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Rapid Generation of Molecular Complexity in the Lewis or Brønsted Acid-Mediated Reactions of Methylenecyclopropanes

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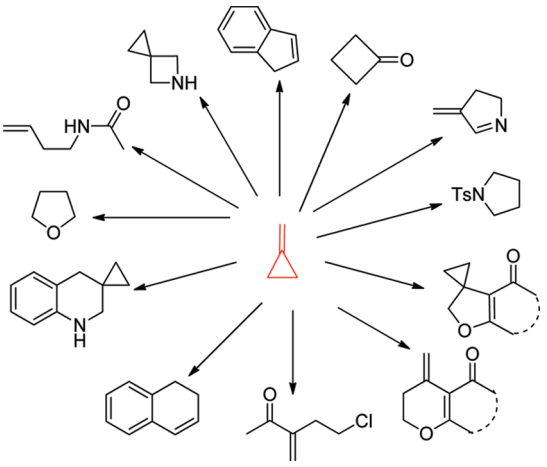
CONSPECTUS

Although they are highly strained, methylenecyclopropanes (MCPs) are readily accessible molecules that have served as useful building blocks in organic synthesis. MCPs can undergo a variety of ring-opening reactions because the release of cyclopropyl ring strain (40 kcal/mol) can provide a thermodynamic driving force for reactions and the π-character of the bonds within the cyclopropane can afford the kinetic opportunity to initiate the ring-opening. Since the 1970s, the chemistry of MCPs has been widely explored in the presence of transition metal catalysts, but less attention had been paid to the Lewis or Brønsted acid mediated chemistry of MCPs. During the past decade, significant developments have also been made in the Lewis or Brønsted acid mediated reactions of MCPs. This Account describes chemistry developed in our laboratory and by other researchers.



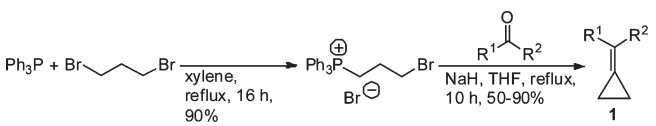
Lewis and Brønsted acids can be used as catalysts or reagents in the reactions of MCPs with a variety of substrates, and substituents on the terminal methylene or on the cyclopropyl ring of MCPs significantly affect the reaction pathways. During the past decade, we and other researchers have found interesting transformations based on this chemistry. These new reactions include the ring expansion of MCPs, cycloaddition reactions of MCPs with aldehydes and imines, cycloaddition reactions of MCPs with nitriles in the presence of strong Brønsted acid, radical reactions of MCPs with 1,3-dicarbonyl compounds, intramolecular Friedel–Crafts reactions of MCPs with arenes, acylation reactions of MCPs, and the reaction of MCPs with 1,1,3-triarylprop-2-yn-1-ols or their methyl ethers.

These Lewis or Brønsted acid mediated reactions of MCPs can produce a variety of new compounds such as cyclobutanones, indenes, tetrahydrofurans, and tetrahydroquinolines. Finally, we have also carried out computational studies to explain the mechanism of the Brønsted acid mediated reactions of MCPs with acetonitrile.

1. Introduction

Methylenecyclopropanes (MCPs) **1** are highly strained but readily accessible molecules that have served as useful building blocks in organic synthesis.[1] Scheme 1 shows one of the most popular methods for the synthesis of MCPs, in which a two-step process is involved including the formation of 3-bromo-triphenylphosphonium bromide from the reaction of 1,3-dibromopropane with triphenylphosphine and a subsequent Wittig reaction with ketones and aldehydes.[2]

SCHEME 1. One of the Most Popular Methods for the Synthesis of MCPs **1**



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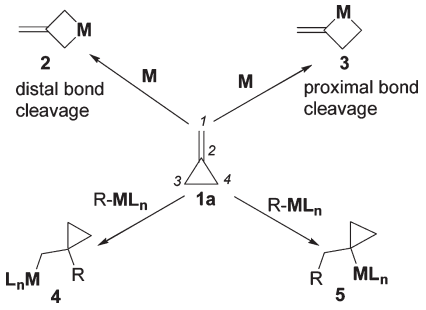


FIGURE 1. Transition metal-catalyzed reaction patterns of MCPs using the parent MCP **1a** as the model.

