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Recent advances in the chemical transformations of functionalized alkylidenecyclopropanes (FACPs)

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During the past several years, functionalized alkylidenecyclopropanes (FACPs) have attracted intensive attention in synthetic chemistry. Many interesting transformations of FACPs have been developed to synthesize a lot of structurally diverse and valuable polycyclic and heterocyclic compounds. This review will classify FACPs into aryl-FACPs, alkyl-FACPs and ring-FACPs for the first time, and recent interesting chemical transformations in these research fields will be included, respectively, from 2011. Moreover, we will pay more attention to the clarification of the reaction mechanism, in which the C–C bond cleavage of alkylidenecyclopropanes (ACPs) will be emphasized.

1. Introduction

Strained small carbocycles have long been the concern of organic chemists. In particular, among them, the cyclopropane subunit plays a prominent role in organic chemistry.[1] In the class of cyclopropanes, methylene- or alkylidenecyclopropanes (MCPs or ACPs) as highly strained but readily accessible molecules can undergo a variety of ring-opening reactions because the relief of ring strain can provide a potent thermodynamic driving force.[2] These ring-opening processes can trigger various reactions of MCPs or ACPs with other substrates, giving efficient access to enhanced molecular complexity in organic syntheses. Generally, the reactivity of MCPs or ACPs has been fully excavated and it includes transition metal-catalyzed reactions,[3] Lewis acid-catalyzed reactions,[4] free radical addition induced rearrangements,[5] thermal induced cyclizations[6] and other types.[7]

In recent years, the development of MCPs or ACPs has emerged as a new direction using novel functionalized alkylidenecyclopropanes (FACPs) as substrates, and many interesting reactions have been explored with these novel FACPs by several groups. These novel FACPs include three types, namely, aryl-functionalized alkylidenecyclopropanes (aryl-FACPs), alkyl-functionalized alkylidenecyclopropanes (alkyl-FACPs) and ring-functionalized alkylidenecyclopropanes (ring-FACPs). Transformations of them to interesting and useful polycyclic compounds effectively expand this field of strained small carbocycles and it is necessary for further exploration to use these transformations to realize the total synthesis of natural products (Scheme 1).

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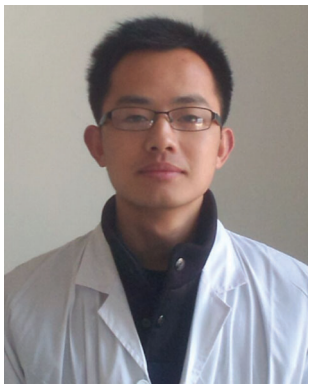

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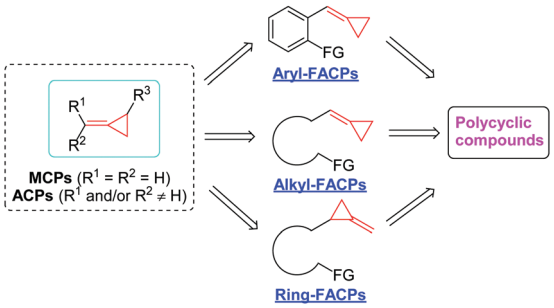


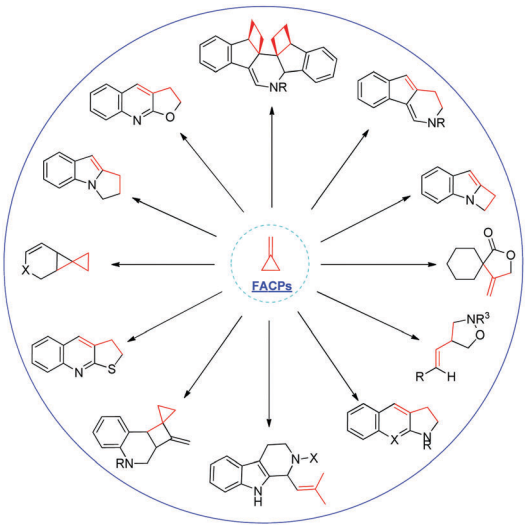
Scheme 1 Classification of functionalized alkylidenecyclopropanes (FACPs).

Recently, several excellent reviews on this fascinating area with regard to the use of MCPs or ACPs in organic synthesis have been published.[2] For example, in 2014, Brandi, Pellissier and Yu summarized the recent progress in this field as a review article, respectively.[2k,l,n] However, a focused review of the chemical transformation of FACPs has never been reported before. This minireview will put the concept of FACPs forward for the first time and mainly focuses on the recent advances in the chemical transformations of FACPs by our group (Scheme 2), along with other groups' findings from 2011. We hope this minireview will satisfy the expectations of the readers who are interested in the field of novel chemical transformation of FACPs.

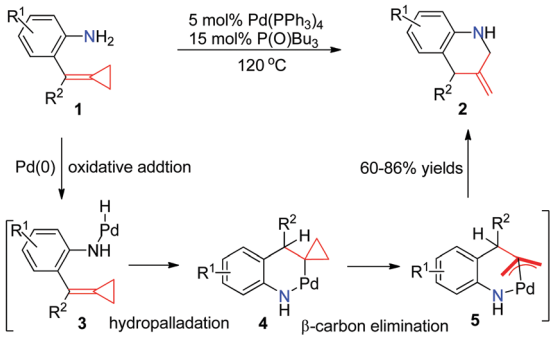
2. Reactivity of FACPs

2.1 Transformations of aryl-FACPs

In early 2005, Yamamoto's group reported the first Pd^0-catalyzed reaction that transforms aniline-tethered alkylidenecyclopropanes **1** to six-membered exomethylene nitrogen heterocycles **2** in good yields (Scheme 3).[8] This reaction starts with the intramolecular oxidative addition of a nitrogen–hydrogen bond of amine onto a zero valent palladium species to produce an amino-palladium species **3**, followed by hydropalladation of alkylidenecyclopropane to give **4**. The cyclopropylpalladium



Scheme 2 Represented examples reported by our group.



Scheme 3 Palladium-catalyzed reaction of FACPs **1**.

species **4** most probably undergoes β-carbon elimination, leading to an allylpalladium intermediate **5**. Subsequent reductive elimination of Pd(II) gives product **2**.

