the presence of H_2SO_4, yielding *N*-aryl-substituted pyrazoles **159** (Scheme 86).[134]



Ar" = Ph, 12 h
161a: Ar = Ph, Ar' = Ph, 92%
161b: Ar = 4-Tol, Ar' = Ph, 93%
161c: Ar = PMP, Ar' = Ph, 95%
161d: Ar = 4-ClC6H4, Ar' = Ph, 88%
161e: Ar = Ph, Ar' = 4-Tol, 90%
161f: Ar = Ph, Ar' = PMP, 92%
161g: Ar = Ph, Ar' = 4-ClC6H4, 90%
161h: Ar = PMP, Ar' = PMP, 95%
Ar" = 4-BrC6H4, 12 h
161i: Ar = Ph, Ar' = Ph, 89%
161j: Ar = Ph, Ar' = PMP, 91%
Ar" = 2,4-(O2N)2C6H3, 8 h
161k: Ar = Ph, Ar' = Ph, 96%
161l: Ar = Ph, Ar' = 4-Tol, 95%
161m: Ar = Ph, Ar' = 4-ClC6H4, 92%
161n: Ar = 2-Th, Ar' = 4-Tol, 92%



Scheme 87 Reaction of 2-aroyl-3-arylcyclopropane-1,1-diesters with arylhydrazines

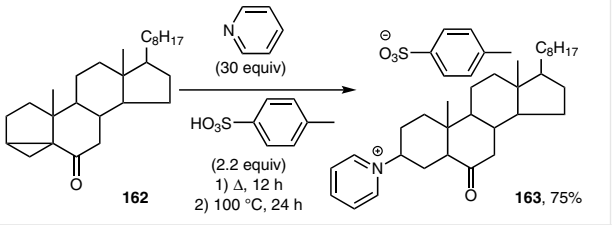
In 2017, Srinivasan et al. demonstrated a similar process involving 2-aroyl-3-arylcyclopropane-1,1-diesters **160** and arylhydrazines under milder conditions that did not result in elimination of the malonyl fragment (Scheme 87).[135] Hence, pyrazolines **161** were produced in high yields. At the same time, the reaction of **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.[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).

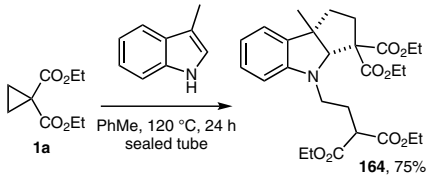


Scheme 88 Ring opening of 3,5-cyclo-cholestan-6-one with pyridine

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**,**e** (Schemes 12 and 13).

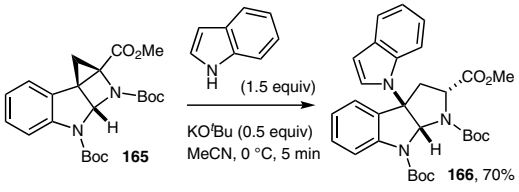
7.2 Ring Opening with Indoles

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-1*H*-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]



Scheme 89 Reaction of **1a** with 3-methyl-1*H*-indole yielding cyclopenta[*b*]indole via (3+2)-cycloaddition/*N*-alkylation

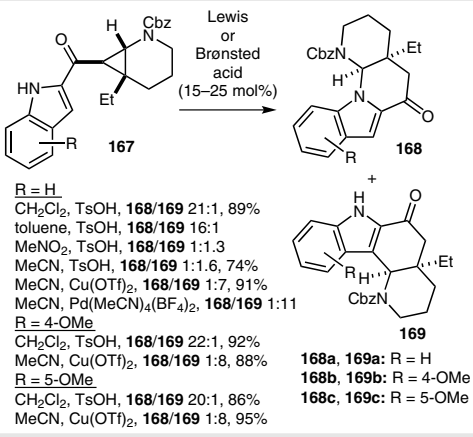
The Rainier group developed a synthesis for the highly strained DA cyclopropane **165**, which underwent ring opening upon treatment with a large series of nucleophiles under very mild conditions.[146] Specifically, it was shown that ring opening of **165** with an indole catalyzed by a base yielded product **166**, and this reaction went to completion in 5 minutes at 0 °C (Scheme 90).



