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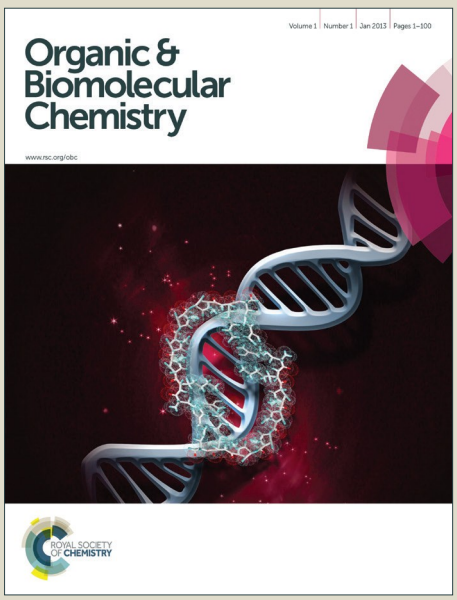

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REVIEW

Heterocycles from Methylenecyclopropanes†

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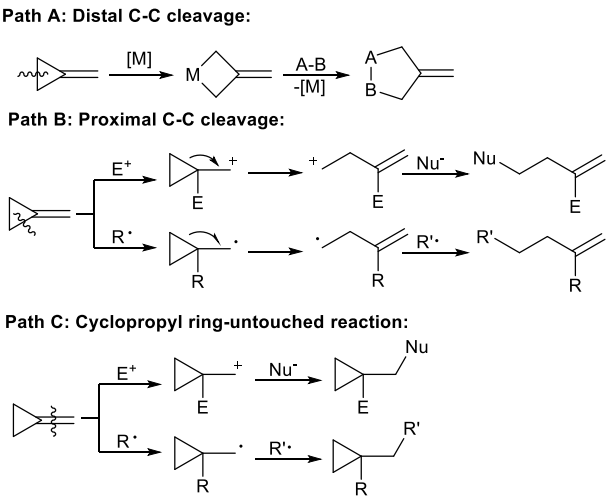
The discoveries of a series of novel organic reactions make methylenecyclopropanes (MCPs) one of the most popular building-blocks in synthetic organic chemistry during the past two decades. Among reported works, constructions of heterocycles from MCPs give new synthetic methodologies that afford more opportunities for the quick synthesis of complicatedly substituted products and should draw enough attentions. However, the reviews in this area are insufficient and the latest monograph on heterocycle-synthesis from MCPs was published 12 years ago. This review aimed to summarize the novel organic reactions of MCPs to produce heterocycles in recent years, which provided particular and powerful tools in organic synthesis.

1. Introduction

Methylenecyclopropanes (MCPs) are a kind of highly strained molecules and were once considered to be unstable in the past. Their stability began to be realized by people after the discovery of many natural products containing MCP skeletons, such as hypoglycine and methylenecyclopropylglycine.[1] The parent structure of MCPs were successfully synthesized in laboratory for the first time in 1953 by treating 3-chloro-(2-chloromethyl)-1-propene with Mg.[2] During the following several decades, a series of comprehensive methodologies for MCP synthesis have been developed,[3] making these highly strained molecules readily accessible materials in laboratory. Nowadays, MCPs have been widely applied in organic synthesis,[4] pharmaceutical chemistry,[5] agricultural chemistry[6] and even material science.[7] Among reported works, the applications of MCPs as building-blocks in organic synthesis are one of the most important topics for the discoveries of many novel reactions that lead to a series of useful organic skeletons more efficiently than traditional methods. MCPs can undergo a variety of reactions, which are facilitated owing to the releasing of their intramolecular strain of the small ring and its exocyclic C=C bond. Generally, the reactions of MCPs underwent through three possible routes: (a) The distal C-C bond cleavage reactions were always catalyzed by transition metals, and led to the allylic derivatives as products (Scheme 1, Path A); (b) The proximal C-C bond cleavage reactions usually happened through electrophilic or free radical mechanisms, and afforded the homo-allylic products (Scheme 1, Path B); (c) There were also many examples of the cyclopropyl ring-untouched reactions, which were indeed the reactions on the C=C bond of MCPs, but were also very useful to synthesize some cyclopropyl ring contained products (Scheme 1, Path C). Scheme 1 concluded the most common classic reaction modes for simple MCPs. But along with the continuous progresses in the field, many functionalized MCPs were prepared and employed as substrates and their reactions might undergo through novel mechanisms.



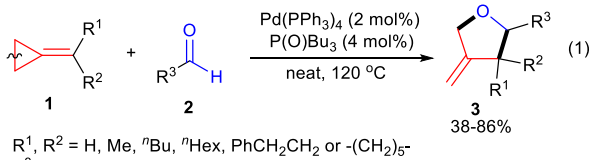
Scheme 1. The classic reaction mechanisms of MCPs

On the other hand, in many reactions, the break of MCPs' three-membered ring is accompanied with the formation of new useful heterocycles such as furans, pyrans, lactones, pyrroles, pyridines and others. Building heterocycles from MCPs afford more opportunities for the quick synthesis of complicatedly substituted products. Thus, topics on the synthesis of heterocycles from MCPs have attracted chemists during the past two decades. However, the reviews in this area are insufficient and cannot well document recent progresses. Although we and others have already published a series of reviews and accounts on the synthesis and applications of MCPs since 2010,[4a-4g] the latest monograph on heterocycle-synthesis from MCPs was published 12 years ago.[4h] Therefore, in this review, we wish to summarize the progresses on

heterocycle-synthesis from MCPs in recent years, which provide novel, particular and powerful synthetic tools for chemists. In order to facilitate the readers for quick reference, the contents are classified by the types of heterocycles from MCPs.

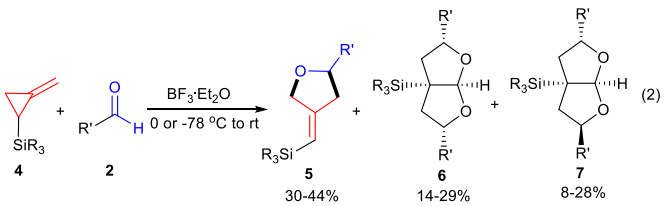
2. Furans from MCPs

The cyclo-additions of aldehydes with simple MCPs are undoubtedly the most direct and universal tools for the construction of furan ring in MCP-chemistry. This synthetic strategy could be realized using palladium as catalyst (eq. 1).[8,9] The [3+2] cyclo-additions of MCPs and carbonyl moieties catalyzed by Pd in neat conditions at 120 °C led to 2-methylene-3,3,4-trisubstituted tetrahydrofurans **3** in 38-86% yields. Unfortunately, the reaction required harsh conditions, which resulted in low functional group tolerance. In addition, the substrate scopes of this reaction were very narrow and were limited in several alkyl-substituted MCPs and electron-rich aldehydes. Reaction of cyclopropylene ring position-substituted MCP with aldehyde was also tried but failed.



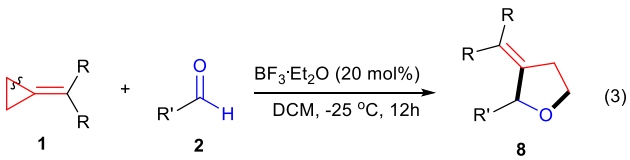
R^1, R^2 = H, Me, ^{n}Bu, ^{n}Hex, $PhCH_2CH_2$ or $-(CH_2)_5-$
R^3 CHO (**2**) = furfural, 5-methylfurfural, 3-furaldehyde, 2-thiophenecarbaldehyde, benzo[*d*][1,3]dioxole-5-carbaldehyde or 4-methoxybenzaldehyde

As electron-rich olefins, MCPs could undergo a series of Lewis acid-promoted reactions, which provided more alternative reaction conditions for the optimizations of the above [3+2] cyclo-additions. Early in 1997, people have already tested the reactions of simple MCPs with aldehydes in the presence of $TiCl_4$. However, instead of the desired cyclo-adducts, the three-membered ring-opened chained compounds were obtained as the major product.[10] Later, Kilburn *et. al.* reported that by introducing a silicon group on cyclopropylene ring and using $BF_3{\cdot}Et_2O$ as catalyst, the reactions could be improved to give cyclo-adducts **5** in 30-44% yields accompanied with the generation of the fused bifurans **6** and **7**, which were the by-products of the reactions of MCPs with two aldehydes (eq. 2).[11] Although the narrow substrate scopes and low product selectivities limited their further applications in organic synthesis, the above two references revealed the possibility of the furan ring-constructions through Lewis acid-catalyzed (or mediated) cycloadditions of MCPs with aldehydes.