Yamamoto's work greatly inspired us to do further research on these kinds of FACPs. In 2012, we reported a convenient

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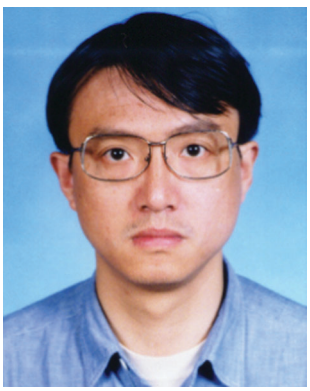
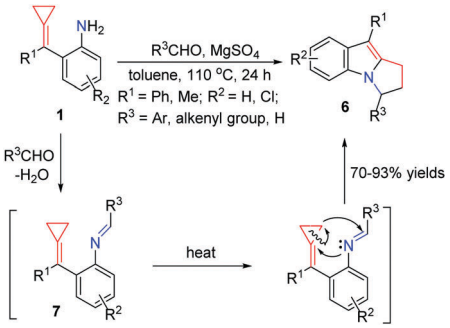


Min Shi

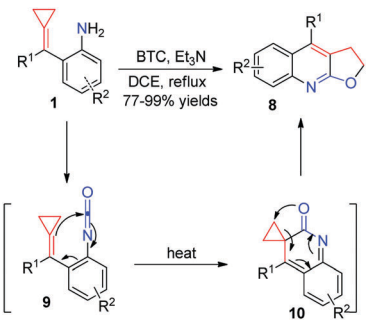
Dr Min Shi was born in 1963 in Shanghai, China. He received his BS in 1984 (Institute of Chemical Engineering of East China) and PhD in 1991 (Osaka University, Japan). He had his postdoctoral research experience with Prof. Kenneth M. Nicholas at the University of Oklahoma (1995–1996) and worked as an ERATO Researcher in Japan Science and Technology Corporation (JST) (1996–1998). He is currently a group leader of the State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry (SIOC).



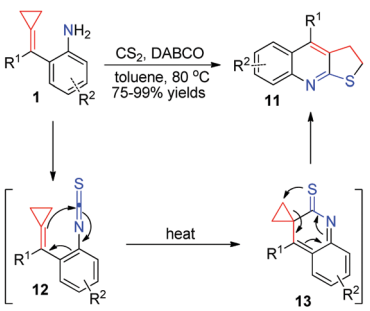
Scheme 4 Thermal-induced cyclization from aldehydes with FACPs **1**.

synthetic method to obtain functionalized pyrrolo[1,2-*a*]indoles **6** in good yields, which are common core structures found in a number of naturally occurring compounds *via* a ring-opening reaction and thermal-induced cyclization from aldehydes with aniline-tethered ACPs **1** (Scheme 4).[9] The reaction of **1** with benzaldehyde in the presence of anhydrous magnesium sulfate afforded imine **7**. When it was heated in toluene at 110 °C, thermal induced [3+2] cyclization took place, leading to the formation of **6** through a three-membered ring-opening pathway.

More recently, for more reaction partners to realize thermal induced [3+2] cyclizations of aniline-tethered ACPs **1**, our group developed a facile method to access a range of furoquinoline and thienoquinoline derivatives **8** and **11** *via in situ* generated isocyanate and isothiocyanate intermediates (Schemes 5 and 6).[10] These reactions produced the desired products in excellent isolated yields and tolerated a broad substrate scope, thus providing a potential application to synthesize some related



Scheme 5 Formation of furoquinoline derivatives from FACPs **1**.



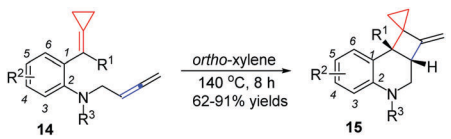
Scheme 6 Formation of thienoquinoline derivatives from FACPs **1**.

natural products and medical candidates. What is more, the production of both **8** and **11** is easy to scale-up to gram scale without loss of reaction efficiency. We proposed a reasonable mechanism, as outlined in Schemes 5 and 6, respectively. It is a common step that isocyanate-tethered ACPs **9** or isothiocyanate-tethered ACPs **12** were first formed based on the general methods. Subsequently, a consecutive 6π-electrocyclization and rearrangement occurred to produce the corresponding furoquinoline and thienoquinoline derivatives **8** and **11**.

For different types of thermal induced cyclization and cycloaddition of FACPs, in 2013, we reported a facile synthetic method for bicyclo[4.2.0] nitrogen heterocycles **15** *via* a thermal induced intramolecular [2+2] cycloaddition reaction of allene-ACPs **14** (Scheme 7).[11] The DFT calculations indicate that this intramolecular [2+2] cycloaddition proceeds *via* a concerted manner and the strained small ring is necessary.

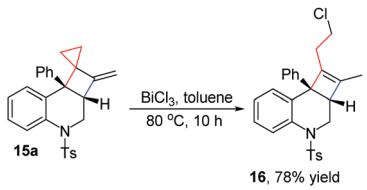
The cyclobutane group in the obtained bicyclo[4.2.0] nitrogen heterocycles **15** can be converted into a cyclobutene group along with the ring opening of cyclopropane. For example, upon treatment of $BiCl_3$ in toluene at 80 °C for 10 h, product **15a** could be easily transformed into product **16** in 78% yield, which is a novel type of 2*a*,3,4,8*b*-tetrahydrocyclobuta[*c*]quinoline derivative that has not been intensively studied so far (Scheme 8).

Recently, our group focused on acrylamide-tethered alkylidenecyclopropanes **17** and disclosed a novel iron or copper catalyzed trifluoromethylation of them with Togni reagent II **18** to construct two types of CF_3-containing tetracyclic benzazepine derivatives **19** and **20** depending on whether or not R^1 is a *para*-methoxy-substituent (Scheme 9).[12] The reaction exhibited high chemoselectivity in which the CF_3 radical preferentially attacked the acrylamide moiety followed by a ring-opening process of ACP. Most functional groups were tolerated, providing the corresponding benzazepine derivatives **19** and **20** in moderate to good yields. It is to be noted that, for the formation of **19**, the electronic effect had a prominent impact on the reaction outcome. Thus, the reactions were carried out with $Cu(MeCN)_4PF_6$ as a catalyst and MeCN as the solvent to improve the reaction

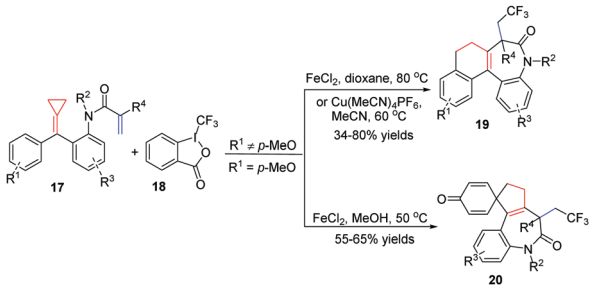


R^1 = C_6H_5, 4-ClC_6H_4, 4-MeC_6H_4, 4-FC_6H_4, Me;
R^2 = 5-Cl, 4-OMe, H;
R^3 = Ts, Ns, Bs, Ac, Bz, SO_2Ph, SO_2(*o*-$NO_2C_6H_4$)

Scheme 7 Thermal induced intramolecular [2+2] cycloaddition of **14**.