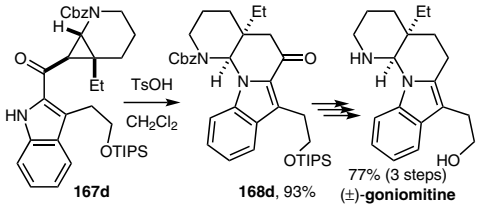
Scheme 90 Ring opening of a strained cyclopropane with indole

For the nucleophilic ring opening of cyclopropyltriphenylphosphonium tetrafluoroborate **152** with indole, see Scheme 98.

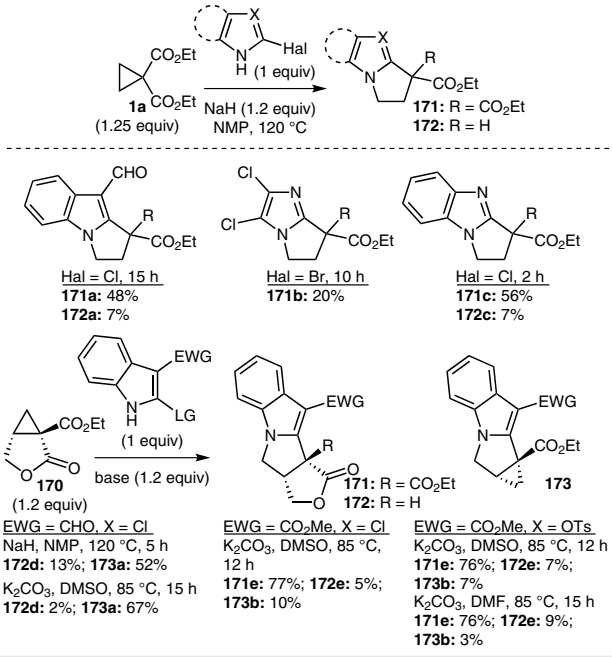
An intramolecular variant of ring opening for DA cyclopropanes **167** upon an *N*-attack by an indole fragment was devised in the Waser group.[17,147] The pathway taken by the reaction was defined by the choice of the catalyst together with the choice of the solvent polarity. Employing largely non-polar CH_2Cl_2 or toluene together with *p*-TsOH as the catalyst gave the products of the *N*-nucleophilic ring open-



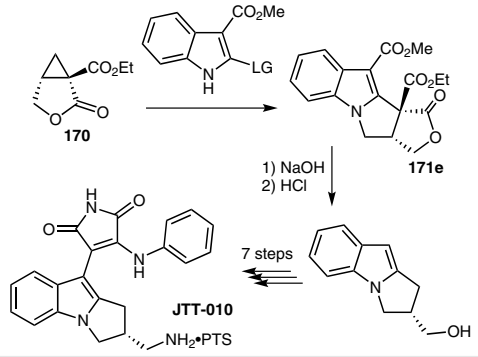
Scheme 91 Intramolecular ring opening of a DA cyclopropane containing an indole substituent



