Synthetic Methods

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A New Golden Age for Donor–Acceptor Cyclopropanes

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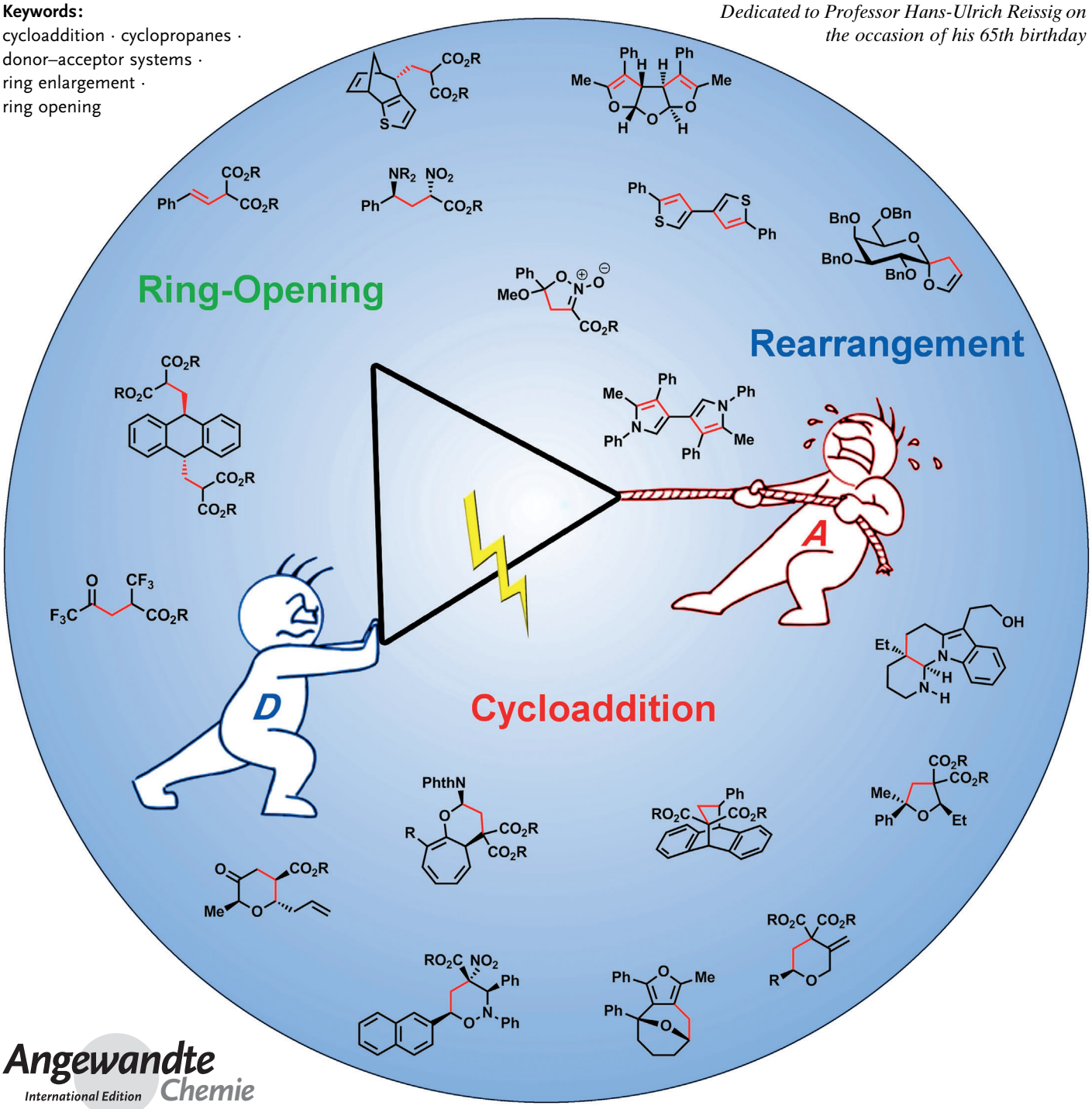
cycloaddition · cyclopropanes · donor–acceptor systems · ring enlargement · ring opening

Dedicated to Professor Hans-Ulrich Reissig on the occasion of his 65th birthday



The effective use of ring strain has been applied to considerable advantage for the construction of complex systems. The focus here is directed towards cyclopropanes as building blocks for organic synthesis. Although thermodynamics should take the side of synthetic chemists, only a specific substitution pattern at the cyclopropane ring allows for particularly mild, efficient, and selective transformations. The required decrease in the activation barrier is achieved by the combined effects of vicinal electron-donating and electron-accepting moieties. This Review highlights the appropriate tools for successfully employing donor–acceptor cyclopropanes in ring-opening reactions, cycloadditions, and rearrangements.

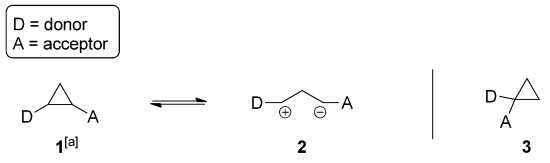
From the Contents

1. Introduction

In the teaching of the basics of organic chemistry there is a *cantus firmus* to decrease strain energy in molecular systems or at least not to create too much thereof. This basic rule, which is naturally based on thermodynamic considerations, serves for understanding many organic reactions. Of course, chemists are also able to prepare highly strained systems, such as cyclopropanes with a ring strain of about 115 kJ mol^{-1}.[1] This, however, often requires substrates which are even higher in energy, such as carbenes, carbenoids, or diradicals.[2] It may be summarized briefly and concisely that cyclopropanes are very high in energy. At the same time, the C–C bonds of this molecule are rather kinetically inert and despite its strain, the molecule does not tend to give up on its cyclic structure. This fact is a prime example for illustrating the essential role kinetics plays in determining reactivity. Cyclopropanes will volountarily undergo reactions such as vinylcyclopropane–cyclopentene rearrangements if given the opportunity. Either a diradicaloid (proceeding via a stabilized intermediate allyl radical) or a concerted mechanism are discussed for this type of reaction.[3] The C–C bond of the cyclopropane may be cleaved even more easily when donors and acceptors are installed in vicinally at the three-membered ring system. When speaking of donor–acceptor (D-A) cyclopropanes, one usually has compounds of type **1** in mind. A geminal substitution of the donor and acceptor, as in compound **3**, is of very little synthetic relevance, even though compounds of type **3** display important structural elements, for example, as amino acids for medicinal chemistry,[4] and play a role in the synthesis of the phytohormone ethene (Scheme 1).[5] The rather weak chemical bond between the donor- and acceptor-substituted carbon atoms of the cyclopropane, which can readily be cleaved heterolytically, may easily be rationalized by a zwitterionic relationship **2**, in which the negative charge is stabilized by the acceptor while the positive charge is stabilized by the donor. This push–pull effect induces a high polarization of the C–C bond, which allows for a multitude of different reactions.[6]

The first investigations on activated cyclopropanes, which at the time were prepared only bearing acceptor groups instead of the typical vicinal donor–acceptor pattern used nowadays, were carried out in the 1960s and 1970s.[7] The research groups of Wenkert and Reissig were responsible for the arrival of a first golden age for D-A cyclopropanes in the 1980s[8] and it was Reissig who termed these entities donor–acceptor cyclopropanes.[8d] All the fundamental types of reactions were reported during this period. They become understandable only when taking the 1,3-zwitterionic relationship into account. Reactions with electrophilic substrates formally lead to the formation of homoenolate products, while conversions with nucleophilic substrates lead to homoconjugated addition products. Saturated or partially unsaturated five-membered ring systems are formed in reactions with systems bearing double or triple bonds (Scheme 2). On the other hand, many acceptors allow the transfer of the negative charge from the C atom, where it was once located, to the acceptor, which leads to the insertion of the acceptor in rearrangement reactions.

For some years now, D-A cyclopropanes have experienced an unexpected renaissance. Formerly uninvestigated donors and acceptors (or their combinations) are in the focus of ongoing investigations, as well as being possibilities for enantioselective transformations, where their very special reactivity can be used as a key step in the total synthesis of various natural products. This Review aims to prove that D-A



[a] Usually *trans*-derivatives are used in case of 1,2-disubstituted cyclopropanes.

Scheme 1. Zwitterionic relationship in vicinally substituted D-A cyclopropanes **1** as well as geminal substitution in three-membered ring **3**.

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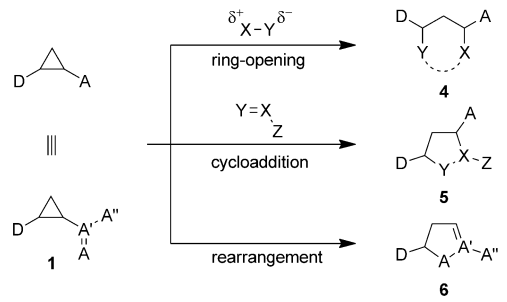


Scheme 2. Different types of reactions of D-A cyclopropanes **1**.

cyclopropanes have indeed reached a second golden age by portraying the most recent developments in this rapidly evolving field.

2. Ring-Opening Reactions

2.1. Ring-Opening Reactions with Nucleophiles

The most basic transformation of a D-A cyclopropane one can imagine is its transformation into an open-chain system. This allows ready access to 1,3-bifunctionalized derivatives. Such ring-opening reactions are usually conducted under Lewis acid catalysis, with the positive charge often captured by heteroatom-containing nucleophiles or electron-rich arenes. The negative charge next to the acceptor substituent is typically neutralized by a proton. The resulting structures have already found widespread application in the synthesis of biologically active molecules.[9]

2.1.1. Addition of Heteroatom Nucleophiles

The opening of enantiomerically enriched D-A cyclopropanes by nucleophilic attack gives rise to the question of whether their enantiomeric excess is retained during this transformation. Studies on ring-opening reactions of aryl-substituted 1-nitrocyclopropanes with heteroatom-containing nucleophiles conducted by Charette and co-workers revealed that a complete retention of the *ee* value is possible in the products **7a** and **7b**. On the one hand, the research group was able to perform reactions of doubly activated cyclopropanes with a variety of phenols by using multiple equivalents of caesium carbonate as a base (Table 1, entry 1).[10] On the other hand, the synthesis of amino-functionalized acyclic products based on enantiomerically enriched D-A cyclopropanes could be achieved by using primary or secondary amines (mostly aniline derivatives) and catalytic amounts of $Ni(ClO_4)_2$ as a Lewis acid (Table 1, entry 2).[11]

A very efficient $TiCl_4$-mediated ring-opening reaction of glycal-based D-A cyclopropanes yielded O,O-acetals **7c** by installing primary alcohols such as methanol, phenol, and allyl alcohol. Yu and Pagenkopf used thiols to successfully carry out a stepwise synthesis of 2-sulfanylpyrans **7d**, which may find application as glycosyl donors in the synthesis of carbohydrates (Table 1, entry 3).[12] Another possibilty to accomplish the synthesis of 1,3-functionalized acyclic products is through the reaction of cyclopropane hemimalonates with ammonium azide. It is assumed that the formation of the carboxyl azide is the initial step in this conversion. This should then be followed by the transfer of the azide to the donor-substituted carbon atom of the cyclopropane through a [3,3] sigmatropic rearrangement, during which a ketene is formed as an intermediate. Under aqueous conditions this intermediate is transformed back into the carboxylic acid and then decarboxylates thermally. Studies on the complete hydrogenation of the obtained azides **7e** to yield esters of γ-aminobutyric acid as well as cyclizations to yield γ-lactams could be carried out successfully (Table 1, entry 4).[13a]

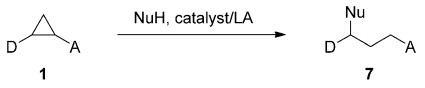
Ring-opening reactions of D-A cyclopropanes have also been established as a method for glycosylation. 3-Ketosubstituted glycal derivatives with an annelated cyclopropane in the 1,2-position undergo reactions with alcohols, in which the six-membered rings of the pyranoses are transformed into sugars containing seven-membered-ring systems.[14]

Daniel B. Werz received his diploma (2000) and PhD (2003, Prof. R. Gleiter) from the University of Heidelberg supported by a scholarship of the Studienstiftung des deutschen Volkes. After postdoctoral research at the ETH Zurich (Prof. P. H. Seeberger) he began his independent research at Georg-August University Göttingen in 2006 (mentor of the habilitation: Prof. L. F. Tietze). Since 2013 he has been associate professor of organic chemistry at the Technical University Braunschweig. His research interests include carbohydrates as well as donor–acceptor-substituted cyclopropanes and investigations concerning catalysis.

Tobias F. Schneider received his diploma in chemistry from Georg-August University in Göttingen with a thesis on oligoannelated THF moieties in 2009. He then carried out PhD studies under the supervision of Prof. Daniel B. Werz on the reactivities of donor–acceptor cyclopropanes as well as synthetic approaches towards tetracoordinated oxygen. He completed his PhD in 2013 and now works as a scientific co-worker in the group of Prof. Daniel B. Werz at the University of Braunschweig.

Johannes Kaschel studied chemistry at the Georg-August University in Göttingen where he received his diploma in 2009. During his PhD (2010–2013) under the supervision of Prof. Daniel B. Werz he focused on rearrangements of donor–acceptor cyclopropanes. After a short stay at the Technical University of Braunschweig he is now carrying out postdoctoral studies in the group of Prof. Richmond Sarpong at UC Berkeley/USA.

Table 1: Ring-opening reactions with heteroatom nucleophiles.[a]



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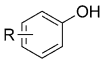
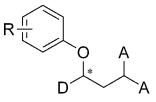
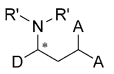
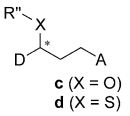
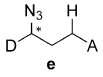
Entry	D	A	Nu	Cat./LA	Main product (**7**)	Max. yield, *de*, *ee*
1[10]	aryl	NO_2, CO_2Me		Cs_2CO_3	 **a**	84%, –, 95% *ee*[b]
2[11]	aryl	NO_2, CO_2Me	HNR'_2	$Ni(ClO_4)_2$	 **b**	94%, –, 92% *ee*[b]
3[12]	*O*-glycal	CO_2Me/Et	R″XH	$TiCl_4$	 **c** (X = O) **d** (X = S)	84%, –, –
4[13a]	aryl	CO_2Me, CO_2H	NH_4N_3[c]	–	 **e**	95%, –, 90% *ee*[b]

[a] Aryl = H/Cl/Br/OMe/NO_2-Ph, 1-naphthyl, styryl; R = *o*/*p*-OMe, *m*-NHBoc, *m*-Cl, *o*-Br, *p*-CF_3; R′ = H, Alk, H; R″ = Me, Ph, Bn, allyl. Bn = benzyl, Boc = *tert*-butoxycarbonyl, Nu = nucleophile, LA = Lewis acid. [b] Use of enantiomerically pure cyclopropanes. [c] Generated in situ from NaN_3 and NH_4Cl.