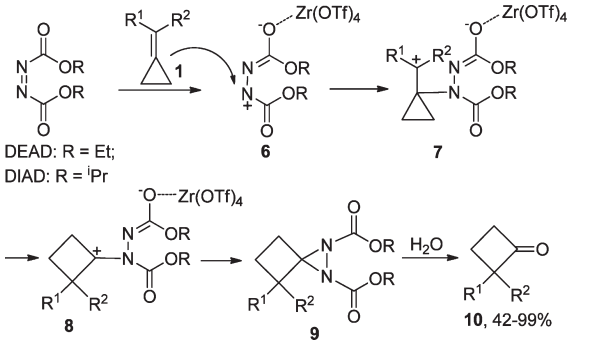
MCPs **1** can undergo a variety of ring-opening reactions because the release of cyclopropyl ring strain (40 kcal/mol)[3] can provide a thermodynamic driving force and the π-character of the ring bonds of the cyclopropane can afford the kinetic opportunity to initiate the unleashing of the strain.[4] Since the 1970s, the chemistry of MCPs **1** has been widely explored in the presence of transition metal catalysts,[5] and the developments in this field have been comprehensively reviewed by Binger,[6] Donaldson,[7] Lautens,[8] Yamamoto,[9] and others.[10] Transition metal-catalyzed reactions of MCPs **1** can be broadly classified as four patterns depicted in Figure 1: the insertion of transition metal M into the distal bond (C3−C4) gives intermediate **2**, while that into the proximal bond (C2−C3 or C2−C4) gives intermediate **3**; when the oxidative addition of organo-transition metal reagent R-MLn to MCPs **1** occurs, two different intermediates **4** and **5** will be achieved via anti-Markovnikov and Markovnikov addition, respectively. The organometallic intermediates **2**−**5** can further react with other substrates, giving the corresponding final products.[9]

Besides transition metal catalysts, Lewis and Brønsted acids can also be used as catalysts or reagents in the reactions of MCPs with a variety of substrates. It has been disclosed that substituents on the terminal of the double bond or cyclopropyl ring of MCPs significantly affect the reaction pathways, and some interesting transformations have been found during the past decade by our group and others. However, this field has not been thoroughly reviewed thus far except one review on the Lewis and Brønsted acid mediated ring-opening reactions of MCPs.[11] In this Account, we will summarize the Lewis or Brønsted acid-mediated reactions of MCPs for the rapid generation of molecular complexity.

2. Lewis or Brønsted Acid Mediated Chemistry of MCPs

2.1. Lewis Acid Mediated Ring-Expansion Reactions of MCPs. It had been reported that cyclobutanones could be

SCHEME 2. Ring-Expansion Reactions of MCPs **1** in the Presence of an Azo Compound and Zr(OTf)$_4$

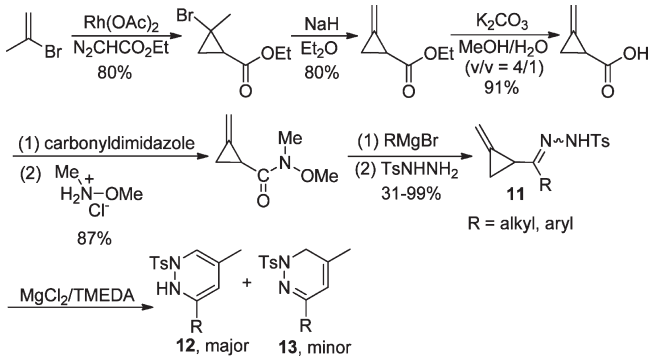


obtained by a two-step transformation starting from MCPs **1** by (1) oxidation with peracid such as MCPBA to give the highly strained oxaspiropentane derivatives and (2) acid- or thermal-induced isomerization of the oxaspiropentanes.[12] In 2004, we found that MCPs **1**, in the presence of an azo compound such as diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD) as a reagent and Lewis acid Zr(OTf)$_4$ as a catalyst in MeCN, could undergo ring-expansion reactions to give cyclobutanones **10** in good to high yields in a one-pot procedure (Scheme 2).[13,14] In these reactions, the Lewis acid activates DEAD or DIAD **6** toward the reaction with MCPs **1** to afford a zwitterion **7**, which furnishes the ring-expansion zwitterion **8** by rearrangement. Intramolecular neutralization generates intermediate **9**, which gives the final products **10** via hydrolysis by adventitious water (Scheme 2). In these ring-expansion reactions of MCPs **1**, substituents such as R^1 and R^2 being electron-rich, -neutral, and -poor aromatic groups are tolerated. In addition, MCPs **1** bearing an aromatic group and an alkyl group are also suitable for these reactions.