Scheme 8 Transformation of compound **15a** to **16**.



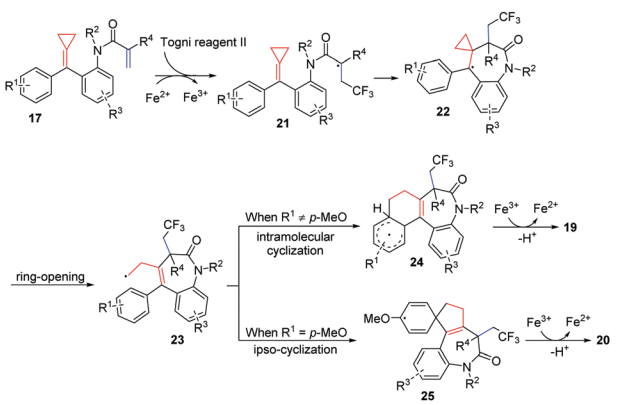
Scheme 9 Iron or copper-catalyzed trifluoromethylation of FACPs **17**.

efficiency and deliver the desired products cleanly when the benzene ring was substituted by a strongly electron-donating methoxyl group. Products **20** were formed in moderate yields in the presence of a catalytic amount of $FeCl_2$ in MeOH within 1 h.

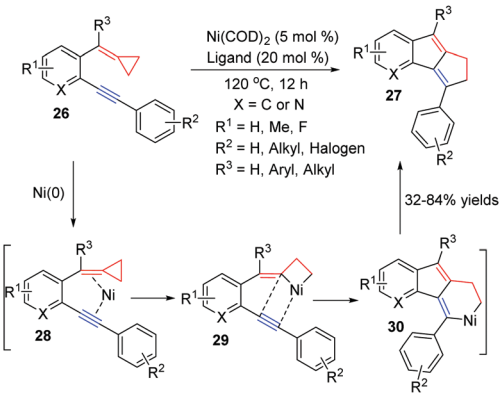
The reaction pathway is proposed in Scheme 10 based on radical trapping experiments and related precedents on trifluoromethylation of activated alkenes. The CF_3 radical generated *via* a single-electron transfer (SET) process reacts chemoselectively with the acrylic moiety of FACPs **17** to give a radical intermediate **21**. Subsequently, radical addition and ring-opening of alkylidenecyclopropane take place, producing homoallyl radical intermediate **23**. Then, intramolecular cyclization of radical intermediate **23** and oxidation deliver product **19**. However, if R^1 is a *para*-methoxy-substituent, an ipso-cyclization occurs forming radical intermediate **25**. Thus, the corresponding spirocyclic benzazepine **20** is obtained after oxidation.

In 2011, Zhang and co-workers developed a new Ni^0-catalyzed [3+2] cycloaddition of ACPs **26** with intramolecular aryl alkynes by the cleavage of a proximal C–C bond to obtain cyclopenta[*a*]indene derivatives **27** in good yields (Scheme 11).[13] A plausible mechanism for the reaction is shown in Scheme 11. Oxidative addition of nickel(0) to the proximal C–C σ bond of cyclopropyl alkene leads to the nickelacyclobutane intermediate **29**. The subsequent intramolecular addition of species **29** into the C–C triple bond generates the six-membered nickel cycle **30**, which undergoes reductive elimination to give the corresponding product **27**.

In 2011, Wu's group discovered a novel Cu^I-catalyzed cascade reaction of 2-ethynylaryl ACPs **31** with sulfonyl azides to generate fused indolines **32** in moderate to good yields (Scheme 12).[14]



Scheme 10 Proposed mechanism for the formation of **19** and **20**.



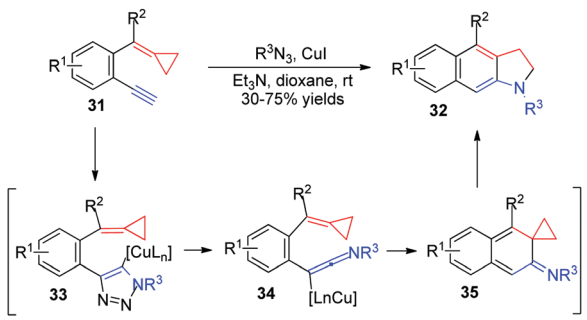
Scheme 11 Nickel-catalyzed cycloaddition of FACPs **26**.

They reasoned that 2-ethynylaryl ACPs **31** would react with sulfonyl azide catalyzed by CuI to afford the triazole intermediates **33**. This intermediate could be transformed into the reactive ketenimines **34** *via* a ring-opening rearrangement. A consecutive 6π-electrocyclization would take place to form intermediates **35**, which subsequently underwent a rearrangement to give the desired products **32**.

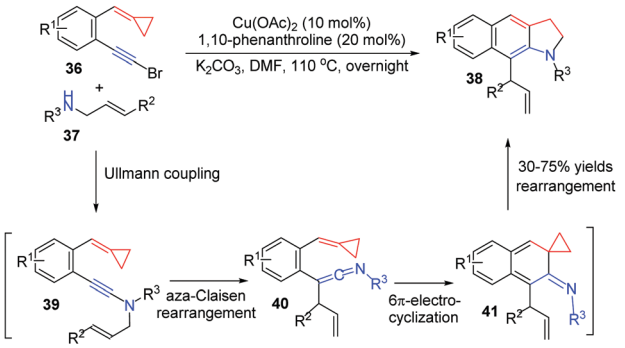
In 2012, Wu's group reported another Cu^{II}-catalyzed tandem reaction of 1-bromoethynyl-2-(cyclopropylidenemethyl)arenes **36** with *N*-allylsulfonamide **37** to afford functionalized benzoindolines **38** in good yields (Scheme 13).[15] The transformation may be a four-step cascade involving Ullmann coupling to get **39**, aza-Claisen rearrangement to form **40**, 6π-electrocyclization to obtain **41** and intramolecular rearrangement to produce benzoindolines **38**.

