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Carbocycles from Donor-Acceptor Cyclopropanes

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This review summarizes research directed towards the formation of carbocyclic adducts from donor-acceptor cyclopropanes. The focus of the review is on annulation and cycloaddition reactions (both inter- and intramolecularly) mediated by Lewis or protic acid, bases, or thermal conditions. Rearrangements resulting in carbocycles and those reactions mediated by transition metal catalysis have been excluded.

Introduction

The toolbox of the synthetic organic chemist benefits greatly from the development of new reactive molecular entities for the construction of complex architectures. In this light, donor-acceptor cyclopropanes have emerged to have a prominent role. The reactivity of these compounds and their use in the total synthesis of natural and unnatural targets continue to be extensively studied and have resulted in numerous reviews.[1]

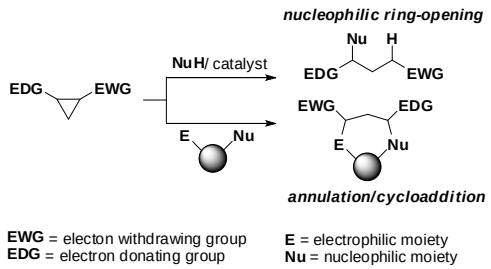


Figure 1: The reactivity of donor-acceptor cyclopropanes.

The reactivity of donor-acceptor (DA) cyclopropanes may be viewed schematically as shown in Figure 1. Simple nucleophilic attack results in what may be viewed as a homo Michael addition. If the nucleophile bears an electrophilic moiety (with orthogonal reactivity to that of the nucleophilic moiety), the nucleophile revealed upon ring-opening may undergo an annulative ring closure in what is a formal cycloaddition. The vast majority of this latter class of reactions involve the formation of heterocycles. This not surprising since the initial ring opening event may be more facile with heteroatom based nucleophilic entities. Such reactive partners are often dipolar in nature. In some cases however, the reaction may involve a partner that is all-carbon resulting in a carbocycle.

This review will cover fairly extensively the annulations and cycloadditions of DA cyclopropanes with all-carbon partners to form carbocyclic products. In order to focus our efforts, we have concentrated on traditional activation of the DA cyclopropane; that is Lewis acid, protic acid, base, or thermal activation. The plethora of elegant methods utilizing transition metal catalysis, have been left aside at this time. In addition, we have chosen to exclude the numerous rearrangement and dimerization reactions of cyclopropanes that result in carbocycles.

1. [3+2] Annulation Reactions of DA Cyclopropanes

The cyclopentane and cyclopentene moieties are common to a wide variety of terpene and alkaloid natural products (Figure 2A).[2] Due to the prevalence and importance of these carbocyclic structures, many strategies have been developed for their construction.[3] For over 50 years, DA cyclopropanes have been synthetically useful 1-3 carbon dipolarophile starting materials for the synthesis of highly substituted 5-membered carbocycles via annulation with alkenes, alkynes, allenes, enol ethers, and enamines (Figure 2B). Herein we discuss the application of DA cyclopropanes in the synthesis of cyclopentane and cyclopentene compounds.

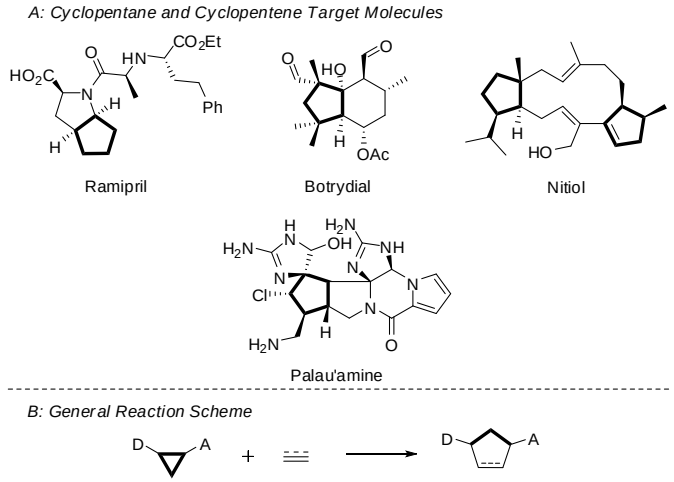
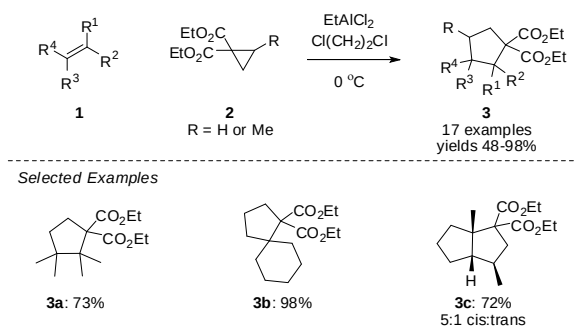


Figure 2: Cyclopentane and Cyclopentene Containing Target Molecules

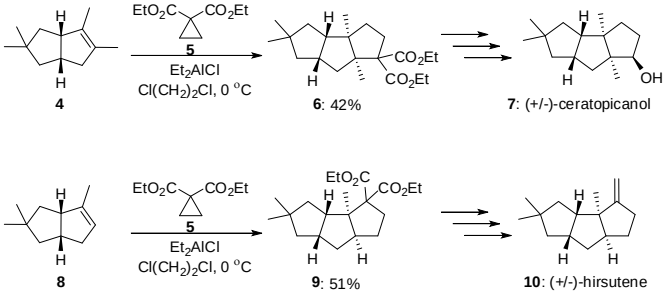
1a. Intermolecular Reactions with Alkenes

One of the first Lewis acid mediated intermolecular annulation reactions for DA cyclopropanes with alkenes was reported in 1986 by Snider et al. (Scheme 1).[4] It was quickly recognized that unlike previous work with DA cyclopropanes[5] the alkene proved too unreactive to partner with cyclopropanes bearing single carbonyl acceptor group, and thus the more reactive 1,1-cyclopropanediester **2** was chosen as the starting material. Two equivalents of $EtAlCl_2$ mediated the reaction between cyclopropane **2** and a selection of di-, tri-, and tetra-substituted alkenes **1** to produce cyclopentanes **3**. The reaction conditions were robust allowing for both acyclic and cyclic (cyclohexene derivatives) olefins to react smoothly, providing access to monocyclic, fused bicyclic, and spirocyclic cyclopentane moieties in moderate to excellent yields. Although the unsubstituted cyclopropanes (R=H) led to higher isolated yields of the product, when an alkyl substituted cyclopropane (R=Me) was employed the products were isolated with reasonable diastereoselectivity (5:1).



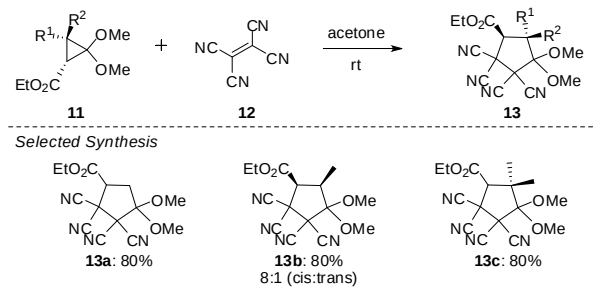
Scheme 1: Reactivity of Cyclopropanes and Alkenes

Over ten year later, Fitjer and co-workers were able to showcase Snider's conditions in the formal synthesis of both (+/-)-ceratopicanol (**7**) and (+/-)-hirsutene (**10**) (Scheme 2).[6] Olefins **4** and **8** underwent smooth transformation to the corresponding tricyclic systems **6** and **9** albeit in lower yields due to isolation of regioisomers in the case of **6** and ring-opened product in the case of **9**. These compounds were easily converted into intermediates that could be advanced to the natural products.[7]



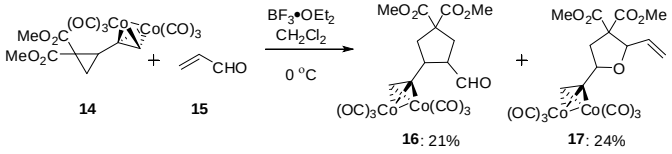
Scheme 2: Synthesis of Ceratopicanol and Hirsutene

Alternatively to Snider's Lewis acid mediated process, conditions were developed by Chiosi for the annulation of tetracyanoethylene **12** with cyclopropane **11** at room temperature in acetone (Scheme 3). While bearing only one acceptor group, this cyclopropane was laden with an extraordinarily powerful acetal donor moiety. This study showed the conversion of three cyclopropanes **11** to the corresponding cyclopentanes **13** in excellent yields and with excellent regioselectivity.[8] The results from Snider were paralleled by showing that additional substituents on the cyclopropane ring resulted in increased reaction times, although contrary to the previous report, yields were not affected. Interestingly, the methoxy acetals were unaffected during the reaction with no evidence of cyclopentanone products.



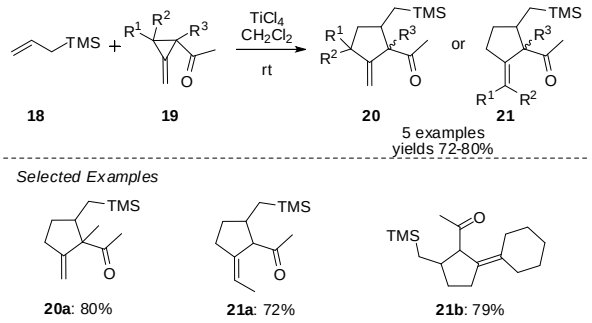
Scheme 3: TCNE Reactions with Cyclopropanes

Further expansion of the reactivity of alkenes with DA cyclopropanes was explored by Christie and Jones when they investigated the use of electron deficient olefins as suitable dipoles for the reaction with cyclopropanes **14** benefitting from a Nicholas type donor activation.[9,10] Although the carbocyclic product **16** was obtained, initial investigations showed that only minor amounts of this product could be formed (Scheme 4) alongside heterocycles **17**. Unable to develop this process for additional electron deficient olefins, the focus of the research continued with the optimization of heterocyclic products.



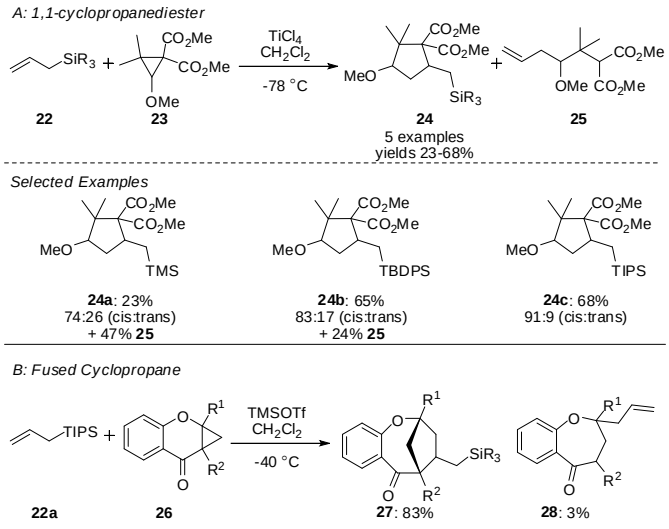
Scheme 4: Annulations with Electron Deficient Olefins

Independently, the groups of Monti and Sugita studied the $TiCl_4$ mediated transformation of allylsilanes with DA cyclopropanes. In two separate reports, Monti showed the reaction of methylenecyclopropylketones **19** with allyltrimethylsilane **18** to produce substituted cyclopentanes **20** and **21** (Scheme 5).[11] Although most examples gave mixtures of **20** and **21** it was determined that product **21** could be formed selectively when R^3=H.



Scheme 5: Reaction of Cyclopropane **19** and Allylsilanes

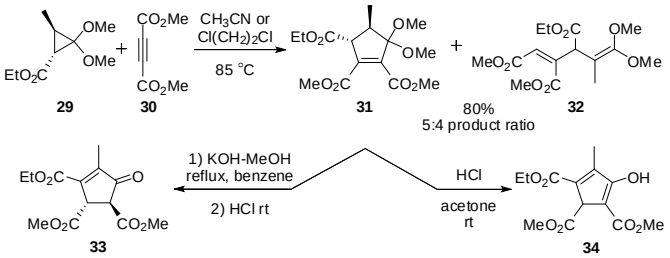
Sugita investigated this transformation with alkoxy-activated cyclopropanes. At low temperatures, $TiCl_4$ promoted the smooth reaction of cyclopropane **23** with a series of allylsilanes **22** (Scheme 6A).[12] General trends showed that higher yields and *cis* selectivities of **24** were achieved when larger silyl groups were employed (TIPS). In the same report, Sugita also showed that this transformation could be expanded to the fused tricyclic cyclopropane **26** to access **27** in the presence of TMSOTf, although lower yields and diastereoselectivity were observed (Scheme 6B).