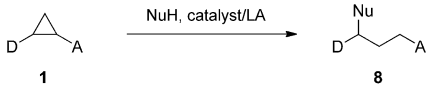
some cases was only successful when carried out under very high pressure (13 kbar; Table 2, entry 2).[13c] At the same time, Waser and co-workers broadened the scope of indole-induced ring-opening reactions by making them also applicable to acceptor-substituted amino cyclopropanes (Table 2, entry 3), even though a D-A cyclopropane carrying a phthalimido donor had been employed in a reaction before under similar conditions without any success. Alkylation at the 3-position was made possible by utilizing $Sc(OTf)_3$ as a Lewis acid to yield **8c** from a variety of substrates. Alkylation with 3-substituted indole derivatives was only observed in the 2-position, as in product **8d**.[16] Furan and pyrrole could also be used in $Sc(OTf)_3$-catalyzed reactions, as shown by Reiser in a highly complex multicomponent reaction that yielded pyrrolidinones.[17]

The conversion of D-A cyclopropanes in the presence of $TiCl_4$ with subsequent addition of allyl trimethylsilanes results

2.1.2. *Addition of Carbon Nucleophiles*

Among the variety of carbon nucleophiles, electron-rich arenes such as indole play a special role. Friedel–Crafts alkylations involving the ring-opening reactions of D-A cyclopropanes usually occur at the 3-position of the indole moiety. Most recent studies in this field are based upon investigations performed by Kerr and co-workers on the indole-induced bond cleavage of D-A cyclopropanes.[13b,c] Subsequent studies by Johnson showed that control could be exerted over the stereocenter formed in this reaction by employing a pybox ligand (pybox*), which enforces a chiral environment upon the Lewis acid MgI_2. The D-A cyclopropanes, which are used as racemic mixtures, are converted into products **8a** with *ee* values of up to 94% by dynamic kinetic resolution (Table 2, entry 1).[15] In 2011, further investigations proved that when employing hemimalonates, that is, substrates with a geminal substitution with ester and acid groups, an additional activation of the carbonyl acceptor is achieved through formation of intramolecular hydrogen bonds. This catalyst-free route to 1,3-functionalized indole derivatives **8b** with remarkable yields in

Table 2: Ring-opening reactions of carbon nucleophiles.



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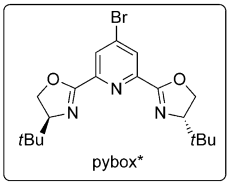
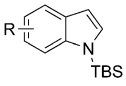
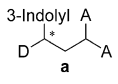
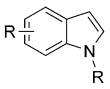
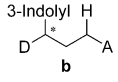
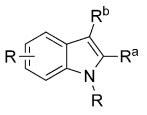
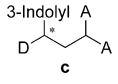
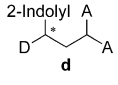
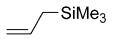
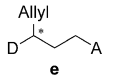
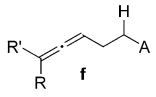
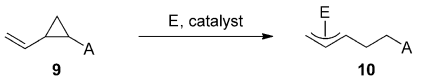


Entry	D	A	Nu	Cat./LA	Main product (**8**)	Max. yield, *de*, *ee*
1[15]	aryl, styryl	2 × CO_2Me		(pybox*)MgI_2	 **a**	96%, –, 94% *ee*[a]
2[13c]	aryl	CO_2Me, CO_2H		–	 **b**	94%, –, –
3[16]	amine	2 × CO_2CHCF_3		$Sc(OTf)_3$	 **c**  **d**	97%, –, –[b] 91%, 88% *de*, –[c]
4[18]	*O*-glycal, OMe	CO_2R		$TiCl_4$	 **e**	87%, 82% *de*, –
5[19]		2 × CO_2Me	R′X	CuCN	 **f**	92%, –, 96% *ee*[a]

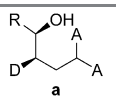
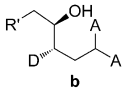
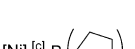
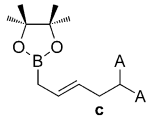
[a] Use of enantiomerically pure cyclopropanes. [b] R^a = H, Alk, R^b = H. [c] R^a = H, $R^b \neq$ H.

in direct allylation in high yields, albeit with rather low selectivity (Table 2, entry 4). Therefore, glycal-based systems as well as some sterically less-demanding three-membered rings with oxygen donors were treated with Lewis acid. The formation of oxocarbenium ions has been postulated. These ions then act as electrophiles and are attacked by the allyl residue, thereby leading to the formation of products **8e**.[18] Besides the commonly observed 1,3-additions, a ring-opening reaction leading to a 1,5-addition was recently carried out. The starting point was an alkyne-substituted cyclopropane, which was treated with an in situ generated organocuprate, thereby establishing a synthetic route towards trisubstituted allenes such as **8f** (Table 2, entry 5).[19]

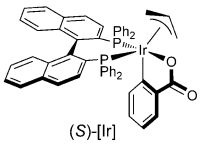
Table 3: Transition-metal-catalyzed ring opening with electrophiles.

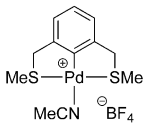


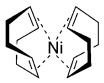
9 **10**

Entry	D	A	E[a,b]	Cat./LA	Main product (**10**)[a]	Max. yield, *de*, *ee*
1[20]	vinyl	2×CO_2Me		(*S*)-[Ir],[c] K_3PO_4	 **a**	89%, 90% *de*, 98% *ee*
2[21]	vinyl	2×CO_2Et		[Pd],[c] $B_2(pin)_2$ *p*-TsOH	 **b**	74%, 100% *de*, –
3[22]	vinyl	H/CO_2Alk/Ac	$B_2(pin)_2$	[Ni],[c]  K_3PO_4	 **c**	85%, 90% *de*, –

[a] R = Ph, piperonyl, styryl, *n*-octyl. [b] E = electrophile.
[c]


(*S*)-[Ir]


[Pd]


[Ni]

2.2. Ring-Opening Reactions with Electrophiles

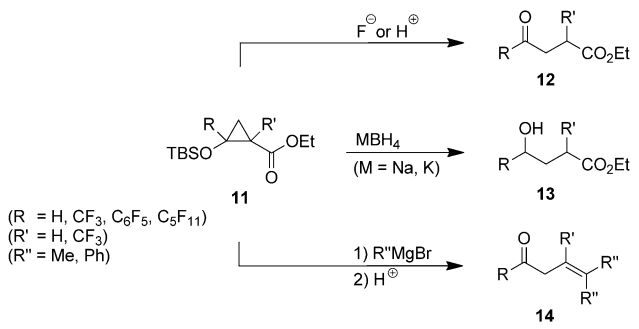
Ring-opening reactions of D-A cyclopropanes with suitable electrophiles—similar to the analogous reactions employing nucleophiles—are another elegant way to synthesize 1,3-substituted acyclic systems. Most recent developments in this field include transition-metal-catalyzed ring-opening reactions of acceptor-substituted vinylcyclopropanes **9**. Therein a nucleophilic π-allyl-metal complex is formed which can undergo further reactions with electrophiles such as carbonyl compounds. The polarity of the donor-substituted carbon atom is formally reversed during this reaction, thus allowing for nucleophilic reactivity.

Krische and co-workers succeeded in effectively employing aldehydes and in some cases even alcohols (which were first dehydrogenated to form aldehydes) as electrophilic coupling partners and conducting these reactions enantioselectively. Iridium complexes based on binap were found to be suitable catalysts for the diastereo- and enantioselective synthesis of homoallylic alcohols **10a**. The thus-obtained products were then directly converted into disubstituted δ-lactones (Table 3, entry 1).[20] Further important insight into this field was gained from studies by Szabó and co-workers on the stabilization of allylic systems by palladium pincer complexes. A prominent example is the reaction of vinylcyclopropane **9** with a palladium catalyst and equivalent amounts of bis(pinacolato)diboron ($B_2(pin)_2$) shown in Table 3, entry 2. The subsequent conversion to afford products **10b** could be achieved by utilizing various aldehydes, which were generated in situ from the corresponding acetals and catalytic amounts of *p*-toluenesulfonic acid (*p*-TsOH).[21] On the basis of these results, vinylcyclopropanes **9** were also optimized for application in [Ni(cod)$_2$] (cod = 1,5-cyclooctadiene) induced borylation reactions, wherein multiple equivalents of base were needed for activation of the diboron derivative. In analogy to the palladium-catalyzed reactions described before, this transformation makes allylic boronic acid esters **10c** accessible with high *E* selectivity, with the desired 1,5-addition taking place exclusively (Table 3, entry 3).[22]

2.3. Ring-Opening Reactions by Activation of the Donor or Acceptor

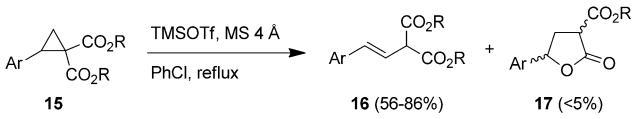
Ring-opening reactions, in which the intermediate is stabilized neither by the addition of nucleophiles nor by conversion with electrophiles, can be initiated by choosing suitable Lewis or Brønsted acids or by deprotection of silyloxy donors. The latter was clearly the focus of recently presented investigations by Gladow and Reissig. By using D-A cyclopropanes **11** as starting materials they achieved the synthesis of γ-ketoesters **12** by a fluoride- or proton-induced deprotection of the silyl group, as well as the direct synthesis of the corresponding hydroxyesters **13** by conversion with metal hydrides. The use of Grignard reagents led to the transformation of compound **11** into a tertiary alcohol, which was then converted into the β,γ-unsaturated ketone **14** by acid catalysis (Scheme 3).[23] Furthermore, such derivatives of three-membered rings are ideal precursors for γ-lactones. Conversion with hydrazine enables the synthesis of dihydropyrazinones, whereas 1,4-formyl ester **12** (R = H) can be employed to obtain a variety of porphyrin analogues.[24,25]

The activation of a carbonyl acceptor of aryl cyclopropanes **15** by using stoichiometric amounts of trimethylsilyl trifluoromethanesulfonate (TMSOTf) as the Lewis acid or catalytic amounts of Sn(OTf)$_2$ facilitates the synthesis of



Scheme 3. Different types of ring-opening reactions based on TBS-protected cyclopropyl ether **11** according to Gladow and Reissig. TBS = *tert*-butyldimethylsilyl.

styryl malonates **16** (Scheme 4). By utilizing various aromatic donors, Melnikov and co-workers were able to obtain a variety of (*E*)-propene derivatives in yields of 56–86 %.[26] Ring-enlargement reactions were often observed to occur as side reactions. Therein, incorporation of the ester functionality is probably the first step, followed by hydrolysis of the formed acetal to give the γ-butyrolactone **17**.



Scheme 4. Ring-opening reactions for the synthesis of (*E*)-styryl malonates **16** according to Melnikov and co-workers.

The improved donor properties of a hydroxy group generated by cleavage of the ester group and the thus-initiated ring opening were utilized as key steps in the total synthesis of several natural products by Reiser and co-workers.[27] This sequence was recently employed in the synthesis of both enantiomers of the natural product arteludovicinolide A (**21**). The oxalylic acid ester **19** was selectively converted with base into the corresponding alcoxide, which carries a vicinal electron-withdrawing ester substituent. Ring opening gave the corresponding carbaldehyde **20**, which retains the steric information almost completely. The natural product **21** was successfully synthesized in only nine steps starting from furan derivative **18** (Scheme 5).[28]

An in situ formed heterovinyl donor has been used in a tungsten(0)-catalyzed cyclodimerization. This route enabled bicycles with annelated three-membered rings bearing an alkyne residue as in **22** to be transformed into dihydrobenzofurans and -indoles. Sarpong and co-workers postulated the formation of metal-vinylidene species **23** from the tungsten complex $W(CO)_5$·THF and a terminal alkyne. Proto-demetalation of the zwitterionic intermediate **24** would lead to the tricyclic intermediate **25**. As the final step, ring opening of the cyclopropane, which bears both an ester acceptor and a formal heterovinyl donor, results in the formation of the isomerization product **26**. After a final proton transfer and aromatization of the five-membered ring, the corresponding heterocycles **27** are obtained almost quantitatively (Scheme 6).[29]

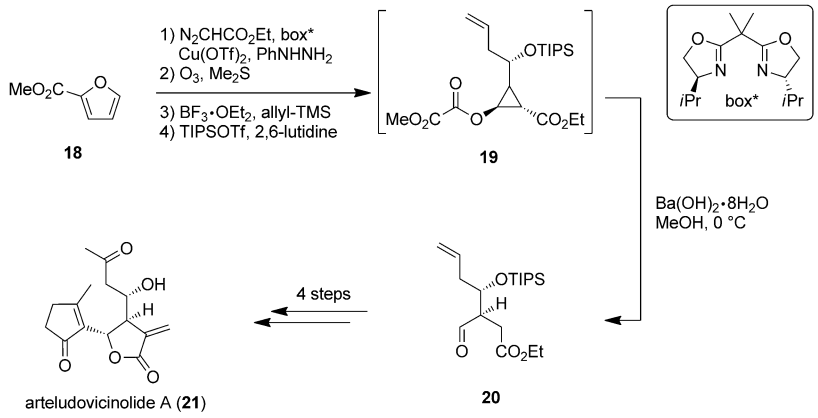
2.4. Cyclodimerizations

In all the reactions mentioned in the previous sections, the D-A cyclopropanes were opened to give acyclic systems. Investigations on Lewis acid induced ring-opening reactions of 2-aryl cyclopropane-1,1-dicarboxylates showed that small amounts of a dimerization product with two three-membered rings were formed.[26] Optimization studies revealed that highly concentrated solutions and often even high reaction temperatures favor cyclodimerizations. Cyclopentanes or cyclohexanes are formed, depending on the mode of cyclization. A multitude of highly substituted cyclic ring systems as well as indanes and dihydroanthracenes are accessible by choosing suitable starting materials.

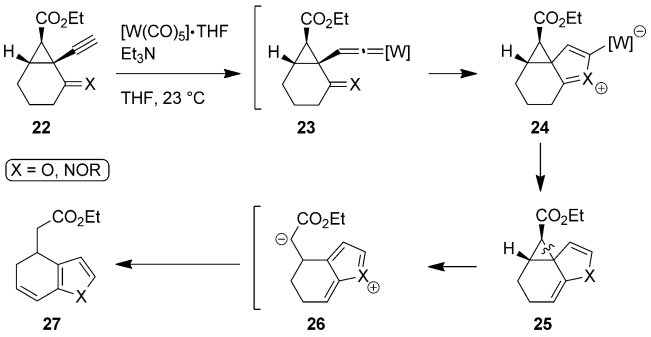
2.4.1. [3+2] Cyclodimerizations

In [3+2] cyclodimerizations two three-membered rings react to form a cyclopentane derivative. One of the cyclopropanes undergoes isomerization to form an open-chain alkene **31**, while the second equivalent of D-A cyclopropane **15** acts as a zwitterionic synthon **28** and reacts with the alkene (Scheme 7). Performing this reaction in the presence of catalytic amounts of Lewis acids such as $Sn(OTf)_2$ or $Yb(OTf)_3$ in chlorobenzene under reflux conditions gave optimal results. The desired cyclodimerization products **32** were obtained exclusively in yields of 50–80 %.[30]

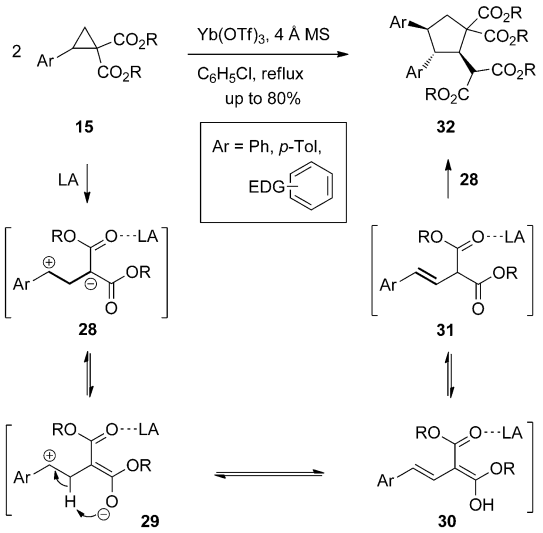
Aryl residues bearing a strong electron donor, such as alkoxy or amino groups, were employed most successfully in these reactions, whereas phenyl or *p*-toluyl substituents already led to a significant increase in the reaction time needed for full conversion. In some cases their use even caused a considerable decrease in diastereoselectivity.