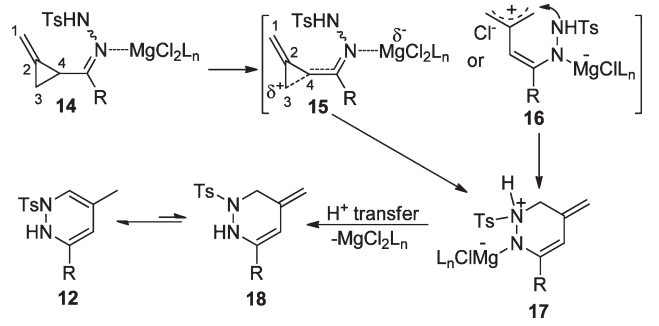
Cyclic diazine derivatives represent an important class of pharmaceutically interesting scaffolds. In 2007, Lautens and co-workers reported the synthesis of methylenecyclopropyl hydrazones **11** and found that the unusual isomeric cyclic diazadienes **12** and **13** can be obtained in good to excellent total yields via the flexible and highly selective Lewis acid $MgCl_2$-mediated ring-expansion reactions of substrates **11** (Scheme 3).[15]

A plausible mechanism for these ring-expansion reactions is shown in Scheme 4. First, Lewis acid $MgCl_2$ coordinates to methylenecyclopropyl hydrazone **11** to form intermediate **14**, which will result in sufficient development of partially positive charge at the C3-position of the cyclopropyl ring of intermediate **15**, and cyclization may occur through this intermediate to form intermediate **17**.

SCHEME 3. Synthesis of MCP Hydrazones **11** and Their Ring-Expansion Reactions in the Presence of Lewis Acid



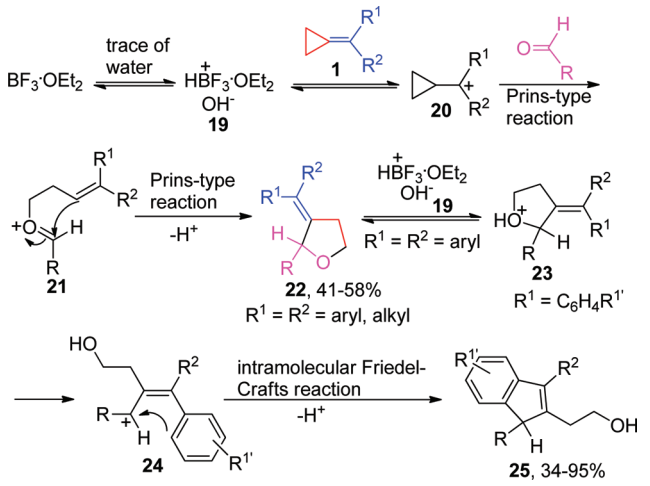
SCHEME 4. A Plausible Mechanism for the Formation of Products **12**



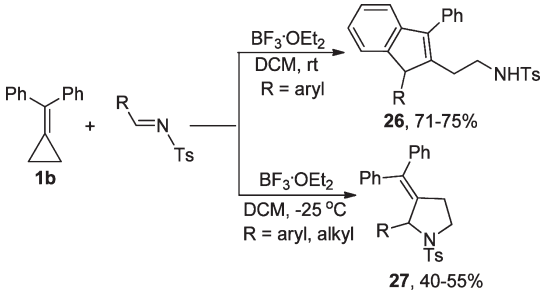
Alternatively, the reaction may proceed via a two-electron disrotatory ring-opening to afford the zwitterion **16**, which can also be transformed to the corresponding cyclization intermediate **17**. Subsequent proton transfer and release of the Lewis acid will afford intermediate **18**. Finally, product **12** will be obtained by isomerization from intermediate **18**.