Transition metal catalyzed intermolecular reactions of carbenes or nitrenes with MCPs have drawn great attention during the past decade. In 2014, we reported a Rh^{II}-catalyzed novel cascade cycloisomerization/aza-Diels–Alder reaction of 1-(cyclopropylidenemethyl)-2-(*N*-sulfonyltriazole)arenes **42**, producing a series of highly functionalized polycyclic N-heterocycles **43** in moderate to good yields (Scheme 14).[16]

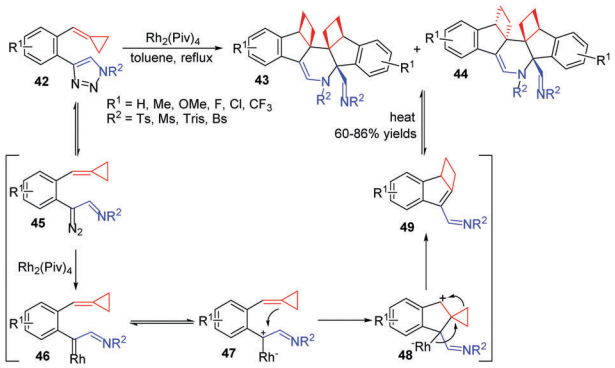
In this reaction, *N*-sulfonyltriazole **42** exists in equilibrium with its diazoimine tautomer **45**. It can be efficiently intercepted by a Rh^{II} catalyst to give rise to highly reactive rhodium(II) azavinyl carbene **46**. This intermediate exists in equilibrium with its diazoimine tautomer **47**, followed by a nucleophilic attack from ACP furnishing intermediate **48**. Subsequent ring expansion



Scheme 12 Cu^I-catalyzed cascade reaction of FACPs **31**.



Scheme 13 Cu^{II}-catalyzed cascade reaction of FACPs **36** with **37**.

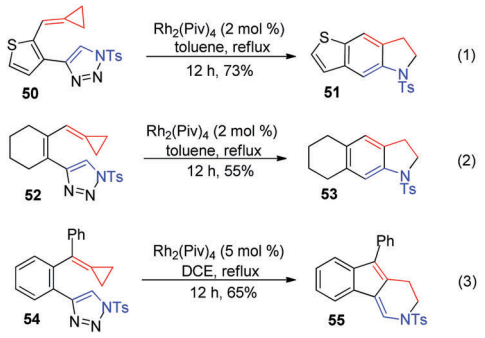


Scheme 14 Rh^{II}-Catalyzed novel cascade reaction of FACPs **42**.

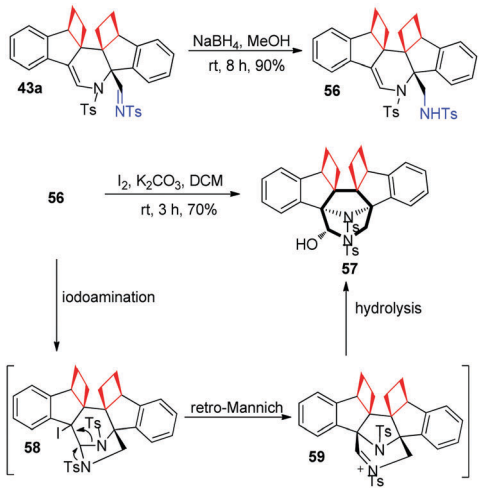
and elimination of the Rh^{II} catalyst generates the α,β-unsaturated imine intermediate **49**, which is very reactive to induce an intermolecular aza-Diels–Alder [4+2] reaction to give products **43** and **44**. When the product mixture is heated at 110 °C, the thermodynamically more stable product **43** can be isolated as the sole product because of the retro-Diels–Alder reaction process.

Next, we aimed to demonstrate the divergent reaction pathways of ACPs with azavinyl carbenes. Thiophene and cycloalkene tethered-triazole-ACPs **50** and **52** were synthesized and treated under standard conditions, only affording the corresponding fused indolines **51** and **53** in 73% and 55% yields, respectively (Scheme 15, eqn (1) and (2)). It is possible that thermal-induced rearrangements of special substrates **50** and **52** are faster than the generation of their rhodium(II) azavinyl carbene intermediates. As for substrate **54**, which has a phenyl substituent on the ACP moiety, formal [3+3] cyclization took place to give product **55** in 65% yield (Scheme 15, eqn (3)).

The imino group of product **43a** could be easily converted to amine **56** upon reduction with $NaBH_4$ in methanol. To our delight, upon treatment of **56** with I_2 and K_2CO_3, 3,8-diazabicyclo[3.2.1]octane derivative **57** could be obtained in 70% yield. This interesting reaction pathway may contain a tandem iodoamination, retro-Mannich reaction and hydrolysis (Scheme 16). Significantly, 3,8-diazabicyclo[3.2.1]octane derivatives usually have valuable biological properties. For example, azaprocin, which has the same core structure as that of **57**, is an opioid analgesic with approximately ten times (10×) the potency of morphine, and a fast onset and short duration of action.



Scheme 15 Further substrate scope study.

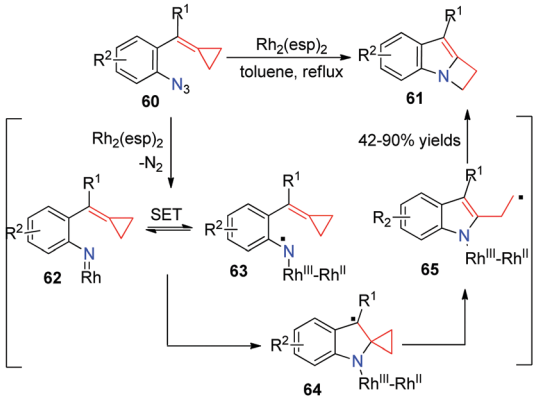


Scheme 16 Transformations of compound **43a** to **56** and **57**.

The reaction of nitrenes with MCPs should be very attractive because the incorporation of a nitrogen atom can potentially give rise to nitrogen containing heterocycles. However, according to the previously reported results, the intermolecular and intramolecular reactions of carbenes or nitrenes with MCPs all lead to the ring expansion of cyclopropane to cyclobutane. Recently, we disclosed a Rh^{II}-catalyzed intramolecular rearrangement of azide-ACPs **60** to form a series of indole-fused azetidines **61** in good yields (Scheme 17).[17]

A plausible mechanism is also outlined in Scheme 17. Coordination of the azide to $Rh_2(esp)_2$ and extrusion of N_2 give the Rh-nitrene intermediate **62**. Next, intramolecular single electron transfer (SET) takes place to form the N-centered radical species **63**. The following radical addition to the C=C bond in the MCP moiety forms intermediate **64**. It undergoes a ring-opening process to furnish homoallylic radical **65**. Subsequent SET from the radical to Rh^{III} and ring-closure gives rise to **61** together with the regeneration of the Rh^{II} catalyst. DFT calculations on the key step explain that cyclization and SET pathways are controlled by a radical clock in intermediate **64**.