Scheme 5. Total synthesis of arteludovicinolide A (**21**) by Reiser and co-workers. TMS = trimethylsilyl, TIPS = triisopropylsilyl.



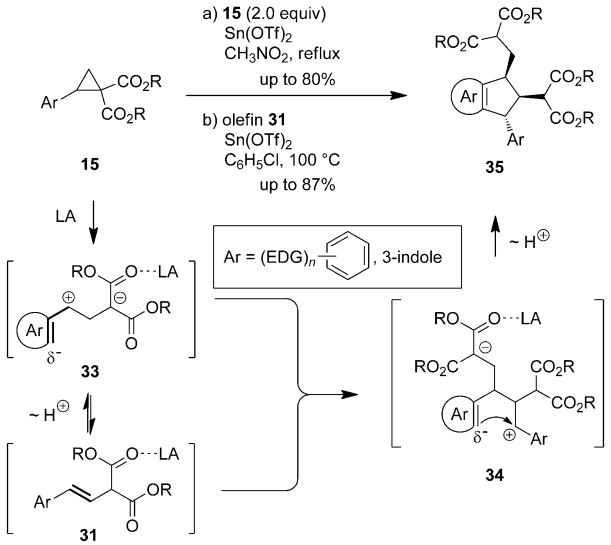
Scheme 6. Proposed mechanism of cyclodimerization to yield 3,4-dihydrobenzofurans and -indols of type **27** according to Sarpong and co-workers.



Scheme 7. Proposed mechanism for the [3+2] cyclodimerization for converting **15** into **32**. MS = molecular sieves, EDG = electron-donating group.

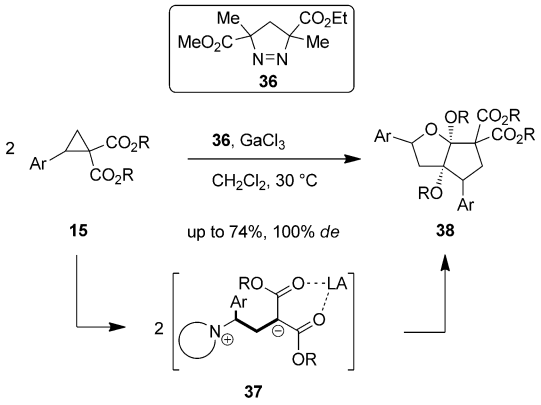
Melnikov and co-workers showed that very electron rich aryl residues such as brenzcatechines allow for an annelation of the formed cyclopentane to obtain indanes and respective heteroarenes. In analogy to the dimerization reactions mentioned before, performing the reaction under conditions a (Scheme 8) leads to bond formation between the zwitterionic species **33** and the in situ generated olefin **31**, thereby resulting in the formation of intermediate **34**. A subsequent Friedel–Crafts alkylation results in the formation of indanes of type **35**. The nucleophilic attack of the aromatic system seems to be favored over a cyclization with the aliphatic residue, which had been observed before. This sequence was expanded by employing nucleophilic heteroarenes such as thiophene, benzofuran, and indole. A crossed version of this cyclodimerization using a variety of aromatic derivatives was also possible, by isolating olefins **31** before performing reactions with D-A cyclopropane **15** (by applying conditions b in Scheme 8).[31]

As recent investigations have demonstrated, it is even possible to include one of the carbonyl groups in the



Scheme 8. [3+2] Cyclodimerization to afford cyclopentane derivatives **35** through annelation of very electron rich arenes.

dimerization process by choosing appropriate conditions. This was made possible by using $GaCl_3$ as a Lewis acidic catalyst as well as a pyrazoline-based organocatalyst **36**, which additionally stabilizes the positive charge in species **37**. Starting from 2-aryl cyclopropane-1,1-dicarboxylates **15** this synthetic strategy provides access to oxabicyclooctanes **38** (Scheme 9).[32]

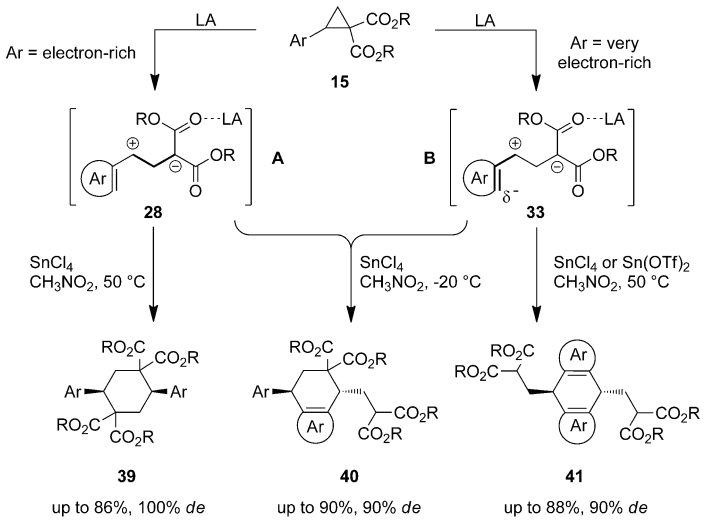


Scheme 9. [3+2] Cyclodimerization to form oxabicyclooctanes **38** in the presence of organocatalyst **36** according to Tomilov and co-workers.

2.4.2. *[3+3] Cyclodimerizations*

The unusual 1,3-zwitterionic relationships that occur during the synthesis of annelated indane systems **35** led to other interesting results. D-A cyclopropanes are not only suitable substrates for [3+2] cyclodimerizations, they can also undergo [3+3] cyclodimerizations. The synthesis of diaryl cyclohexanes **39**, tetrahydronaphthalenes **40**, and in some cases even the synthesis of dihydroanthracenes **41** was achieved starting from the conversion of aryl cyclopropane-1,1-dicarboxylates **15** with strongly activating Lewis acids

such as tin(IV) or titanium(IV) chloride. In all these reactions very electron rich arenes such as substituted methoxybenzenes were employed as the starting material. Cylohexanes and dihydroanthracenes **39** and **41** could be synthesized by utilizing stoichiometric amounts of $SnCl_4$ or catalytic amounts of $Sn(OTf)_2$ in solvents such as nitromethane or chloroform, respectively, at about 50 °C. The formation of anthracene derivatives was only observed in a few cases where special substitution patterns with up to three electron-donating methoxy groups were present (Scheme 10).



Scheme 10. Postulated reaction mechanism for different types of [3+3] cyclodimerizations of electron-rich aryl cyclopropane-1,1-dicarboxylates **15**.

Carrying out the reactions at significantly lower temperatures of −40 °C or −20 °C under the conditions shown in Scheme 10 gave the desired tetrahydronaphthalenes **40** without any side products. Except for the synthesis of cyclohexanes **39**, which is completely diastereoselective, all the reactions could be carried out with selectivities ranging from rather poor 10% up to excellent 90%, depending on the choice of substrates. The thermodynamically favored *trans* isomer was formed in all these reactions. However, the multiple equivalents of Lewis acid required in these conversions as well as the rather unreproducible yields in some of them and the limitation of using electron-rich arenes clearly demonstrate a further need for optimization.[33]

3. Cycloadditions

Cycloadditions of activated D-A cyclopropanes with dipolarophiles, 1,3-dipoles, or dienes are a valuable tool for accessing highly functionalized five-, six-, or seven-membered-ring systems. A very high regioselectivity is observed in all these reactions, as the partially negatively charged center of the reaction partner preferentially attacks the donor-substituted carbon atom of the three-membered ring. Diastereo- and enantioselective reactions are possible when utilizing chiral substrates, chiral Lewis acids, or dynamic kinetic asymmetric transformations. Although a variety of donors have been described for application in these reactions, thus far geminal ester groups have been virtually the only acceptors described.

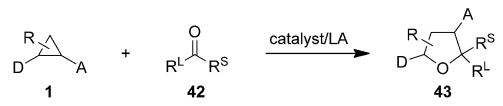
3.1. Cycloadditions with Aldehydes and Ketones

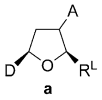
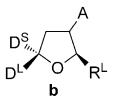
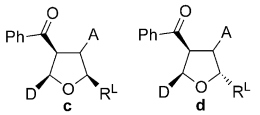
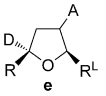
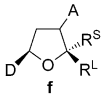
Cycloadditions of D-A cyclopropanes with ketones or aldehydes lead to the formation of THF derivatives. When the first investigations of D-A cyclopropanes were carried out in the 1980s and 1990s, alkoxy groups were almost the only donors used in these reactions.[34] More recently the use of alkyl, aryl, and amino donors has also been reported. Johnson and co-workers observed a high diastereoselectivity in the $Sn(OTf)_2$- or $SnCl_4$-catalyzed reactions of aldehydes with aryl- or alkyl-substituted cyclopropanes, respectively. Therein 2,5-*cis*-configured tetrahydrofurans **43a** were obtained as the main products, which the authors ascribe to an unusual S_N2 mechanism (Table 4, entries 1 and 2).[35] Enantiomerically pure products can be obtained by using enantiomerically pure substrates as well as by employing a dynamic kinetic asymmetric transformation (DyKAT). In this process a (pybox^2*)Mg^{II} catalyst was used, which both mediates the inner transformation of the racemic mixture of the cyclopropyl substrate and also catalyzes the reaction of one of the enantiomers with the aldehyde (Table 4, entry 3).[36] In reactions of D-A cyclopropanes bearing two donors, products **43b** are obtained, in which the sterically more demanding donor (D^L) is in the *cis* position to the residue R^L of the former aldehyde (Table 4, entry 5).[37]

Instead of aryl or alkyl residues, Waser and co-workers used nitrogen as a donor for synthesizing amino-substituted tetrahydrofurans in an iron(III)-catalyzed [3+2] addition of aminocyclopropanes with aldehydes. The diastereoselectivity of this reaction to form 2,5-*cis* products **43a** was again very pronounced when carried out using electron-poor aldehydes (Table 4, entry 4).[38] When $SnCl_4$ was used as the catalyst even ketones could be inserted successfully and a stereoselective preparation of aminotetrahydrofuran derivatives **43f** bearing quarternary stereocenters was possible (Table 4, entry 9).[39]

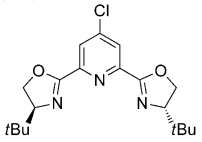
Yang et al. succeeded in synthesizing the 2,5-*trans*-configured products by adding catalytic amounts of $AlCl_3$. The choice of aldehyde, however, turned out to be a crucial factor in determining the outcome of this reaction. Although the use of electronically neutral or electron-poor aryl aldehydes also resulted in the formation of 2,5-*cis* products **43c**, the less-common *trans* products **43d** were obtained when using electron-rich aryl aldehydes (Table 4, entry 6).[40] The formation of 2,5-*trans*-derivatives (with respect to the donor) **43e** was also observed in the Ca^{II}-catalyzed cycloadditions reported by Niggemann and co-workers, in which an alkyne acts as the donor. This result was dependent on neither the steric demand nor on the electronic influence of the residue R in the geminal position to the donor (Table 4, entry 7).[41] Similar results could be obtained when using a Ru^{II} catalyst.

Table 4: Cycloaddition of D-A cyclopropanes with aldehydes and ketones.[a]

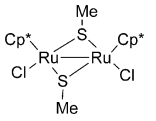


Entry	D	A	Cat./LA	Main product (**43**)	Max. Yield, *de*, *ee*
1[35]	aryl	2×CO_2R	$Sn(OTf)_2$		100%, 98% *de*, 99% *ee*[a]
2[35]	alkyl	2×CO_2R	$SnCl_4$	 **a**	100%, 97% *de*, 96% *ee*[a]
3[36]	aryl, styryl	2×CO_2R	(pybox^{2*})MgI_2		75%, 96% *de*, 94% *ee*
4[38]	NPhth	2×CO_2R	$FeCl_3$ Al_2O_3		99%, 89% *de*, –
5[37]	alkyl, aryl, vinyl, allyl	2×CO_2R	$Sn(OTf)_2$	 **b**	91%, 94% *de*, 86% *ee*[a]
6[40]	aryl	2×CO_2R	$AlCl_3$	 **c** **d** R^L = electron-poor R^L = electron-rich	88%, 97% *de*, 96% *ee*[b]
7[41]	alkynyl	2×CO_2R	$Ca(NTf_2)_2$/ Bu_4NPF_6		95%, 94% *de*, –
8[42]	alkynyl	2×CO_2R	{Cp*RuCl-(η^2-SMe)}$_2$ BF_3 OEt_2	 **e**	88%, 33% *de*, –
9[39]	NPhth	2×CO_2R	$SnCl_4$	 **f**	99%, 90% *de*, –

[a] Cp* = C_5Me_5, NPhth = phthalimidoyl, NTf_2 = bistriflylamide. [b] Use of enantiomerically pure cyclopropanes.



pybox^{2*}



{Cp*RuCl-(η^2-SMe)}$_2$

As only terminal alkynes could be used in this process, it might be assumed that a Ru-allenylidene complex is formed as the key intermediate. The proposed mechanism of this reaction differs significantly from those reactions based on Lewis acid catalysis described before. These assumptions are also supported by DFT studies (Table 4, entry 8).[42]

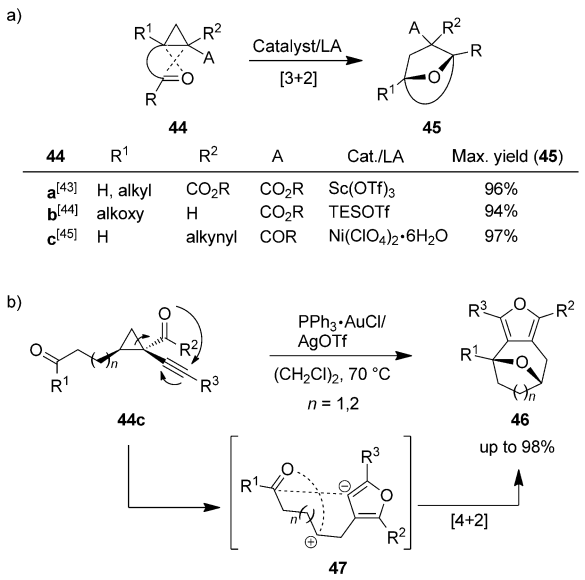
Bicyclic systems **45**, which are a widespread structural motif in natural products, are accessible when [3+2] cycloadditions of this kind are performed in an intramolecular fashion. This idea was implemented by Wang and co-workers in reactions involving alkyl-,[43] alkoxy-,[44] as well as alkynyl-substituted[45] cyclopropanes as starting materials. Although carbonyl substituents were the most commonly used acceptors in these transformations, a very specific catalyst system was required in all cases (Scheme 11 a). The choice of catalyst was particularly crucial for obtaining the desired products when alkynyl-substituted cyclopropanes **44 c** were used as substrates. A [4+2] cycloaddition was observed instead of a [3+2] cycloaddition when a catalyst system consisting of $Ph_3P{\cdot}AuCl$ and AgOTf was chosen for this conversion. The reaction of the geminal carbonyl group with the activated triple bond as the first step of this transformation led to the formation of the furan moiety in **47**. The subsequent [4+2] cycloaddition then furnished the tricyclic product **46** in yields of up to 98% (Scheme 11 b).[45]

The multitude of total syntheses which utilize [3+2] cycloadditions of cyclopropanes as a key step indicates that these reactions are highly reliable transformations with a wide range of applications. Natural products such as (+)-virgatosine,[46] (−)-allosecurinine,[47] (+)-isatisine A,[48] and (+)-polyanthelline A[49] could be prepared successfully by using such cycloadditions.