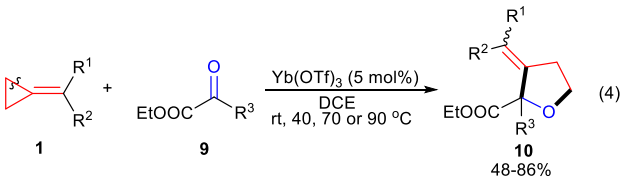


R_3 = ^{i}Pr$_3$ or Ph$_2{}^t$Bu; R' = ^{i}Pr or 4-$NO_2C_6H_4$

The Lewis acid-catalyzed cyclo-additions of simple MCPs with aldehydes were developed by Shi *et. al.* in 2004.[12] The reactions were performed at low temperature in DCM with $BF_3{\cdot}Et_2O$ as catalyst, giving cyclo-adducts 2-substituted-3-methylene-tetrahydrofurans **8** in moderate yields (eq. 3). Similarly, reactions of simple MCPs **1** with electron-withdrawing group (EWG)-activated aldehydes or ketones **9** led to the tetrahydrofuran derivatives **10** in moderate to good yields.[13] The required reaction temperatures varied from r.t. to 90 °C, depending on the substrates (eq. 4). The application scopes of these Lewis acid-catalyzed reactions were more comprehensive than the previously reported palladium-catalyzed ones (eq. 1) and both electron-rich and -deficient MCPs were suitable substrates. It was noticeable that the ring-open modes of these cyclo-additions were quite different (as marked in each equation). The former (eq. 1) proceeded through a distal C-C bond cleavage in cyclopropylene ring while in the later reactions (eq. 3 and 4), the proximal C-C bond of the ring break. These phenomena were caused by the different reaction mechanisms (Scheme 1), which were well summarized in original references as well as our previous reviews.[9]

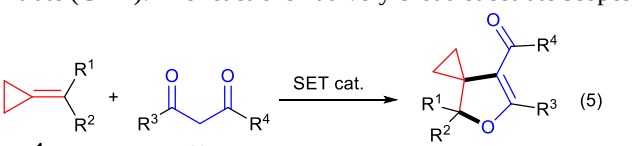


R = Ph, 4-MeC_6H_4, 4-ClC_6H_4, ^{n}Bu; R' = ^{n}Bu, ^{i}Bu, ^{i}Pr



R^1, R^2 = H, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 3-PhC_6H_4, or 4-ClC_6H_4; R^3 = H or COOEt

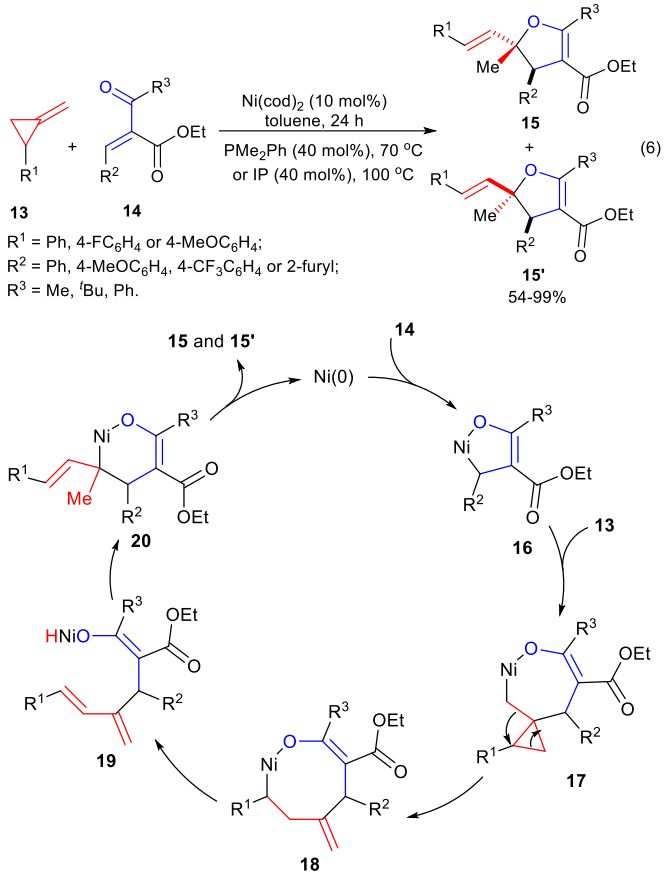
Besides transition metal- or Lewis acid-catalyzed cyclo-additions, single electron transfer (SET) reactions could also construct the furan rings from MCPs. In the presence of SET catalysts, simple MCPs **1** and 1,3-dicarbonyl compounds **11** underwent a cyclopropyl ring-untouched reaction to provide spirocyclopropyl dihydrofurans **12** (eq. 5).[14] These reactions were performed in HOAc, MeOH or MeCN/THF solutions and the SET catalysts were multiple-valent transition metal salts, such as manganese(III) acetate and cerium(IV) ammonium nitrate (CAN). The reactions had very broad substrate scopes.



R^1, R^2 = aryl, alkyl or H; R^3, R^4 = aryl, alkyl or OR;
SET cat. = $Mn(OAc)_3{\cdot}2H_2O$ or CAN.

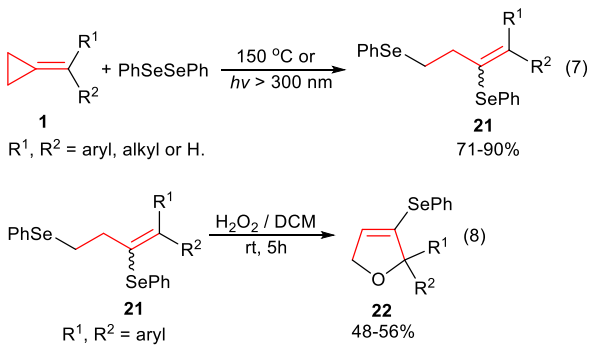
[4+1] cycloadditions of MCPs **13** with enones **14** also led to furan derivatives. The reactions were catalyzed by nickel in the presence of phosphorus ligands such as PMe_2Ph or iminophosphine (IP), giving 2-vinyl-4-ester substituted dihydrofurans **15** and **15'** in moderate to excellent yields (eq. 6).[15] Although the application scopes of this reaction were narrow both in substrates and products, this methodology led to a direct construction of certain specially substituted furan skeletons for drug discovery. In the reaction, enones **14** first reacted with Ni(0) to give the intermediate metal complex **16**. Then, the MCPs **13** reacted with **16** through the insertion of their methylene C=C into C-Ni bond to afford the spirocyclopropyl organometallic cycles **17**. Ring enlargement of **17** led to the intermediate **18**, which soon generated **19** through β-H elimination. Insertion of methylene into Ni-H bond in **19** afforded the six membered organometallic cycle **20**,

which regenerated Ni(0) species and gave the final product **15** and **15'** (Scheme 2).

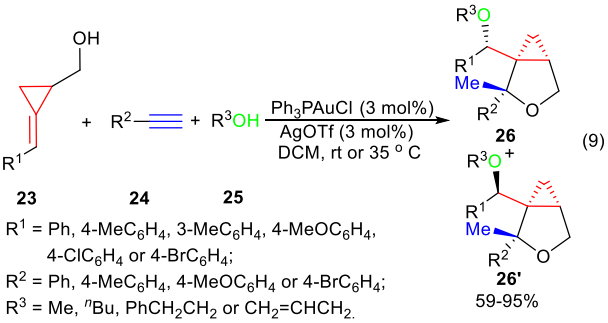


Scheme 2 Possible mechanisms for [4+1] cycloadditions of MPCs with enone.

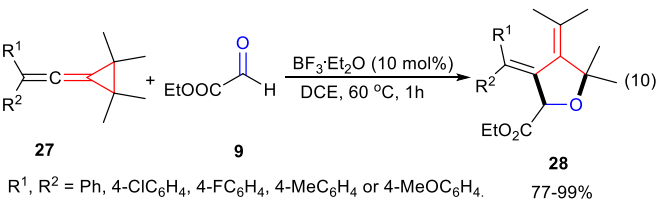
Furan derivatives could also be synthesized from simple MCPs through multiple steps. For example, reactions of MCPs **1** under heat or visible light irradiation led to 2,4-diphenylselenyl-1-butenes **21** in good yields (eq. 7).[16] Treating **21** with H_2O_2 under mild conditions afforded 2-phenylselenyl dihydrofurans **22** rapidly (eq. 8).[16a] Although the substrates limited in diaryl-substituted MCPs for the second step of reactions, this methodology provided a quick access to selenium-contained multi-substituted furan derivatives, which were difficult to obtain through traditional ways.