Scheme 6: Annulation of Allylsilanes and Cyclopropanes

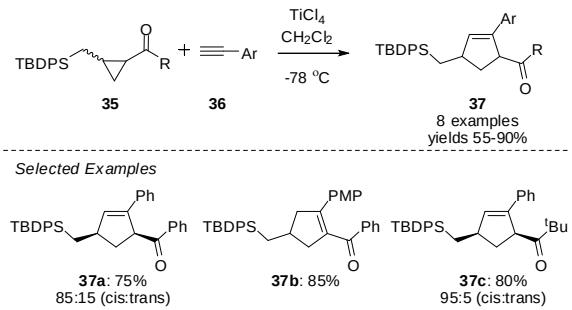
1b. Intermolecular Reactions with Alkynes

Initial surveys into the reactions of DA cyclopropanes with alkynes were similar to the alkene work of Chiosi[8] requiring no external additives and being performed only under thermal conditions. The reaction of dimethyl acetylenedicarboxylate (DMAD) **30** and cyclopropane **29** led to the formation of cyclopentene **31** plus the ring-opened product **32** (Scheme 7).[13] Changing solvents and temperature led to an increase in the formation of **32** and under ideal conditions only a 5:4 (**31**:**32**) product ratio could be obtained. The cyclopentene product was then efficiently converted into cyclic enone **33** and cyclopentadiene **34** which showcased the utility of this method to access structurally unique carbocyclic scaffolds.



Scheme 7: Thermal Reaction of DMAD with Cyclopropanes

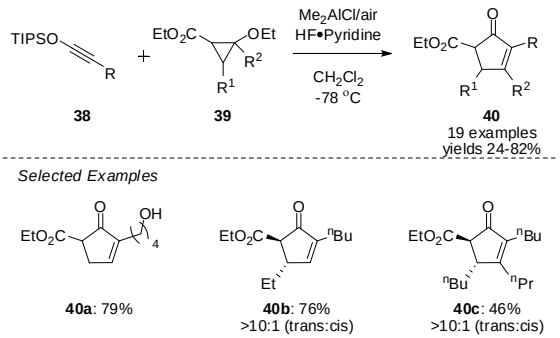
Yadav was able to display the reactivity of carbonyl-substituted cyclopropanes with aryl acetylenes under stoichiometric Lewis acid conditions.[14] A variety of aryl acetylenes **36** were treated with cyclopropane **35** in the presence of $TiCl_4$ to give cyclopentenes **37** in serviceable yields and *cis* selectivities up to 95:5 (Scheme 8). When p-methoxyphenylacetylene was used, acid-catalysed double bond migration happened readily; however, this could be supressed by the addition of K_2CO_3. Although a moderate substrate scope was explored, electron withdrawing aromatic acetylenes produced lower yields while alkyl and propargyl alkynes did not show the desired reactivity. Finally, the scope was expanded to include spirobicyclic cyclopropanes, which underwent the annulation in excellent yields and *cis* selectivities.



Scheme 8: Lewis Acid Mediated Annulation of Alkynes and Cyclopropanes

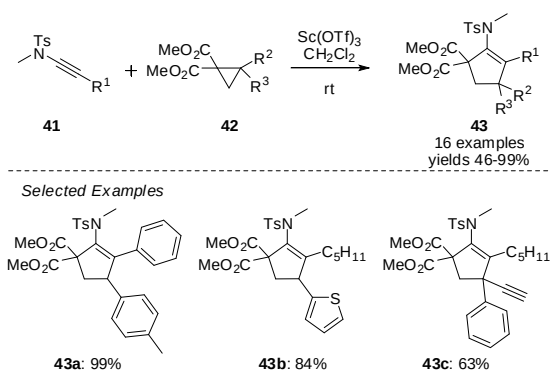
In 2008, Ready advanced the use of alkynes in this annulation to include ynol ethers.[15] Alkoxy activated cyclopropanes **39**

reacted modestly with silyl ynol ethers **38** in the presence of stoichiometric Me_2AlCl in air with a HF•Pyridine additive to access cyclopentenone **40** (Scheme 9). The active Lewis acid was presumed to be (MeO)$AlMeCl$[16] and the use of the additive was important for complete desilylation of the initial cycloadduct to give the desired enone. The reaction conditions were suitable for a range of alkyl ynols; however, low yields were observed for aromatic substrates. Additional trends showed that when the R^1 position of the cyclopropane was substituted, the product was obtained with diastereoselectivity towards the *trans* product (>10:1), and when the R^2 position was substituted, the product was obtained in lower overall yields.



Scheme 9: Cyclopropanes and Ynol ethers

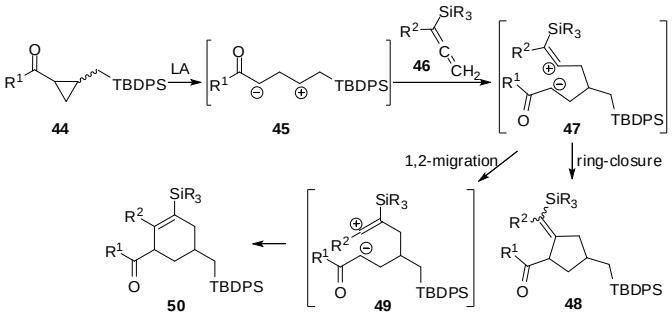
In related work, Johnson recently reported the Lewis acid catalysed annulation of ynamides **41** and cyclopropanes **42** to access substituted cyclopentenes **43** (Scheme 10).[17] In contrast to Ready's work, catalytic $Sc(OTf)_3$ was efficient in promoting the annulative transformation, and aromatic substitution on the ynamide was well tolerated. Electron rich aromatic substituted cyclopropanes underwent the reaction resulting in excellent yields of isolated product (up to 99%); however, electron poor, highly electron rich aromatic (p-NMe_2Ph), vinyl, and alkyl-substituted cyclopropanes were unreactive under the reaction conditions. Although optically enriched cyclopropanes showed product conversion with no erosion of enantiomeric excess under standard reaction conditions, typical DYKAT reaction conditions (MgI_2, pybox) proved ineffective with this system.[18]



Scheme 10: Cyclopropanes and Ynamides

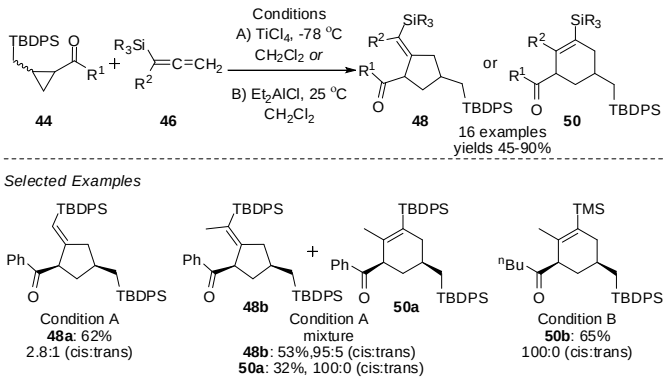
1c. Intermolecular Reactions with Allenes

To date, only one example of a Lewis acid-mediated intermolecular allene annulation has been reported.[19] Building on their success with alkynes, Yadav and co-workers have shown the synthesis of cyclopentane **48** and cyclohexene **50** via a Lewis acid mediated reaction of carbonyl cyclopropane **44** with allenylsilanes **46**. A proposed mechanism for the formation of both products is shown in Scheme 11. **48** was formed through the expected annulation pathway, while the cyclohexene **50** was formed presumably through a 1,2-migration of the allenylsilicon intermediate **47** to **49**.



Scheme 11: Proposed Mechanism for the Formation of **48** and **50**

The reactive $TiCl_4$ Lewis acid conditions readily promoted protodesilylation during the reaction leading to lower yields of isolated product. This process was able to be slowed by using larger silyl groups and through the use of Et_2AlCl. The formation of cyclopentane was favoured in modest to excellent yields by employing low reaction temperatures with $TiCl_4$ (**48b** vs **50a**) and could selectively be formed when there was no substitution on the allenylsilanes (e.g. **48a**) (Scheme 12). The cyclohexene product could be formed selectively in good yields when Et_2AlCl and higher temperatures were employed (e.g. **50b**). In most cases, regardless of the conditions used, the *cis* adducts were isolated (cyclopentanes up to 95:5 and cyclohexene up to 100:0 *cis*:*trans*).

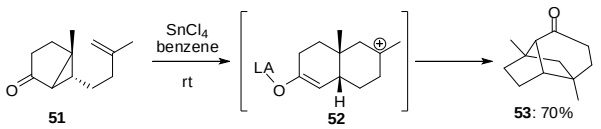


Scheme 12: Reaction of DA Cyclopropanes and Allenes

1d. Intramolecular Reactions

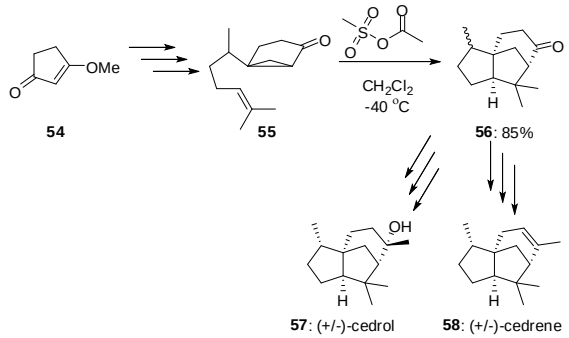
Although there has been great progress toward intermolecular reaction of DA cyclopropanes with carbon dipoles, much of

these advances would not be possible without the preliminary investigations by Stork[5,20] and Corey[21] on the intramolecular reaction of DA cyclopropanes to form polycyclic carbocycles.



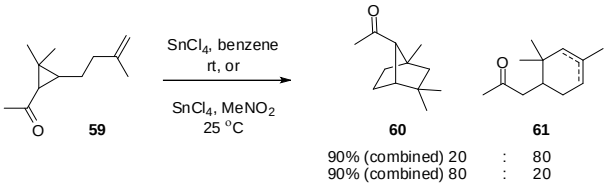
Scheme 13: Stork's Initial Results of the Intramoleular Reaction of Cyclopropane and Alkenes

Seminal work by Stork (Scheme 13) showed it was possible for ring-opening of acylcyclopropane **51** to occur followed by trapping of the corresponding intermediate **52** with the enolate to form bridged bicyclic compound **53** under the mediation of stoichiometric $SnCl_4$. Although only one substrate was evaluated, Stork insisted, "this efficient cyclization should be a fairly general route to various bicycle[2.2.1]heptanes." Corey investigated the use of these conditions with a similar acylcyclopropane **55** system in the formal synthesis of (+/-)-cedrene **57** and (+/-)-cedrol **58** (Scheme 14). Initial investigations showed that only small amounts of the desired bridged bicycle **56** were obtained using $SnCl_4$ and other protic or Lewis acids. Fortunately, annulation was achieved using a reactive acetylating agent resulting in a high yield of **56**. When optically enriched cyclopropane was exposed to the reaction conditions, a cyclization product was obtained as a single stereoisomer. This result agrees with the work of Stork that the cyclization occurs synchronously with cleavage of the cyclopropane ring.



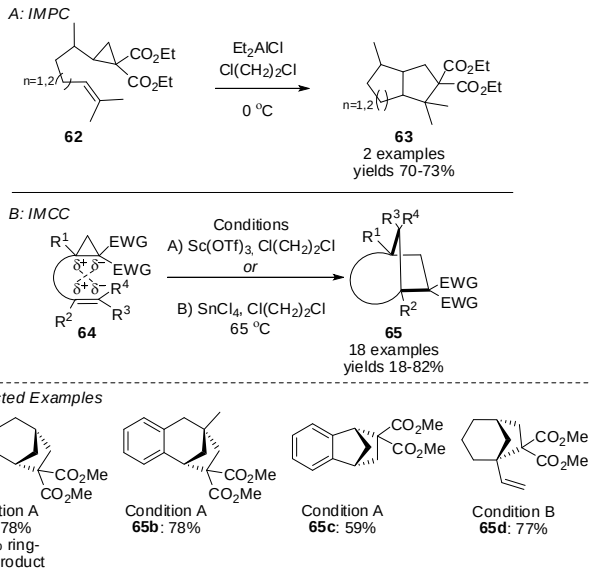
Scheme 14: Synthesis of Cedrol and Cedrene

Grieco displayed an expansion of this chemistry to non-rigid acylcyclopropanes **59** in 1974.[22] It was determined that solvents had a large effect on the product distribution of the desired bridged bicyclic product **60** and cyclohexene **61** (Scheme 15). When the reaction was performed in non-polar solvents, cyclohexene **61** was the major product; however, when more common polar cycloaddition solvents were employed the **60** was isolated as the major product. This work showed versatile access to simple bridged bicyclic compounds and was an influential example to the development of this field.