A different reactivity is observed when tropone derivatives **48** instead of ketones are used in these conversions. The strong zwitterionic character of the tropone system leads to a formal [8+3] cycloaddition and to the formation of bicyclic products **50**. DFT studies support the assumption of a stepwise mechanism, with the zwitterionic compound **51** formed as the main intermediate (Scheme 12). This synthetic strategy was first developed with a nitrogen-based donor,[50] but was later also successfully carried out with a variety of different donors such as aryl, heteroaryl, and vinyl substituents.[51]

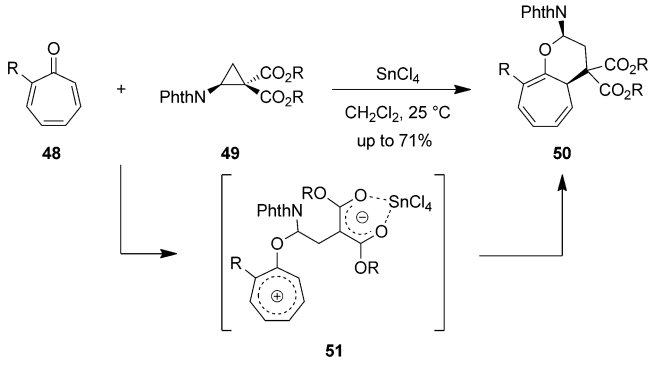
3.2. Cycloadditions with Imines, Oximes, and Hydrazones

Carbonyl compounds undergo [3+2] cycloadditions with D-A cyclopropanes to yield tetrahydrofurans, while the nitrogen-containing heteroanalogous carbonyl systems such as imines and oximes allow for the synthesis of tetrahydropyrroles. MgI_2 was employed as a catalyst for these conversions in the pioneering studies performed by Carreira and co-workers.[52] Later, Carson and Kerr showed that catalytic amounts of $Yb(OTf)_3$ also lead to a formal [3+2] cycloaddition (Table 5, entry 1).[53] A dynamic kinetic process (DyKAT) with a chiral magnesium catalyst even enables an asymmetric synthesis from a racemic mixture of the cyclopropane (Table 5, entry 2).[54] Furthermore, a simple change in the reaction conditions led to the formation of bicyclic 2,5-



44	R^1	R^2	A	Cat./LA	Max. yield (**45**)
a[43]	H, alkyl	CO_2R	CO_2R	$Sc(OTf)_3$	96%
b[44]	alkoxy	H	CO_2R	TESOTf	94%
c[45]	H	alkynyl	COR	$Ni(ClO_4)_2 \cdot 6H_2O$	97%

Scheme 11. a) Synthesis of bicycles of type **45**; b) intramolecular ring-enlargement reactions starting from *gem*-carbonyl-alkynyl-cyclopropanes **44c**.



Scheme 12. Formal [8+3] cycloaddition of D-A cyclopropanes with tropone substrates **48**.

cis products **53c** instead of the usual 2,5-*trans* tetrahydropyrroles **53b**. The order in which the reagents were added proved to be crucial to the outcome of this reaction. The *cis* product **53c** was obtained exclusively when the catalyst was added to the D-A cyclopropane first and the reaction partner second. Adding the reaction partner first and the catalyst second resulted in the *trans* products **53b** (Table 5, entry 3).[55] Intramolecular insertion of an in situ generated hydrazone to afford bicyclopyrazolidines was achieved by $Yb(OTf)_3$ catalysis.[56]

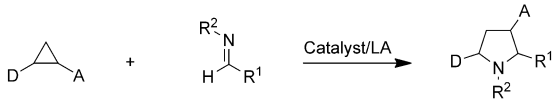
The reactivity of electron-poor pyridine derivatives with D-A cyclopropanes to give indolizines **56** proved to be similar to the reactivity of the commonly used imines. It is remarkable that the pyridine ring exhibits a higher reactivity than the electron-withdrawing group (EWG, for example, a nitrile group; Scheme 13, compare Section 3.4). Although the methoxy group, which acts as the donor in this compound, is already eliminated during the cycloaddition with formation of one double bond, subsequent addition of MnO_2 is necessary to afford full aromatization of the product. Not only pyridine but also electron-poor quinolines could successfully be employed for the preparation of benzoindolizines.[57]

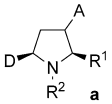
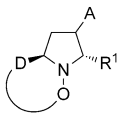
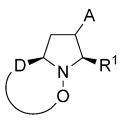
Such a [3+2] cycloaddition was used as the key step in the total synthesis of the alkaloid FR901483 to access the oligocyclic structure.[58]

3.3. Cycloadditions with Enes, Allenes, and Dienes

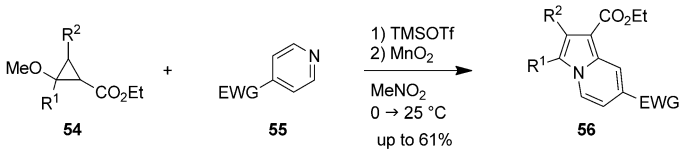
Strongly polarized ene components are required to gain synthetic access to the analogous carbocyclic five-membered-ring systems by [3+2] cycloadditions. Silyl enol ethers or enamines are usually suitable reactants for such transformations. The reaction of arylcyclopropanes with silyl enol ethers catalyzed by Cu^{II} yielded cyclopentanes **57a**, which can, however, also undergo ring-opening reactions in the presence of the catalyst. To prevent this unwanted side reaction, supplementary addition of a bisoxazoline/Zn^{II} complex was necessary (Table 6, entry 1).[59] A similar ring opening was also observed in the reaction of aminocyclopropanes with silyl enol ethers, in which the use of $SnCl_4$ as a catalyst gave the best yields of the desired aminocyclopentanes **57b** (Table 6, entry 2).[60] A high steric demand of the acceptor substituent as well as of the silyl groups turned out to be the determining factors for further improving the diastereoselectivities of these transformations. In combination with DFT studies, these observations led Qu et al. to the assumption that this formal [3+2] cycloaddition is indeed a stepwise reaction, in which the intramolecular cyclization is the second and rate-determining step.[61] Further investigations of this reaction by using chiral bisoxazoline ligands also facilitated asymmetric conversions with an enantiomeric excess of up to 99% *ee* (Table 6, entries 3 and 4).[62]

Table 5: Cycloadditions of D-A cyclopropanes with imines and oximes.



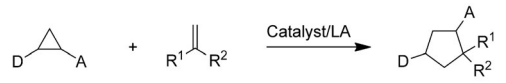
Entry	D	A	Cat./LA	Main product (**53**)	Max. yield, *de*, *ee*
1[53]	aryl	$2\times CO_2R$	$Yb(OTf)_3$	 **a**	96%, 98% *de*, –
2[54]	aryl, styryl	$2\times CO_2R$	$(pybox^{2*})MgI_2$		86%, 98% *de*, 96% *ee*
3[55]	alkyl	$2\times CO_2R$	$Yb(OTf)_3$	 **b**  **c**	99%, 100% *de*, 99% *ee*[a]

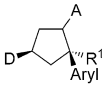
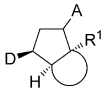
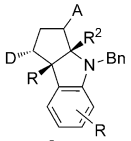
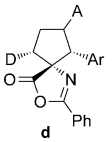
[a] Use of enantiomerically pure cyclopropanes.



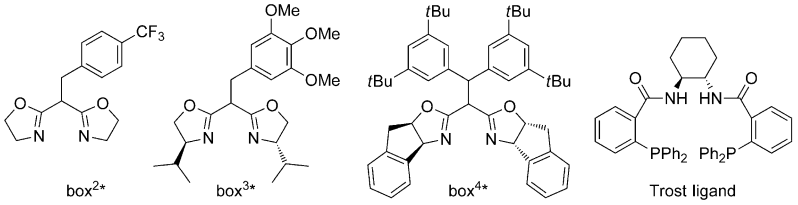
Scheme 13. Cycloaddition of electron-poor pyridine derivatives **55** with D-A cyclopropanes.

Table 6: Cycloadditions of D-A cyclopropanes with enes.



Entry	D	A	R^1	Cat./LA	Main product (**57**)	Max. yield, *de*, *ee*
1[59]	aryl	2×CO_2R	$OSiR_3$	$Cu(SbF_6)_2$ $Zn(box^{2*})_2$	 **a**	99%, 92% *de*, 77% *ee*
2[60]	NR_2	2×CO_2R	$OSiR_3$, alkoxy	$SnCl_4$		99%, 90% *de*, 94% *ee*[a]
3[62]	aryl	2×CO_2R	$OSiR_3$	$CuBr_2$, $AgSbF_6$ box^{2*}	 **b**	95%, 98% *de*, –
4[62]	aryl	2×CO_2R	$OSiR_3$	$Cu(ClO_4)_2$ box^{3*}		94%, 98% *de*, 99% *ee*
5[63]	aryl, vinyl, styryl	2×CO_2R	NR_2	$Cu(OTf)_2$ box^{4*}	 **c**	97%, 96% *de*, 96% *ee*
6[64]	vinyl	2×CO_2R	NR	$[Pd_2dba_3]$ $CHCl_3$[b] Trost ligand	 **d**	87%, 90% *de*, 98% *ee*

[a] Use of enantiomerically pure cyclopropanes. [b] dba = *trans,trans*-dibenzylideneacetone.



Tricyclic products **57c** are accessible by using indoles as reaction partners. As a consequence of its very high diastereo- and enantioselectivity, the aforementioned reaction catalyzed by a Cu^{II}-bisoxazoline complex has been put to excellent use in the syntheses of some natural products (Table 6, entry 5).[63] Furthermore, racemic mixtures of vinylcyclopropanes can be converted into spiro-annelated cyclopentanes **57d** through an asymmetric formal [3+2] cycloaddition by using the Pd^0-(*S,S*)-DACH-Trost complex with prochiral Michael compounds (Table 6, entry 6).[64]

The $SnCl_4$-catalyzed reaction of aryl-substituted cyclopropanes with alkenes led in many cases to a [3+2] annelation, during which the aryl residue was included to give indanes **60**, instead of the expected [3+2] cycloaddition. Products of type **61** were obtained only when less-nucleophilic aryl groups were used as donors or the reaction temperature was lowered to about −30 °C. In some cases the formation of indane derivatives **60** was facilitated by adding BF_3·OEt_2 as the Lewis acid (Scheme 14).[65]

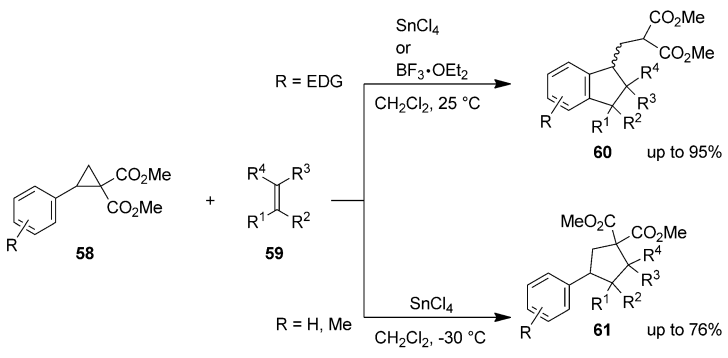
Recently, Wang and co-workers even succeeded in employing allenes as a 2π component in an intramolecular [3+2] cycloaddition. This gave rise to the question which of the two double bonds of the allene would react first and whether such a regioselectivity might be controlled by choosing suitable reaction conditions. One possibility would lead to the formation of bicyclo[3.2.1]octane structures and the other would afford bicyclo[4.3.0]nonane structures. Both scaffolds are widespread structural motifs in natural products. Although allenic substrates **62** gave the products of a parallel cycloaddition in good or even excellent yield in the presence of $Sc(OTf)_3$ as the catalyst, the use of $Yb(OTf)_3$ led to the formation of the crossed product **65** instead (Scheme 15). Cation **63** is expected to be formed as an intermediate during the course of the reaction. Two distinct modes of cyclization can be considered: Pathway a leads to the formation of **64**, whereas pathway b yields the crossed product **65**.[66]

To date, formal [4+3] cycloadditons of D-A cyclopropanes bearing diene moieties have remained limited to using 1,3-diphenylisobenzofurans and anthracenes as reaction partners. Not only does the diene have to be very reactive in Diels–Alder type reactions, but it also has to be sterically hindered in a way that makes it unreactive in possible [3+2] cycloadditions. The predominant formation of the respective *exo* isomer makes it seem plausible that the observed stereochemistry is the consequence of a concerted reaction proceeding under orbital control (Table 7).[67]

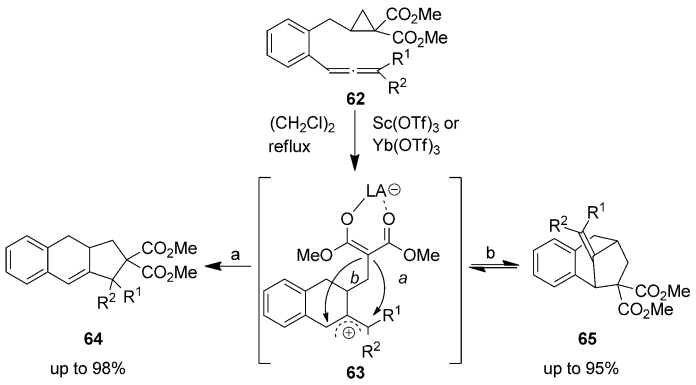
Reactions of heteroaryl-substituted cyclopropanes **68** with cyclopentadiene (**69**) did not give any products of [4+3] cycloadditions, but instead afforded products **70** or **71** resulting from [4+3] annelations. As already observed in reactions with alkenes, these transformations showed that aryl-substituted cyclopropanes act as amphiphilic synthons, with their nucleophilic position not only located in the cyclopropane, but also in the aryl residue (Scheme 16).[68]

3.4. Cycloadditions with Nitriles and Heterocumulenes

While systems bearing double bonds undergo [3+2] cycloadditions to afford saturated five-membered-ring sys-

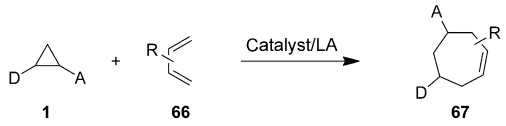


Scheme 14. Reaction of aryl cyclopropanes with alkenes.

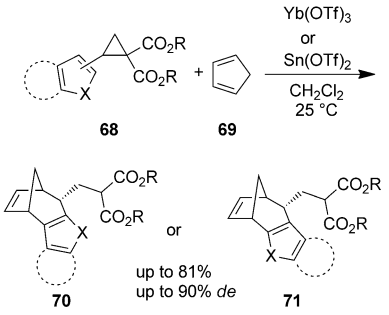


Scheme 15. Intramolecular [3+2] cycloaddition with allenes.

Table 7: Cycloadditions of D-A cyclopropanes with dienes.