Scheme 92 Total synthesis of (±)-goniomitine



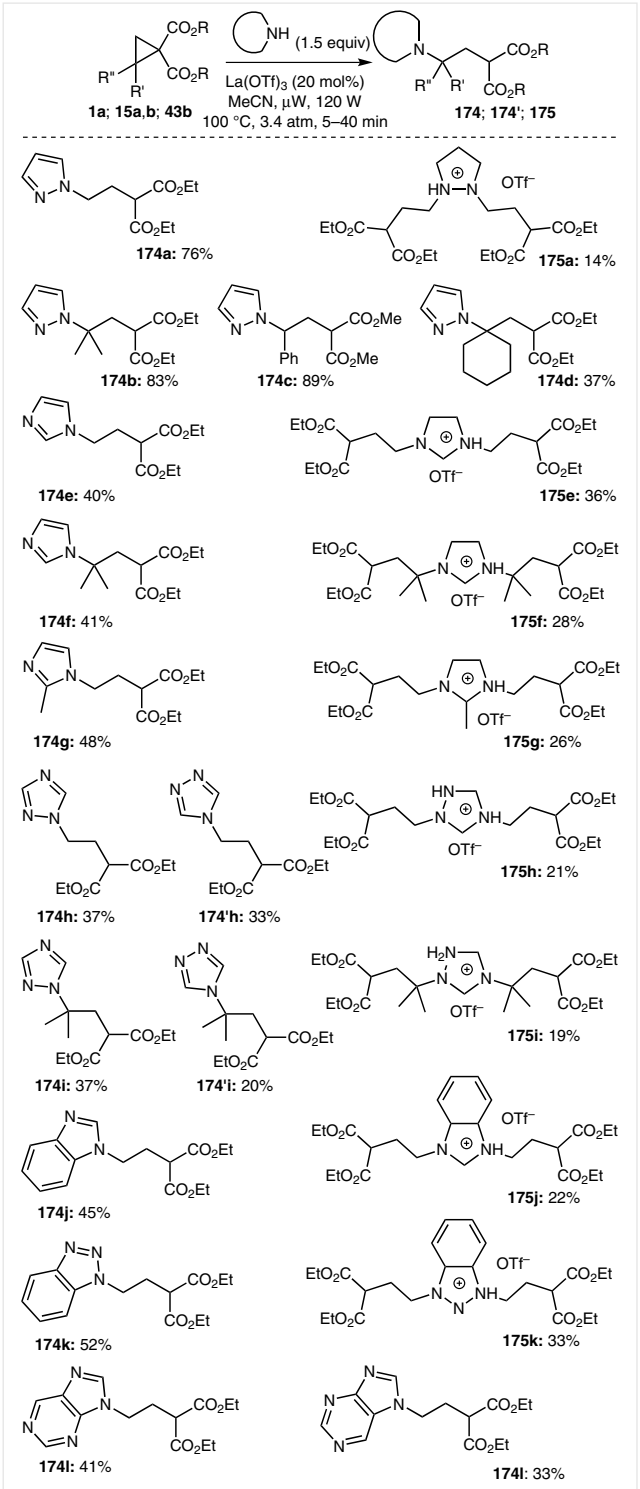
Scheme 93 Conversion of cyclopropanecarboxylates into polyheterocycles via nucleophilic ring opening/nucleophilic substitution



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

ing of **167** yielding **168**, whereas employing MeCN and soft Lewis acids as the catalyst yielded the products **169** of *C*3-nucleophilic ring opening (homo-Nazarov cyclization) (Scheme 91). *N*-Nucleophilic ring opening was used in the total synthesis of alkaloid goniomitine (Scheme 92).

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



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

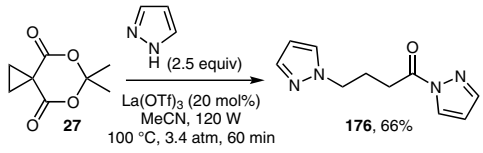
opening of cyclopropanes **1** or **170**, followed by nucleophilic substitution and leading to **171–173** (Scheme 93).[148] Analogous processes were carried out for imidazoles and benzimidazoles. Based upon this reaction, they devised a synthesis of the protein kinase C-β inhibitor JTT-010 (Scheme 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.

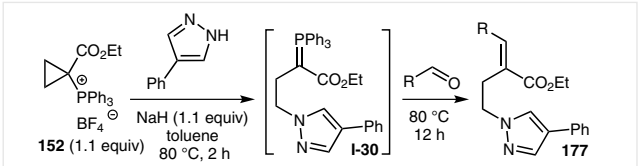
Under similar conditions, Danishefsky's cyclopropane **27** reacted with excess pyrazole via nucleophilic ring opening and subsequent amidation by the second equivalent of pyrazole yielding **176** (Scheme 96).



Scheme 96 Conversion of Danishefsky's cyclopropane into a bis-pyrazole derivative

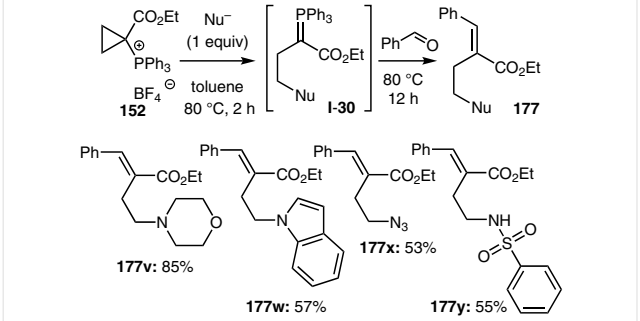
Chung and co-workers designed a process relying on the ring opening of cyclopropyltriphenylphosphonium tetrafluoroborate **152** with pyrazoles in basic medium with a subsequent Wittig reaction between intermediate phosphorus ylide **I-30** and an aliphatic or aromatic aldehyde.[150] This technique allowed the exclusive synthesis of pyrazole-substituted 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; MgI_2 as the catalyst gave N7-adducts **178a–l** while $AlCl_3$ gave N9 adducts **179a–k** (Scheme 99).