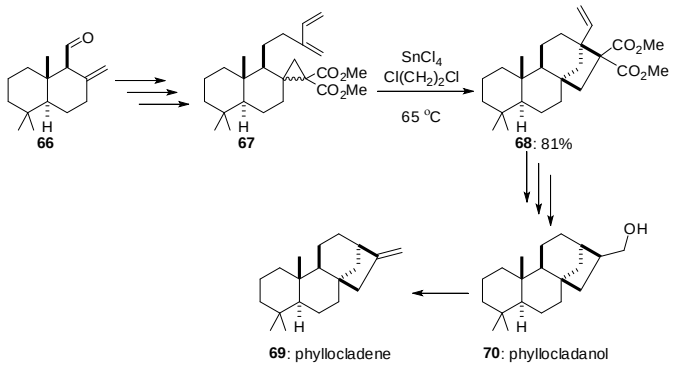
Scheme 15: Intramolecular Annulation of Non-rigid Cyclopropanes with Alkenes

In 1986, Snider was able to show the use of their previously described conditions (see Scheme 1) for the related intramolecular parallel cycloaddition (IMPC) of 1,1-cyclopropanediester **62** to gain access to fused bicarbocycle **63** in good yields (Scheme 16A).[4] More recently, Wang and co-workers showed the first Lewis acid catalysed intramolecular reaction of alkenes with cyclopropanes (Scheme 16B).[23] Moreover, they showed they could manipulate the regiochemical outcome of the product by modifying the directing effects of the alkene, thus allowing for bridged bicyclic compounds **65** to be formed through an intramolecular cross cycloaddition (IMCC) pathway.



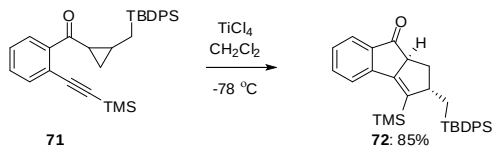
Scheme 16: IMPC and IMCC Reactions of Alkene-Substituted Cyclopropanes

The reaction conditions developed by Wang were suitable for a variety of styrenyl connected cyclopropanes allowing access to **65** in average to excellent yields regardless of the substitution pattern. Typically, the [3.2.1] bridged bicycles were isolated in higher yields than the [2.2.1] systems (e.g. **65b** vs **65c**). Additionally, the reaction conditions showed no erosion of *ee* when optically enriched cyclopropanes were used. Alkyl tethered cyclopropanes also proved to be effective substrates; however, they required additional activation by two methods: 1) incorporation of a vinyl substituent was required, and 2) a hard Lewis acid catalyst ($SnCl_4$) was required to promote efficient activation (e.g. **65d**). In the same report, Wang also presented the application of this method to the synthesis of two terpenoid natural products phyllocladanol (**70**)[24] and phyllocladene (**69**)[25] (Scheme 17).



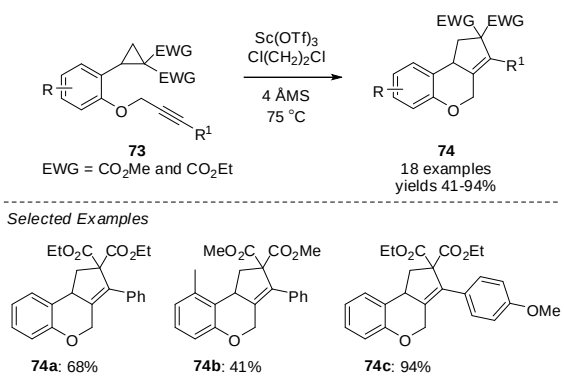
Scheme 17: Synthesis of Phyllocladene and Phyllocladanol

Unlike their alkene counterpart, little research has been undertaken into the Lewis/protic acid intramolecular reaction of alkynes with cyclopropanes. The first example was reported in Yadav's original alkyne annulation paper with carbonyl cyclopropylmethylsilanes.[14] $TiCl_4$ mediated cyclization of **71** furnished **72** in 85% yield with excellent *cis* selectivity (Scheme 18).



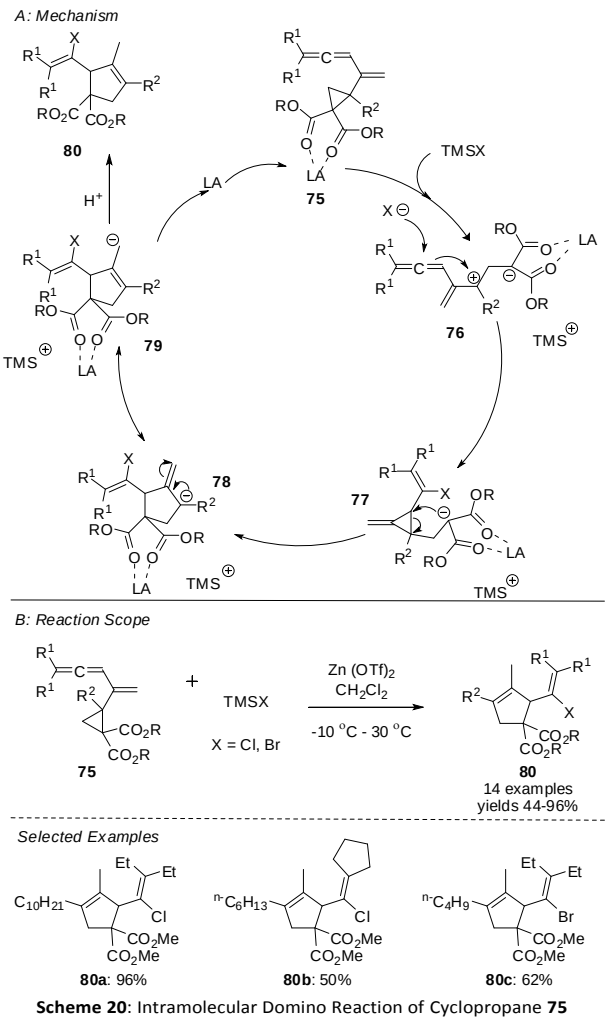
Scheme 18: Intramolecular Annulation of Alkyne-Substituted Cyclopropane **71**

Work by Liang and co-workers, showed that 1,1-cyclopropanediesters **73** could undergo Lewis acid catalysed intramolecular cyclization providing a direct route to cyclopenta[*c*]chromene **74** (Scheme 19).[26] In general, the reaction conditions were robust; electron-donating groups on the benzene ring resulted in the highest yields, while electron-withdrawing groups gave lower yields or were not tolerated. Yields were significantly decreased when ortho-substituents on the benzene ring were explored (e.g. **74b**), likely due to steric interactions. Although the reaction could have been performed on large scale, only aromatic substitution on the alkyne was tolerated (alkyl and terminal show no reactivity). Finally, Liang was able to show that a nitrogen atom could be incorporated into the tether to access nitrogen based products.



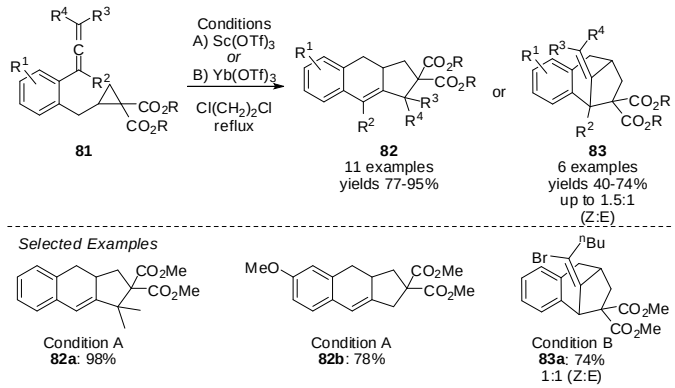
Scheme 19: Synthesis of Cyclopenta[*c*]chromene *via* an Intramolecular Reaction

Over the last few years, the Ma group has made great strides in the area of zinc catalysed intramolecular domino reactions of allene-substituted cyclopropanes **75** to afford vinyl cyclopentenes **80**.[27] The formation of **80** can be understood by the proposed mechanism (Scheme 20A). Initial ring-opening via Lewis acid bond cleavage would form 1,3-zwitterionic intermediate **76**. Next, nucleophilic attack of halide X^- followed by intramolecular cyclopropanation would form intermediate **77**, which could then be opened by the stabilized enolate to give **78**. Finally, protonation would give product **80**. The reaction conditions worked efficiently for a large array of substitutions on the allene as well as quaternary cyclopropane substitution (Scheme 20B). Lower yields were reported with TMSBr (e.g. **80c**) in comparison to TMSCl and when cyclic allenes were explored (e.g. **80b**). This unusual transformation allowed for construction of unique highly substituted cyclopentene rings with a versatile vinyl functional handle that will undoubtedly allow for this method to be utilized in the synthesis of complex target molecules.



Scheme 20: Intramolecular Domino Reaction of Cyclopropane **75**

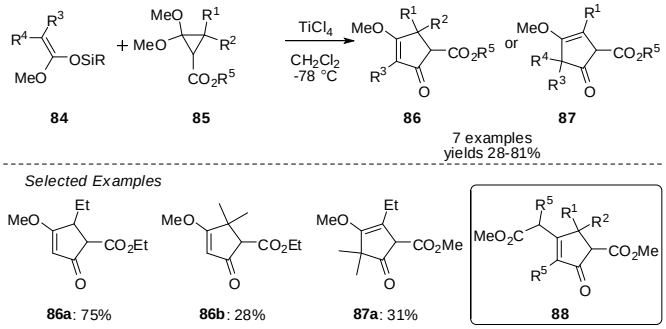
The most recent intramolecular transformation of allenes and cyclopropanes was reported by the Wang group in their exploration of the intramolecular utility of 1,1-cyclopropanediesters.[28] Wang discovered that, much like the intramolecular alkene annulations, cyclopropane **81** could follow a parallel (IMPC) or cross (IMCC) reaction pathway to produce fused [4.3.0]nonane bicycles **82** or bridged [3.2.1]octane bicycles **83**, respectively (Scheme 21). By varying the Lewis acid catalyst, Wang showed the product could be biased towards one product over the other. When $Sc(OTf)_3$ conditions were engaged, bicyclo[4.3.0]nonanes **82** were isolated selectively. These conditions were tolerant of a range of substitution on the cyclopropane starting material, with the exception of bulky substituents on the terminal allene position of the cyclopropane which favoured the formation of the [3.2.1]octane bicycles. When $Yb(OTf)_3$ conditions were employed, [3.2.1]octane bicycles **83** were accessed with moderate regioselectivity up to 2.2:1 (**83**:**82**). The selectivity could be improved by simply adding a halogen to the terminal end of the allene starting material, allowing for complete conversion to the [3.2.1]octane bicycles (**83a**).



Scheme 21: IMPC and IMCC Reaction of Allenylcyclopropane **81**

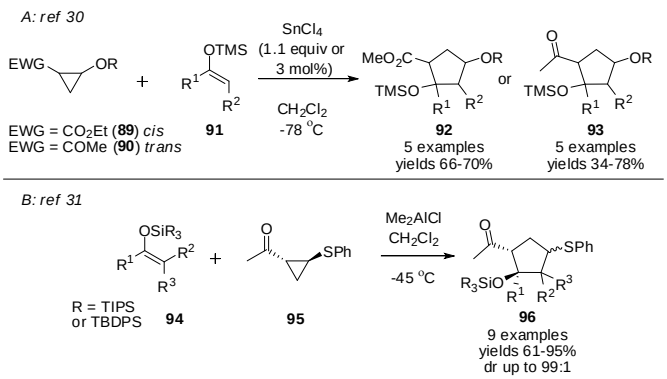
1e. Reactions with Enol Ethers

Over the last 25 years, there has been significant interest in the use of enol ethers and ketene acetals as dipoles for the annulation reaction with cyclopropanes. Studies have revealed successful reactivity with a large array of different DA cyclopropanes, and both diastereoselective and enantioselective methods have been developed. One of the first reports in this field was presented in 1990, showcasing the use of 2,2-dialkoxycyclopropanes **85** with a series of silyl ketene acetals to access the desired cyclopentenone **86** or **87** depending on the cyclopropane used (Scheme 22).[29] While $TiCl_4$ mediated conditions allowed for practical conversion to the desired products, the reaction conditions proved to be non-selective, typically leading to a mixture of four diastereomers. In some cases, when excess ketene was used, addition product **88** was also observed in small quantities.



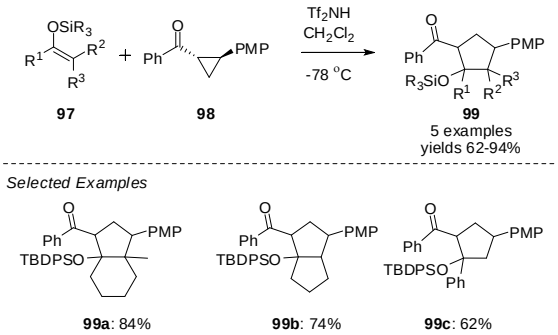
Scheme 22: Preliminary Investigations into the Reaction of DA Cyclopropanes and Silyl Enol Ethers

Shortly after this seminal work, Kuwajima and co-workers published two papers on the exploration of the use of alkoxy and phenylsulfide activated cyclopropanes as reaction partners with silyl enol ethers (Scheme 23A/B). In the case of alkoxycyclopropane esters **89**, product formation (**92**) could be attained in good overall yields as a mixture of stereoisomers with stoichiometric amounts of $SnCl_4$ (Scheme 23A).[30] These conditions were accepting of a wide range of silyl enol ethers including disubstituted and cyclic examples (from cyclohexanone etc.); however, trisubstituted enol ethers proved unreactive. In the same report, it was determined that alkoxycyclopropane ketones **90** were too reactive for the use of stoichiometric amounts of $SnCl_4$ leading to dimerization of the starting material. To overcome this issue, a catalytic amount of the Lewis acid were used allowing for low to moderate product conversion with silyl enol ethers. While this report did show the first Lewis acid catalysed addition of enol ethers and DA cyclopropanes, the selectivity of the reaction was poor leading to complex mixtures of stereoisomers.