The active radical intermediate **64** led us to question what would happen instead of ring-opening when there was no radical clock. Different ring sized azide-methylenecycloalkanes as well as dimethyl substituted alkenes were investigated. These reactions

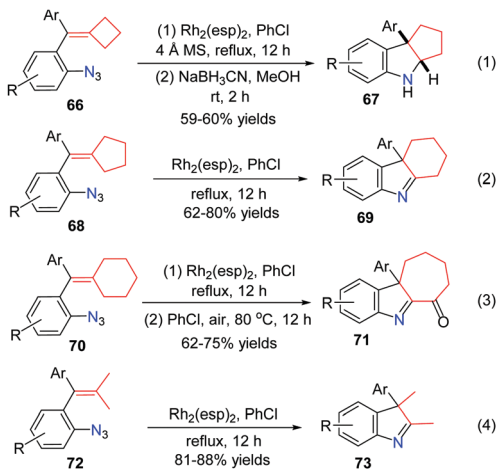


Scheme 17 Rh^{II}-Catalyzed intramolecular rearrangement of azide-ACPs **60**.

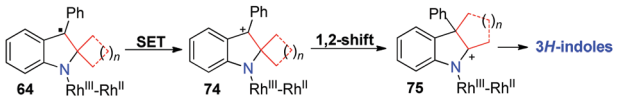
went on smoothly in chlorobenzene under reflux for 12 h to obtain a series of 3*H*-indoles in moderate to good yields. The reactions of methylenecyclobutanes **66** proceeded smoothly, affording hexahydrocyclopenta[*b*]indoles **67** in moderate yields after reduction by $NaBH_3CN$ (Scheme 18, eqn (1)). As for substrates **68**, the corresponding tetrahydro-1*H*-carbazoles **69** were obtained in 62–80% yields (Scheme 18, eqn (2)). Specifically, in the case of methylenecyclohexanes **70**, the reactions proceeded smoothly and the desired products were easily oxidized by air, affording ketones **71** in 62–75% yields (Scheme 18, eqn (3)). When substrates **72** bearing two methyl substituents reacted under the standard reaction conditions, the products **73** were formed after 1,2-alkyl migration in good yields (Scheme 18, eqn (4)).

A plausible pathway accounting for these reactions is outlined in Scheme 19. Without the radical clock in this reaction, ring-opening of intermediate **64** cannot take place and it undergoes another SET to give spirocyclic cationic intermediate **74**. A consecutive 1,2-alkyl shift occurs to afford the fused indole **75**, which produces the corresponding 3*H*-indole products.

The active intermediate **62** also attracted our attention strongly and the multicomponent tandem reaction of Rh-nitrenes with ACPs should be very attractive because the incorporation of a nitrogen atom can potentially give rise to novel N-containing



Scheme 18 Further substrate scope study.

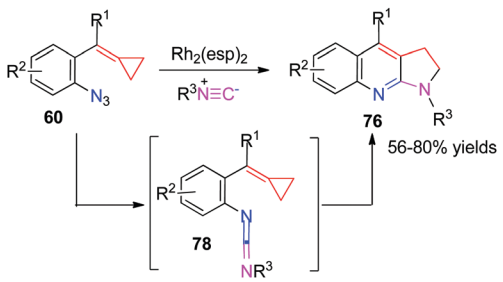


Scheme 19 A plausible mechanism for the formation of 3*H*-indoles.

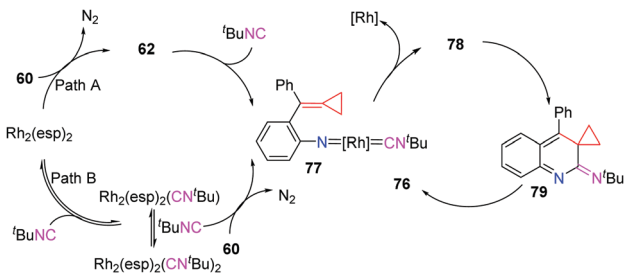
heterocycles. Furthermore, extended application to intercept the *in situ* generated rhodium nitrene to embed the 3C synthon of MCPs into other ring systems, especially heterocycles instead of the indole-fused azetidine **61** formation, seems to be challenging and interesting. As a result, we found that azide-MCPs **60** could undergo intermolecular cyclization with isonitriles catalyzed by the Rh^{II} catalyst to produce a series of pyrrole-fused quinolines **76** in good yields *via* carbodiimide intermediates **78** (Scheme 20).[18]

Two plausible pathways accounting for this intermolecular cascade reaction are outlined in Scheme 21. In path A, the denitrogenation process gives Rh-nitrene **62**, which reacts with ^{t}BuNC to afford the key intermediate **77**. Alternatively (path B), the reaction of $Rh_2(esp)_2$ with ^{t}BuNC gives $Rh_2(esp)_2(CN^tBu)_2$, which is not very stable and decomposes into $Rh_2(esp)_2(CN^tBu)$ at the same time. Upon regeneration of the catalyst, key intermediate **77** can also be afforded from azide-ACP **60**. After the regeneration of the Rh^{II} catalyst, **77** is transformed to carbodiimide **78**. A consecutive 6π-electrocyclization occurs to afford intermediate **79**, which subsequently undergoes a thermal-induced rearrangement to produce pyrrole-fused quinolines **76**.

Next, we carried out some transformations of products **76** to improve the applicability of this methodology. For example, after removal of the PMB of product **76a** and further condensation with 3,4,5-trimethoxybenzoic acid, DU-145 cell inhibitor **80** could be obtained in 80% yield. It showed the best IC_{50} value (0.114 μM)



Scheme 20 Rh^{II}-Catalyzed intermolecular cyclization with isonitriles of azide-ACPs **60**.



Scheme 21 A plausible mechanism for this reaction.

and may be used as a novel anti-cancer agent in prostate cancer therapy (Scheme 22).