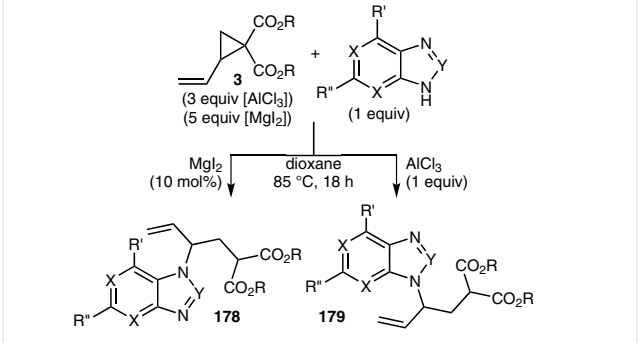


177a: R = Ph, 91%
177b: R = 4-Tol, 80%
177c: R = 3-Tol, 75%
177d: R = 2-Tol, 56%
177e: R = 4-ClC$_6$H$_4$, 82%
177f: R = 3-ClC$_6$H$_4$, 83%
177g: R = 2-ClC$_6$H$_4$, 86%
177h: R = 4-O$_2$NC$_6$H$_4$, 90%
177i: R = 2-O$_2$NC$_6$H$_4$, 83%
177j: R = 4-MeOC$_6$H$_4$, 43%
177k: R = 3-MeOC$_6$H$_4$, 43%
177l: R = 2-MeOC$_6$H$_4$, 32%
177m: R = H, 85%
177n: R = 3-Py, 50%
177o: R = 3-Py(CH$_2$)$_2$, 50%
177p: R = 2-(5-MePy)(CH$_2$)$_2$, 27%
177q: R = 4-(*N*-Et)Imid, 36%
177r: R = ^{i}Bu, 53%
177s: R = ^{c}Pent, 10%
177t: R = ^{c}Pr, 55%
177u: R = ^{c}Pent(CH$_2$)$_2$, 90%

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



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

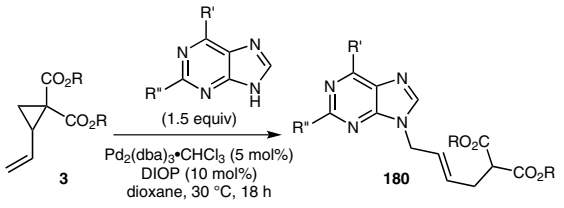


X = N, Y = CH
178a: R = Et, R′ = Cl, R″ = H, 72%
178b: R = Me, R′ = Cl, R″ = H, 84%
178c: R = ^{i}Pr, R′ = Cl, R″ = H, 64%
178d: R = ^{t}Bu, R′ = Cl, R″ = H, 41%
178e: R = Me, R′ = I, R″ = H, 31%
178f: R = Me, R′ = Cl, R″ = Cl, 33%
X = CH, Y = N
178g: R = Et, R′ = H, R″ = H, 82%
X = CH, Y = CH
178h: R = Et, R′ = H, R″ = H, 88%
X = CH, Y = CMe
178i: R = Et, R′ = H, R″ = H, 71%

X = N, Y = CH
179a: R = Et, R′ = Cl, R″ = H, 79%
179b: R = Me, R′ = Cl, R″ = H, 87%
179c: R = ^{i}Pr, R′ = Cl, R″ = H, 67%
179d: R = ^{t}Bu, R′ = Cl, R″ = H, 63%
179e: R = Me, R′ = I, R″ = H, 44%
179f: R = Et, R′ = OEt, R″ = H, 48%
179g: R = Et, R′ = *N*-Pip, R″ = Cl, 89%
179h: R = Et, R′ = *n*-Pent, R″ = H, 62%
179i: R = Et, R′ = 9-Phen, R″ = H, 82%
X = CH, Y = CH
179j: R = Et, R′ = H, R″ = H, 61%
X = CH, Y = N
179k: R = Et, R′ = H, R″ = H, 87%

Scheme 99 Lewis acid triggered ring opening of 2-vinylcyclopropane-1,1-dicarboxylates with purines

Catalytic amounts of $Pd_2(dba)_3$·$CHCl_3$ 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 famcidovir) which have potential for anti-HIV activity.