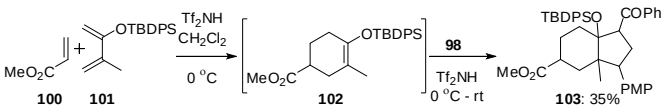
Scheme 23: Reactions of Alkoxy- and Phenylsulfide-subsituted Cyclopropanes with Silyl Enol Ethers

Kuwajima next showed a diastereoselective process using 2-phenylthiocyclopropane **95** (Scheme 23B).[31] It was determined that increasing the steric bulk of the silyl group (TIPS or TBDPS) led to diastereoselective product formation (**96**) up to 99:1. Additionally, the rate of starting material dimerization could be minimized using aluminum reagents instead of tin, leading to overall higher yields and larger substrate scopes than previously reported.



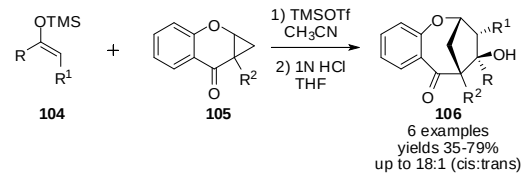
Scheme 24: Triflimide Catalysed Reactivity of Cyclopropylketones

In a similar manner to the work of Kuwajima, the Ihara group showed the triflic imide catalysed annulation of silyl enol ethers and p-methoxyphenyl (PMP) activated cyclopropanes **98** to access cyclopentanes **99** (Scheme 24).[32] The conditions were favourable for cyclic silyl enol ethers (cyclohexanone derived) and diminished yields were seen for acetophenone derived enol ethers. Results paralleled that of Kuwajima's first report, showing little to no diastereoselectivity under these reaction conditions. To showcase the diversity of their catalytic conditions, the group applied them to a multi-component sequential Diels-Alder/[3+2] annulation reaction to produce highly substituted **103** in modest overall yield (Scheme 25).



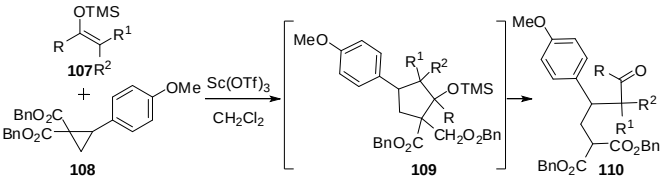
Scheme 25: Multi-component Sequential Diels-Alder/[3+2] Annulation Reaction

In 1999, Sugita et al. highlighted once again the use of catalytic TMSOTf conditions in the synthesis of bridged[4.2.1] bicycles. This catalytic method allowed a range of silyl enol ethers to react with fused cyclopropane **105** to give low to serviceable isolated yields of the desired product with usable *cis/trans* ratios up to 18:1 (Scheme 26).[33] The report gave a small substrate scope indicating that substitution on the cyclopropane greatly decreased the yield of the desired product and increased yields of the ring-opened product.



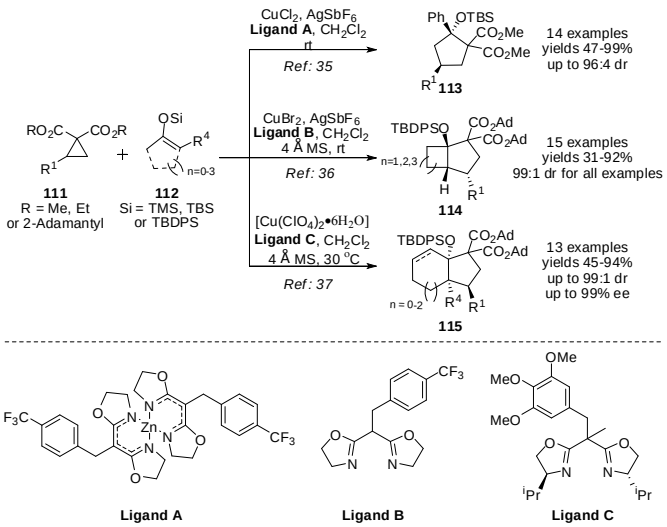
Scheme 26: TMSOTf Catalysed Reaction of **104** and **105**

Near the end of 2008, investigations by Wang[34] showed the annulation of cyclopropane **108** with silyl enol ethers to be rather difficult, as the cyclic products **109** readily underwent retro-aldol reactions to produce high yields of the acyclic product **110** under Lewis acid conditions (Scheme 27). Under optimal conditions, only a few cyclic products could be isolated and in very low yields.



Scheme 27: Initial Investigations into the Reaction of 1,1-cyclopropanediesters with Enol Ethers

The Tang group began investigations on the reactivity of 1,1-cyclopropanediesters in the hopes of developing a highly enantioselective process for the [3+2] annulation reaction with silyl enol ethers. Their initial exploration into this field required finding ideal conditions for the suppression of acyclic by-product **110** (Scheme 27). It was quickly discovered that the acyclic by-product of the annulation process could be minimized by modifying two simple aspects of the reaction: 1) by changing the Lewis acid, and 2) by increasing the steric bulk of the silyl group.[35] Making both of these modifications showed a significant increase in yield and the selectivity now favoured the desired cyclopentane ring over the acyclic product. Finally, they discovered that if both changes were made along with the addition of a bulky bisoxazoline dimer ligand (**A**), not only was the acyclic product suppressed completely but the desired products **113** were isolated with good to excellent diastereomeric ratios (Scheme 28). The reaction conditions were compatible with a variety of aromatic substituted cyclopropanes with lower yields observed for the less stable vinyl and heteroaromatic substituted cyclopropanes. The silyl enol ether could also be changed; however, when cyclic examples were employed (cyclohexanone derived), a decrease in yield and loss of diastereoselectivity was observed.

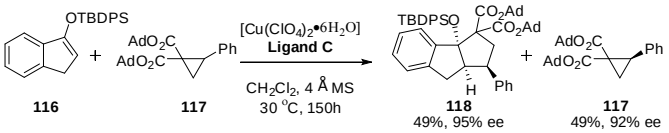


Scheme 28: Tang's Work Towards the Enantioselective Reaction of Cyclopropanes and Silyl Enol Ethers

In hopes of overcoming this selectivity problem and gaining access to fused bicyclic cyclopentane derivatives, Tang needed to develop a new set of reaction conditions.[36] Once again, they exploited the idea of steric bulk. By surveying an assortment of

different ester-substituted cyclopropanes, it was discovered that when sterically bulky 2-adamantyl diester cyclopropanes **111** were employed with silyl enol ethers containing large silyl groups (TDBPS), smooth annulation occurred with excellent diastereoselectivity (Scheme 28). Again, by utilizing a bisoxazoline ligand (**B**), the bicyclic products **114** could be isolated in high yields and near perfect diastereoselectivity. The conditions were tolerant of a range of aromatic cyclopropanes with lower yields again being observed for the less stable vinyl and heteroaromatic substituted cyclopropanes. A variety of different ring sized silyl enol ethers could also be used with the trend that the smaller ring sizes gave higher product yields.

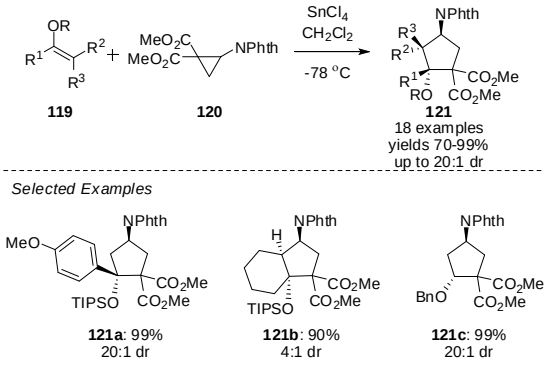
The most recent stage of Tang's research focused on enantioselective conditions for the synthesis of cyclopentanes from cyclopropanes and silyl enol ethers. In 2013, such enantioselective conditions for the dynamic kinetic asymmetric transformation (DYKAT) were discovered (Scheme 28).[37] The conditions worked well for highly activated electron rich aromatic cyclopropanes (almost exclusively) allowing access to cyclopentanes **115** in good to excellent yields with moderate to excellent diastereoselectivity and overall excellent enantiomeric excess. Again, a similar trend was shown for the cyclic silyl enol ethers, where the smaller ring sizes gave overall higher yields and greater diastereoselectivity. Additionally, the conditions developed worked for less electron rich aromatic cyclopropanes (**117**); however, they proceeded in a kinetic resolution fashion and typically required increased reaction times (Scheme 29). Further exploration into this process is currently underway.



116 **117** **118** 49%, 95% ee **117** 49%, 92% ee

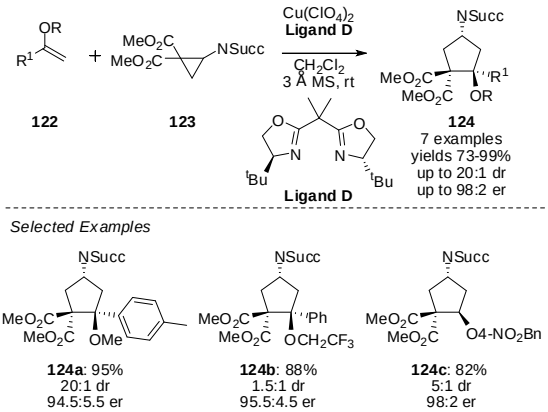
Scheme 29: Kinetic Resolution of Less Activated DA Cyclopropanes with Silyl Enol Ethers (for ligand C see Scheme 28)

Recently, Waser became engaged in investigating the reactivity of amino-activated cyclopropanediesters toward the same [3+2] reaction process with enol ethers. In 2011, the first of two papers in this area were published showing the first catalytic [3+2] annulation of aminocyclopropanes (Scheme 30).[38] The appropriate phthalimidocyclopropane **120** was discovered to be the ideal cyclopropane starting material for this transformation. Unlike previous reports by Kuwajima[30,31] and Ihara,[32] it was found that the mono-carbonyl cyclopropanes were unreactive to a variety of reaction conditions. Initial Lewis acid screening proved very important to find a suitable catalyst that would minimize the formation of any unwanted acyclic products. $SnCl_4$ was selected as the best catalyst allowing for great conversion to the corresponding cyclopentanes **121** in excellent yields with modest to great diastereoselectivity up to 20:1. The reaction conditions were tolerant of many different substituted silyl enol and alkyl enol ethers, and in contrast to Tang's work, the size of the silyl group had little to no effect on the selectivity of the reaction. Although a large substrate scope was evaluated, a few examples resulted in diminished yields and selectivities, including trisubstituted, aliphatic substituted, and cyclic silyl enol ethers, as well as 3,4-dihydropyran enol ethers. It was also shown that when optically enriched phthalimidecyclopropane **120** was subjected to the reaction conditions with a series of silyl enol ethers, little to no erosion of enantiomeric purity was observed.



Scheme 30: Diastereoselective Annulation of Enol Ethers and Aminocyclopropanes

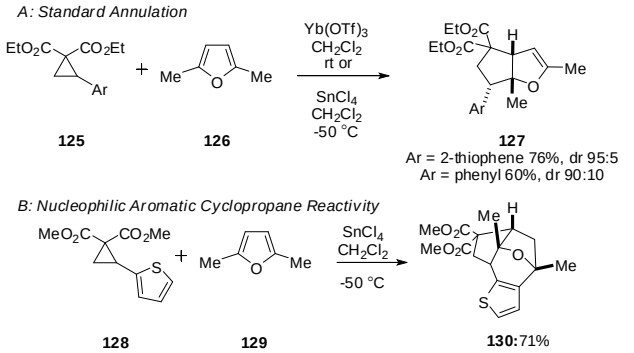
Waser next explored a DYKAT method for the synthesis of aminosubstituted cyclopentanes. This result was realized in early 2014 by utilizing a succinimidocyclopropane **123**, a bulky bisoxazoline ligand (**D**), and by replacing the silyl group on the enol ether with an alkyl group (Scheme 31).[39] Parallel to Tang's result, the overall [3+2] annulation worked well with a variety of different enol ethers, giving high yields, moderate to excellent diastereomeric ratios, and excellent enantiomeric excess in most cases. The reaction could be performed on gram scale without significant loss of yield or stereocontrol. Further experiments are underway to establish the origin of asymmetric induction.