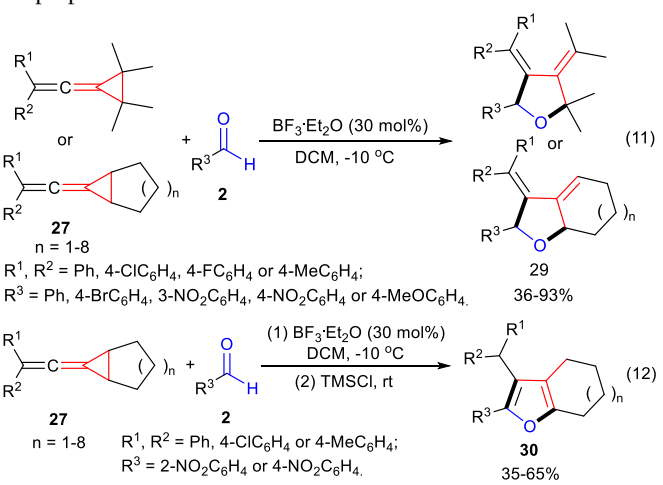
Multi-component reactions of MCPs were also reported to synthesize furans. Treating MCPs **23**, Alkynes **24** and alcohol **25** in DCM in the presence of gold and silver catalyst afforded product **26** and **26'** in moderate to good yields (eq. 9).[17] This three-component reaction provided a quick synthesis of cyclopropyl-fused tetrahydrofurans under mild conditions.



The cyclo-additions of vinylidenecyclopropanes (VCPs) **27** were also powerful tools in heterocycle-synthesis. As more complicated derivatives in MCP families, VCPs were more activated building-blocks with more reaction positions. However, reactions of VCPs always had good selectivity in spite of their high reactivities. For example, the [3+2] cyclo-addition of VCPs **27** with EWG-activated aldehydes **9** generated 3,4-dimethylene tetrahydrofurans **28** rapidly (eq. 10).[18] The reactions were catalyzed by $BF_3{\cdot}Et_2O$ in DCE and had excellent product yields (>90%), except for electron-rich VCPs (R^1=R^2=4-$MeOC_6H_4$), which rearranged in reaction conditions and led to a lower product yield in 77%.

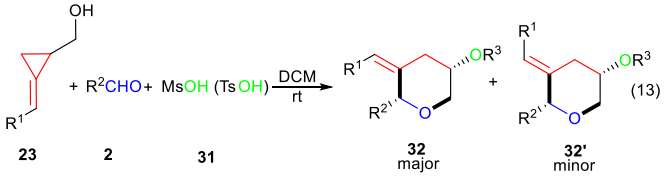


Reactions of VCPs with simple aldehyde were also reported in the next year. Huang group found that catalyzed by $BF_3{\cdot}Et_2O$ under low temperature, the [3+2] cyclo-additions of VCPs **27** with simple aldehyde **2** led to 3,4-dimethylene tetrahydrofurans **29** in moderate to excellent yields (eq. 11).[19] Treating the reactions of medium or large ring-fused VCPs **27** with TMSCl further led to the corresponding ring-fused furans **30** in moderate yields (eq. 12).[19] These reactions had very broad substrate scopes, giving common synthetic methodologies for the preparation of certain furan derivatives.



3. Pyrans from MCPs

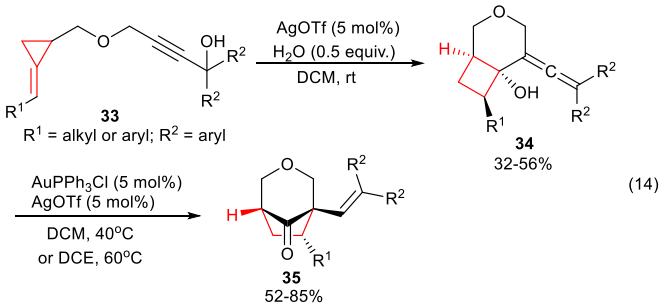
There are few examples for pyran-synthesis from simple MCPs and in many cases they were observed as the by-products.[14a] However, after modification, functionalized MCPs can undergo a series of interesting reactions to construct pyran-contained skeletons. For example, cyclopropylene-functionalized MCPs **23** underwent multi-component reactions with aldehydes and sulfonic acids to give a facile access to methylene tetrahydropyrans **32** and **32'** smoothly under mild conditions (eq. 13).[20]



23 **2** **31** **32** major **32'** minor

R^1= aryl; R^2 = alkyl or aryl; R^3 = Ms or Ts 42-95%

MCPs **33**, which were derived from **23**, led to cyclobutyl-fused pyranallenes **34** through silver-catalyzed intramolecular cyclizations and ring enlargement of MCP skeleton under mild conditions. In the presence of gold and silver catalysts, compoumd **34** could further rearrange to bridged tetrahydropyranones **35** (eq. 14).[21]

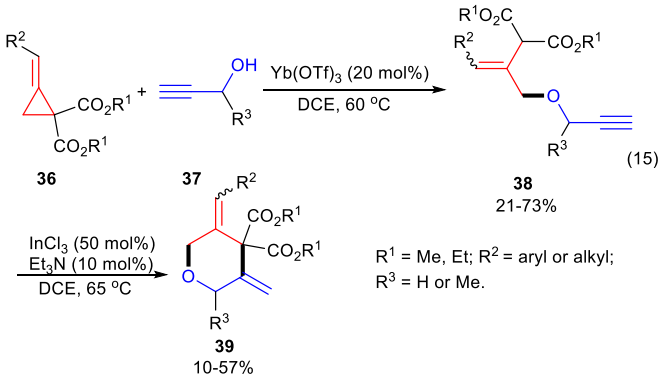


33 R^1 = alkyl or aryl; R^2 = aryl

34 32-56%

35 52-85%

$Yb(OTf)_3$-catalyzed additions of MCPs **36** with **37** led to cyclopropylene-opened products **38**, which were able to construct 3,5-dimethylene tetrahydropyrans **37** by heating with $InCl_3$ and Et_3N in DCE at 65 °C (eq. 15).[22] The direct synthesis of **39** from **36** and **37** using $Yb(OTf)_3/InCl_3/Et_3N$ multi-catalyst system was also tried but failed, resulting in both low product yields and narrow application scopes.

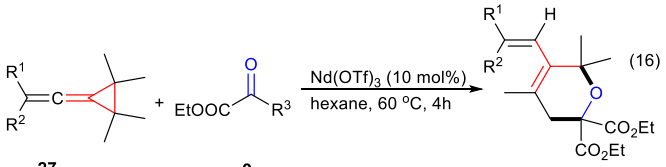


36 **37** **38** 21-73%

39 10-57%

R^1 = Me, Et; R^2 = aryl or alkyl; R^3 = H or Me.

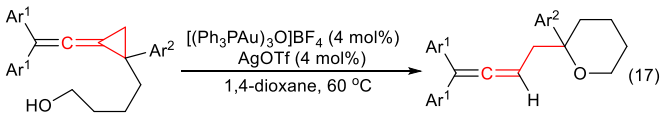
VCPs were also employed to synthesize pyrans. When R^3 = COOEt, the cyclo-additions of EWG-activated ketones **9** with VCPs **27** led to vinyl dihydropyrans **40** in moderate yields (eq. 14).[18] The reactions were performed in hexane with $Nd(OTf)_3$ as catalyst and proceeded through ene reaction mechanism, which resulted in different products from the [3+2] cyclo-additions (eq. 16 *vs.* 10).[9]



27 **9** **40** 30-67%

R^1, R^2 = Me, Ph, 4-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 3,4-$Me_2C_6H_3$;
R^3 = COOEt

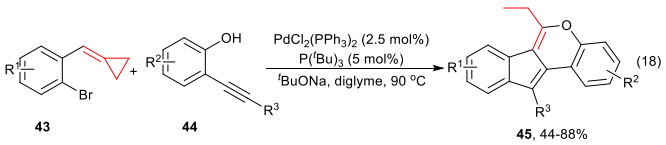
Moreover, cyclopropylene-modified VCPs **41** afforded allene-subsituted tetrahydropyrans **42** through their intramolecular cyclizations (eq. 17).[23] The rearrangements were catalyzed by gold, which broke the C-C bond in cyclopropylene ring first. The following nucleophilic attack of the proximal hydroxide broke the three membered ring and generated the furan ring, giving **42** in moderate yields.[9] Containing activated allene skeletons, **42** might be useful intermediates in organic synthesis.



41 **42** 45-69%

Ar^1, Ar^2, Ar^3 = Ph, 3-BrC_6H_4, 4-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-MeC_6H_4 or 4-$MeOC_6H_4$

The palladium-catalyzed reactions of MCPs to prepare pyrans were also developed. Recently, Wu group reported that the MCPs **43**, bearing an bromo on the *ortho*-position of their aryl rings, were able to react with the 2-alkynylphenol **44** to give the aryl-fused pyrans **45** (eq. 18).[24] The starting material **43** are easily available from the direct Wittig reaction of 2-bromobenzaldehyde with cyclopropylidene ylid, but the products **45** inevitably bear an ethyl on the pyran ring, which comes from the MCPs and restricts the application scopes of the reaction.