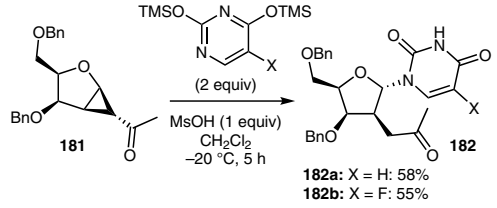


R' = Cl, R" = H
180a: R = Et, 82%
180b: R = Me, 82%
180c: R = ^{i}Pr, 75%
180d: R = ^{t}Bu, 56%
180e: R = CF_3CH_2, 37%
180f: R = Et, R' = 9-Phen, R" = H, 69%
180g: R = Me, R' = I, R" = H, 63% S^2
180h: R = Et, R' = ^{n}PrS, R" = H, 92%
180i: R = Et, R' = *N*-pyrrolidino, R" = Cl, 67%
180j: R = Et, R' = *N*-piperidino, R" = Cl, 89%
180k: R = Et, R' = *N*-morpholino, R" = Cl, 51%

Scheme 100 Palladium(II)-catalyzed ring opening of 2-vinylcyclopropane-1,1-dicarboxylates with purines

7.4 Ring Opening with Pyrimidines

Another approach to structural analogues of nucleosides by Shao et al.[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.



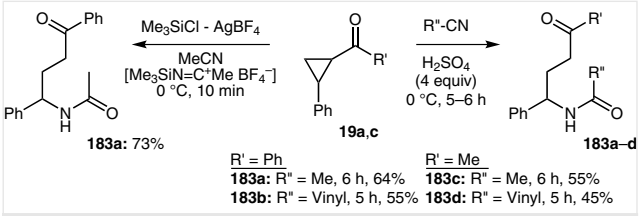
182a: X = H: 58%
182b: X = F: 55%

Scheme 101 Nucleophilic ring opening of a cyclopropanated lyxose with pyrimidines

8 Ring Opening with Nitriles (Ritter Reaction)

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.[153] The efficiency of this reagent was demonstrated in the ring opening of ketocyclopropane **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.[154]

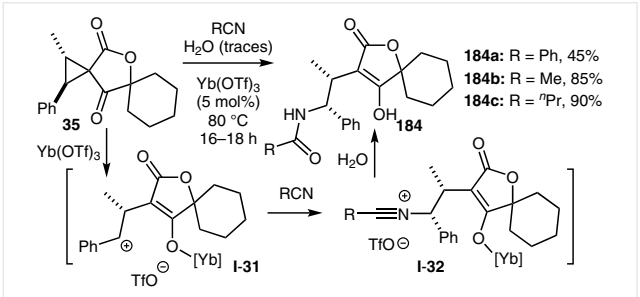


R' = Ph
183a: R" = Me, 6 h, 64%
183b: R" = Vinyl, 5 h, 55%

R' = Me
183c: R" = Me, 6 h, 55%
183d: R" = Vinyl, 5 h, 45%

Scheme 102 Ring opening of ketocyclopropanes with nitriles

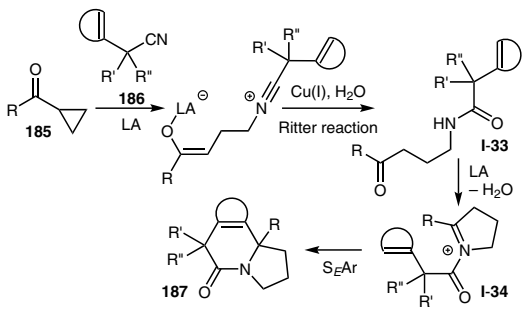
Schobert et al.[74] found that spiro-activated DA cyclopropanes **35** react with nitriles in a reaction catalyzed by ytterbium(III) triflate, a Lewis acid of average strength (Scheme 103).