Scheme 31: DYKAT Reaction of Aminoactivated Cyclopropanes and Enol Ethers

Finally, 2,5-dimethylfuran had also been shown to be a suitable dipole for the [3+2] annulation of cyclopropanes, although only a limited substrate scope had been displayed (Scheme 32A). In fact, only 2-thienyl and phenyl substituted cyclopropanes **125**

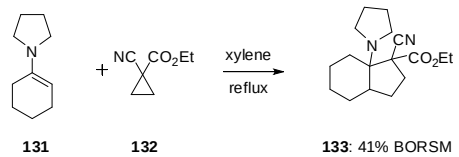
underwent cyclization with furan **126** to give the desired cycloadduct **127** under $Yb(OTf)_3$ or $SnCl_4$ conditions, respectively.[40] Additionally, it was shown that when thienyl cyclopropane **125** was subjected to $SnCl_4$ conditions, the desired cycloadduct underwent a subsequent electrophilic aromatic substitution reaction with the furan ring to give **130** (Scheme 32B).



Scheme 32: Reactions with 2,5-dimethylfuran

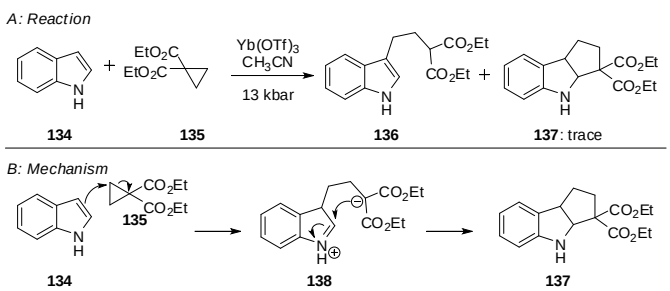
1f. Reactions with Enamines

Since the historical discovery of the thermal enamine annulation with cyclopropanes displayed by Dolfini (Scheme 33),[41] this field of research has been dominated by one type of enamine: the highly reactive indole.



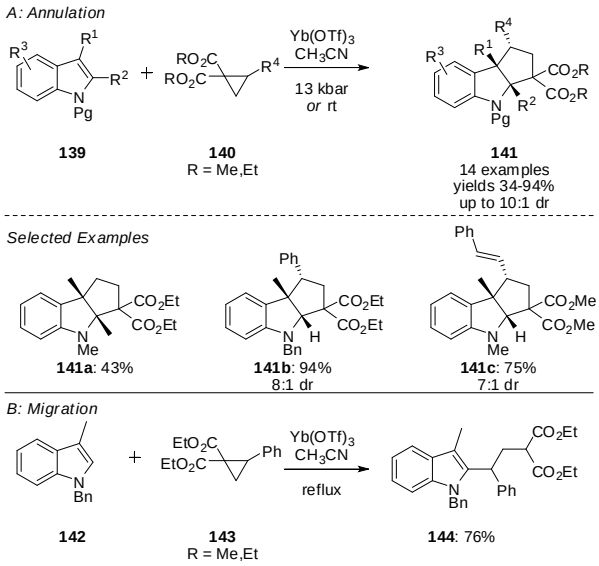
Scheme 33: Seminal Reaction of Enamines with Cyclopropanes

During the development of a follow up project on the alkylation of indoles with α,β–unsaturated ketones,[42] Kerr et al. explored the use of DA cyclopropanes as a homologous evolution of this work. Their preliminary results showed that when using catalytic $Yb(OTf)_3$ under high pressure conditions, indole **134** could open cyclopropane **135** (Scheme 34A);[43] however, a trace amount of the **137** was formed as well, presumably through nucleophilic ring-opening followed by Mannich type trapping by the corresponding malonic enolate (Scheme 34B).[44]



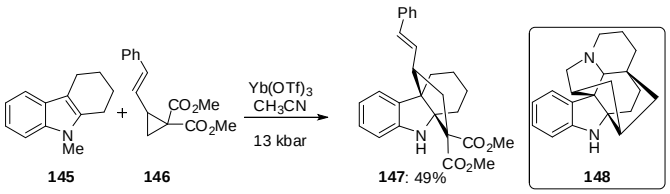
Scheme 34: Preliminary Investigation into the Annulation of Indoles with Cyclopropanes

Encouraged by the formation of **137**, the Kerr group next set out to optimize this [3+2] annulation process. It was discovered that placing a substituent on the three position of the indole allowed for direct conversion to the annulated **141** product using both thermal and hyperbaric conditions (Scheme 35A).[45] The reaction proceeded well with 2- and 3-substituted indoles and various substituted cyclopropanes to access the cyclic **141** as the major product.However when high temperature conditions were utilized, the formation of migration product **144** became a competing and sometimes major product (Scheme 35B). It was later determined that when cyclic product **141** was heated under Lewis acid conditions, conversion to **144** was observed providing evidence for the reversibility of this process.[45b]



Scheme 35: Annulation of DA Cyclopropanes with 3-substituted Indoles

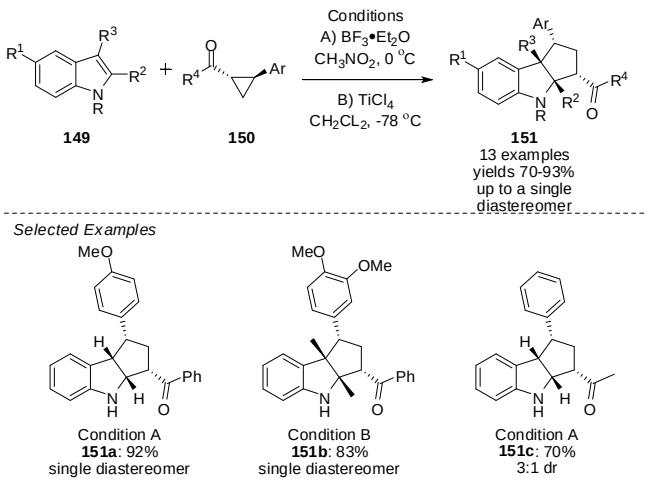
When less activated cyclopropanes were used (R^4 = Me or H), hyperbaric conditions resulted in the highest yields. When more activated cyclopropanes were used (R^4 = phenyl, vinyl, or styrenyl), ambient room temperature conditions resulted in higher yields. To display the utility of this transformation, the key tetracyclic subunit of the kopsane alkaloid **148** was synthesized by the reaction of cyclopropane **146** with tetrahydrocarbazole **145** (Scheme 36).



Scheme 36: Synthesis of the Kopsane Core

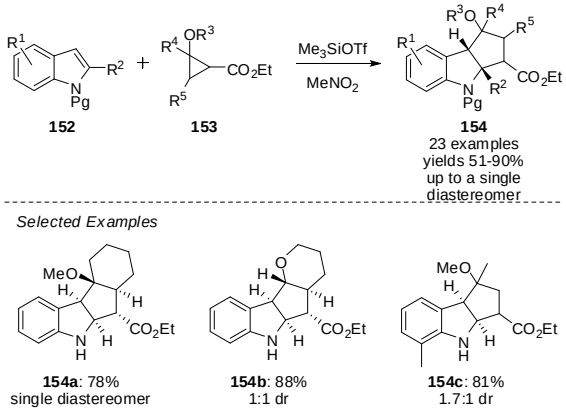
The groups of Ila and Pagenkopf then showed expansions of this chemistry with different DA cyclopropanes. In 2006, Ila showed that *trans* cyclopropylketones **150** could undergo annulations with indoles to give products **151** in highly

diastereoselective yields under BF_3•Et_2O mediated conditions (Scheme 37).[46] Electron rich aromatic substituents on the cyclopropane led to isolated products as a single diastereomer, while electron neutral (Ar = phenyl) cyclopropanes led to diastereomeric mixtures, similar to that seen by Kerr. When highly activated (Ar = 3,4-dimethoxyphenyl) cyclopropanes were used, modified $TiCl_4$ conditions were required. To expand the scope of their study, the reaction conditions were applied to the 1,1-cyclopropanediester starting material and similar results to those of Kerr were observed. It is noteworthy that under these reaction conditions, little to no migration product was observed as in the case with $Yb(OTf)_3$. This result can presumably be attributed to the low reaction temperatures employed.



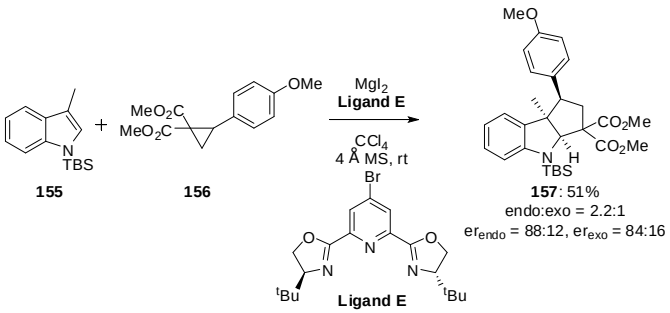
Scheme 37: Reactivity of Cyclopropylketones with Indoles

In 2007, Pagenkopf showed that alkoxy-activated cyclopropanes could undergo annulation reactions with indoles in the presence of TMSOTf.[47] In contrast to previous reports, the annulation of cyclopropanes **153** was achieved in high yields using 2,3-unsubstituted and 2-substituted indoles **152** (Scheme 38); in fact, when 3-substituted indoles were employed under these reaction conditions, only the migration and elimination products were observed. The reaction conditions were suitable for a series of alkoxy-activated cyclopropanes with highest diastereoselectivities (single diastereomer) coming from structurally restricted cyclopropanes (e.g. **154a**). In general, the unfused cyclopropanes resulted in the lowest yields (e.g. **154c**) while the fused cyclopropanes gave good to excellent yields of the product. Additionally, the reaction conditions were tolerant of many different substituents on the benzenoid ring of the indole.



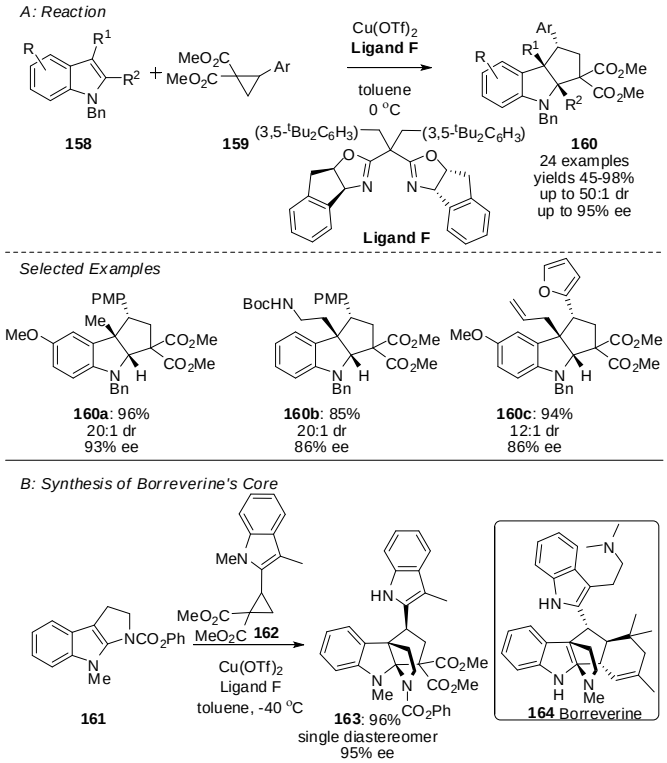
Scheme 38: Reactivity of Alkoxycyclopropanes with Indoles

The next progression in this vein was the development of asymmetric reaction conditions for the synthesis of enantioenriched cyclopentan[*b*]indoles. While continuing their work on dynamic kinetic asymmetric transformation reactions of DA cyclopropanes,[48] Johnson reported the first asymmetric synthesis of indole homo-Michael adducts via cyclopropanes.[49] This DYKAT method using pybox ligand (**E**) and catalytic MgI_2 was very efficient for the alkylation of indoles with cyclopropanes (er up to 97:3). While not the focus of this work, Johnson did show that this process could be applied to the annulation process when 3-methyl indole was employed (Scheme 39).



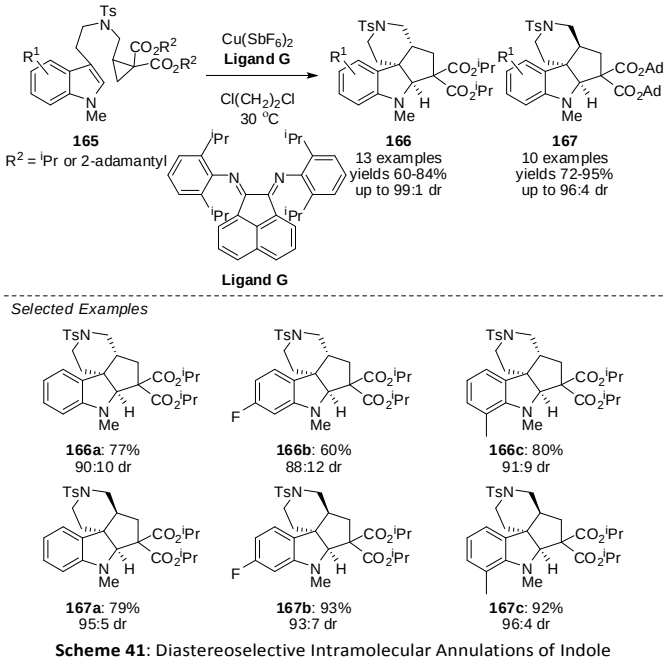
Scheme 39: Preliminary Results for the Asymmetric Reaction of Indoles and Cyclopropanes

In 2013, Tang was able to develop a highly enantioselective cyclopentannulation reaction of indoles and DA cyclopropanes (Scheme 40A).[50] Much like their work with enol ethers, this process worked well with activated (p-methoxyphenyl) cyclopropanes **159** in almost all cases, giving good diastereoselectivity and high enantioselectivity of **160**. Lower yields and selectivities were observed when less activated cyclopropanes were utilized (e.g. 2-furyl, vinyl, p-iodophenyl). To showcase this method, Tang devised a short synthesis to the core of Borreverine **164** in very high yield and as a single diastereomer (Scheme 40B).