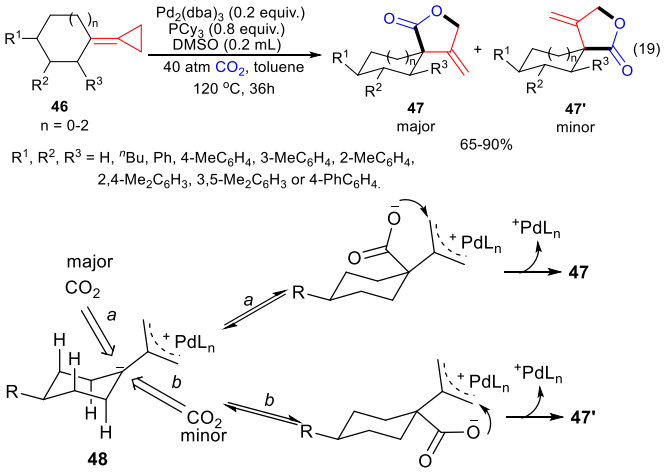
43 **44** **45**, 44-88%

4. Lactones from MCPs

Lactones can be taken as the derivatives of furans or pyrans. But considering that there are many examples of lactone-synthesis in MCP-chemistry and lactones themselves are so important compounds that should not be ignored, we wish to discuss the preparations of lactones from MCPs as an independent section.

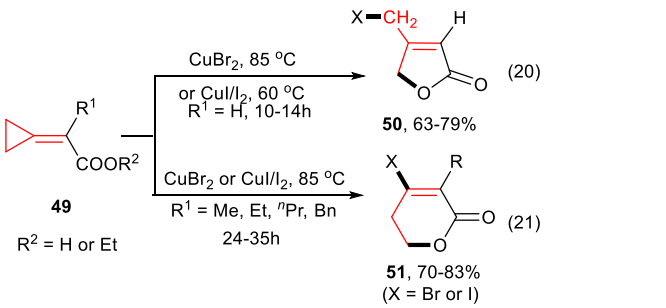
Undoubtly, the [3+2] cyclo-additions of MCPs with carbon dioxide are the most efficient strategy to construct lactone skeletons. In 2011, Shi group found that treating cyclopropylidene-cycloalkanes at 120 °C under 40 atm of CO_2 in the presence of palladium catalyst led to spirocycloalkyl lactones **47** and **47'** in moderate to excellent yields (eq. 19).[25a] In those reactions, palladium first broke the distal C-C bond of cyclopropylene but not the proximal one, giving allylic metal complexes **48**. The reaction positions of **48** with CO_2 determined the product selectivity, giving **47** or **47'** from the

two different positions (Scheme 3). Unfortunately, the reaction had very narrow substrate scope, which limited only in cycloalkylene-substituted MCPs. Otherwise, the product yields were very low due to the lower substrate ring-strain.[25b, 25c]

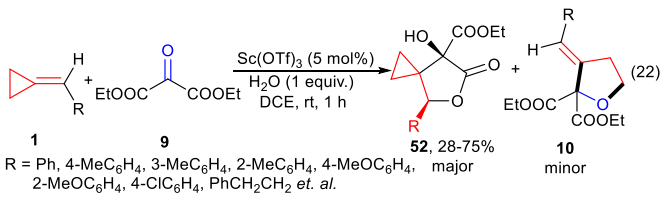


Scheme 3 Mechanisms for the [3+2] cyclo-additions of MCPs with CO_2.

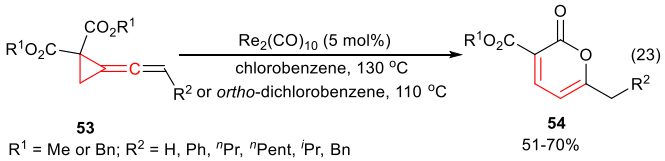
Lactones were also accessible through the copper mediated intramolecular cyclization of cyclopropylideneacetic acid derivatives **49**, a type of functionalized MCPs.[26] The reactions afforded furan-2(5*H*)-ones **50** first (*eq.* 20), but when reaction times extended, 5,6-dihydropyran-2-ones **51** were generated (*eq.* 21). Generations of the two possible products were caused by the different ring break methods of MCPs: the distal C-C bond cleavage led to **50**, while the proximal cleavage afforded **51**.



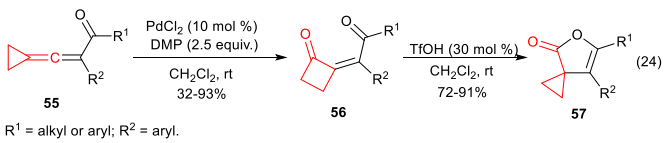
During the investigations on the Lewis acid-catalyzed reactions of MCPs **1** to prepare furan derivatives (eq. 3 and 4), Shi *et. al.* found that the reactions of mono-substituted MCPs **1** with diethyl 2-oxomalonate **9** led to an interesting spirocycloproyl lactone derivatives **52**, while the expected alkylene tetrahydrofurans **10** were obtained as the minor products (eq. 22).[27] This unexpected reaction afforded novel opportunities to prepare certain spirocycloproyl lactones with high efficiency.



VCPs were also applied to prepare lactones. $Re_2(CO)_{10}$-catalyzed intramolecular tandem ring-open and cyclization of VCPs **53** led to lactones **54** in moderate yields (eq. 23).[28] In this reaction, rhenium first coordinated with the carbonyl group and allene moiety simultaneously. The following ring break, 1,2-H shift and cyclization afforded the final product **53**. The methodology provided a short synthesis for certain 2,5-disubstituted lactones, but unfortunately, it required halogen solvents which were harmful to environment. Parallel conditional optimization reactions performed in other solvents such as toluene, xylene, DMF, dioxane and *et. al.* resulted in rather low product yields.[28]

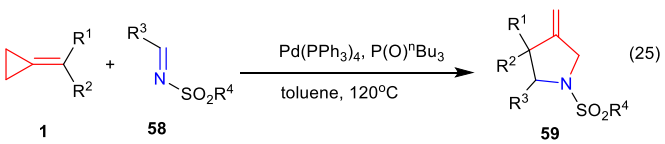


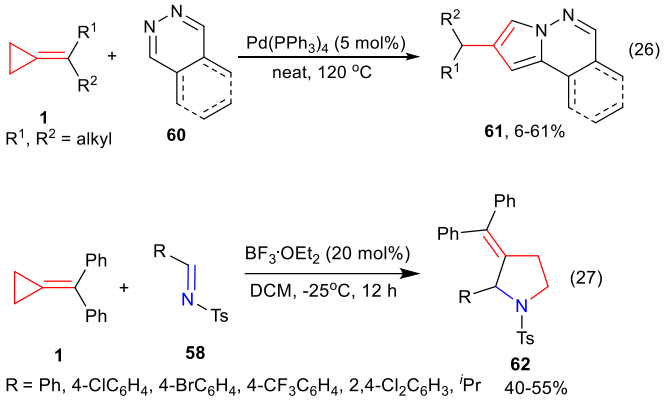
The ring expansion of 3-cyclopropylideneprop-2-en-1-ones **55** led to methylenecyclobutanone (MCBone) derivatives **56**, which could produce spirocyclopropyl lactones **57** in moderate to excellent yields catalyzed by TfOH (eq. 24).[29] Since the synthetic methodologies of MCBones have been well developed by us recently through the simple Aldol condensations,[30] compounds **57** are now easily prepared from available starting materials in fewer steps.

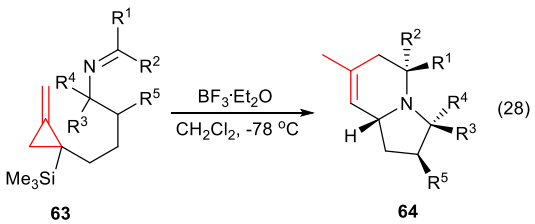


5. Pyrroles from MCPs

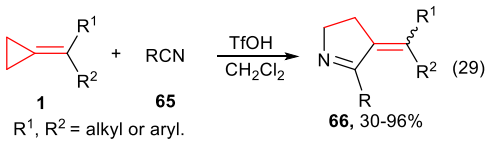
As C3 building-blocks, MCPs were also employed to construct the useful pyrrole skeletons through the [3+2] cyclo-additions. The reactions of MCPs **1** with imine derivatives **58** to synthesize pyrrole derivatives **59** were first reported by the Yamamoto group, using palladium catalyst and phosphorus ligand. The reactions were performed in toluene at 120 °C, affording 3-methylenepyrrolidines in moderate to good yields (eq. 25).[31] Similarly, the [3+2] cycloadditions of MCPs 1 with 1,2-diazines **60** gave a direct access to the 5-Azaindolizine derivatives (eq. 26).[32] Latter, Shi *et. al.* found that the reactions of MCPs 1 with imine derivatives **58** could also be catalyzed by the cheaper $BF_3{\cdot}OEt_2$ without any additives at low temperature (eq. 27).[12] Furthermore, the Lewis acid-catalyzed intramolecular *endo*-cyclization of trimethylsilyl methylenecyclopropyl imines **63** selectively gave the multi-substituted indolizidines **64** (eq. 28).[33] Undoubtly, construction of pyrroles through the [3+2] cyclo-addition of simple MCPs with imines should be an effective synthetic methodology owning to its directness as well as the accessible starting materials.