Entry	D	A	Cat./LA	Main product (**67**)	Max. yield, *de*, *ee*
1[67]	aryl	2×CO_2R	$Yb(OTf)_3$	**a**	92%, 72% *de*, –
2[67]	aryl	2×CO_2R	$TiCl_4$ *or* $SnCl_4$	**b**	85%, –, –



Scheme 16. [4+3] Annelation by reaction of cyclopentadiene with aryl-substituted cyclopropanes.

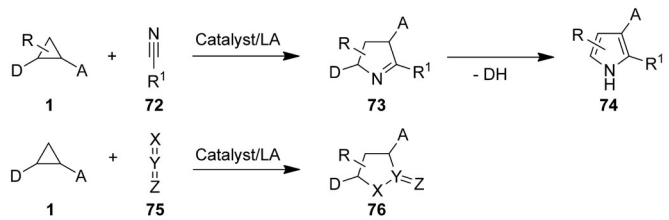
tems, the use of systems with a triple bond makes structures including one unsaturated bond accessible. This approach allows alkoxy-substituted cyclopropanes to be transformed with nitriles to eliminate alcohols and directly yield pyrrole derivatives **74a**, whereas 1-pyrrolines, which are formed when using aryl donors, do not undergo spontaneous aromatization (Table 8, entries 1 and 2).[70] In contrast, the reaction of D-A cyclopropanes with isothiocyanates did not yield any pyrrolidine derivatives, but exclusively led to the formation of thiolactames **76a** (Table 8, entries 3 and 4). NMR spectroscopy was rather unreliable for identifying products, but the products were verified by Stoltz and co-workers by IR and crystal-structure data.[71] Previously, the formation of pyrrolidine-2-thiones had been assumed.[72] Nevertheless, formal [3+2] cycloadditions can lead to the synthesis of nitrogen-containing heterocyclic structures, as demonstrated by employing carbodiimides and isocyanates as reactants (Table 8, entries 5 and 6).[71]

3.5. Cycloadditions with Nitrones and Nitronates

Most of the cycloaddition reactions discussed so far utilized a 1,2-dipole to form a five-membered ring, that is, they are formal [3+2] cycloadditions. When 1,3-dipoles are employed instead, reactions with D-A cyclopropanes lead to formal [3+3] cycloadditions, which result in the formation of six-membered-ring systems. Nitrones and nitronates were used in such reactions, which allowed for the preparation of tetrahydro-1,2-oxazines **78**. The use of the Lewis acid $Yb(OTf)_3$ mainly led to the formation of products in which the substituents in the 3- and 6-positions are in a *cis* arrangement (Table 9, entry 1).[73] The use of MgI_2 results in the formation of significant amounts of the corresponding *trans* products, although the 3,6-*cis* compound still remains the major product in all the transformations. Ganton and Kerr attributed the difference in product formation to a higher kinetic stability of the magnesium malonate compared to the Yb adduct, which increases the probability for the transformation of an open-chain intermediate into a *trans* arrangement of the two substituents (Table 9, entry 2).[74] The nitrone can also be generated in situ from a carbonyl compound and a hydroxylamine in a one-pot synthesis.[75]

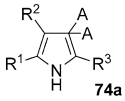
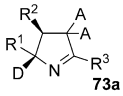
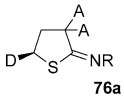
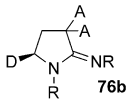
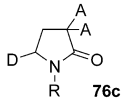
The first enantioselective method for preparing tetrahydro-1,2-oxazines by employing chiral Ni^{II} catalysts was reported by Sibi et al. (Table 9, entry 3).[76] Only a few months later Tang and co-workers succeeded in significantly increasing the observed diastereoselectivity by switching from

Table 8: Cycloadditions of D-A cyclopropanes with nitriles **72** and heterocumulenes **75**.



1 72 73 74

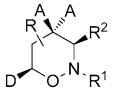
1 75 76

Entry	D	A	Cat./LA	Main product	Max. Yield, *de*, *ee*
1[70]	alkoxy	CO_2R	TMSOTf	 **74a**	98%, –, –
2[70]	aryl	$2\times CO_2R$	$SnCl_4$	 **73a**	90%, 100% *de*, –
3[72]	aryl, vinyl	$2\times CO_2R$	$FeCl_3$	 **76a**	67%, –, –
4[71]	aryl, vinyl	$2\times CO_2R$	$Sn(OTf)_2$		99%, –, 95% *ee*[a]
5[71]	aryl	$2\times CO_2R$	$Sn(OTf)_2$	 **76b**	99%, –, 98% *ee*[a]
6[71]	aryl	$2\times CO_2R$	$FeCl_3$	 **76c**	78%, –, –

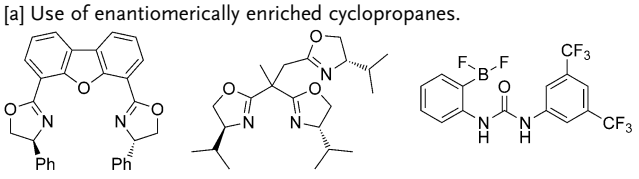
[a] Use of enantiomerically pure cyclopropanes.

Table 9: Cycloadditions of D-A cyclopropanes with nitrones.

1 77 78

Entry	D	A	Cat./LA	Main product	Max. Yield, *de*, *ee*
1[73]	H, aryl, vinyl	$2\times CO_2R$	$Yb(OTf)_3$	 **78**	96%, –, –
2[74]	H, alkyl, aryl, vinyl	$2\times CO_2R$	MgI_2		99%, 88% *de*, –
3[76]	alkyl, aryl	$2\times CO_2R$	(dbfox*)/$Ni(ClO_4)_2$		99%, 88% *de*, 95% *ee*
4[77]	Ph, vinyl, styryl	$2\times CO_2R$	(box[5]*)/$Ni(ClO_4)_2$		99%, 86% *de*, 97% *ee*
5[78]	aryl, vinyl	CO_2R, NO_2	urea*		99%, 33% *de*, 91% *ee*[a]

[a] Use of enantiomerically enriched cyclopropanes.



bisoxazoline-Ni^{II} catalysts to trisoxazoline-Ni^{II} catalysts (Table 9, entry 4).[77]

The most recent results concerning the synthesis of oxazinanes **78** bearing an additional stereocenter in the 4-position were obtained by the simultaneous use of two different acceptor groups. Mattson and co-workers replaced one of the ester groups by a nitro group and carried out the desired reaction in the presence of a urea catalyst (Table 9, entry 5).[78]

Furo[3,4-*d*]-[1,2]oxazepines **82** were prepared by Zhang et al. in a formal [4+3] cycloaddition catalyzed by Au^I using 1-(1-alkynyl)cyclopropylketones **80** and nitrones **79** as the starting materials. It can be assumed that the Au^I catalyst preferentially coordinates to the alkyne and not to the carbonyl acceptor (also compare Scheme 11b). Such coordination leads to the initial formation of the furan unit by nucleophilic attack of the carbonyl group on the vinyl-Au moiety. Subsequent reaction with the nitrone and elimination of the catalyst generate a seven-membered heterocyclic system. If $Sc(OTf)_3$ is used instead as a hard Lewis acid, which preferentially coordinates to the carbonyl group, the familiar reactivity of the alkyne-substituted D-A cyclopropane can be observed to give tetrahydro-1,2-oxazines **81** (Scheme 17).[79]

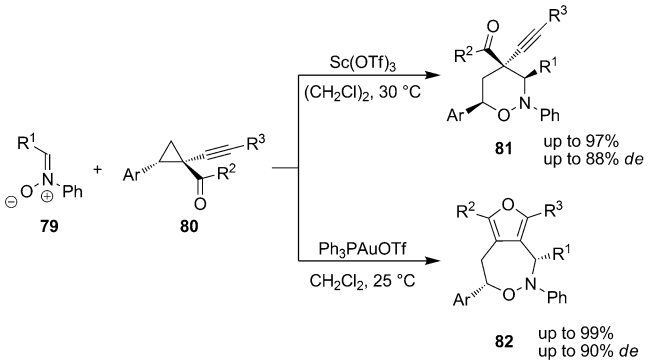
Cyclic nitronates **83** can be used in formal [3+3] cycloadditions to prepare bicyclic nitroso acetales **85** by using $Yb(OTf)_3$ as a catalyst (Scheme 18).[80] Tetrahydro-1,2-oxazines prepared from D-A cyclopropanes and nitrones have played an important role in the synthesis of highly substituted pyrroles[81] as well as in the total synthesis of the complex natural product (+)-nakadomarin A.[82]

3.6. Cycloadditions with Azomethine Imines

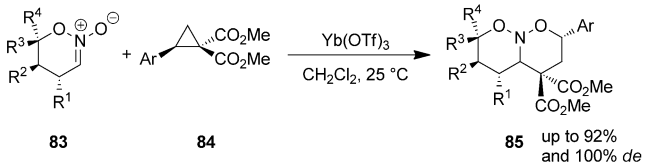
Aromatic azomethine imines are another class of substrates which undergo formal [3+3] cycloadditions with D-A cyclopropanes to afford tetrahydropyrazines. Thus far, *N*-iminoquinoline ylides **86** have been the only substrates employed in this reaction. The resulting dihydroquinoline derivatives **87** could be obtained with high enantioselectivity by using a chiral trisoxazoline ligand (Table 10).[83]

3.7. Formal [3+3] Annelations

Towards the end of this section on cycloadditions we would like to focus on a class of reactions which lead to the

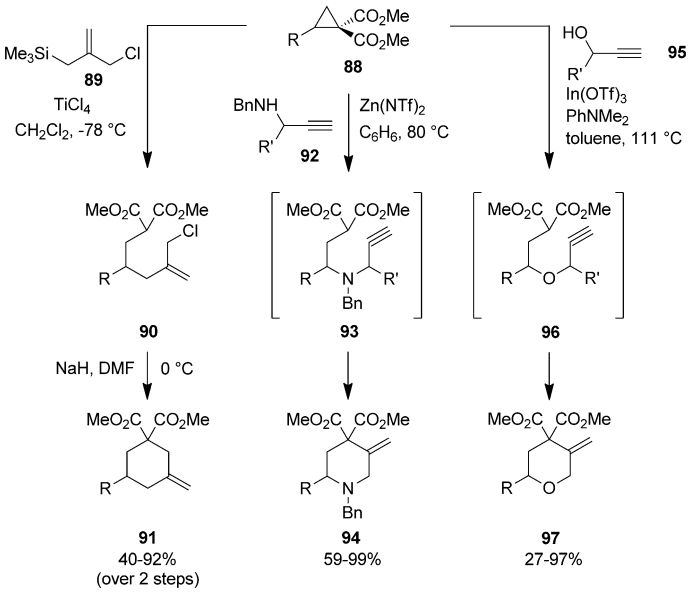


Scheme 17. Preparation of nitrones using *gem*-carbonyl-alkynyl-substituted cyclopropanes **80**.



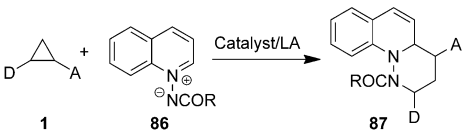
Scheme 18. Synthesis of bicyclic nitroso acetals **85** according to Ioffe and co-workers.

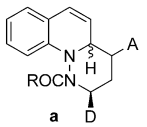
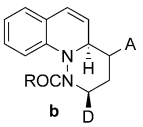
formation of six-membered-ring systems by [3+3] annelation, but always proceed in two steps and in some cases even require the addition of further reagents after the first step. Sapeta and Kerr excelled in this field by preparing substituted cyclohexanes as well as the corresponding piperidines and tetrahydropyrans. One cyclopropane with two ester groups as acceptor and one aryl group as donor was used in each of these conversions. **89** was employed as a synthetic equivalent for trimethylenemethane to obtain cyclohexane derivatives. Ring opening of cyclopropane **88** in the presence of $TiCl_4$ leads to the formation of the open-chain compound **90**, which affords the six-membered ring **91** in the presence of NaH (Scheme 19).[84] Similar transformations could be performed when propargylic amines **92** were used as the substrates in the presence of Zn^{II} salts as catalysts. As a main difference, the intermediate **93** which is formed after ring opening is not isolated but immediately undergoes a Conia-ene reaction to yield piperidine **94**.[85] The analogous reaction of propargylic alcohols **95**, which give the respective tetrahydropyran **97** via intermediate **96**, could also be carried out successfully.[86]

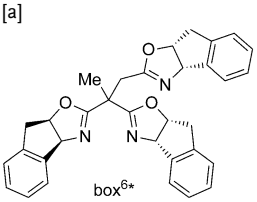


Scheme 19. [3+3] Annelation to yield cyclohexanes, piperidines, and tetrahydropyrans according to Sapeta and Kerr.

Table 10: Cycloadditions of D-A cyclopropanes with *N*-iminochinoline ylides **86**.



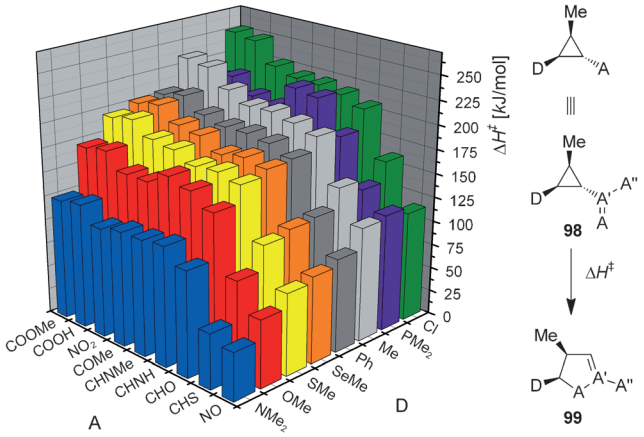
Entry	D	A	Cat./LA	Main product (**87**)	Max. Yield, *de*, *ee*
1[83a]	aryl, vinyl	2×CO_2R	$Ni(ClO_4)_2$	 **a**	84%, 74% *de*, –
2[83b]	aryl, vinyl	2×CO_2R	$Ni(ClO_4)_2$ box^{6*} [a]	 **b**	99%, 90% *de*, 98% *ee*

[a] 

4. Rearrangements

Ring enlargements of D-A cyclopropanes to form a heterocyclopentene are formally heteroanalogous reactions of the vinylcyclopropane–cyclopentene rearrangement discussed in Section 1. Long before the pure CH system was investigated (Neureiter 1959),[87] the first rearrangements of cyclopropylimines (Cloke 1929)[88] and cyclopropylcarbaldehydes (Wilson 1947)[89] had been described. However, these reactions did not find a broad range of applications. One reason for this

fact may be found in the high temperatures (200 °C up to 500 °C) needed for these conversions to overcome the high activation barriers arising from the lack of donor substituents in the substrates. Using D-A cyclopropanes made it possible to perform a multitude of rearrangement reactions under very mild conditions. The first fundamental investigations in this field were carried out by Wenkert and Reissig in the 1980s. More recent studies often utilize Lewis or Brønsted acids, which coordinate to the acceptor group and lead to further activation of the substrate. This causes an intramolecular attack of the acceptor on the donor-substituted carbon atom of the cyclopropane. In many cases, the influence of a very strong acceptor is sufficient to initiate ring-enlargement reactions without any catalyst. Theoretical investigations revealed that nitrogen, chalcogen, and aryl substituents are the most suitable donors, whereas nitroso, carbonyl, and imino groups should be used as the acceptors to effectively lower the activation barrier for the desired rearrangements.[90] The latter two have found broad application, whereas not a single system with a nitroso group has been prepared to date. The activation barrier determined by DFT studies for the ring enlargement of 72 D-A cyclopropanes **98** is shown in Scheme 20. These investigations have also shown that these



Scheme 20. Theoretically calculated activation barriers (without solvent effects) for the rearrangement reaction of different D-A cyclopropanes to heterocyclopentenes (calculations are based on B3LYP/6-311G(d)).

transformations occur in a concerted process when no catalyst is present. The corresponding zwitterionic or biradicaloid intermediates were shown to have higher activation barriers in all cases. For some selected systems the effect of different solvents was also included in the calculations using the PCM model. The model system Me_2N/CHO showed that the activation barrier decreases by 16–41 kJ mol^{-1} as the polarity of the respective solvent increases (toluene, CH_2Cl_2, DMSO).