Scheme 40: Synthesis of **160** *via* a DYKAT Reaction of Cyclopropanes and Indoles

In a recent expansion of this work, Tang has developed a highly switchable diastereoselective intramolecular [3+2] annulation of cyclopropanes and indoles.[51] Extensive optimization led to the use of diimine ligand (**G**) and catalytic copper, which provided modest diastereoselectivity of the products **166** (83:17 dr). Upon further optimization, when the esters were changed from methyl to isopropyl, an increase in diastereoselectivity was observed (90:10). Additionally, when larger adamantyl groups were used, the selectivity reversed to the other diastereomer **167**. Both esters were tested with a variety of benzenoid substitutions, leading to high yields and excellent selectivities of both isomers of the unique pentacyclic structure (Scheme 41).



Scheme 41: Diastereoselective Intramolecular Annulations of Indole

2. 6-Membered Carbocycles from DA Cyclopropanes

Much like their five membered counterpart, the cyclohexane ring is an important structural moiety in natural products. Its structure is ubiquitous in a variety of naturally, pharmaceutically, and historically relevant molecules (Figure 3)[52] and thus synthetic methods devoted to the synthesis of cyclohexanes are of high interest and value. In contrast to cyclopentanes, less research has been devoted to the [3+3] annulation of cyclopropanes to access cyclohexanes.

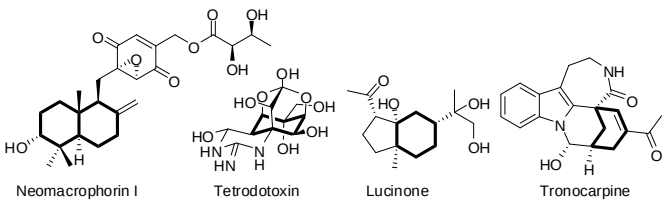
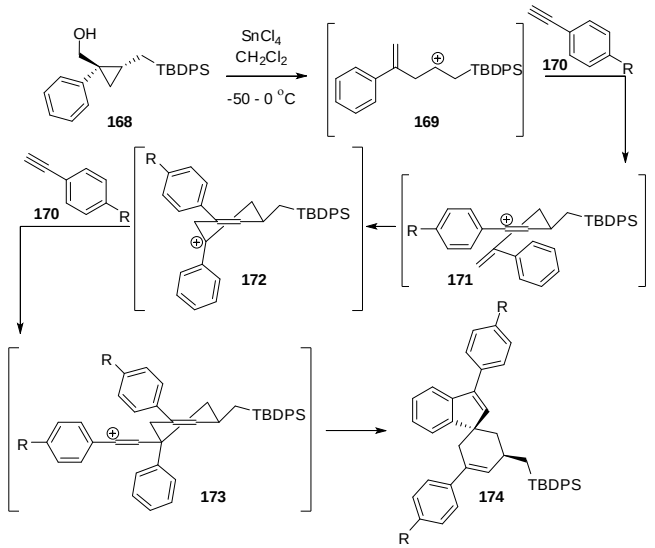


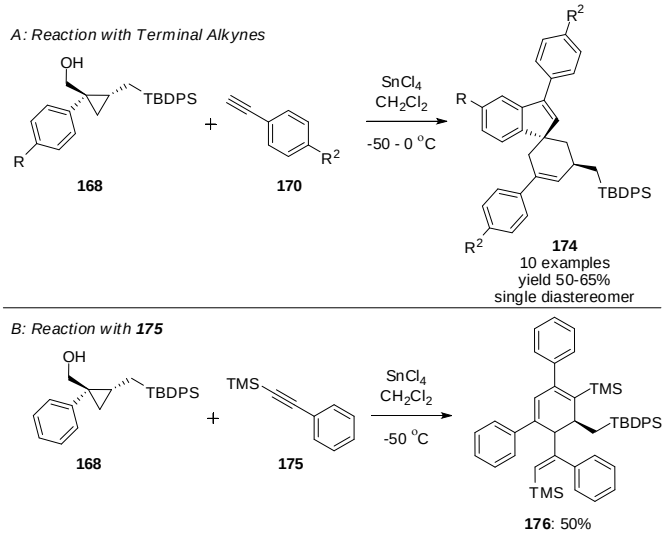
Figure 3: Cyclohexane Containing Target Molecules

Yadav reported the addition of two equivalents of alkynes with cyclopropane **168** to access spriocyclic compounds **174** (Scheme 42).[53] Ring-opening of the cyclopropane with $SnCl_4$ led to silicon stabilized cation **169** which could react with an alkyne to give arylvinyl cation **171** followed by trapping with the newly formed olefin. Styrenyl cation **172** could then be attacked by another equivalent of alkyne to give arylvinyl cation **173**, which could then be trapped by the aromatic ring (from the cyclopropane) to give the observed product.



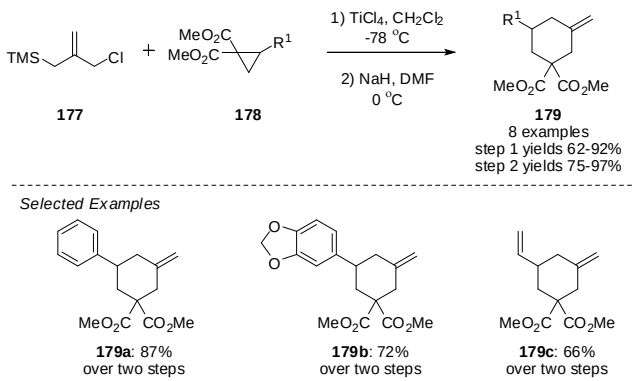
Scheme 42: Mechanism for the Formation of Spirocycle **174**

The conditions worked well for electron neutral aromatic cyclopropanes reacting with a series of electron neutral alkynes giving diastereomerically pure products **174** in reasonable yields (Scheme 43A). The stability of the vinyl cation intermediates was presumably the reason electron poor alkynes were ineffective. When TMS phenyl alkyne **175** was used under the standard reaction conditions, cyclohexadiene **176** was formed in a modest yield (Scheme 43B). It is proposed that **176** was formed through the elimination of a **172** type intermediate followed by a subsequent reaction with another equivalent of alkyne.



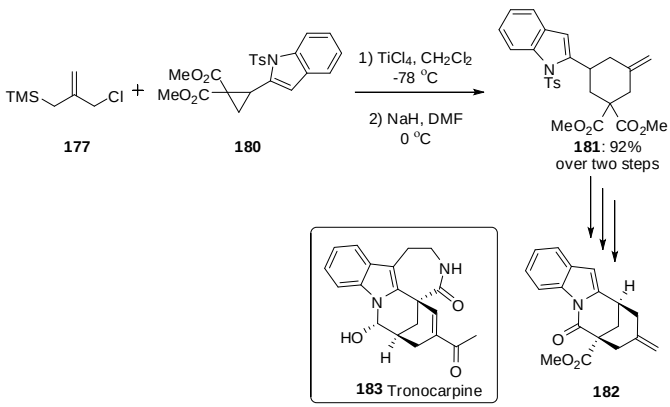
Scheme 43: Reactivity of Cyclopropane **168**

In 2009, Kerr and co-workers reported the reaction of 1,1-cyclopropanediesters **178** with 2-(chloromethyl)-3-trimethylsilyl-1-propane **177** as a trimethylenemethane (TMM)[54] equivalent in the synthesis of exo-methylenecyclohexanes **179** (Scheme 44).[55] After various attempts to promote this reaction via one-step palladium catalysis had proven unsuccessful, a sequential two-step Lewis acid mediated ring-opening followed by a base mediated ring closure was invoked to access the cyclohexane **179**.



Scheme 44: Reactions with 2-(chloromethyl)-3-trimethylsilyl-1-propane (**177**)

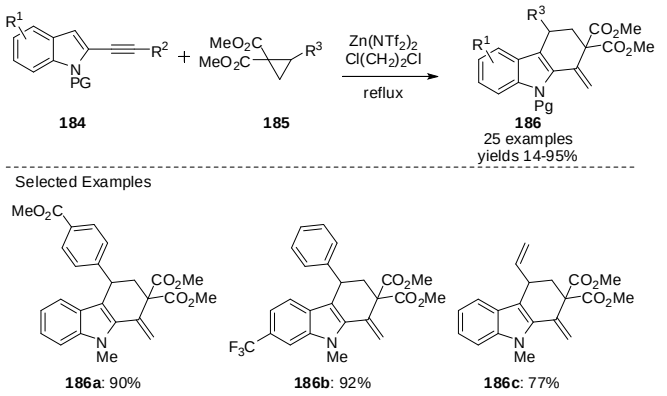
Ring-opening worked in modest yields with a variety of aromatic and vinyl cyclopropanes, while ring closure worked in excellent yields for almost all substrates. Lower yields were seen for the ring-opening of 2-thienyl cyclopropane presumably due to the stability of the cyclopropane under $TiCl_4$ conditions. Alkyl substituted cyclopropanes did not undergo ring-opening/allylation due to the lack of stability of the putative ring-opened intermediate.[56] In the same paper, the utility of this reaction was displayed in the rapid synthesis of tronocarpine's core **183** (Scheme 45).



Scheme 45: Core Synthesis of Tronocarpine

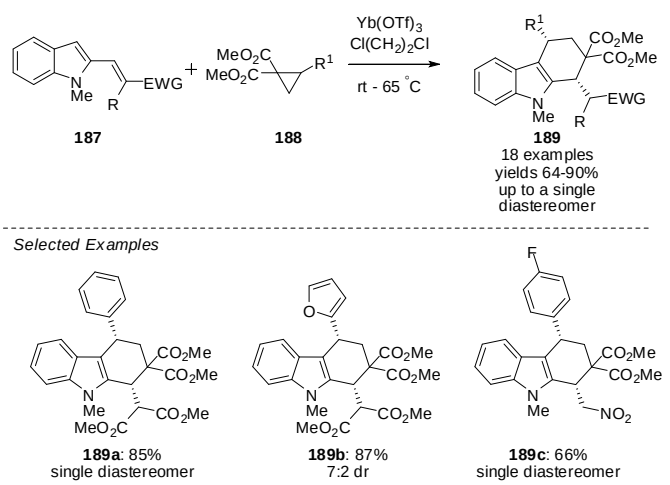
A few years later, Kerr was able to expand the developing area of tandem cyclopropane ring-opeing/Conia-ene reactions[57] to access the cyclohexene ring of tetrahydrocarbazoles by using 2-alkynylindoles as a 1-3 dipole surrogate. Zinc catalysed ring-opening of cyclopropane **185** with alkynylindole **184** followed by an in situ Conia-ene cyclization led to a variety of substituted tetrahydrocarbazoles **186** (Scheme 46).[58] The reaction conditions were suitable for a range of cyclopropanes with lower yields observed for 2-furyl cyclopropane. Once again, alkyl substituted-cyclopropanes were not reactive towards ring-opening. Substitution on the alkyne shut down the Conia-ene process and only ring-opened products were isolated.

To overcome this limitation, it was found the ester substitution on the alkyne would allow for cyclization to occur in a tandem Michael addition type fashion. When optically enriched cyclopropanes were subjected to the reaction conditions, little to no erosion in *ee* was observed. Interestingly, the tetrahydrocarbazoles could be easily converted into the corresponding carbazole compounds through a two-step process, thus allowing quick access to the core framework of a range of natural products.



Scheme 46: Tandem Ring-opening/Conia-ene Reactions

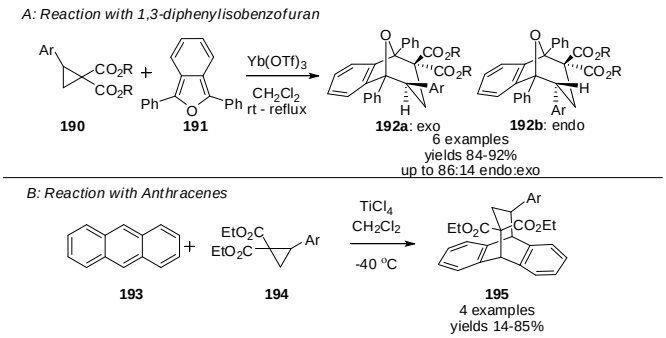
Advancement of this chemistry to the highly diastereoselective tandem ring-opening/Michael addition has recently been reported by Ghorai.[59] Reaction of indole **187** with 1,1-cyclopropanediester **188** under $Yb(OTf)_3$ catalysis yielded the corresponding tetrahydrocarbazole **189** in average to excellent yields with good diastereoselectivity (in most cases as a single diastereomer) (Scheme 47). It was proposed that the selectivity was achieved after ring-opening in which the Michael acceptor favoured the pseudoaxial half-chair conformation leading to the *cis* isomer. Overall, the reaction conditions were efficient for a variety of aromatic cyclopropanes with lower yields and selectivity when styrenyl substituted cyclopropanes were used. In general, the malonate acceptor groups gave higher yields than the corresponding nitro acceptors.