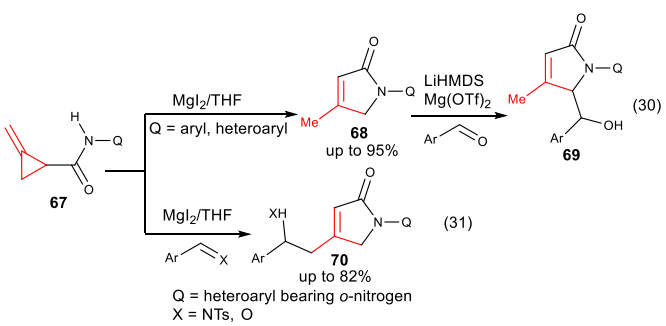




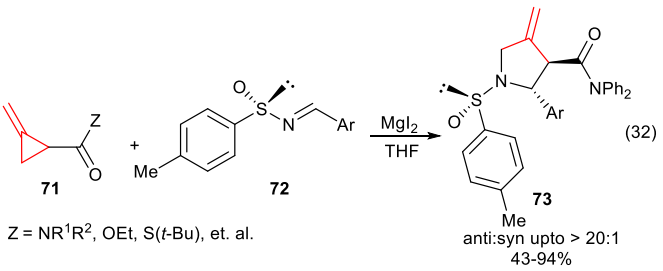
Besides imines, pyrroles were also available through the reactions of simple MCPs **1** with nitriles **65** (eq. 29)[34] The reactions were promoted by TfOH and proceeded quickly. Since nitriles are accessible and abundant chemicals, the methodology provided a practical access to pyrroles and might have very broad application scopes.



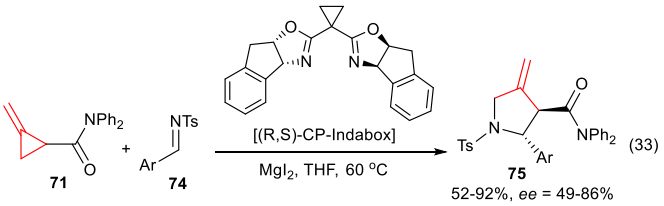
The functionalized MCPs are much more activated and can undergo a series of reactions to prepare useful organic compounds including pyrroles. In 2003, the Lautens group reported that promoted by MgI_2, methylenecyclopropyl amides **67** underwent the ring expansion to give the 4-methylpyrrol-2-one derivatives **68**, which afforded the γ-hydroxy-alkylated products **69** through the reactions with aldehydes (eq. 30). The methylenecyclopropyl amides **67** could directly led to the alkylated products **70** through the MgI_2-catalyzed alkylative ring expansion (eq. 31).[35a]



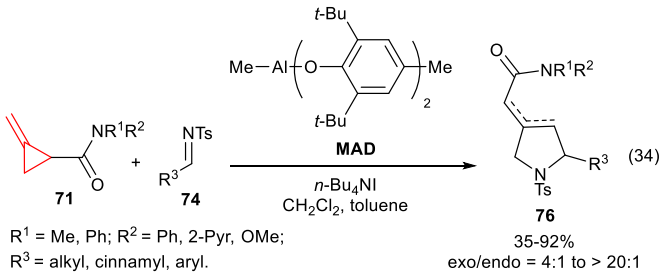
In the next year, they reported the MgI_2-promoted addition of methylenecyclopropyl amide derivatives **71** with chiral aromatic sulfinimines **72** to synthesize 2,3,4-trisubstituted pyrrolidines **72** (eq. 32),[35b,35c] which were then employed in the total synthesis of (-)-(α)-Kainic Acid.[35d]



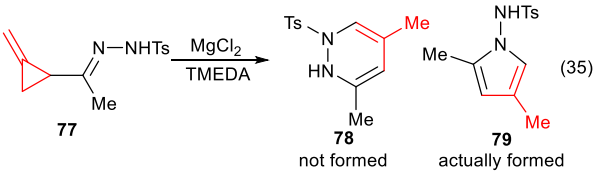
The application scopes of the reactions were further expanded. Using chiral Lewis acid, the reactions of methylenecyclopropyl amides **71** with simple aromatic sulfinimines **74** led to the pyrrolidines **75** with moderate to good enantioselectivity (eq. 33).[35e]



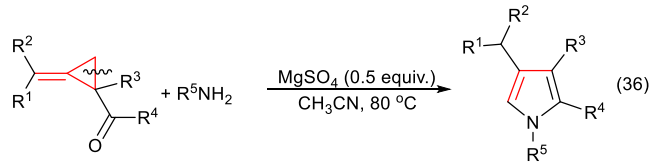
Latter, they found that using MAD as the catalyst directed the reaction of methylenecyclopropyl amides **71** with sulfinimines **74** to the γ-position and gave pyrrolidines **76** as products (eq. 34).[35f]



Catalyzed by $MgCl_2$, rearrangement of MCPs **77** occurred. The product was once assigned to be the pyridazine derivative **78**,[35g] but finally confirmed to be pyrrole **79** based on the computational results and ^{13}C NMR analyses (eq. 35).[35h]

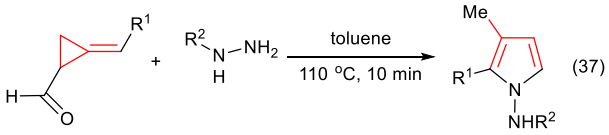


The reaction of MCPs **80** with amines **81** proceeded smoothly in the presence of $MgSO_4$ under mild conditions, affording an efficient synthesis of 2,3,4-trisubstituted pyrroles **82** (eq. 36).[36] The carbonyl substituted MCPs **83** were also able to react with hydrazines **84** in toluene at 110 °C without any catalyst or additive, giving the unique 1H-pyrrol-1-amines **85** quickly in moderate yields (eq. 37).[37]



80 **81** **82** 36-86%

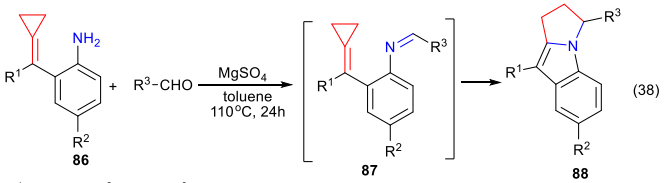
R^1, R^2 = H, alkyl; R^3 = H, COOEt, SO_2Ph;
R^4 = CH_3, Ph, CF_3; R^5 = Bn, *p*-MeOBn, ^{n}Bu, ^{t}Bu



83 **84** **85** 53-75%

R^1 = aryl, alkyl, H
R^2 (EWG) = PhCO, Ts, COOMe

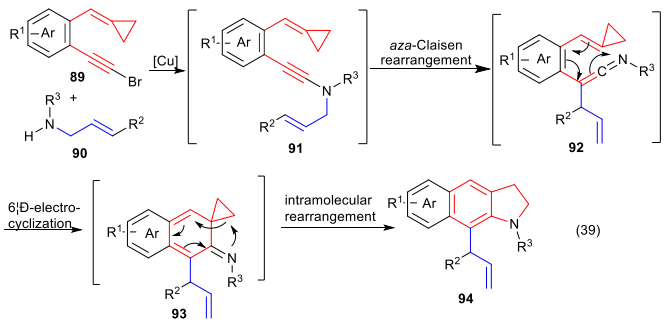
Bearing an *ortho*-amino on their aryl rings, the MCPs **86** reacted with aldehydes quickly and led to the intermediate **87**. Further cyclizations afforded the interesting fused pyrrole derivatives **88** in moderate to impressively high yields (eq. 38).[38]



86 **87** **88** 70-99%

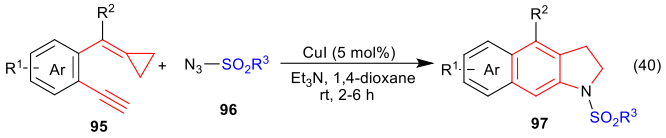
R^1 = Ph, Me; R^2 = H, Cl; R^3 = aryl, alkenyl, H

In 2012, Wu group designed and synthesized the complex MCPs **89** with an *ortho*-bromoalkynyl group on the aryl ring. They were then employed to react with allylic amine **90** to prepare the aryl-fused pyrrolidines **91** (eq. 39).[39] The reaction proceeded through multiple steps: The copper-catalyzed cross-coupling of the terminal alkynyl bromo with amine **90** first led to the intermediate **91**, which then afforded **92** through an *aza*-Claisen rearrangement. Further intramolecular *6π*-electro-cyclization of **92** gave the spiro-cyclopropyl intermediate **93**, which then rearranged to aryl-fused pyrrolidines **94** (eq. 39).