2.2. Lewis Acid-Promoted Cycloaddition Reactions of MCPs with Aldehydes. We further developed the Lewis acid catalyzed reactions of MCPs **1** with aldehydes. As can be seen from Scheme 5, Lewis acid $BF_3 \cdot OEt_2$-mediated reactions of MCPs **1** with aldehydes can give the corresponding indene derivatives **25** at room temperature, while THF derivatives **22** were formed as the sole product when the same reactions were carried out at −25 °C.[16] The initial reaction of $BF_3 \cdot OEt_2$ with a trace of water in the system generates the Brønsted acid type catalyst **19**.[17] The reaction of catalyst **19** with MCPs **1** gives intermediate **20** (the corresponding counterion of $BF_3 \cdot OEt_2$, that is HO^-, has been omitted in all of the intermediates involved for convenience). The intermediate **20** can probably form an oxonium-type cationic intermediate **21** with an aldehyde by a Prins-type reaction.[18] The subsequent intramolecular Prins-type reaction of intermediate **21** gives the corresponding THF

SCHEME 5. Lewis Acid Catalyzed Cycloaddition Reactions of MCPs **1** with Aldehydes



SCHEME 6. $BF_3 \cdot OEt_2$-Catalyzed Reactions of MCP **1b** with *N*-Tosyl Imines

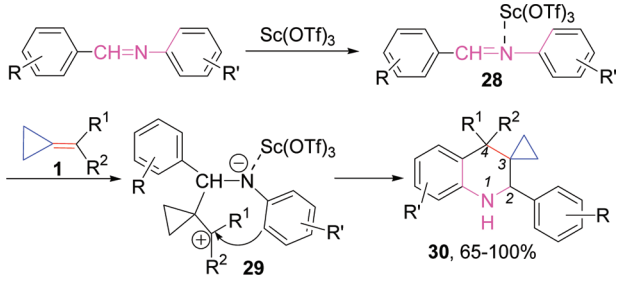


derivatives **22**. When $R^1 = R^2 =$ aryl group, protonation at the oxygen atom of **22** by the Brønsted acid type catalyst **19** affords the cationic intermediate **23**, which when followed by the intramolecular Friedel–Crafts reaction,[19] presumably via the corresponding intermediate **24**, furnishes indene derivatives **25**. For the reactions in the formation of THF derivatives **22**, MCPs **1**, in which both R^1 and R^2 are electron-rich, -neutral, and -poor aromatic groups, even when both R^1 and R^2 are alkyl groups, are tolerated, while for the formation of indene derivatives **25**, R^1 and R^2 should be electron-rich or -neutral aromatic groups probably to facilitate the final intramolecular Friedel–Crafts reaction.

2.3. Lewis Acid Catalyzed Cycloaddition Reactions of MCPs with Imines. Lewis acid catalyzed reactions of MCP **1b** ($R^1 = R^2 =$ Ph) with *N*-tosyl imines can give the indene and pyrrolidine derivatives **26** and **27** in moderate to good yields at different temperatures, respectively (Scheme 6).[16a,b,20]

In addition, if *N*-aryl imines were used instead of *N*-tosyl ones, it was found that tetrahydroquinoline derivatives **30** were formed via formal aza-Diels–Alder reactions of MCPs **1**

SCHEME 7. $Sc(OTf)_3$-Mediated Reactions of MCPs **1** with *N*-Aryl Imines

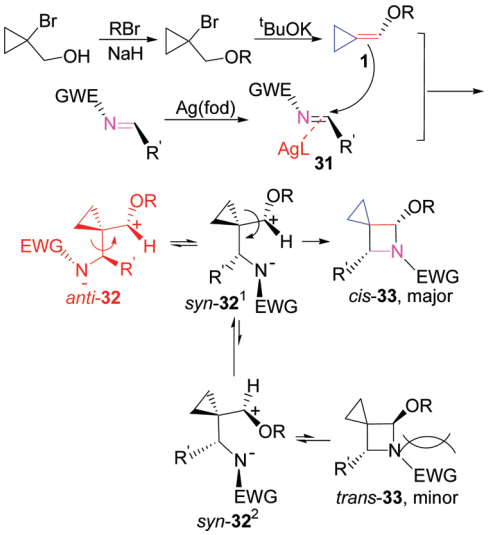


in the presence of Lewis acid $Sc(OTf)_3$ (Scheme 7).[21] For a range of imines derived from aromatic amines and arylaldehydes, the reactions proceeded smoothly to give the corresponding formal aza-Diels–Alder products **30** in good to excellent yields with the unsubstituted cyclopropyl ring at the 3,3′-position.