4.1. Ring Enlargements of Discrete Cyclopropanes

Uncatalyzed vinylcyclopropane–cyclopentene rearrangements require high reaction temperatures. A Ni^0-NHC catalyst lowers the activation barrier for the desired rearrangement, so that the formation of cyclopentenes **100a** become observable at room temperature in most cases (Table 11, entry 1).[91] Even though this example does not resemble a proper D-A cyclopropane it was included here as a native CH system for the sake of completeness. Besides choosing suitable catalysts, installing a donor substituent and employing two geminal acceptors is sufficient to lower the activation barrier of rearrangements. For example, *gem*-nitro-imino-substituted cyclopropanes yield dihydropyrrole derivatives **100b**, which result from rearrangement of the imino substituent (Table 11, entry 2).[92]

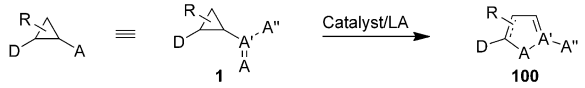
Derivatives of dihydrofuran and furan are obtained in excellent yields when carbonyl groups are used as acceptors in these transformations. The effect of various donors such as vinyl, aryl, amino, and alkoxy groups has also been investigated (Table 11, entries 3–8).[93] The reaction conditions chosen for these conversions often caused spontaneous aromatization of the products. After rearrangement of an in situ generated imino acceptor, elimination of the alkoxy donor occured, which could be found attached to the side chain of pyrrole derivative **100h** after completion of the reaction (Table 11, entry 8).[94]

When donor-substituted cyclopropanes bearing geminal nitro and ester groups are used, a rearrangement which incorporates the nitro group into the formed heterocyclic structure **100i** occurs instantaneously. The various donor substituents influence the obtained yields (best yields were obtained using OR and NR_2, lowest values were obtained using SR), but do not lead to the formation of a ketene acetal structure by incorporation of the ester group (Table 11, entry 9).[95] Theoretical calculations proved that both thermodynamics as well as kinetics are in favor of the cyclic nitronate formed in this conversion. Li, Shao, and co-workers demonstrated that arrangements which are often considered to be concerted reactions occur as a stepwise process when performed in the presence of $BiCl_3$, which makes additional incorporation of a nucleophilic reagent possible (Table 11, entry 10).[96] Werz and co-workers had also reported that the course of the reaction can be significantly influenced by utilizing Lewis acids. The addition of $Yb(OTf)_3$ during the synthesis of [5.*n*]spiroketals **100k** mostly resulted in higher yields, but also led to considerable decreases in the observed diastereoselectivity. This result can easily be rationalized if one considers the Lewis acid to cause a change in the mechanism of the conversion, so that it no longer proceeds through a concerted mechanism but in a stepwise manner (Scheme 21).[97] The open-chain intermediate **104** may now attack the oxonium ion either from the top or from the bottom. This possibility does not exist in a concerted mechanism.

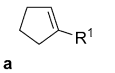
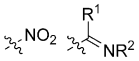
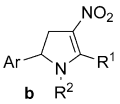
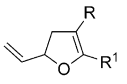
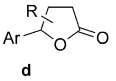
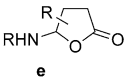
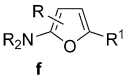
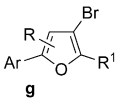
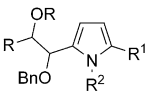
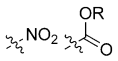
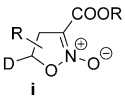
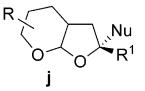
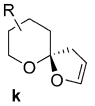
4.2. Rearrangements of Two Adjacent Cyclopropanes

The use of furan derivative **105**, which bears cyclopropane groups on both sides, allows the complexity of the products formed to be significantly increased through simultaneous rearrangement of the two adjacent cyclopropane rings. Tricyclic bisacetals **106** could be prepared at room temper-

Table 11: Rearrangement reactions of D-A cyclopropanes to yield (hetero)cyclopentenes.



1 100

Entry	D	A	Cat./LA	Main product (**100**)	Max. yield
1[91]	H		$[Ni(cod)_2]$, IPr[a]	 **a**	96%
2[92]	aryl		–	 **b**	99%
3[93a]	vinyl		$[Ni(cod)_2]$, bipy[a] or PPh_3	 **c**	99%
4[93b–d]	aryl		LiCl, Me_3N HCl	 **d**	91%
5[93e]	N(Ac)R N(Boc)R		1) TFA[a] 2) NaOH	 **e**	50%[b]
6[93f]	NR_2		–	 **f**	76%
7[93g]	aryl		Al_2O_3 (acidic)	 **g**	90%[c]
8[94]	alkoxy		$InBr_3$	 **h**	95%
9[95]	OR, SR, NR_2, aryl		–	 **i**	96%
10[96]	alkoxy		$BiCl_3$	 **j**	91%
11[97]	alkoxy		–	 **k**	87%

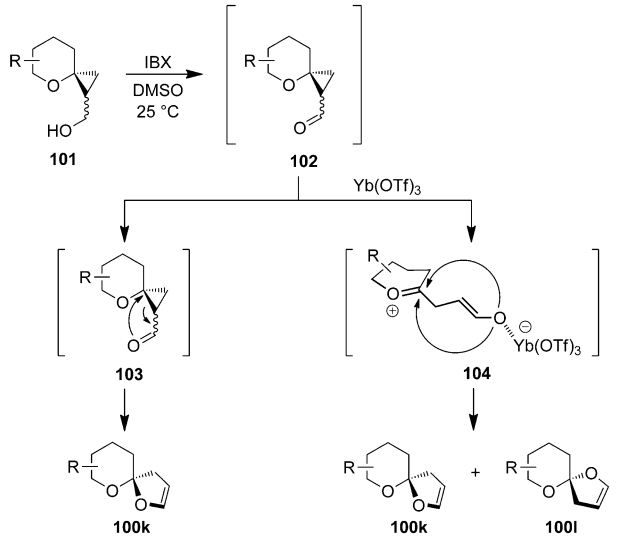
[a] Bipy = 2,2′-bipyridine, IPr = 1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidene, TFA = trifluoroacetic acid. [b] Deprotection of the amine donor using TFA leads to a ring-opened product. Subsequent conversion with NaOH results in lactone **100e**, yield over 2 steps. [c] Application of dibromo-substituted D-A cyclopropanes results in furan derivative **100g** after elimination of HBr.

ature without any catalyst when aldehyde acceptors (which can be generated in situ from the corresponding alcohols) were employed in these transformations.[98] Similar substrates bearing ketone substituents showed a higher activation barrier, and only afforded the corresponding products **107** at higher temperatures (100 °C) and in the presence of catalytic amounts of acids.[99] If similar rearrangements of thioketone- or imino-substituted cyclopropanes are performed, spontaneous elimination of water from the intermediate bis-S,O- or bis-N,O-acetals **108** and **110** occurs. This difference in behavior can be attributed to a higher stabilization of the formed pyrroles and thiophenes compared to the corresponding furans. Very few examples of such 3,3′-linked bisthiophenes **109**[100] and bispyrroles **111**[101] exist in the literature, even though their very reactive free 2-position makes them highly intriguing synthetic building blocks (Scheme 22). The concept described above was also applicable when *N*-Boc-pyrrole was used as the starting material, which yielded bis-N,O-acetals. The use of thiophene as the starting material, however, represents a greater challenge, as it is far less reactive towards rearrangements and up to now only one side could be cyclopropanated successfully.[99]

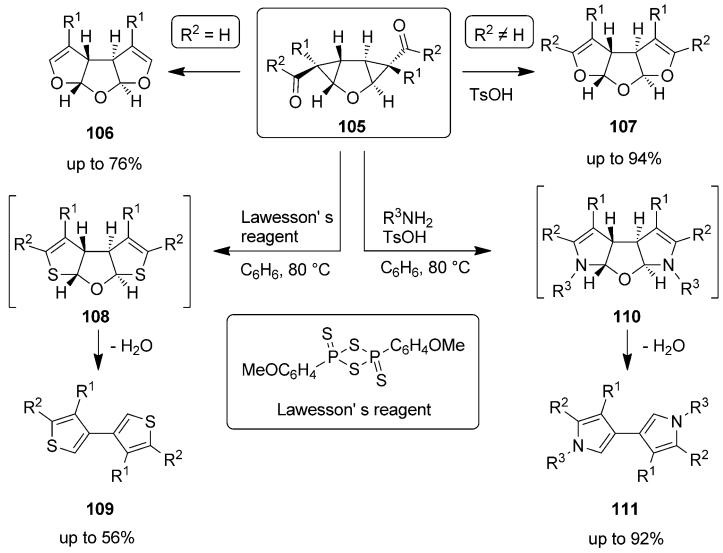
4.3. Ring Enlargement through Catalytic Homo-Nazarov Cyclizations

Homo-Nazarov cyclizations have been known since the 1980s, when Murphy reported the use of a fourfold excess of $SnCl_4$ as a Lewis acid to effect reactions of this type.[102] However, it took until 2009 before Waser reported a catalytic version under mild conditions. Therein cyclopropylketone **112** was treated with catalytic amounts of *p*-TsOH to initiate a ring enlargement that yielded six-membered-ring systems **113** (Scheme 23).[103]

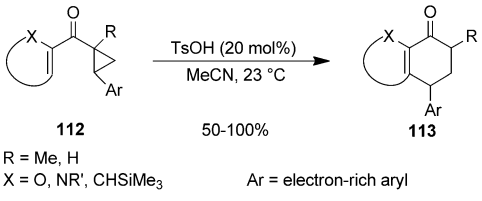
Homo-Nazarov cyclizations have also been utilized in the synthesis of various natural products. Waser and co-workers developed a formal total synthesis of the alkaloid aspidospermidine, during which intermediate **117** is subjected to a $Cu(OTf)_2$-catalyzed homo-Nazarov cyclization. The use of different conditions allows for the preparation of aminal **119**. This conversion did not lead to the anticipated formation of a five-membered ring by attack of the carbonyl oxygen atom on the three-membered ring of intermediate **117** (see Section 4.1), instead the attack of the indole nitrogen atom leads to the formation of a six-membered ring (Scheme 24). The resulting aminal **119** can be converted in three more steps into the natural product (±)-goniomitine (**120**).[104] Conceptionally similar reactions were employed by France and co-workers for preparing pyridoindoles and related compounds.[105]



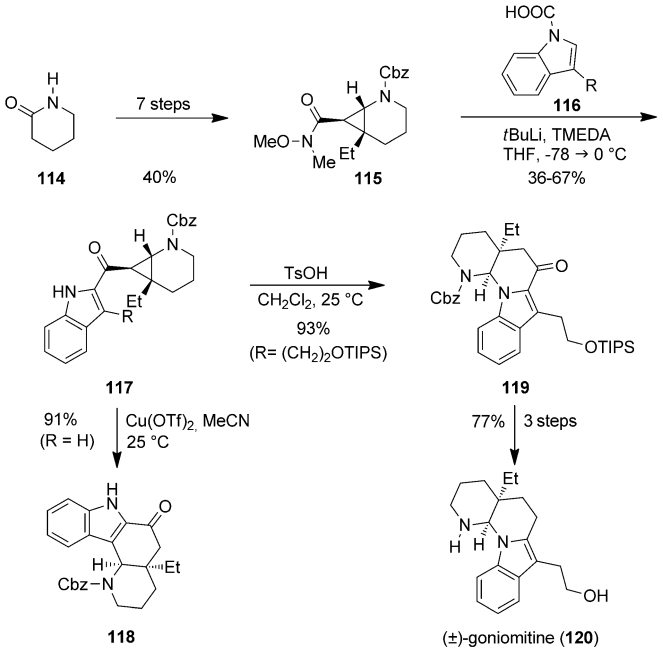
Scheme 21. Influence of a Lewis acid on the different reaction mechanisms for the rearrangement of **102**. IBX = 2-iodoxybenzoic acid.



Scheme 22. Rearrangement of tricyclic furan-based D-A cyclopropanes **105** used for the formation of oligoacetals **106** and **107** as well as 3,3′-linked heterocyclic frameworks **109** and **111**.



Scheme 23. Catalytic homo-Nazarov cyclization according to Waser and co-workers.



Scheme 24. Synthesis of an aspidospermidine precursor and total synthesis of (±)-goniomitine (**120**) by Waser and co-workers. Cbz = benzyloxycarbonyl, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

5. Conclusion and Outlook

The last few years have brought great advances in the chemistry of donor–acceptor-substituted cyclopropanes. On the one hand, new donor–acceptor combinations were investigated by experimental and theoretical means and thus provided access to essential structural motifs. On the other hand, catalytic enantioselective variations were most notably examined in the field of ring-opening and cycloaddition reactions. D-A cyclopropanes have often even been used in total syntheses of biologically active natural products to generate the respective five-membered heterocycles with a clearly defined stereoselectivity. Complex bicyclic systems can be established easily and highly effectively by intramolecular versions of cycloaddition reactions. In contrast, rearrangement reactions of D-A cyclopropanes lead to partially unsaturated five-membered heterocycles—thus, appropriate substrates offer metal-free access to connected heterocyclic frameworks.

Important challenges remain for the future. In addition to many hitherto unknown donor–acceptor combinations, which open up a wide field, enantioselective modifications have not been established for a large number of already studied transformations. Deeper mechanistic insights should provide clarity on how regio-, stereo-, and enantioselectivities arise and thus form the basis to extend so far very specific solutions to other donors and acceptors. Especially in the field of cycloadditions and ring enlargements, the focus has been put on the generation of five-membered rings. Although there are a few examples of higher cycloadditions, they have hardly been explored thus far. To date, rearrangement reactions of

D-A cyclopropanes have always been implemented to extend a three- to a five-membered ring. Expanded acceptor–systems should eventually provide access to six- and seven-membered rings with unusual substitution patterns. Not least, the question arises to what extent this chemistry based on cyclopropanes could be translated to donor–acceptor cyclobutanes, which have only slightly lower strain energies than their three-membered ring analogues.[106] Initial studies have shown encouraging results and demonstrate that at least some reactions could be accomplished in a similar way.[107]

It is astonishing, and at the same time also encouraging for synthetic chemistry in general, that 30 years after the first fundamental investigations by Wenkert and Reissig, a relatively old area of research, which had in principle been well understood, is experiencing such a revitalization. As we have learned from history, making a discovery alone is often not sufficient. It needs a broad range of further investigations to sustainably establish an area, to make it applicable and draw conclusions for the future. Donor–acceptor-substituted cyclopropanes have now arrived at this stage.

We are grateful to all of our globally active colleagues who dedicated themselves to this highly interesting—destructive—art of cyclopropane chemistry, and thus have laid the foundations of this Review. At the same time we wish to apologize if we did not include some examples or should even have overlooked some. Our work in this field was financially supported by the German Research Foundation (Emmy Noether and Heisenberg Fellowships to D.B.W.), the German-Israeli Foundation (G.I.F. Young Scientists' Program), and the Fonds der Chemischen Industrie (Dozentenstipendium to D.B.W.); we are thus obliged in all respects to these funding institutions. For her help with the translation, we thank Marie Bergner, Göttingen.