89 **90** **91** **92** **93** **94**

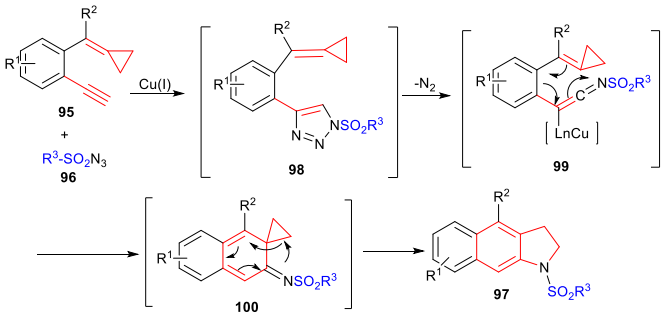
Aryl-fused pyrrolidines were also available from MCPs using sulfonyl azide as the nitrogen source. For example, catalyzed by copper, the MCPs **95** reacted with sulfonyl azides **96** smoothly to give the aryl-fused N-sulfonylpyrrolidines **97** at room temperature (eq. 40).[40]



95 **96** **97** 27-75%

R^1 = H, 5-OMe, 4,5-OMe, 4-Me, 4-Cl, 5-F, 4-F, R^2 = H, Me,
R^3 = 4-MeC_6H_4, C_6H_5, 4-BrC_6H_4, 4-$NO_2C_6H_4$, Me,

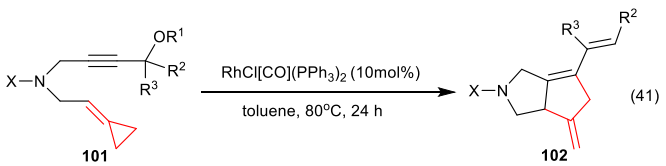
Undoubtly, the copper-catalyzed click reaction of **95** with **96** was the first step, affording the triazole intermediate **98**, which then led to **99** quickly after the release of an N_2. The intramolecular cyclization of **99** gave the spiro-cyclopropyl intermediate **100**, which then rearranged to the final product **97** (Scheme 4).



95 **96** **98** **99** **100** **97**

Scheme 4. Possible mechanisms for the reaction of **95** with **96**.

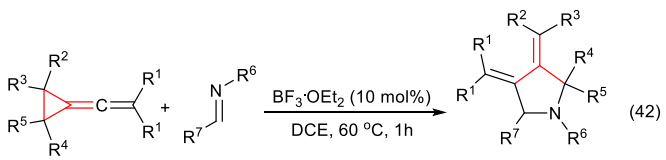
The pyrrolidine rings could also be constructed as "additional result" in MCPs' reactions. For example, in the Rh-catalyzed [3C+2C] reaction of the well-designed MCPs **101**, the pyrrolidine ring in **102** was generated along with the methylenecyclopentene cycle (eq. 41). [41]



101 **102** 36%-60%

R^1=$COCF_3$, Bz, Ac,
R^2= Me, Et, 4-PhBr, 4-Cl, 3-Cl, cyclohexane, cyclopentane
R^3=Me, H
X=Ts, Bs, Ns

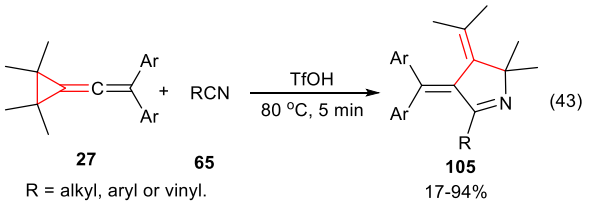
Pyrroles were also accessible from VCPs. Catalyzed by Lewis acid such as the metal triflates and $BF_3{\cdot}OEt_2$, the simple VCPs **27** reacted with imines **103** smoothly to give 3,4-dimethylene pyrrolidines **104** in moderate to excellent yields under mild conditions (eq. 42).[42] It should be noticed that the substitutes on nitrogen was the key to control the reaction selectivity: the electron-deficient aryl afforded pyrrolidines **104**, while the electron-enriched aryl benefited the generation of pyridine derivatives, which will be discussed in the next section.



27 **103** **104** 64-99%

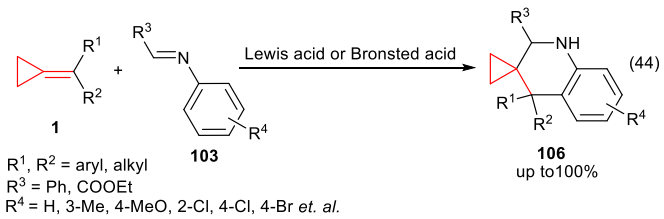
R^1, R^2, R^3, R^4, R^5 = H, alkyl, aryl
R^6 = aryl of Ts; R^7 = aryl or COOEt.

The [3+2] cycloadditions of VCPs **27** with nitriles **65** were also able to generate pyrroles. The reactions were promoted by Brønsted acid and proceeded at a impressively quick speed, giving the dialkylenepyrrole derivatives **105** in upto excellent yields (eq. 43).[43]

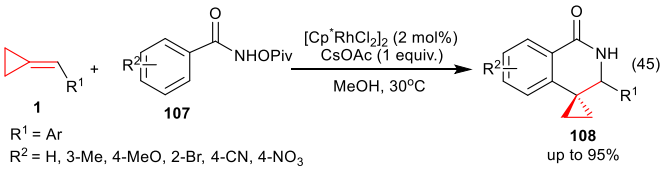


6. Pyridines from MCPs

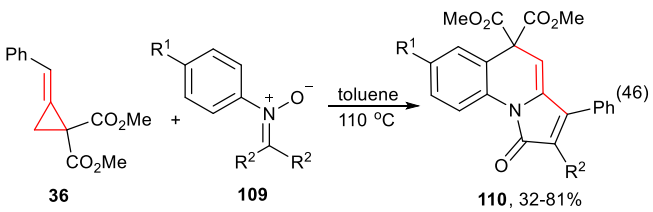
The Lewis acid- or Brønsted acid-catalyzed *aza*-Diels-Alder reaction of simple MCPs **1** with imines **103** provided an efficient synthetic methodology for quinoline derivatives **106** (eq. 44).[44] The catalyst could be metal triflates, $BF_3{\cdot}OEt_3$ or Brønsted acids such as CF_3SO_3H and $C_8F_{17}SO_3H$. The imines directly added to the C=C bond of MCPs while the cyclopropyl ring was untouched.

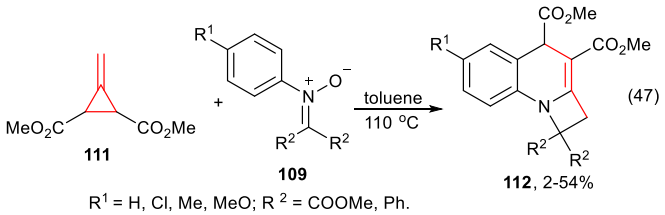


Recently, Cui *et. al.* reported that the Rh-catalyzed C–H activation/cycloaddition of mono-substituted MCPs **1** with benzamides **107** afforded the aryl-fused piperidinones **108** in up to impressively excellent yield (eq. 45).[45] In the reaction, the three-membered ring was untouched and kept intact as spiro-cyclopropyl in products.