2.2 Transformations of alkyl-FACPs

ACPs and MCPs have proven to be versatile three-carbon synthons for an array of metal-catalyzed annulation reactions. Mascareñas and López reported that FACPs could be used in Pd-catalyzed [3+2+2] cycloadditions with activated alkenes involving ACP proximal bond cleavage.[19] The same group also reported Ni-catalyzed intramolecular [3+2+2] cycloaddition with similar substrates.[20] It should be noted that Evans and colleagues reported the first example of intermolecular Rh^{I}-catalyzed [3+2+2] carbocyclization of FACPs **81** with activated alkynes **82** to get bicycloheptadienes **83** and **84** in good yields in 2008 (Scheme 23).[21]

In 2014, López and Mascareñas achieved the Rh^{I}-catalyzed [3+2+2] cycloaddition of FACPs **85** with intramolecular alkenes and alkynes. The transformation afforded synthetically relevant 5,7,5-fused tricyclic systems **86** and/or **87** with moderate or good yields, good versatility, and high diastereoselectivities (Scheme 24).[22] In the same year, they also reported highly diastereo- and chemoselective Ni^{0}-catalyzed intramolecular [3+2+2] cycloaddition of similar FACPs **85**. The reaction proceeded *via* proximal cleavage of cyclopropane and made it possible to construct relevant 6,7,5-tricyclic frameworks **88** in a one-pot reaction manner. They also pointed out that the characteristics of the nickel ligands were important to the reaction outcome (Scheme 25).[23]

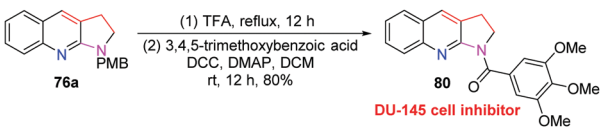
In 2012, Evans's group reported a novel Rh^{I}-catalyzed [3+2+1] carbocyclization of carbo- and heteroatom-tethered FACPs **81** with CO to realize the stereoselective construction of *cis*-fused bicyclohexenones **89** in good yields (Scheme 26).[24]

Thereafter, the development of the Rh^{I}-catalyzed [(3+2)+1] carbocyclization reaction of alkynylidenecyclopropanes **81** with carbon monoxide to construct polysubstituted phenols **90** is described by the groups of Evans and Chung, respectively (Scheme 27).[25] This work offers a convenient method for the selective formation of 5,6-bicyclic phenols, which provide important intermediates for the target directed synthesis of natural products such as benfluron and MN100.

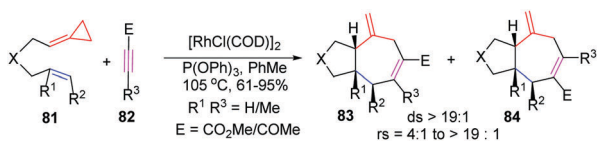
In 2012, in the absence of reaction partners, such as activated alkynes and carbon monoxide, they reported the novel diastereoselective Rh^{I}-catalyzed ene-cycloisomerization (ECI) reactions of alkenylidenecyclopropanes **81** to provide an atom-economical approach to five-membered carbo- and heterocycles **91** that contain two new stereogenic centers in good yields (Scheme 28).[26]

More importantly, the isolation and characterization of a novel rhodacycle intermediate **92** implicated in the Rh^{I}-catalyzed reactions of FACPs was achieved by Evans's group (Scheme 29).[27] The structure of the metallacycle was unambiguously determined by X-ray crystallography. The metallacycle **92** is catalytically competent in Rh^{I}-catalyzed carbocyclization with alkynes and carbon monoxide along with Rh^{I}-catalyzed ene-cycloisomerization (ECI) in the absence of a π-component under standard conditions. These reactions proceeded through the Rh^{III} metallacycle. They isolated the metallacycle and provided important insight into the ligand requirements for the insertion of π components. Furthermore, they also described a novel [(3+2)+2] carbocyclization reaction of the metallacycle **92** with an activated allene to produce **93**.

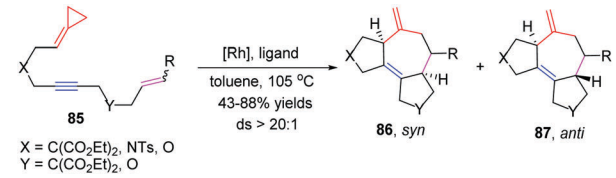
In 2013, our group developed a new Rh^{I}-catalyzed intramolecular cycloisomerization reaction of nitrogen-tethered indoles with FACPs **94** to provide easy access to tetrahydro-β-carboline derivatives **95** in good yields (Scheme 30).[28] The reaction mechanism is proposed on the basis of isotopic labeling and control experiments, and is also supported by DFT calculations.



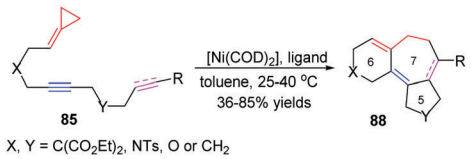
Scheme 22 Transformation of compound **76a** to **80**.



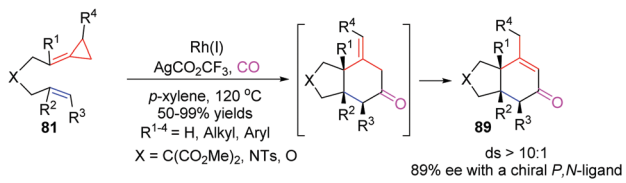
Scheme 23 Rh^{I}-Catalyzed [3+2+2] carbocyclization of FACPs **81** with activated alkynes **82**.



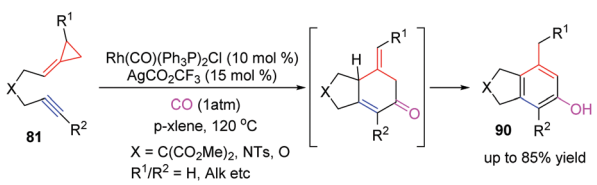
Scheme 24 Rh^{I}-Catalyzed [3+2+2] cycloaddition of FACPs **85**.



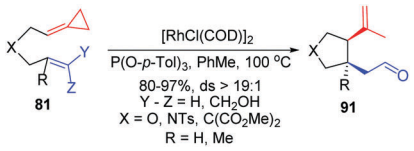
Scheme 25 Ni^{0}-Catalyzed [3+2+2] cycloaddition of FACPs **85**.



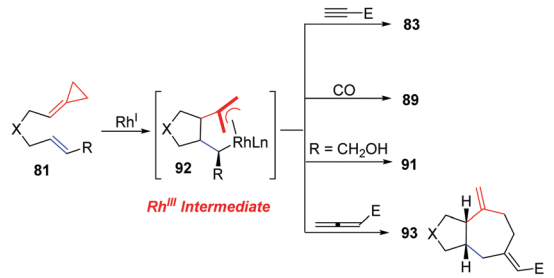
Scheme 26 Rh^{I}-Catalyzed [3+2+1] carbocyclization of FACPs **81** with CO.



Scheme 27 Rh^{I}-Catalyzed [(3+2)+1] carbocyclization reaction of FACPs **81** with CO.



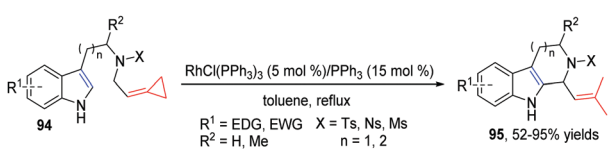
Scheme 28 Rh^{I}-Catalyzed ene-cycloisomerization (ECI) reactions of FACPs **81**.