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[1] A. de Meijere, *Angew. Chem.* **1979**, *91*, 867 – 884; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 809 – 826.

[2] a) A. Wurtz, *Ann. Chem. Pharm.* **1855**, *96*, 364 – 375; b) H. E. Simmons, R. D. Smith, *J. Am. Chem. Soc.* **1958**, *80*, 5323 – 5324; c) H. E. Simmons, R. D. Smith, *J. Am. Chem. Soc.* **1959**, *81*, 4256 – 4264; d) E. J. Corey, M. Chaykovsky, *J. Am. Chem. Soc.* **1965**, *87*, 1353 – 1364; e) M. P. Doyle, *Chem. Rev.* **1986**, *86*, 919 – 939; f) M. Brookhart, W. B. Studabaker, *Chem. Rev.* **1987**, *87*, 411 – 432; g) T. Ye, M. A. McKervey, *Chem. Rev.* **1994**, *94*, 1091 – 1160; h) H. E. Zimmerman, D. Armesto, *Chem. Rev.* **1996**, *96*, 3065 – 3112; i) D. F. Harvey, D. M. Sigano, *Chem. Rev.* **1996**, *96*, 271 – 288; j) H.-W. Frühauf, *Chem. Rev.* **1997**, *97*, 523 – 596; k) O. G. Kulinkovich, A. de Meijere, *Chem. Rev.* **2000**, *100*, 2789 – 2834; l) H. Lebel, J.-F. Marcoux, C. Molinaro, A. B. Charette, *Chem. Rev.* **2003**, *103*, 977 – 1050.

[3] a) E. W. Schlag, B. S. Rabinovitch, *J. Am. Chem. Soc.* **1960**, *82*, 5996 – 6000; b) Z. Goldschmidt, B. Crammer, *Chem. Soc. Rev.* **1988**, *17*, 229 – 267; c) J. J. Gajewski, L. P. Olson, M. R. Willcott, *J. Am. Chem. Soc.* **1996**, *118*, 299 – 306; d) K. N. Houk, M. Nendel, O. Wiest, J. W. Storer, *J. Am. Chem. Soc.* **1997**, *119*, 10545 – 10546; e) J. E. Baldwin, *Chem. Rev.* **2003**, *103*, 1197 – 1212.

[4] F. Brackmann, A. de Meijere, *Chem. Rev.* **2007**, *107*, 4493 – 4537.

[5] a) S. F. Yang, N. E. Hoffman, *Annu. Rev. Plant Physiol.* **1984**, *35*, 155 – 189; b) H. Kende, *Annu. Rev. Plant Physiol. Plant Mol. Biol.* **1993**, *44*, 283 – 307.

[6] a) H.-U. Reissig, *Top. Curr. Chem.* **1988**, *144*, 73 – 135; b) H.-U. Reissig, R. Zimmer, *Chem. Rev.* **2003**, *103*, 1151 – 1196; c) M. Yu, B. L. Pagenkopf, *Tetrahedron* **2005**, *61*, 321 – 347; d) D. Agrawal, V. K. Yadav, *Chem. Commun.* **2008**, 6471 – 6488; e) C. A. Carson, M. A. Kerr, *Chem. Soc. Rev.* **2009**, *38*, 3051 – 3060; f) F. De Simone, J. Waser, *Synthesis* **2009**, 3353 – 3374; g) M. J. Campbell, J. S. Johnson, A. T. Parsons, P. D. Pohlhaus, S. D. Sanders, *J. Org. Chem.* **2010**, *75*, 6317 – 6325; h) T. P. Lebold, M. A. Kerr, *Pure Appl. Chem.* **2010**, *82*, 1797 – 1812; i) J. Kaschel, D. B. Werz, *Nachr. Chem.* **2011**, *59*, 729 – 733; j) M. Y. Mel′nikov, E. M. Budynina, O. A. Ivanova, I. V. Trushkov, *Mendeleev Commun.* **2011**, *21*, 293 – 301; k) Z. Wang, *Synlett* **2012**, *23*, 2311 – 2327; l) M. A. Cavitt, L. H. Phun, S. France, *Chem. Soc. Rev.* **2014**, *43*, 804 – 818.

[7] a) G. Stork, M. Gregson, *J. Am. Chem. Soc.* **1969**, *91*, 2373 – 2374; b) G. Stork, P. A. Grieco, *J. Am. Chem. Soc.* **1969**, *91*, 2407 – 2408; c) G. Stork, M. Marx, *J. Am. Chem. Soc.* **1969**, *91*, 2371 – 2373; d) G. Stork, P. A. Grieco, *Tetrahedron Lett.* **1971**, *12*, 1807 – 1810; e) E. Corey, R. Balanson, *Tetrahedron Lett.* **1973**, *14*, 3153 – 3156; f) S. Danishefsky, J. Dynak, E. Hatch, M. Yamamoto, *J. Am. Chem. Soc.* **1974**, *96*, 1256 – 1259; g) S. Danishefsky, M. Y. Tsai, J. Dynak, *J. Chem. Soc. Chem. Commun.* **1975**, 7 – 8; h) S. Danishefsky, R. McKee, R. K. Singh, *J. Am. Chem. Soc.* **1977**, *99*, 7711 – 7713; i) S. Danishefsky, *Acc. Chem. Res.* **1979**, *12*, 66 – 72; j) S. Danishefsky, J. Regan, R. Doehner, *J. Org. Chem.* **1981**, *46*, 5255 – 5261.

[8] a) E. Wenkert, M. E. Alonso, B. L. Buckwalter, K. J. Chou, *J. Am. Chem. Soc.* **1977**, *99*, 4778 – 4782; b) E. Piers, H.-U. Reissig, *Angew. Chem.* **1979**, *91*, 857 – 858; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 791 – 792; c) E. Wenkert, *Acc. Chem. Res.* **1980**, *13*, 27 – 31; d) H.-U. Reissig, E. Hirsch, *Angew. Chem.* **1980**, *92*, 839 – 840; *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 813 – 814; e) H.-U. Reissig, *Tetrahedron Lett.* **1981**, *22*, 2981 – 2984; f) C. Brückner, H.-U. Reissig, *J. Chem. Soc. Chem. Commun.* **1985**, 1512 – 1513; g) C. Brückner, H.-U. Reissig, *Angew. Chem.* **1985**, *97*, 578 – 579; *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 588 – 589; h) E. L. Grimm, R. Zschiesche, H. U. Reissig, *J. Org. Chem.* **1985**, *50*, 5543 – 5545; i) H.-U. Reissig, I. Reichelt, H. Lorey, *Liebigs Ann. Chem.* **1986**, *1986*, 1924 – 1939; j) C. Brueckner, H. U. Reissig, *J. Org. Chem.* **1988**, *53*, 2440 – 2450; k) H.-U. Reissig, H. Holzinger, G. Glomsda, *Tetrahedron* **1989**, *45*, 3139 – 3150; l) B. Hofmann, H.-U. Reissig, *Synlett* **1993**, 27 – 29; m) B. Hofmann, H.-U. Reissig, *Chem. Ber.* **1994**, *127*, 2327 – 2335.

[9] a) S. Tanimori, M. Tsubota, M. He, M. Nakayama, *Biosci. Biotechnol. Biochem.* **1995**, *59*, 2091 – 2093; b) G. Bose, P. Langer, *Tetrahedron Lett.* **2004**, *45*, 3861 – 3863; c) M. Tanaka, M. Ubukata, T. Matsuo, K. Yasue, K. Matsumoto, Y. Kajimoto, T. Ogo, T. Inaba, *Org. Lett.* **2007**, *9*, 3331 – 3334.

[10] O. Lifchits, D. Alberico, I. Zakharian, A. B. Charette, *J. Org. Chem.* **2008**, *73*, 6838 – 6840.

[11] O. Lifchits, A. B. Charette, *Org. Lett.* **2008**, *10*, 2809 – 2812.

[12] M. Yu, B. L. Pagenkopf, *Tetrahedron* **2003**, *59*, 2765 – 2771.

[13] a) P. Harrington, M. A. Kerr, *Tetrahedron Lett.* **1997**, *38*, 5949 – 5952; b) M. R. Emmett, M. A. Kerr, *Org. Lett.* **2011**, *13*, 4180 – 4183; c) M. R. Emmett, H. K. Grover, M. A. Kerr, *J. Org. Chem.* **2012**, *77*, 6634 – 6637.

[14] a) P. R. Sridhar, P. Venukumar, *Org. Lett.* **2012**, *14*, 5558 – 5561; b) P. Venukumar, C. Sudharani, P. R. Sridhar, *Chem. Commun.* **2014**, *50*, 2218 – 2221.

[15] S. M. Wales, M. M. Walker, J. S. Johnson, *Org. Lett.* **2013**, *15*, 2558 – 2561.

[16] F. de Nanteuil, J. Loup, J. Waser, *Org. Lett.* **2013**, *15*, 3738 – 3741.
[17] S. Roy, O. Reiser, *Angew. Chem.* **2012**, *124*, 4801 – 4804; *Angew. Chem. Int. Ed.* **2012**, *51*, 4722 – 4725.
[18] M. Yu, B. L. Pagenkopf, *Org. Lett.* **2003**, *5*, 4639 – 4640.
[19] P. Cérat, P. J. Gritsch, S. R. Goudreau, A. B. Charette, *Org. Lett.* **2010**, *12*, 564 – 567.
[20] J. Moran, A. G. Smith, R. M. Carris, J. S. Johnson, M. J. Krische, *J. Am. Chem. Soc.* **2011**, *133*, 18618 – 18621.
[21] a) S. Sebelius, V. J. Olsson, K. J. Szabó, *J. Am. Chem. Soc.* **2005**, *127*, 10478 – 10479; b) S. Sebelius, V. J. Olsson, O. A. Wallner, K. J. Szabó, *J. Am. Chem. Soc.* **2006**, *128*, 8150 – 8151; c) N. Selander, K. J. Szabó, *Chem. Commun.* **2008**, 3420 – 3422.
[22] Y. Sumida, H. Yorimitsu, K. Oshima, *Org. Lett.* **2008**, *10*, 4677 – 4679.
[23] D. Gladow, H.-U. Reissig, *Synthesis* **2013**, *45*, 2179 – 2187.
[24] D. Gladow, H.-U. Reissig, *Helv. Chim. Acta* **2012**, *95*, 1818 – 1830.
[25] a) M. H. Beyzavi, D. Lentz, H.-U. Reissig, A. Wiehe, *Eur. J. Org. Chem.* **2013**, 269 – 282; b) M. H. Beyzavi, C. Nietzold, H.-U. Reissig, A. Wiehe, *Adv. Synth. Catal.* **2013**, *355*, 1409 – 1422.
[26] A. O. Chagarovskiy, O. A. Ivanova, E. R. Rakhmankulov, E. M. Budynina, I. V. Trushkov, M. Y. Melnikov, *Adv. Synth. Catal.* **2010**, *352*, 3179 – 3184.
[27] a) C. Böhm, O. Reiser, *Org. Lett.* **2001**, *3*, 1315 – 1318; b) B. Nosse, R. B. Chhor, W. B. Jeong, C. Böhm, O. Reiser, *Org. Lett.* **2003**, *5*, 941 – 944; c) S. Kalidindi, W. B. Jeong, A. Schall, R. Bandichhor, B. Nosse, O. Reiser, *Angew. Chem.* **2007**, *119*, 6478 – 6481; *Angew. Chem. Int. Ed.* **2007**, *46*, 6361 – 6363.
[28] A. Kreuzer, S. Kerres, T. Ertl, H. Rücker, S. Amslinger, O. Reiser, *Org. Lett.* **2013**, *15*, 3420 – 3423.
[29] E. L. Fisher, S. M. Wilkerson-Hill, R. Sarpong, *J. Am. Chem. Soc.* **2012**, *134*, 9946 – 9949.
[30] A. O. Chagarovskiy, O. A. Ivanova, E. M. Budynina, I. V. Trushkov, M. Y. Melnikov, *Tetrahedron Lett.* **2011**, *52*, 4421 – 4425.
[31] a) O. A. Ivanova, E. M. Budynina, A. O. Chagarovskiy, E. R. Rakhmankulov, I. V. Trushkov, A. V. Semeykin, N. L. Shimanovskii, M. Y. Melnikov, *Chem. Eur. J.* **2011**, *17*, 11738 – 11742; b) O. A. Ivanova, E. M. Budynina, D. A. Skvortsov, M. Limoge, A. V. Bakin, A. O. Chagarovskiy, I. V. Trushkov, M. Y. Melnikov, *Chem. Commun.* **2013**, *49*, 11482 – 11484.
[32] R. A. Novikov, V. P. Timofeev, Y. V. Tomilov, *J. Org. Chem.* **2012**, *77*, 5993 – 6006.
[33] O. A. Ivanova, E. M. Budynina, A. O. Chagarovskiy, I. V. Trushkov, M. Y. Melnikov, *J. Org. Chem.* **2011**, *76*, 8852 – 8868.
[34] a) S. Shimada, Y. Hashimoto, A. Sudo, M. Hasegawa, K. Saigo, *J. Org. Chem.* **1992**, *57*, 7126 – 7133; b) S. Shimada, Y. Hashimoto, K. Saigo, *J. Org. Chem.* **1993**, *58*, 5226 – 5234; c) S. Shimada, Y. Hashimoto, T. Nagashima, M. Hasegawa, K. Saigo, *Tetrahedron* **1993**, *49*, 1589 – 1604.
[35] a) P. D. Pohlhaus, J. S. Johnson, *J. Am. Chem. Soc.* **2005**, *127*, 16014 – 16015; b) P. D. Pohlhaus, J. S. Johnson, *J. Org. Chem.* **2005**, *70*, 1057 – 1059; c) P. D. Pohlhaus, S. D. Sanders, A. T. Parsons, W. Li, J. S. Johnson, *J. Am. Chem. Soc.* **2008**, *130*, 8642 – 8650.
[36] A. T. Parsons, J. S. Johnson, *J. Am. Chem. Soc.* **2009**, *131*, 3122 – 3123.
[37] A. G. Smith, M. C. Slade, J. S. Johnson, *Org. Lett.* **2011**, *13*, 1996 – 1999.
[38] F. Benfatti, F. de Nanteuil, J. Waser, *Org. Lett.* **2012**, *14*, 386 – 389.
[39] F. Benfatti, F. de Nanteuil, J. Waser, *Chem. Eur. J.* **2012**, *18*, 4844 – 4849.
[40] a) G. Yang, Y. Shen, K. Li, Y. Sun, Y. Hua, *J. Org. Chem.* **2011**, *76*, 229 – 233; b) G. Yang, Y. Sun, Y. Shen, Z. Chai, S. Zhou, J. Chu, J. Chai, *J. Org. Chem.* **2013**, *78*, 5393 – 5400.
[41] S. Haubenreisser, P. Hensenne, S. Schröder, M. Niggemann, *Org. Lett.* **2013**, *15*, 2262 – 2265.
[42] Y. Miyake, S. Endo, T. Moriyama, K. Sakata, Y. Nishibayashi, *Angew. Chem.* **2013**, *125*, 1802 – 1806; *Angew. Chem. Int. Ed.* **2013**, *52*, 1758 – 1762.
[43] S. Xing, W. Pan, C. Liu, J. Ren, Z. Wang, *Angew. Chem.* **2010**, *122*, 3283 – 3286; *Angew. Chem. Int. Ed.* **2010**, *49*, 3215 – 3218.
[44] S. Xing, Y. Li, Z. Li, C. Liu, J. Ren, Z. Wang, *Angew. Chem.* **2011**, *123*, 12813 – 12817; *Angew. Chem. Int. Ed.* **2011**, *50*, 12605 – 12609.
[45] Y. Bai, W. Tao, J. Ren, Z. Wang, *Angew. Chem.* **2012**, *124*, 4188 – 4192; *Angew. Chem. Int. Ed.* **2012**, *51*, 4112 – 4116.
[46] S. D. Sanders, A. Ruiz-Olalla, J. S. Johnson, *Chem. Commun.* **2009**, 5135 – 5137.
[47] A. B. Leduc, M. A. Kerr, *Angew. Chem.* **2008**, *120*, 8063 – 8066; *Angew. Chem. Int. Ed.* **2008**, *47*, 7945 – 7948.
[48] a) A. Karadeolian, M. A. Kerr, *Angew. Chem.* **2010**, *122*, 1151 – 1153; *Angew. Chem. Int. Ed.* **2010**, *49*, 1133 – 1135; b) A. Karadeolian, M. A. Kerr, *J. Org. Chem.* **2010**, *75*, 6830 – 6841.
[49] M. Campbell, J. Johnson, *Synthesis* **2010**, 2841 – 2852.
[50] A. R. Rivero, I. Fernández, M. Á. Sierra, *Org. Lett.* **2013**, *15*, 4928 – 4931.
[51] R. Tejero, A. Ponce, J. Adrio, J. C. Carretero, *Chem. Commun.* **2013**, *49*, 10406.
[52] a) P. B. Alper, C. Meyers, A. Lerchner, D. R. Siegel, E. M. Carreira, *Angew. Chem.* **1999**, *111*, 3379 – 3381; *Angew. Chem. Int. Ed.* **1999**, *38*, 3186 – 3189; b) A. Lerchner, E. M. Carreira, *J. Am. Chem. Soc.* **2002**, *124*, 14826 – 14827; c) C. Meyers, E. M. Carreira, *Angew. Chem.* **2003**, *115*, 718 – 720; *Angew. Chem. Int. Ed.* **2003**, *42*, 694 – 696.
[53] C. A. Carson, M. A. Kerr, *J. Org. Chem.* **2005**, *70*, 8242 – 8244.
[54] A. T. Parsons, A. G. Smith, A. J. Neel, J. S. Johnson, *J. Am. Chem. Soc.* **2010**, *132*, 9688 – 9692.
[55] S. K. Jackson, A. Karadeolian, A. B. Driega, M. A. Kerr, *J. Am. Chem. Soc.* **2008**, *130*, 4196 – 4201.
[56] T. P. Lebold, M. A. Kerr, *Org. Lett.* **2009**, *11*, 4354 – 4357.
[57] N. A. Morra, C. L. Morales, B. Bajtos, X. Wang, H. Jang, J. Wang, M. Yu, B. L. Pagenkopf, *Adv. Synth. Catal.* **2006**, *348*, 2385 – 2390.
[58] C. A. Carson, M. A. Kerr, *Org. Lett.* **2009**, *11*, 777 – 779.
[59] J.-P. Qu, C. Deng, J. Zhou, X.-L. Sun, Y. Tang, *J. Org. Chem.* **2009**, *74*, 7684 – 7689.
[60] F. de Nanteuil, J. Waser, *Angew. Chem.* **2011**, *123*, 12281 – 12285; *Angew. Chem. Int. Ed.* **2011**, *50*, 12075 – 12079.
[61] J.-P. Qu, Y. Liang, H. Xu, X.-L. Sun, Z.-X. Yu, Y. Tang, *Chem. Eur. J.* **2012**, *18*, 2196 – 2201.
[62] H. Xu, J.-P. Qu, S. Liao, H. Xiong, Y. Tang, *Angew. Chem.* **2013**, *125*, 4096 – 4099; *Angew. Chem. Int. Ed.* **2013**, *52*, 4004 – 4007.
[63] H. Xiong, H. Xu, S. Liao, Z. Xie, Y. Tang, *J. Am. Chem. Soc.* **2013**, *135*, 7851 – 7854.
[64] B. M. Trost, P. J. Morris, S. J. Sprague, *J. Am. Chem. Soc.* **2012**, *134*, 17823 – 17831.
[65] Y. A. Volkova, E. M. Budynina, A. E. Kaplun, O. A. Ivanova, A. O. Chagarovskiy, D. A. Skvortsov, V. B. Rybakov, I. V. Trushkov, M. Y. Melnikov, *Chem. Eur. J.* **2013**, *19*, 6586 – 6590.
[66] Z. Wang, J. Ren, Z. Wang, *Org. Lett.* **2013**, *15*, 5682 – 5685.
[67] a) O. A. Ivanova, E. M. Budynina, Y. K. Grishin, I. V. Trushkov, P. V. Verteletskii, *Angew. Chem.* **2008**, *120*, 1123 – 1126; *Angew. Chem. Int. Ed.* **2008**, *47*, 1107 – 1110; b) O. A. Ivanova, E. M. Budynina, Y. K. Grishin, I. V. Trushkov, P. V. Verteletskii, *Eur. J. Org. Chem.* **2008**, 5329 – 5335.
[68] O. A. Ivanova, E. M. Budynina, A. O. Chagarovskiy, A. E. Kaplun, I. V. Trushkov, M. Y. Melnikov, *Adv. Synth. Catal.* **2011**, *353*, 1125 – 1134.
[69] a) M. M. A. R. Moustafa, B. L. Pagenkopf, *Org. Lett.* **2010**, *12*, 3168 – 3171; b) M. Yu, B. L. Pagenkopf, *Org. Lett.* **2003**, *5*,