Scheme 47: Highly Diastereoselective Tandem Ring-opening/Michael addition

3. [4+3] Annulation Reactions of DA Cyclopropanes

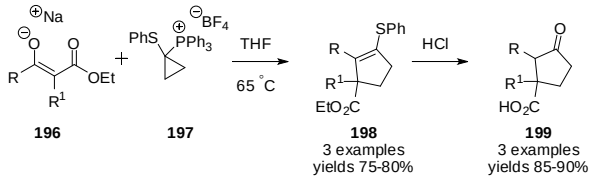
The research field of [4+3] annulations of DA cyclopropanes is in its infancy as few reports have been described for both heterocyclic and carbocyclic processes. This is in part due to the fact that most 1,4-dipoles are also 1,2-dipoles and can also undergo a more facile [3+2] annulation event. Over the past few years, Ivanova has reported success in this area leading to a [4+3] annulation process of cyclopropanes to access a carbocyclic frame work (Scheme 48A/B). Initial investigation used 1,3-diphenylisobenzofuran **191** as a suitable starting material for the reaction with aryl substituted cyclopropanes **190** (Scheme 48A).[60] The catalytic conditions were suitable for a series of aromatic and heteroaromatic cyclopropanes leading to the bridged bicyclic compound **195** in excellent yields in most cases. Although the yields of this reaction were fairly high, the diastereoselectivity of the products were modest in the best cases (electron rich aromatic) in favour of the less stable *exo* product. In the same year, Ivanova published work reporting the reaction of anthracene **193** with cyclopropanes **194** to access carbocycle **195** (Scheme 48B).[61] Unlike the previous report, this work was very selective toward cyclopropane substitution and thus only a small scope was achieved with low to moderate yields.



Scheme 48: Formal [4+3] Cycloadditons

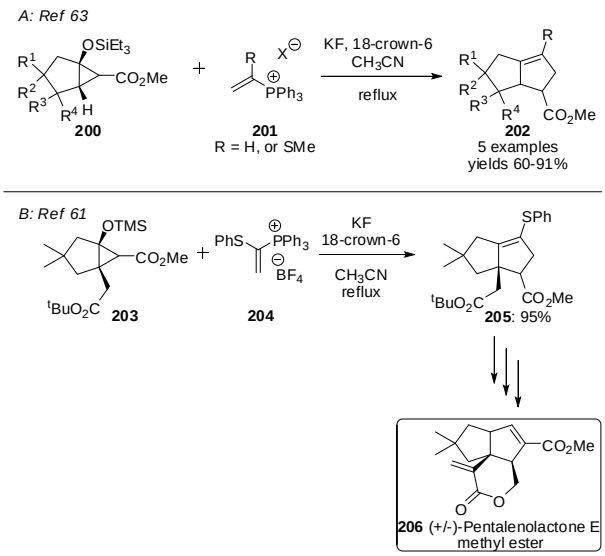
4. Miscellaneous Reactions of DA Cyclopropanes

In 1975, Marino reported a base-mediated tandem cyclopropane ring-opening Wittig reaction with ethylacetoacetate derivatives **196** and triphenylphosphonium cyclopropane **197** to access cyclopentene **198** (Scheme 49).[62] The small substrate scope showed the reaction was compatible with several different keto-esters (i.e. R = Phenyl or alkyl). Additionally, the cyclopentene products could be hydrolysed to give the corresponding cyclopentanone **199**. This initial report led to a variety of different studies investigating the tandem ring-opening Wittig reaction of cyclopropanes.



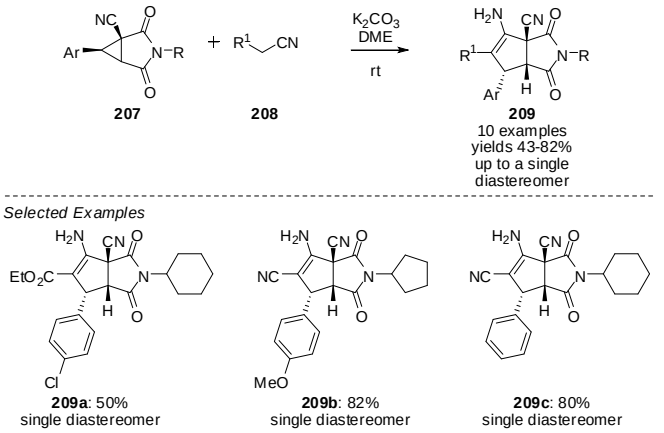
Scheme 49: Tandem Ring-opening/Wittig Reactions of Cyclopropane **197**

In a similar manner, Marino next explored the tandem process with alkoxy activated cyclopropanes **200** and triphenylphosphonium alkenes **201** to give the corresponding fused bicyclic system **202** (Scheme 50A).[63,64] Again, the cyclopentene sulfides could easily be hydrolysed. In comparison to the seminal, the switch in location of the phosphonium salt resulted in higher yields of the desired cycloadduct. This method was exploited in the total synthesis of (+/-)-pentalenolactone E methyl ester **206** in excellent yield (Scheme 50B).[65]



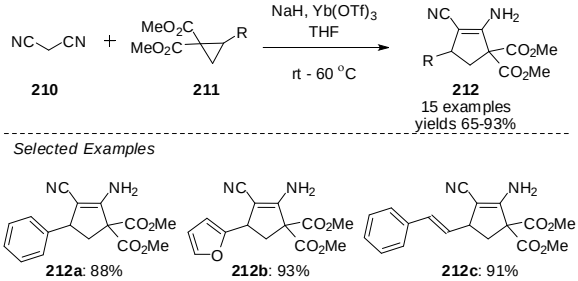
Scheme 50: Tandem Ring-opening/Wittig Reactions with Alkenylphosphoniums

Wang revealed in 2008, the synthesis of bicyclic dicarboximides **209** from the unique reaction of cyclopropane **207** and malononitriles and alkyl cyanoacetate (Scheme 51).[66] Under basic conditions, product formation was achieved efficiently with excellent diastereoselectivity (in almost all cases only one isomer was isolated) when malononitriles were used; however, yields were significantly lower when the cyanoacetate starting material was used. In hopes of getting improved yields, the reaction temperatures were increased; however, this led to decomposition.



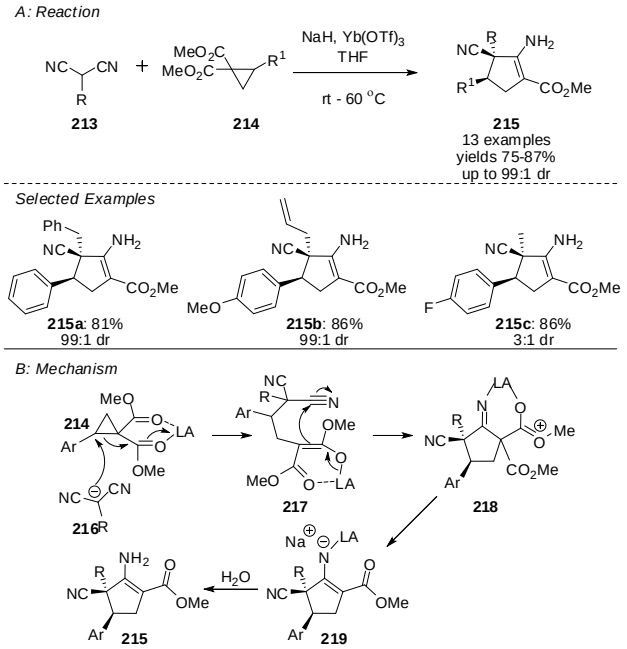
Scheme 51: Synthesis of Bicyclic Dicarboximides

In another example of this chemistry, the Ghorai group showed the analogous reaction of malononitriles with 1,1-cyclopropane diesters **211**, under NaH and Lewis acid conditions to give carbocyclic enaminonitriles **212** (Scheme 52).[67] A large scope was displayed and in general the yields were high. Additionally, the reaction conditions were suitable for not only aromatic cyclopropanes, but also heteroaromatic and styrenyl examples.



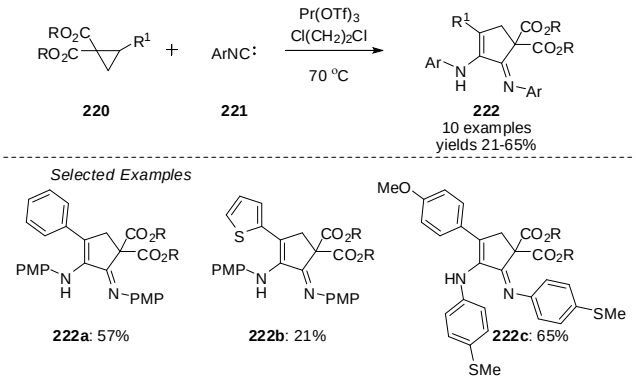
Scheme 52: Reactions with Malononitirles

In an interesting follow up to this work, Ghorai showed a tandem ring-opening cyclization decarboxylation approach when substituted malononitriles **213** were employed (Scheme 53A).[68] The proposed mechanism suggests ring-opening of the cyclopropane by **216** followed by ring-closure to give intermediate **218**. This intermediate could undergo a facile demethoxycarbonylation to give **219**, ultimately leading to the product **215** (Scheme 53B). This reaction worked well with a variety of different cyclopropane substitutions in moderate to excellent yields, and diastereoselectivity (up to a single diastereomer). Lower selectivities were reported for styrenyl examples and the reaction conditions were not compatible with aromatic substitution on the malononitrile, perhaps due to both steric effects and the stability of the resulting anion.



Scheme 53: Tandem Annulation Decarboxylation with Substituted Malononitriles

In 2006, de Meijere developed a novel formal [3+1+1] cycloadditon reaction of two equivalents of arylisocyanides **221** with cyclopropanes **220** to access dinitrogen substituted cyclopentenes **222** (Scheme 54).[69] Mechanistically, the reaction was presumed to go through two sequential insertion operations, initially to form an activated 2-iminocyclobutane (although no indications of this product were isolated during the reaction) followed by a second addition to give the desired cyclopentene product.[70] The reaction conditions produced low to moderate yields and were not shown to work with alkyl cyclopropanes or alkyl isocyanides. In order for future synthetic applications of this chemistry to be utilized, conditions will have to be altered to obtain more serviceable yields of the product.



Scheme 54: Reactions with Arylisocyanides

Conclusions

The number of useful synthetic transformations resulting from annulations and cyclizations of DA cyclopropanes is staggering and ever expanding. Most usually, the products have been heterocycles; however, recently there has been a surge in the use of all carbon reaction partners to form carbocyclic adducts. In this review, we have attempted to cover the literature concerning progress in this area, focussing on acid, base, or thermal mediated conditions. We hope that this review will be a useful tool to the organic chemist with interest in this area.

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Notes and references

[a] The University of Western Ontario, Department of Chemistry, London, Ontario, Canada N6A 5B7.

[1] (a) Schneider, T.; Kaschel, J.; Werz, D. *Angew. Chem. Int. Ed.* **2014**, *53*, 5504. (b) Cavitt, M.; Phun, L.; France, S. *Chem. Soc. Rev.* **2014**, *43*, 804. (c) Mack, D.; Njardarson, J. *ACS Catal.* **2013**, *3*, 272. (d) Tang, P.; Qin, Y. *Synthesis* **2012**, 2969. (e) Wang, Z. *Synlett*, **2012**, 2311. (f) De Simone, F.; Saget, T.; Benfatti, F.; Alemida, S.; Waser, J. *Chem. Eur. J.* **2011**, *17*, 14527. (g) Reisman, S.; Nani, R.; Levin, S. *Synlett* **2011**, 2437. (h) Mel'nikov, M.; Budynina, E.; Ivanova, O.; Trushkov, I. *Mendeleev Commun*. **2011**, *21*, 293. (i) Campbell, M.; Johnson, J.; Parsons, A.; Pohlhaus, P.; Sanders, S. *J. Org. Chem.* **2010**, *75* 6317. (j) Lebold, T.; Kerr, M. *Pure Appl. Chem.* **2012**, *82*, 1797. (k) De Simone, F.; Waser, J *Synthesis* **2009**, 3353. (l) Carson, C.; Kerr, M. *Chem. Soc. Rev.* **2009**, *38*, 3051. (m) Agrawal, D.; Yadav, V. *Chem. Commun.* **2008**, 6471. (n) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117. (o) Yu, M.; Pagenkopf, B. *Tetrahedron*, **2005**, *61*, 321. (p) Reissig, H-U.; Zimmer, R. *Chem. Rev.* **2013**, *103*, 1151. (q) Wong, H.; Hon, M-Y.; Tse, C-W.; Yip, Y-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165.