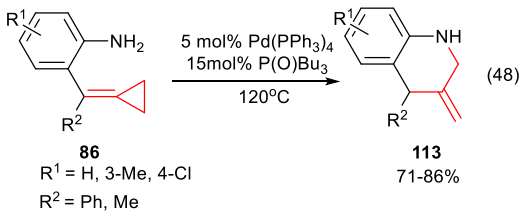


The C,C-disubstituted ketonitrones were also able to react with MCPs to prepare pyrroles. The reactions underwent smoothly in toluene at reflux and generated two possible products, depending on the structure of the starting MCPs: The MCPs **36** gave pyrrolo[1,2-*a*]quinolines **110** (eq. 46), while the MCPs **111** led to the 2,4-dihydro-1H-azeto[1,2-*a*]quinoliness **112** (eq. 47). [46]

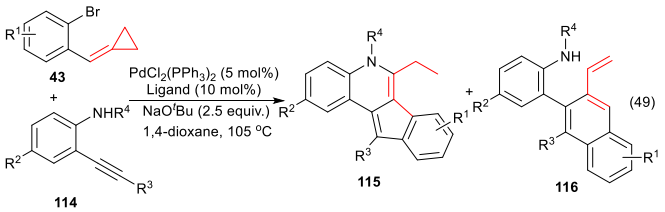




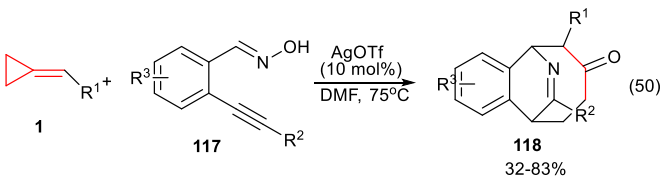
Pyridines could also be constructed along with the cyclopropyl ring break of MCPs. As shown in eq. 48, the MCPs **86**, bearing *ortho*-amino on their aryl rings, were able to rearrange to quinoline derivatives **113** in the presence of palladium catalyst.[47]



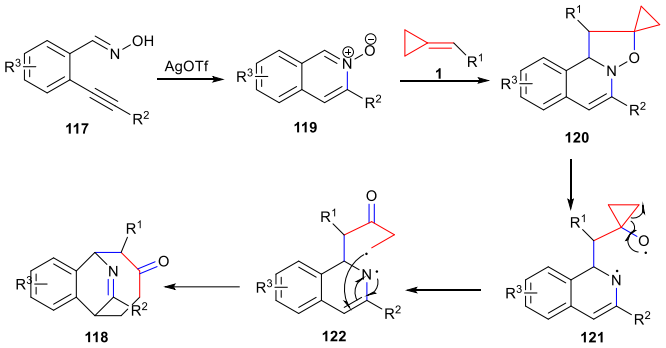
The reaction of 1-bromo-2-(cyclopropylidenemethyl)benzene **43** with 2-alkynyl aniline **114** led to fused quinoline derivatives **115** and the amine **116** simultaneously (eq. 49).[48] Ligands were found to be the key to control the selectivity. Generally, the carbene ligand afforded quinolines **115** as the major product, while the phosphine ligand benefited the generation of **116**.



Aldoximes could also be employed as nitrogen source and react with MCPs to synthesize pyridines. Catalyzed by AgOTf, the reaction of the simple mono-substituted MCPs **1** with 2-alkynyl benzaldehyde oxime **117** afforded the interesting bridged isoquinoline derivatives **118** (eq. 50).[49]

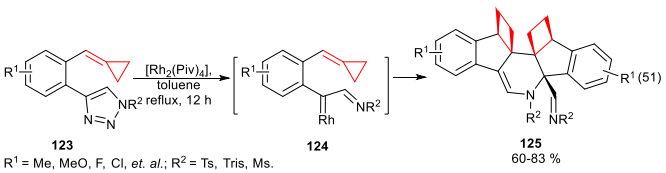


Catalyzed by AgOTf, 2-alkynyl benzaldehyde oxime **117** first rearranged to the intermediate isoquinoline oxide **119**, which then led to **120** through the [3+2] cycloaddition with MCPs **1**. The homo-cleavage of N-O bond in **120** afforded the biradical **121**, which afforded the intermediate biradical **122** after the cyclopropyl ring break. The intramolecular free radical addition of **122** gave the final bridged product **118** (Scheme 5).

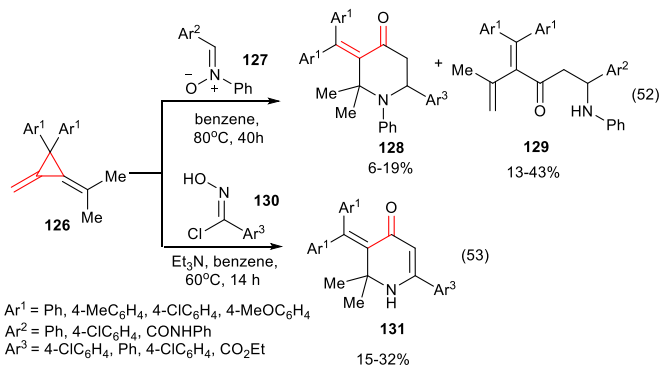


Scheme 5. Possible mechanisms for the reaction of **1** with **117**.

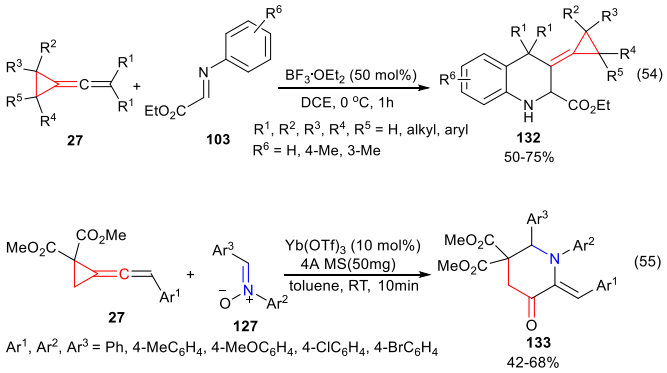
Very recently, Shi group reported an interesting Rhodium (II)-catalyzed intramolecular cycloisomerizations of MCPs with N-sulfonyl-1,2,3-triazoles. In the reaction, the MCPs **123** were first transformed to the rhodium azavinyl carbene intermediate **124** and then cycloisomerized to the highly functionalized polycyclic pyridine derivatives **125**. The MCP moieties finally rearranged to the fused cyclobutyl rings. Although the reactions proceeded through multiple steps and generated very complex products, the yields were still good and could reach 80% generally, providing a shortcut for the synthesis of those potentially applicable analogues (eq. 51). [50]



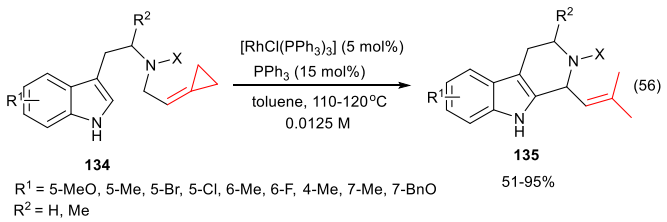
The dimethylenecyclopropanes **126** were also employed to synthesize pyridines. The reactions with diarylnitrones **127** led to the piperidinones **128** and chain product **129** (eq. 52), while the reaction with nitrile oxides **130** afforded the 2,3-dihydropyridin-4(1H)-ones **131** (eq. 53).[51] Unfortunately, the product yields of these reactions were too low to meet the requirement of organic synthesis.

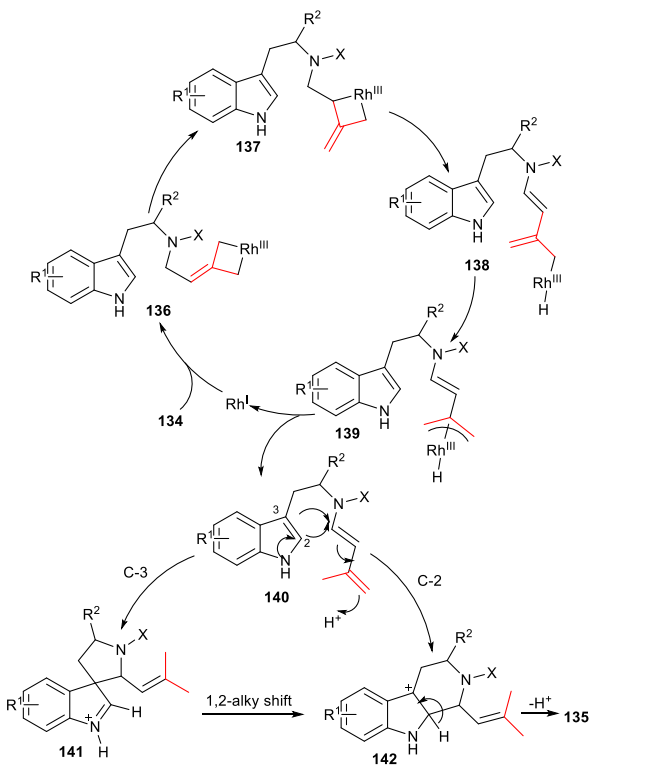


VCPs were also employed to synthesize pyridines. In the Lewis-catalyzed reactions of VCPs **27** with imines **103**, the interesting cyclopropylidene tetrahydroquinolines **132** were obtained when electron-enriched aryl substituted imines **96** were employed (eq. 54).[52] The Lewis acid-catalyzed reactions of VCPs **27** with diarylnitrones **127** afforded the piperidinones **133** in moderate yields (eq. 55).[52]



Pyridine structured could also be constructed in the MCP contained substrates but beyond the MCP moieties. For example, the Rh-catalyzed cyclization of substrate **134** generated a piperidine ring without the MCP skeleton (eq. 56).[53]





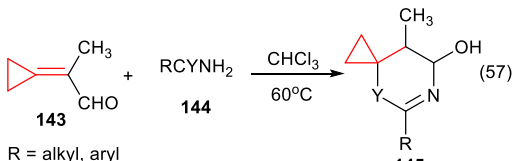
Scheme 6. Possible mechanisms for the intramolecular reaction of **134**.