Scheme 103 Ytterbium(III)-catalyzed ring opening of spiro-activated DA cyclopropanes with nitriles

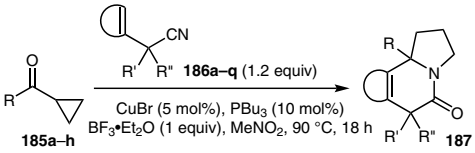
The proposed mechanism involves the coordination of the Lewis acid with the EWG in **35** as well as opening the three-membered ring to give intermediate **I-31**. Subsequent attack of the nitrile upon the flat carbocationic center in **I-32** along the path with lower steric hindrance produces (*R**,*R**)-acetamides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

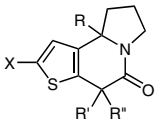
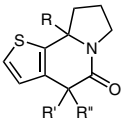
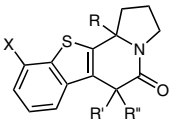
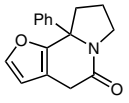
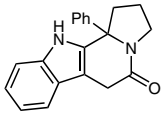
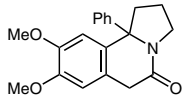
In 2013, the Jiang group developed a new, efficient synthetic approach to the derivatives of indolizinone **187**, based on the domino reaction between ketocyclopropanes



Scheme 104 Proposed mechanism for the formation of indolizinones

Table 3 Ring Opening of Ketocyclopropanes with Benzonitriles Yielding Indolizinone Derivatives



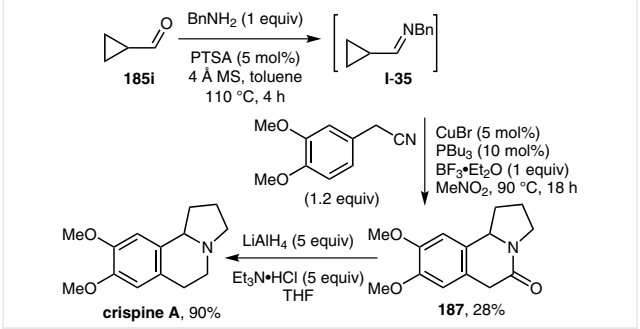
	R′, R′′ = H, X = H				R = Ph, X = H		
	R	Yield (%)		Yield (%)	R′	R′′	Yield (%)
	Ph	80	R	85	-$(CH_2)_2$-		32
	4-FC_6H_4	85	3-FC_6H_4	70	-$(CH_2)_3$-		66
	4-ClC_6H_4	84	3-ClC_6H_4	66	-$(CH_2)_4$-		60
	4-Tol	72	1-naphthyl	55	-$(CH_2)_5$-		50
	R′, R′′ = H, X = Br				Bn	Bn	47
	Ph	69	4-FC_6H_4	70	allyl	allyl	55
	R′, R′ = H				R = Ph		
	R		Yield (%)		R′	R′′	Yield (%)
	Ph		84		Me	H	76
	4-FC_6H_4		90		Me	Me	71
	4-ClC_6H_4		84		allyl	allyl	60
	R′, R′′ = H, X = H				R′, R′′ = H, X = Cl		
	R		Yield (%)		R		Yield (%)
	Ph		72		Ph		55
	4-ClC_6H_4		60				
	Yield (%) 57			Yield (%) 40			Yield (%) 66

185a–h and benzonitriles **186a–q** which contained (hetero)aromatic EDG (Table 3).[155] 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).

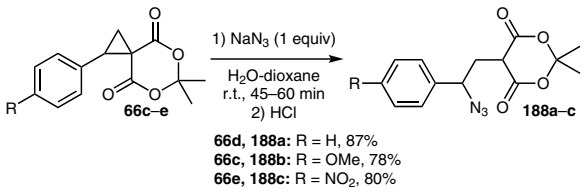
This approach was applied to the total synthesis of anticancer alkaloid (±)-crispine A (Scheme 105).

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_3 group and the EWG. The first example of this type of reaction was reported by Bernabé in 1985.[90] 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).

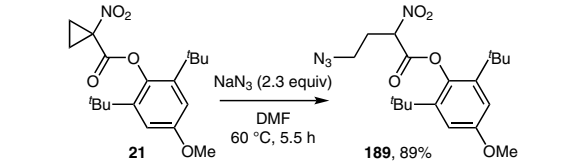


Scheme 105 Total synthesis of alkaloid (±)-crispine A



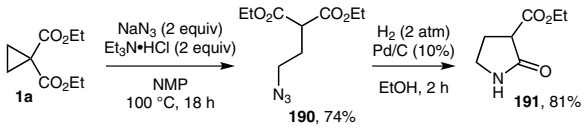
Scheme 106 Ring opening of spiro-cyclopropanes with the azide ion

Seebach et al. conducted a similar reaction, employing 1-nitrocyclopropane-1-carboxylate **21**.[67] In this case, complete conversion of **21** into acyclic azide **189** required heating at 60 °C in DMF (Scheme 107).