[2] (a) Kinnel, R.; Gehrken, H.-P.; Scheuer P. *J. Am. Chem. Soc.* **1993**, *115*, 3376. (b) Kinnel, R.; Gehrken, H.-P.; Swali, R.; Skoropowski, G.; Scheuer, P. *J. Org. Chem.* **1998**, *63*, 3281. (c) Yusuf, S.; Teo, K.; Pogue, J.; Dyal, L.; Copland, I.; Schumacher, H.; Ingelheim, B.; Dagenais, G.; Sleight, P.; Anderson, C.; *N. Engl. J. Med.* **2008**, *358*, 1547. (d) Reino, J.; Duran-Patron, R.; Segura, I.; Hernadez-Galan, R.; Riese, H.; Collado, I. *J. Nat. Product.* **2003**, *66*, 344. (e) Kawahara, N.; Nozawa, M.; Kurata, A.; Hakamatsuka, T.; Sekita, S.; Satake, M. *Chem. Pharm. Bull.* **1999**, *47*, 1344.

[3] For selected reviews on the synthesis of cyclopentane rings: (a) Heasley, B. *Current Org. Chem.* **2014**, *18*, 641. (b) Aitken, D.; Eijsbeg, H.; Frongi, A.; Olliver, J.; Piras, P. *Synthesis*, **2014**, *46*, 1. (c) Gimazetdinov, A.; Ivanova, N.; Miftakhov, M. *Nat. Prod. Comm.* **2013**, *8*, 981. (d) Rouce, S.; Aitken, D. *Eur. J. Org. Chem.* **2010**, 5339. (e) Kurteva, V.; Afonso, C. *Chem. Rev.* **2009**, *109*, 6890. (f) Hudlicky, T.; . Price, J. *Chem. Rev.* **1989**, *89*, 1467.

[4] Beal, R.; Dombroski, M.; Snider, B. *J. Org. Chem.* **1986**, *51*, 4391.

[5] Stork, G.; Grieco, P. *J. Am. Chem. Soc.* **1969**, *91*, 2407.

[6] Anger, T.; Graalmann, O.; Schroder, H.; Gerke, R.; Kaiser, U.; Fitjer, L.; Noltemeyer, M. *Tetrahedron* **1998**, *54*, 10713.

[7] (a) Clive, D.; Magnuson, S. *Tetrahedron Lett.* ***1995***, 15. (b) Clive, D.; Magnuson, S.; Manning, H.; Mayhew, D. *J. Org. Chem.* **1996**, *61*, 2095. (c) Cohen, T.; McNamara, K.; Kuzemko, M.; Ramig, K.; Landi, J.; Dong, Y. *Tetrahedron*, **1993**, *49*, 7931.

[8] Graziano, M.; Chiosi, S. *J. Chem. Res.* **1989**, 44.

[9] Christie, S.; Davoile, R.; Jones, R. *Org. Biomol. Chem.* **2006**, *4*, 2683.

[10] Lebold, T.; Carson, C.; Kerr, M. *Synlett*, **2006**, *3*, 364.

[11] a) Monti, H.; Rizzotto, D.; Leandri, G. *Tetrahedron Lett.* **1994**, *35*, 2885. b) Monti, H.; Rizzotto, D.; Leandri, G. *Tetrahedron* **1998**, *54*, 6725.

[12] Sugita, Y.; Yanadoi, S.; Hosoya, H.; Yokoe, I. *Chem. Pharm. Bull.* **2001**, *49*, 657.

[13] Graziano, L.; Iesce, R.; Cermola, F.; Cimminello, G. *J. Chem. Res.* **1992**, 4.

[14] Yadav, V.; Sriramurthy, V. *Angew. Chem. Int. Ed.* **2004**, *43*, 2669.

[15] Qi, X.; Ready, J. *Angew. Chem. Int. Ed.* **2008**, *47*, 7068.

[16] a) Fried, J.; Sih, J. *Tetrahedron Lett.* **1973**, 3899. b) Daniewski, A.; Wovkulich, P.; Uskokivic, M. *J. Org. Chem.* **1992**, *57*, 7133.

[17] Mackay, W.; Fistikci, M.; Carris, R.; Johnson, J. *Org. Lett.* **2014**, *16*, 1626.
[18] (a) Steinreiber, J.; Faber, K.; Griengl, H. *Chem. Eur. J.* **2008**, *14*, 8060. (b) Parsons, A.; Johnson, J. *J. Am. Chem. Soc.* **2009**, *131*, 3122. (c) Parsons, A.; Smith, G.; Neel, J.; Johnson, J. *J. Am. Chem. Soc.* **2010**, *132*, 9688.
[19] Yadav, V.; Sriramurthy, V. *Org. Lett.* **2004**, *6*, 4495.
[20] Stork, G.; Grieco, P. *Tetrahedron Lett.* **1971**, 1807.
[21] Corey, E.; Balanson, R. *Tetrahedron Lett.* **1973**, 3153.
[22] Grieco, P.; Finkelhor, R. *Tetrahedron Lett.* **1974**, 527.
[23] Zhu, W.; Fang, J.; Liu, Y.; Ren, J.; Wang, Z. *Angew. Chem. Int. Ed.* **2013**, *52*, 2032.
[24] McAlees, A.; McCrindle, R. *Can. J. Chem.* **1973**, *51*, 4103.
[25] Briggs, L.; Cain, F.; Cambie, R.; Davis, B. *J. Chem. Soc.* **1962**, 1840.
[26] Xia, X-F.; Song, X-R.; Liu, X-Y; Liang, Y-M. *Chem. Asian J.* **2012**, *7*, 1538.
[27] Yu, Q.; Ma, S. *Chem Commun.* **2012**, *48*, 11784.
[28] Wang, Z.; Ren, J.; Wang, Z. *Org. Lett.* **2013**, *15*, 5682.
[29] Saigo, K.; Shimada, S.; Shibasaki, T.; Hasegawa, M. *Chem. Lett.* **1990**, 1093.
[30] Komatsu, M.; Suehiro, I.; Horiguchi, Y.; Kuwajima, I. *Synlett* **1991**, 771.
[31] Horiguchi, Y.; Suehiro, I.; Sasaki, A.; Kuwajima, I. *Tetrahedron Lett.* **1993**, *34*, 6077.
[32] Takasu, K.; Nagao, S.; Ihara, M. *Adv. Synth. Catal.* **2006**, *348*, 2376.
[33] Sugita, Y.; Kawai, K.; Hosoya, H.; Yokoe, I. *Heterocycles*, **1999**, *51*, 2029.
[34] Fang, J.; Ren, J.; Wang, Z. *Tetrahedron Lett.* **2008**, *49*, 6659.
[35] Qu, J-P.; Deng, C.; Zhou, J.; Sun, X-L.; Tang, Y *J. Org. Chem.* **2009**, *74*, 7684.
[36] Qu, J-P.; Liang, Y.; Xu, H.; Sun, X-L.; Yu, Z-X.; Tang, Y. *Chem. Eur. J.* **2012**, *18*, 2196.
[37] Xu, H.; Qu, J-P.; Liao, S.; Xiong, H.; Tang, Y. *Angew. Chem. Int. Ed.* **2013**, *52*, 4004.
[38] Nanteuil, F.; Waser, J.; *Angew. Chem. Int. Ed.* **2011**, *50*, 12075.
[39] Nanteuil, F.; Serrano, E.; Perrotta, D.; Waser, J. *J. Am. Chem. Soc.* **2014**, *136*, 6239.
[40] Chagarovskiy, A.; Budynina, E.; Ivanova, O.; Grishin, Y.; Trushkov, I.; Verteletskii, P. *Tetrahedron* **2009**, *65*, 5385.
[41] Dolfini, J.; Menich, K.; Corliss, P. *Tetrahedron Lett.* **1966**, *37*, 4421.
[42] Harrington, P.; Kerr, M. *Synlett*, **1995**, 1047.
[43] Harrington, P.; Kerr, M. *Tetrahedron Lett.* **1997**, *38*, 5949.
[44] Similar results have been reported in recent indole alkylation with cyclopropane papers; Dulin, C.; Murphy, K.; Nolin, K. *Tetrahedron Lett.* **2014**, *55*, 5280.
[45] (a) Kerr, M.; Keddy, R. *Tetrahedron Lett.* **1999**, *40*, 5671 (b) England, D.; Kuss, T.; Keddy, R.; Kerr, M. *J. Org. Chem.* **2001**, *66*, 4704.
[46] Venkatesh, C.; Singh, P.; Ila, H.; Junjappa, H. *Eur. J. Org. Chem.* **2006**, 5378.
[47] Bajtos, B.; Yu, M.; Zhao, H.; Pagenkopf, B. *J. Am. Chem. Soc.* **2007**, *129*, 9631.
[48] (a) Parsons, A.; Johnson, J. *J. Am. Chem. Soc.* **2009**, *131*, 3122. (b) Parsons, A.; Smith, A.; Neel, A.; Johnson, J. *J. Am. Chem. Soc.* **2010**, *132*, 9688. (c) Campbell, M.; Johnson, J.; Parsons, A.; Pohlhaus, P.; Sanders, S. *J. Org. Chem.* **2010**, *75*, 6317.
[49] Wales, S.; Walker, M.; Johnson, J. *Org. Lett.* **2013**, *15*, 2558.
[50] Xiong, H.; Xu, H.; Liao, S.; Xie, Z.; Tang, Y. *J. Am. Chem. Soc.* **2013**, *135*, 7851.
[51] Zhu, J.; Liang, Y.; Wang, .l; Zheng, Z-B.; Houk, K.; Tang, Y. *J. Am. Chem. Soc.* **2014**, *136*, 6900.
[52] (a) Hirose, A.; Hayato, M.; Akio, T.; Tastsuo, N.; Masaru, H. *Tetrahedron* **2014**, *70*, 1458. (b) Tahara, Y. *J. Pharm. Soc. Jpn.* **1909**, *29*, 587. (c)Tahara, Y. *Biochem. Z.* **1911**, *30*, 255. (d) Castillo, L.; Lanza, A.; Faure, R.; Debrauwer, L.; Elias, R.; Balansard, G. *Phytochemistry*, **1995**, *40*, 1193. (e) Kam, T.-S.; Sim, K.-M.; Lim, T.-M. *Tetrahedron Lett.* **2000**, *15*, 2733.
[53] Yadav, V.; Kumar, N.; Parvez, M. *Chem. Commun.* **2007**, 2281.
[54] For a review of Pd-TMM cycloadditions see: (a) Trost, B. *Angew. Chem., Int. Ed.* **1986**, *25*, 1. (b) Trost, B.; Chan, D. *J. Am. Chem. Soc.* **1979**, *101*, 6429.
[55] Sapeta, K.; Kerr, M. *Org. Lett.* **2009**, *11*, 2081.
[56] Vriesen, M.; Grover, H.; Kerr, M. *Synlett* **2014**, *25*, 428.
[57] (a) Lebold, T.; Leduc, A.; Kerr, M. *Org. Lett.* **2009**, *11*, 3770. (b) Leduc, A.; Lebold, T.; Kerr, M. *J. Org. Chem.* **2009**, *74*, 8414.
[58] Grover, H.; Lebold, T.; Kerr. M. *Org. Lett.* **2011**, *13*, 220.
[59] Talukdar, R.; Tiwari, W.; Saha, A.; Ghorai, M. *Org. Lett.* **2014**, *16*, 3954.
[60] Ivanova, O.; Budynina, E.; Grishin, Y.; Trushkov, I.; Verteletskii, P. *Angew. Chem. Int. Ed.* **2008**, *47*, 1107.
[61] Ivanova, O.; Budynina, E.; Grishin, Y.; Trushkov, I.; Verteletskii, P. *Eur. J. Org. Chem.* **2008**, 5329.
[62] Marino, J.; Landick, R. *Tetrahedron Lett.* **1975**, *51*, 4531.
[63] Marino, J.; Laborde, E. *J. Am. Chem. Soc.* **1985**, *107*, 734.
[64] Marino, J.; Laborde, E. *J. Org. Chem.* **1987**, *52*, 1.
[65] (a) Marino, J.; Silveira, C.; Comasseto, J.; Petragnani, N. *J. Org. Chem.* **1987**, *52*, 4139. (b) Marino, J.; Silveira, C.; Comasseto, J.; Petragnani, N. *J. Braz. Chem. Soc.* **1996**, *7*, 51.
[66] Ren, Z.; Cao, W.; Lu, Y.; Wang, Y.; Wang, S. *Synthetic Commun.* **2008**, *38*, 2215.
[67] Ghorai, M.; Talukdar, R.; Tiwari, D. *Chem. Commun.* **2013**, *49*, 8205.
[68] Ghorai, M.; Talukdar, R.; Tiwari, D. *Org. Lett.* **2014**, *16*, 2204.
[69] Korotkov, V.; Larionov, O.; Meijere, A. *Synthesis* **2006**, *21*, 3542.
[70] Precedence for the described mechanism: Bez, G.; Zhao, C.-G. *Org. Lett.* **2003**, *5*, 4991.