A plausible mechanism for this type of formal aza-Diels–Alder reactions is shown in Scheme 7.[22] The cyclopropylmethyl cation in intermediate **29** is further stabilized by two substituents (R^1 and R^2 with at least one aromatic group) on the double bond.[23] Thus, the intramolecular Friedel–Crafts reactions quickly take place to give the corresponding formal aza-Diels–Alder adducts **30** rather than the cyclopropylmethyl cation rearranged products. In this type of formal aza-Diels–Alder reaction of MCPs **1** with *N*-aryl imines, in order to obtain a stabilized carbocationic intermediate such as **29**, both R^1 and R^2 should be electron-rich or -neutral aromatic groups or at least one of them should be an electron-rich or -neutral aromatic group and the other can be an alkyl group. For MCP **1c** ($R^1 = R^2 = 4\text{-}ClC_6H_4$), in which both R^1 and R^2 are electron-poor aromatic groups, no reaction occurred for a series of *N*-aryl imines tested.

As stated above, several interesting cycloaddition reactions of MCPs **1** with imines have been explored in the presence of Lewis acid, Brønsted acid, or solid acid during the past years. For instance, [3 + 2] cycloadditions occurred in the reactions of MCPs **1** with *N*-tosyl imines under mild conditions.[16a,b] Moreover, [4 + 2] cycloadditions took place smoothly in the reactions of MCPs **1** with *N*-aryl imines or ethyl (arylimino)acetates.[21,24] Furthermore, in 2006, Nakamura and co-workers reported another type of reaction of MCPs **1**, that is, [2 + 2] cycloaddition reactions of alkoxymethylenecyclopropanes **1** with activated imines to afford 2-alkoxyazetidine derivatives **33** in good to high yields with high *cis* stereoselectivity in the presence of Lewis acid catalyst Ag(fod) (fod =6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato) (Scheme 8).[25] In these reactions, R is

SCHEME 8. Silver Salt-Catalyzed [2 + 2] Cycloaddition Reactions of MCPs **1** with Activated Imines



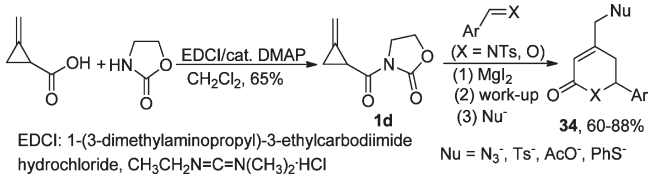
an alkyl group and R′ can be electron-rich, -neutral, or -poor aryl groups and alkyl groups. In addition, only activated imines in which the EWG is a strong electron-poor group such as Ts, Ms, and SO_2Ph showed good activity. These [2 + 2] cycloaddition reactions are proposed to proceed in two steps via the well-stabilized 1,4-zwitterionic intermediate **32**. The silver complex certainly acts as a Lewis acid and enhances the electrophilicity of the imines as in intermediate **31**, and C–N bond formation would lead to the *anti*-oriented zwitterionic intermediate *anti*-**32**, which, after internal rotation, cyclizes to the azetidine *cis*-**33** or *trans*-**33**. Apparently, the ring closure is reversible, and *cis*-**33** is the thermodynamically more stable isomer.

Lautens and co-workers found that different substituents on the cyclopropyl ring of MCPs **1** also dramatically affected the reaction patterns of these substrates with *N*-tosyl imines and aldehydes. For instance, MCP **1d**, bearing an electron-withdrawing oxazolidinone group on the cyclopropyl ring, reacted smoothly with *N*-tosyl imines or aldehydes in the presence of a stoichiometric amount of MgI_2 in refluxing THF, affording a δ-lactam bearing an allylic iodo substituent and lacking the oxazolidinone group as the exclusive product. Since the resulting iodides were unstable to chromatography on silica gel, the products **34** of the reactions were usually isolated after displacement of the iodide with nucleophiles (Scheme 9).[26]