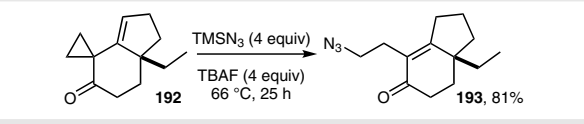
Scheme 107 Ring opening of 1-nitrocyclopropane-1-carboxylate with the azide ion

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 $Et_3N{\cdot}HCl$, **1a** was not converted into **190**. The reduction of azide **190** was accompanied by γ-lactamization, yielding pyrrolidone **191**.



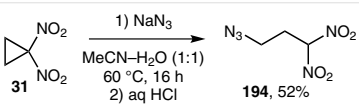
Scheme 108 Conversion of diethyl cyclopropane-1,1-dicarboxylate into a pyrrolidone via nucleophilic ring opening with the azide ion followed by reductive cyclization

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]



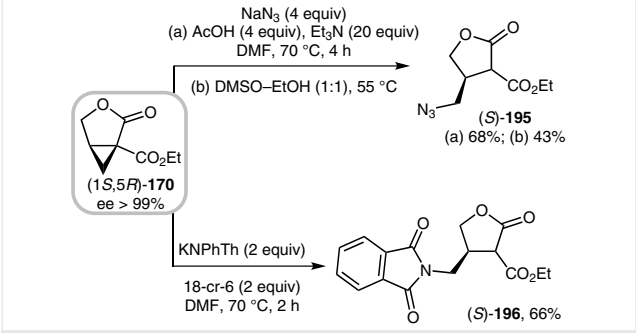
Scheme 109 Ring opening of a ketocyclopropane with the $TMSN_3$/TBAF system

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]



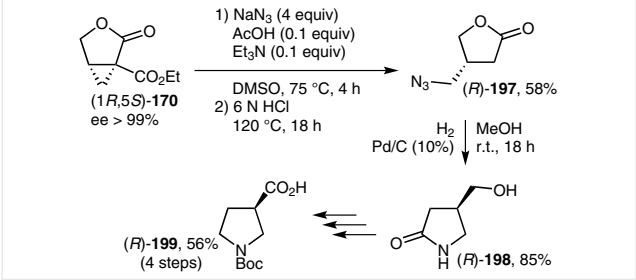
Scheme 110 Ring opening of 1,1-dinitrocyclopropane with the azide ion

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**.



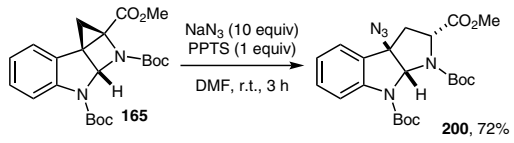
Scheme 111 Synthesis of optically active γ-butyrolactones

On this basis, the Lee group synthesized optically pure *N*-Boc-β-proline **199** (Scheme 112).[159]



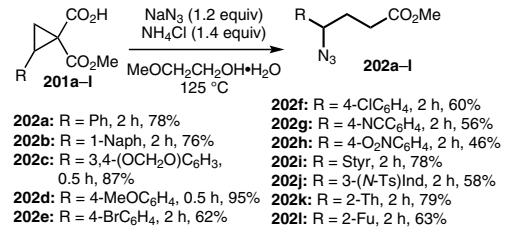
Scheme 112 The synthesis of *N*-Boc-β-proline

Nucleophilic ring opening of the highly strained DA cyclopropane **165** by the azide ion yielded azidopyrroloindoline **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.



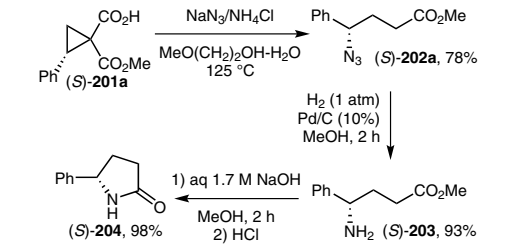
Scheme 113 Ring opening of a highly strained DA cyclopropane with the azide ion

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-diesters did not react with sodium azide under these conditions.



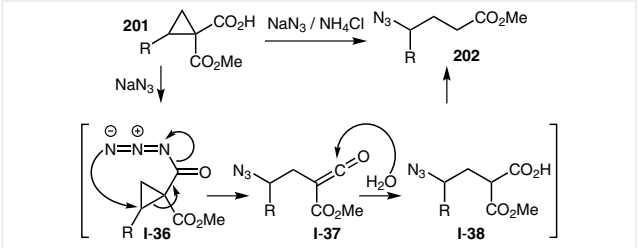
Scheme 114 Ring opening of cyclopropanecarboxylic acids with the azide ion

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 $[\alpha]_D$ of **202a** was compared that determined for optically active lactam **204** (Scheme 115).