In the reaction, the oxidation-addition of substrate **134** with Rh^{I} break the cyclopropyl ring and afforded the organometallic intermediate **136**, which then rearranged to **137**, **138** and the allylic Rh^{III} intermediate **139** sequently. The reduction-

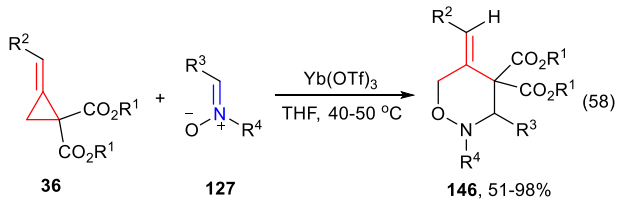
elimination in **139** released the Rh^I catalyst and generated the intermediate **140**. Reactions of **140** at C-3 and C-2 position afforded the tautomeric intermediate **141** and **142** respectively, which then led to the final product **135** after the proton releasing (Scheme 6).

7. Other heterocycles from MCPs

There are also many examples using MCPs as building-blocks to construct other kinds of heterocycles. For example, In 2005, we reported the tandem Michael–nucleouphilic addition of thioamides or selenoamides **144** to 2-cyclopropylidene propionaldehyde **143** to synthesize the spirocyclopropane-annulated heterocycles **145** (eq. 57).[54] The reaction proceeded smoothly in $CHCl_3$ to give the corresponding products in moderate to excellent yields. Although the cyclopropyl ring kept intact after the reaction, it might help to improve the reactivity of the substrates, since simple α, β-unsaturated aldehydes were much more difficult to undergo similar reactions under mild conditions.

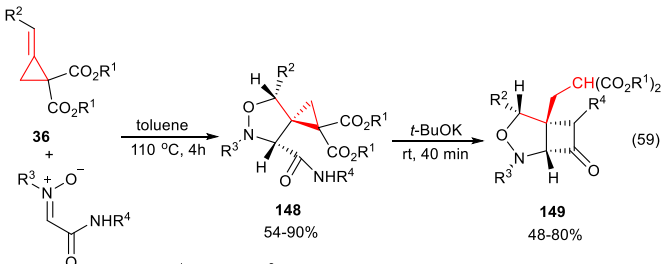


Oxazinanes were also available from MCPs. The Lewis acid-catalyzed reactions of MCPs **36** with nitrones **127** afforded the 5-methylene-1,2-oxazinanes **146** in moderate to excellent yields (eq. 58).[55]



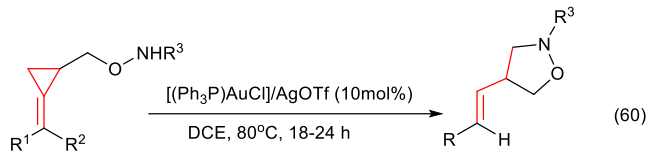
R^1 = Me, Et; R^2 = alkyl or aryl;
R^3 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, 4-IC_6H_4, 2-furyl;
R^4 = Me, 4-ClC_6H_4, 3-ClC_6H_4, 4-BrC_6H_4, 4-MeC_6H_4.

The reactions of MCPs **36** with nitrones **147** first gave the spirocyclopropyl isoxazolidines **148**, which then rearranged to the cyclobutone fused isoxazolidines **149** when treated by t-BuOK (eq. 59).[56]



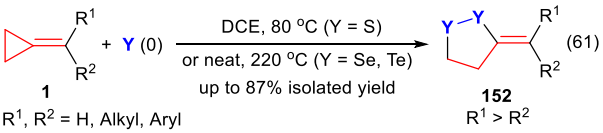
R^1 = Me, Et; R^2 = Ph, 4-MeC_6H_4, 4-ClC_6H_4;
R^3 = Ph, 4-MeC_6H_4; R^4 = Ph, 4-$MeOC_6H_4$.

Catalyzed by Au, the cyclopropyl functionalized MCPs **150** underwent an intramolecular cyclization along with the break of their cyclopropyl ring, giving alkenyl isoxazolidines **151** in moderate to good yields (eq. 60).[57]

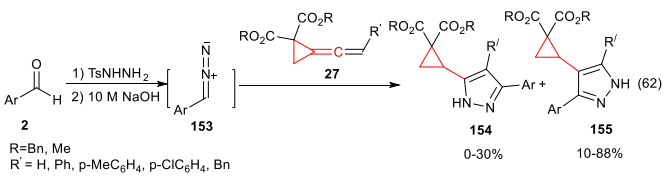


R^1 = aryl; R^2 = H, 4-BrC_6H_4
R^3 = Ts, Bs, Ns,

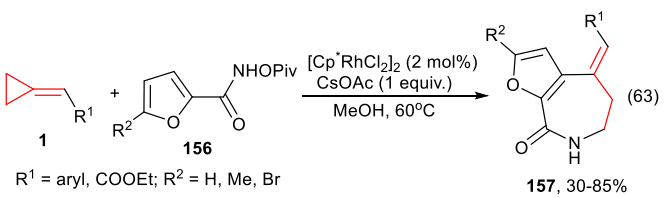
Very recently, we accidently found an interesting [3+2] cycloaddition of simple MCPs **1** with elemental chalcogens, giving heterocycles **152** in moderate to good yields (eq. 61).[58] The selectivity of the reaction was controlled by the steric-hindrance of substituents on MCPs **1**. It should be noticed that the heterocycles **152** might have bioactivities and widely existed in natural products, such as the nereistoxin and guinesines, which were isolated from *Lumbricomerereis hateropoda* and *Cassipourea guianensis* respectively.[59] In addition, preparing heterocycles directly from elemental chalcogens should be an effective and economic synthetic methodology because of the abundant chalcogen starting materials.[60]



VCPs were also employed to synthesize the multi-heteroatom cycles. The reaction of VCPs **27** led to the cyclopropyl substituted pyrazoles **154** and **155** through the reactions with **153**, which was available from aldehydes **2** and $TsNHNH_2$ (eq. 62).[61]

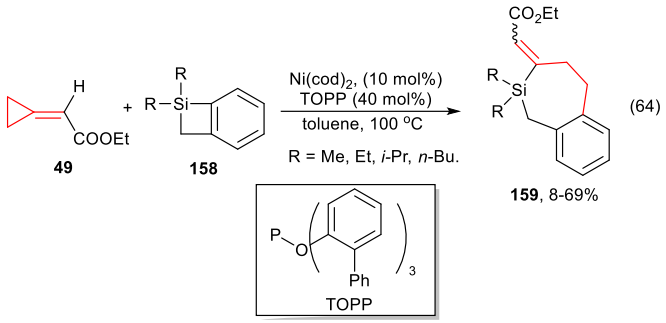


It is possible to build the large rings from MCPs as well. For example, in the Rh-catalyzed C–H activation/cycloaddition of simple MCPs **1** with amides, the cyclopropyl ring broke and led to large heterocycles **157** when the more activated furan-2-carboxamides **156** were employed (eq. 63).[45]



R^1 = aryl, COOEt; R^2 = H, Me, Br

The Ni-catalyzed [3+4] cycloaddition of MCPs **49** with benzosilacyclobutenes **158** afforded the interesting silicon-contained large ring compounds **159**, which were difficult to obtain through traditional methodologies (eq. 64).[62]



Conclusions

In conclusion, MCPs are versatile building-blocks in heterocycle synthesis. The reactions of MCPs bring more opportunities to develop novel and efficient methodologies to synthesize heterocycle compounds, including furans, pyrans, lactones, pyrroles, pyridines and other multi-heteroatom contained cycles or large rings. The MCP chemistry today is now developing rapidly and compared with that of ten years ago, people now are more tend to design and synthesize complex and functionalized MCPs and applied them in heterocycle synthesis. This area is amazing for the unexpected novel reaction discoveries.

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Notes and references

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