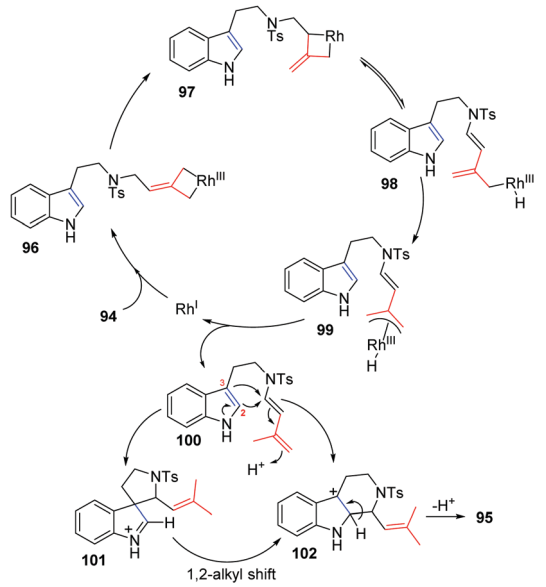
Scheme 29 Stereoselective Rh^{I}-catalyzed [(*m*+*n*)+*o*] carbocyclizations and ene-cycloisomerizations (ECI) of FACPs **81** *via* intermediates **92**.

A plausible mechanism for this reaction is outlined in Scheme 31. Initial insertion of the metal at the distal position of alkylidenecyclopropane **94** gives metallacyclobutene **96**, followed by isomerization to form intermediate **97** through a trimethylenemethane (TMM)-like transition state. Intermediate **97** undergoes β-H elimination to give Rh–H species **98**, which can isomerize to produce π-allylic Rh^{III} complex **99**. Conjugated diene **100** can be obtained from intermediate **99** through reductive elimination along with regeneration of the Rh^{I} complex. There are two competing pathways for cyclization in the Pictet–Spengler reaction, since both the indole C2- and C3-positions are nucleophilic. Through an indole C3-position attack on the conjugate diene, spiroindolenine intermediate **101** is formed, which can further undergo a 1,2-alkyl shift to afford the six-membered-ring intermediate **102**. Alternatively, nucleophilic attack of the indole C2-position on the diene moiety leads directly to intermediate **102**, followed by deprotonation to give **95**.

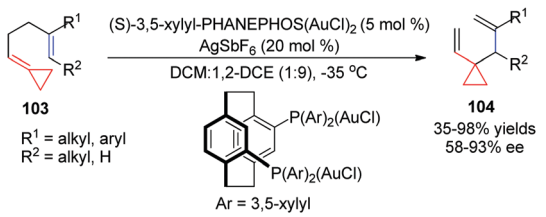
Taking advantage of the ring strain relief strategy, Gagné's group recently reported several Au^{I}-catalyzed rearrangements of FACPs. In 2012, they found the first enantioselective Au^{I}-catalyzed Cope rearrangement from achiral 1,5-dienes **103** to form products **104** (Scheme 32).[29] Subsequently, they investigated ACP-containing cyclic 1,5-dienes **105** and disclosed an Au^{I}-catalyzed ring-expanding cycloisomerization of **105** to produce the corresponding bicyclo[4.2.0]oct-1-enes **106** in good yields (Scheme 33).[30] Based on this result, novel ACP-bearing 1,5-enynes such as **107** were synthesized, and under the catalysis of PPh_3AuNTf_2, bicyclo[4.2.0]dienes **108** were obtained through a sequential 6-*endo*-dig-cyclization/ring



Scheme 30 Rh^{I}-Catalyzed cycloisomerization reaction of FACPs **94**.



Scheme 31 A plausible mechanism for this reaction.

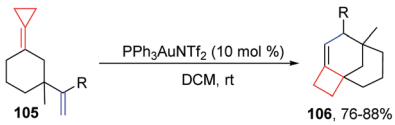


Scheme 32 Au^{I}-Catalyzed Cope rearrangement of FACPs **103**.

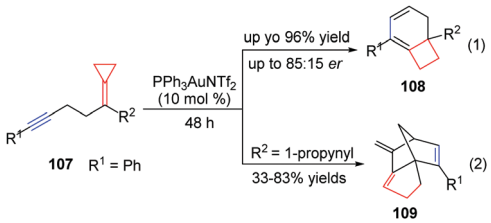
expansion/net 1,2-hydrogen shift process (Scheme 34, eqn (1)).[31] It is worth noting that when FACPs **107** (R^2 = 1-propynyl) were treated with PPh_3AuNTf_2 (10 mol%) in 1,2-dichloroethane at 50 °C, the expected bicyclic products **108** were not formed. Instead, the tricyclic compounds **109** were obtained as a single diastereomer in 33–83% yields (Scheme 34, eqn (2)).[32]

Recently, we have also developed another example of Au^{I}-catalyzed cycloisomerization of nitrogen and oxygen-tethered alkylidenecyclopropanes **81** to provide easy access to tricyclic compounds or bicyclo[4.1.0]heptene derivatives **110** in high yields under very mild conditions (Scheme 35).[33] The reaction may initially form cyclopropyl gold–carbene intermediate **111**, which equilibrates with intermediate **112**, followed by a 1,2-hydride shift process.

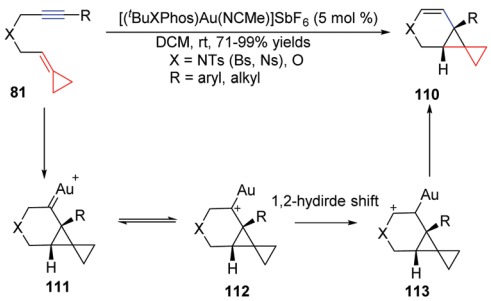
Moreover, our group also prepared triazole-tethered alkyl-FACPs **114** and **116**, and azavinyl carbenes also reacted smoothly with alkylidenecyclopropane to furnish two structurally valuable products, **115** and **117**.[16] Tricyclic aldehyde **115** was formed in 70%



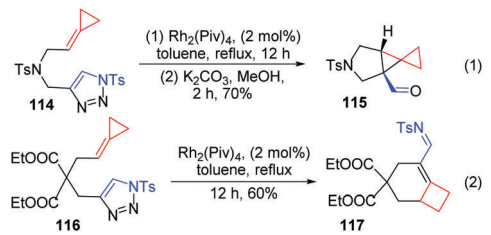
Scheme 33 Au^{I}-Catalyzed ring-expanding cycloisomerization of FACPs **105**.



Scheme 34 Au^{I}-Catalyzed rearrangements of FACPs **107**.



Scheme 35 Au^{I}-Catalyzed cycloisomerization of FACPs **81**.