5099 – 5101; c) M. Yu, G. D. Pantos, J. L. Sessler, B. L. Pagenkopf, *Org. Lett.* **2004**, *6*, 1057 – 1059.
[70] G. Sathishkannan, K. Srinivasan, *Org. Lett.* **2011**, *13*, 6002 – 6005.
[71] A. F. G. Goldberg, N. R. O'Connor, R. A. Craig, B. M. Stoltz, *Org. Lett.* **2012**, *14*, 5314 – 5317.
[72] H. Wang, W. Yang, H. Liu, W. Wang, H. Li, *Org. Biomol. Chem.* **2012**, *10*, 5032 – 5035.
[73] I. S. Young, M. A. Kerr, *Angew. Chem.* **2003**, *115*, 3131 – 3134; *Angew. Chem. Int. Ed.* **2003**, *42*, 3023 – 3026.
[74] M. D. Ganton, M. A. Kerr, *J. Org. Chem.* **2004**, *69*, 8554 – 8557.
[75] I. S. Young, M. A. Kerr, *Org. Lett.* **2004**, *6*, 139 – 141.
[76] M. P. Sibi, Z. Ma, C. P. Jasperse, *J. Am. Chem. Soc.* **2005**, *127*, 5764 – 5765.
[77] Y.-B. Kang, X.-L. Sun, Y. Tang, *Angew. Chem.* **2007**, *119*, 3992 – 3995; *Angew. Chem. Int. Ed.* **2007**, *46*, 3918 – 3921.
[78] A. M. Hardman, S. S. So, A. E. Mattson, *Org. Biomol. Chem.* **2013**, *11*, 5793.
[79] Y. Zhang, F. Liu, J. Zhang, *Chem. Eur. J.* **2010**, *16*, 6146 – 6150.
[80] E. O. Gorbacheva, A. A. Tabolin, R. A. Novikov, Y. A. Khomutova, Y. V. Nelyubina, Y. V. Tomilov, S. L. Ioffe, *Org. Lett.* **2013**, *15*, 350 – 353.
[81] W. J. Humenny, P. Kyriacou, K. Sapeta, A. Karadeolian, M. A. Kerr, *Angew. Chem.* **2012**, *124*, 11250 – 11253; *Angew. Chem. Int. Ed.* **2012**, *51*, 11088 – 11091.
[82] I. S. Young, M. A. Kerr, *J. Am. Chem. Soc.* **2007**, *129*, 1465 – 1469.
[83] a) C. Perreault, S. R. Goudreau, L. E. Zimmer, A. B. Charette, *Org. Lett.* **2008**, *10*, 689 – 692; b) Y.-Y. Zhou, J. Li, L. Ling, S.-H. Liao, X.-L. Sun, Y.-X. Li, L.-J. Wang, Y. Tang, *Angew. Chem.* **2013**, *125*, 1492 – 1496; *Angew. Chem. Int. Ed.* **2013**, *52*, 1452 – 1456.
[84] K. Sapeta, M. A. Kerr, *Org. Lett.* **2009**, *11*, 2081 – 2084.
[85] T. P. Lebold, A. B. Leduc, M. A. Kerr, *Org. Lett.* **2009**, *11*, 3770 – 3772.
[86] A. B. Leduc, T. P. Lebold, M. A. Kerr, *J. Org. Chem.* **2009**, *74*, 8414 – 8416.
[87] N. Neureiter, *J. Org. Chem.* **1959**, *24*, 2044 – 2046.
[88] J. B. Cloke, *J. Am. Chem. Soc.* **1929**, *51*, 1174 – 1187.
[89] C. L. Wilson, *J. Am. Chem. Soc.* **1947**, *69*, 3002 – 3004.
[90] T. F. Schneider, D. B. Werz, *Org. Lett.* **2011**, *13*, 1848 – 1851.
[91] G. Zuo, J. Louie, *Angew. Chem.* **2004**, *116*, 2327 – 2329; *Angew. Chem. Int. Ed.* **2004**, *43*, 2277 – 2279.
[92] R. P. Wurz, A. B. Charette, *Org. Lett.* **2005**, *7*, 2313 – 2316.
[93] a) R. K. Bowman, J. S. Johnson, *Org. Lett.* **2006**, *8*, 573 – 576; b) R. Weisser, W. Yue, O. Reiser, *Org. Lett.* **2005**, *7*, 5353 – 5356; c) K. Harrar, O. Reiser, *Chem. Commun.* **2012**, *48*, 3457 – 3459; d) H. K. Grover, M. R. Emmett, M. A. Kerr, *Org. Lett.* **2013**, *15*, 4838 – 4841; e) G. Özüduru, T. Schubach, M. M. K. Boysen, *Org. Lett.* **2012**, *14*, 4990 – 4993; f) Y. Jiang, V. Z. Y. Khong, E. Lourdusamy, C.-M. Park, *Chem. Commun.* **2012**, *48*, 3133 – 3135; g) E. Gopi, I. N. N. Namboothiri, *J. Org. Chem.* **2013**, *78*, 910 – 919; h) S. J. Gharpure, M. K. Shukla, U. Vijayasree, *Org. Lett.* **2009**, *11*, 5466 – 5469; i) S. J. Gharpure, L. N. Nanda, M. K. Shukla, *Eur. J. Org. Chem.* **2011**, 6632 – 6635; j) S. J. Gharpure, U. Vijayasree, S. R. B. Reddy, *Org. Biomol. Chem.* **2012**, *10*, 1735 – 1738.
[94] P. Wang, S. Song, Z. Miao, G. Yang, A. Zhang, *Org. Lett.* **2013**, *15*, 3852 – 3855.
[95] C. D. Schmidt, J. Kaschel, T. F. Schneider, D. Kratzert, D. Stalke, D. B. Werz, *Org. Lett.* **2013**, *15*, 6098 – 6101.
[96] X. Ma, Q. Tang, J. Ke, J. Zhang, C. Wang, H. Wang, Y. Li, H. Shao, *Chem. Commun.* **2013**, *49*, 7085 – 7087.
[97] C. Brand, G. Rauch, M. Zanoni, B. Dittrich, D. B. Werz, *J. Org. Chem.* **2009**, *74*, 8779 – 8786.
[98] a) T. F. Schneider, J. Kaschel, B. Dittrich, D. B. Werz, *Org. Lett.* **2009**, *11*, 2317 – 2320; b) T. F. Schneider, J. Kaschel, S. I. Awan, B. Dittrich, D. B. Werz, *Chem. Eur. J.* **2010**, *16*, 11276 – 11288.
[99] J. Kaschel, T. F. Schneider, P. Schirmer, C. Maaß, D. Stalke, D. B. Werz, *Eur. J. Org. Chem.* **2013**, 4539 – 4551.
[100] J. Kaschel, C. D. Schmidt, M. Mumby, D. Kratzert, D. Stalke, D. B. Werz, *Chem. Commun.* **2013**, *49*, 4403 – 4405.
[101] a) J. Kaschel, T. F. Schneider, D. Kratzert, D. Stalke, D. B. Werz, *Angew. Chem.* **2012**, *124*, 11315 – 11318; *Angew. Chem. Int. Ed.* **2012**, *51*, 11153 – 11156; b) J. Kaschel, T. F. Schneider, D. Kratzert, D. Stalke, D. B. Werz, *Org. Biomol. Chem.* **2013**, *11*, 3494 – 3509.
[102] a) W. S. Murphy, S. Wattanasin, *Tetrahedron Lett.* **1980**, *21*, 1887 – 1890; b) W. S. Murphy, S. Wattanasin, *J. Chem. Soc. Perkin Trans. 1* **1981**, 2920 – 2926; c) W. S. Murphy, S. Wattanasin, *J. Chem. Soc. Perkin Trans. 1* **1982**, 1029 – 1035.
[103] a) F. De Simone, J. Andrès, R. Torosantucci, J. Waser, *Org. Lett.* **2009**, *11*, 1023 – 1026; b) F. De Simone, T. Saget, F. Benfatti, S. Almeida, J. Waser, *Chem. Eur. J.* **2011**, *17*, 14527 – 14538.
[104] a) F. De Simone, J. Gertsch, J. Waser, *Angew. Chem.* **2010**, *122*, 5903 – 5906; *Angew. Chem. Int. Ed.* **2010**, *49*, 5767 – 5770; b) F. De Simone, J. Gertsch, J. Waser, *Angew. Chem.* **2011**, *123*, 4124.
[105] a) D. V. Patil, L. H. Phun, S. France, *Org. Lett.* **2010**, *12*, 5684 – 5687; b) D. V. Patil, M. A. Cavitt, P. Grzybowski, S. France, *Chem. Commun.* **2011**, *47*, 10278 – 10280; c) L. H. Phun, D. V. Patil, M. A. Cavitt, S. France, *Org. Lett.* **2011**, *13*, 1952 – 1955.
[106] a) J. C. Namyslo, D. E. Kaufmann, *Chem. Rev.* **2003**, *103*, 1485 – 1538; b) Z. Z. Rappoport, J. F. Liebman, *The Chemistry of Cyclobutanes*, Wiley, Chichester, **2005**; c) T. Seiser, T. Saget, D. N. Tran, N. Cramer, *Angew. Chem.* **2011**, *123*, 7884 – 7896; *Angew. Chem. Int. Ed.* **2011**, *50*, 7740 – 7752.
[107] a) A. T. Parsons, J. S. Johnson, *J. Am. Chem. Soc.* **2009**, *131*, 14202 – 14203; b) M. M. A. R. Moustafa, B. L. Pagenkopf, *Org. Lett.* **2010**, *12*, 4732 – 4735; c) B. Machin, B. L. Pagenkopf, *Synlett* **2011**, 2799 – 2802; d) A. C. Stevens, C. Palmer, B. L. Pagenkopf, *Org. Lett.* **2011**, *13*, 1528 – 1531.