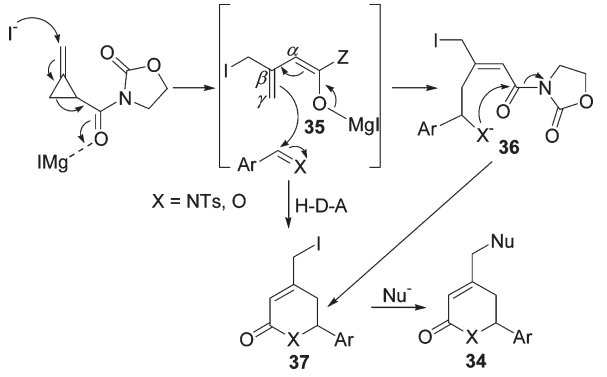
The formation of products **34** can be interpreted based on a common-type magnesium dienolate intermediate **35**, which is formed initially by MgI_2-induced ring opening of the cyclopropyl ring of the substrate **1d**. Thus, intermediate

36 would be formed by nucleophilic attack of intermediate **35** to the C=N or C=O double bond through alkylation of the γ-carbon atom. Intermediate **36** eventually leads to products **34** via intermediate **37** by 5-*exo* cyclization and displacement of the iodide anion by nucleophiles. In an alternative way, a hetero-Diels–Alder (H-D-A) process of intermediate **35** with imines or aldehydes would also account for the formation of intermediate **37** (Scheme 10).

SCHEME 9. MgI_2-Mediated Reactions of MCP **1d** with *N*-Tosyl Imines or Aldehydes



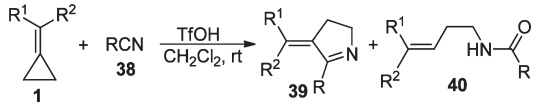
SCHEME 10. A Plausible Mechanism for the Formation of Products **34**



2.4. Brønsted Acid Catalyzed Reactions of MCPs 1 with Nitriles. The strong Brønsted acid freshly distilled TfOH catalyzed reactions of MCPs **1** with nitriles were also investigated. We found that the [3 + 2] cycloaddition products, namely, 3,4-dihydro-2*H*-pyrrole derivatives **39**, could be obtained in good to high yields as the major products along with the Ritter-type products **40** as the byproduct in a few cases (Table 1).[27] MCPs **1** in which both R^1 and R^2 are aromatic groups or one is an aromatic group and the other is an alkyl group are suitable for these reactions (Table 1, entries 1–7 and 9–15). It should be noted here that MCP **1j** bearing two butyl groups was not a good partner, and the reaction was sluggish to give complex mixtures under identical conditions (Table 1, entry 8). No desired product was obtained for the reaction of MCP **1k** bearing a phenyl group and a hydrogen atom with benzonitrile (Table 1, entry 16). Therefore, two aromatic groups or one aromatic group and one alkyl group for MCPs **1** is essential for these [3 + 2] cycloaddition reactions.

A plausible mechanism for the formation of products **39** and **40** is shown below: protonation of Brønsted acid with MCPs **1** and electrophilically assisted nucleophilic ring opening by RCN gives intermediate **41**. Subsequent intramolecular electrophilic attack takes place to give intermediate **42**, which gives the [3 + 2] cycloaddition products **39** via

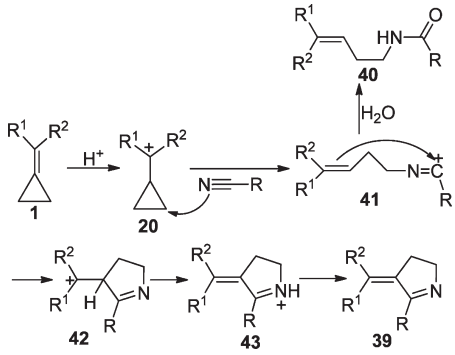
TABLE 1. Reactions of MCPs **1** (1.0 equiv) with Nitriles **38** (2.0 mL) in CH_2Cl_2 (1.0 mL) in the Presence of TfOH (1.0 equiv)