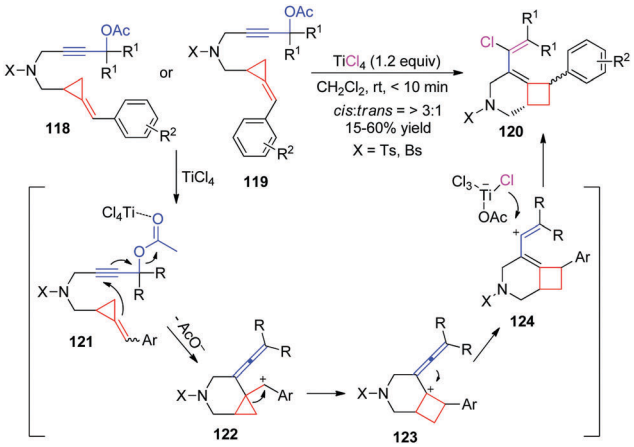
Scheme 36 Rh-Catalyzed triazole-tethered FACPs **114** and **116**.

yield after cyclopropanation and hydrolysis when *N*-tethered-triazole-ACP **114** was used as a substrate (Scheme 36, eqn (1)). Interestingly, the reaction of substrate **116** delivered *trans*-α,β-unsaturated imine product **117** in 60% yield (Scheme 36, eqn (2)).

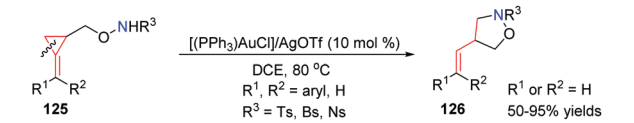
2.3 Transformations of ring-FACPs

When functional groups are introduced at the ring of MCPs or ACPs, the ring-opening or ring-expansion of FACPs may take place in a very special and different manner. In 2011, our group reported a $TiCl_4$-mediated intramolecular ring enlargement of FACPs **118** and **119** with propargylic esters to afford the corresponding chlorinated bicyclo[4.2.0]oct-5-ene derivatives **120** in moderate to good yields (Scheme 37).[34]

We proposed a plausible reaction mechanism for this $TiCl_4$-mediated carbocyclization in Scheme 38. Coordination of the ester group to $TiCl_4$ gives intermediate **121**. Nucleophilic intramolecular addition of the pendant methylenecyclopropane to the alkyne moiety along with the release of an acyloxy group affords carbocation **122**, which contains a vinylidene moiety. Subsequently, carbocationic intermediate **122** undergoes intramolecular ring enlargement of cyclopropane *via* 1,2-migration giving intermediate **123** which can give vinyl cationic intermediate **124** through isomerization. Then, a chloride ion is



Scheme 37 $TiCl_4$-Mediated intramolecular ring enlargement of FACPs **118** or **119**.

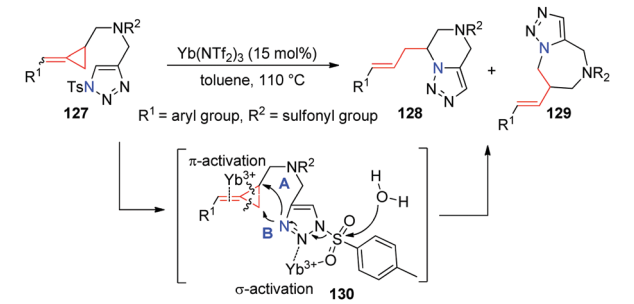


Scheme 38 Au^{I}-Catalyzed reaction of FACPs **125**.

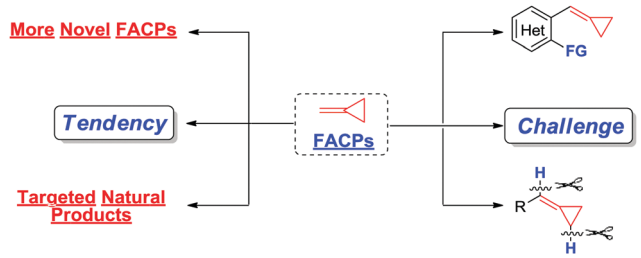
transferred to a vinyl cation from the *in situ* generated metal complex, affording the corresponding chlorinated bicyclo[4.2.0]oct-5-ene **120**. It should be noted that carbocation **122** can be stabilized by the neighboring aryl unit, which can serve as a driving force for this transformation. Moreover, as can be seen from Scheme 38, *E*- and *Z*-methylenecyclopropanes **118** or **119** give the same benzylic cation **122** under identical conditions. This can explain why the same products could be formed using **118** and **119** as the substrates.

In 2012, our group reported an interesting and novel Au^{I}-catalyzed intramolecular hydroamination and ring-opening of sulfonamide-substituted 2-(arylmethylene)cyclopropylcarbinols **125**. A variety of 4-substituted isoxazolidine derivatives **126** were obtained in good to high yields through highly regioselective cleavage of a C–C single bond in the cyclopropane unit (Scheme 38).[35]

Recently, our group successfully prepared a series of novel methylenecyclopropane-triazoles **127**. Intramolecular nucelophilic cyclizations of them have been explored in the presence



Scheme 39 $Yb(NTf_2)_3$ catalyzed intramolecular nucelophilic cyclizations of FACPs **127**.



Scheme 40 Tendency and challenge of the development of FACPs.

of a $Yb(NTf_2)_3$ catalyst, giving the corresponding triazole containing six- and seven-membered heterocycles **128** and **129** in good yields upon heating in toluene (Scheme 39).[36] In this reaction, Lewis acid $Yb(NTf_2)_3$ first coordinates to the Ts-triazole moiety through σ-activation and the alkene moiety in MCP parts *via* π-activation to give intermediate **130**, which may then undergo intramolecular cyclization *via* two possible pathways along with the hydrolysis of a sulfonyl group by ambient water to give the corresponding products **128** (path A) and **129** (path B).

3. Conclusion and outlook

In summary, the development of FACP chemistry has attracted widespread attention from chemists. Different types of FACP, which can be easily prepared, emerge as endless useful substrates in organic synthesis. The reaction products of FACPs have important structure motifs in organic and medicinal chemistry. These new findings subsequently enrich the strained small carbocyclic chemistry at the present stage. Furthermore, these novel synthetic methodologies have some potential applications in the synthesis of natural products and bioactive compounds. As a result, designing and discovering more novel types of FACP and using them to synthesize targeted natural products is gradually becoming the tendency in the field of FACP chemistry. Furthermore, investigating the reactivity of heterocyclic FACPs and realizing the C–H bond activation instead of C–C bond activation of some special FACPs will be more challenging and interesting (Scheme 40).

Acknowledgements

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