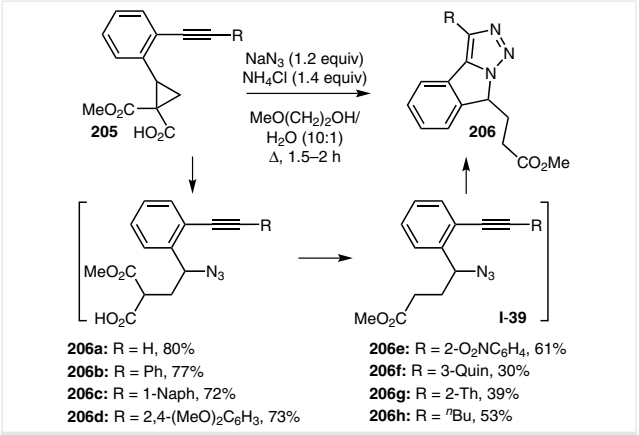
Scheme 115 Conversion of (*S*)-**201a** into pyrrolidone (*S*)-**204**

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.



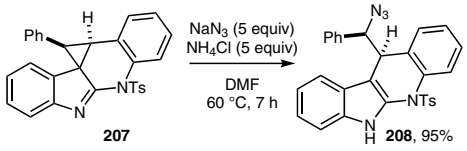
Scheme 116 Proposed mechanism for the transformation of **201** into **202**

2-(*o*-Alk-1-ynylphenyl)cyclopropane-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]



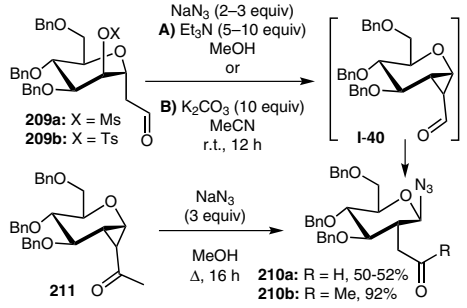
Scheme 117 Cascade transformation of DA cyclopropanes into tricyclic triazoles

Activated cyclopropane **207**, wherein the amidine fragment of the indoloquinolinic system acts as an EWG, underwent diastereoselective ring opening upon treatment with NaN_3/NH_4Cl (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 S_N2-like.



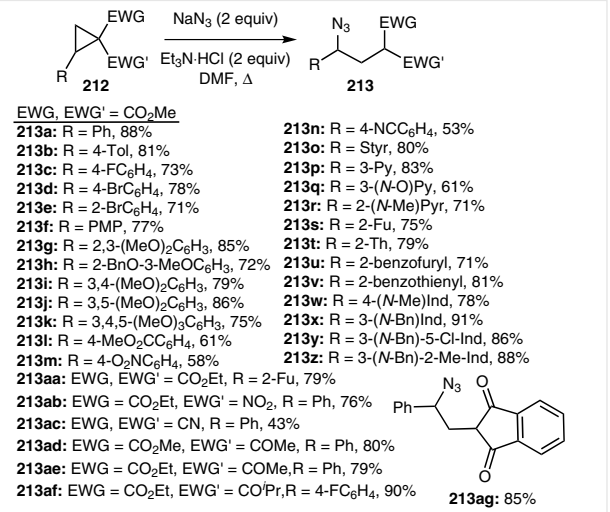
Scheme 118 Ring opening of an activated cyclopropane by the azide ion by an S_N2-like mechanism

The Zou group examined the nucleophilic ring opening of activated cyclopropanes annulated to glucopyranoside.[163,164] Ring opening of unstable cyclopropanecarbaldehyde **I-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.



Scheme 119 Ring opening of carbonyl-substituted DA cyclopropanes with the azide ion

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.[165–167] 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 ester, acyl, nitro, and cyano groups as EWG with the azide ion (Scheme 120).[165] The experimental data showed that the reaction proceeded via an S_N2-like mechanism with reversal of configuration at the electrophilic center of cyclopropane **212**.[165] We localized S_N2-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.



Scheme 120 Ring opening of DA cyclopropanes with the azide ion

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.

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