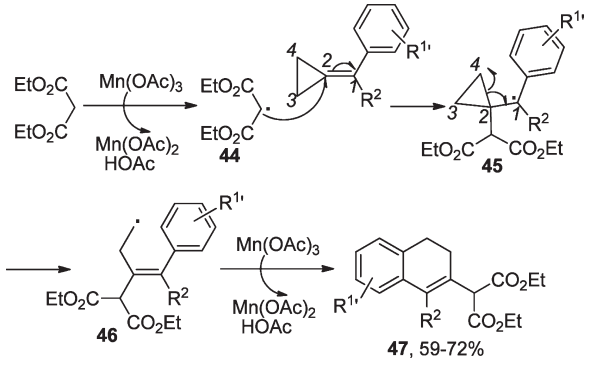
			yield/%[a]	
entry	**1** (R^1/R^2)	**38** (R)	**39**	**40**
1	**1b** (Ph/Ph)	**38a** (Me)	**39a**, 86	**40a**, 2
2	**1c** (4-ClC_6H_4/4-ClC_6H_4)	**38a**	**39b**, 85	**40b**, 10
3	**1e** (4-FC_6H_4/4-FC_6H_4)	**38a**	**39c**, 75	**40c**, trace
4	**1f** (4-MeC_6H_4/4-MeC_6H_4)	**38a**	**39d**, 73	**40d**, trace
5	**1g** (4-$MeOC_6H_4$/4-$MeOC_6H_4$)	**38a**	**39e**, 88	**40e**, trace
6	**1h** (2-ClC_6H_4/C_6H_5)	**38a**	**39f**, 60 (14:1)[b]	**40f**, 21 (14:1)[b]
7	**1i** (4-$EtOC_6H_4$/Me)	**38a**	**39g**, 56 (3:1)[b]	
8	**1j** (Bu/Bu)	**38a**	complex mixture of products	
9	**1b**	**38b** (Ph)	**39h**, 87	**40g**, 5
10	**1c**	**38b**	**39i**, 93	**40h**, trace
11	**1e**	**38b**	**39j**, 96	**40i**, trace
12	**1f**	**38b**	**39k**, 91	**40j**, trace
13	**1g**	**38b**	**39l**, 85	**40k**, trace
14	**1h**	**38b**	**39 m**, 42 (2:1)[b]	**40l**, 56 (2:1)[b]
15	**1i**	**38b**	**39n**, 30 (4:1)[b]	
16	**1k**(Ph/H)	**38b**	complex mixture of products	

[a]Isolated yields. [b]Mixtures of (*E*)- and (*Z*)-isomers (ratio = *E*/*Z*).

SCHEME 11. A Plausible Mechanism for the Formation of Products **39** and **40**



SCHEME 12. $Mn(OAc)_3$-Mediated Radical Reactions of MCPs **1** with Malonic Acid Diethyl Ester

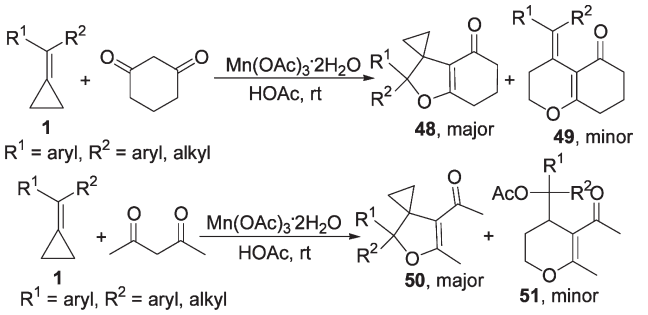


deprotonation with usual workup. The intermediate **41** reacts with adventitious water to give the ring-opened Ritter-type reaction products **40**[28] (Scheme 11). More details about the mechanism are illustrated in the third section based on computational studies.

Catalyzed by TfOH[27] and H_2SO_4,[28] the different products in the reactions of MCPs **1** with nitriles can be explained by the following reasons: (1) H_2SO_4 is more hydrophilic than TfOH and usually contains higher amounts of H_2O under ambient conditions, which results in the Ritter-type reaction products **40** as the sole isolated products; in contrast, in the presence of freshly distilled TfOH, less H_2O exists in the reaction system and intramolecular electrophilic attack of intermediate **41** took place dominantly, giving the [3 + 2] cycloaddition products **39** as the major ones.

2.5. Lewis Acid Mediated Radical Reactions of MCPs with 1,3-Dicarbonyl Compounds. Lewis acid $Mn(OAc)_3$ mediated radical reactions of MCPs **1** with malonic acid diethyl ester were first reported by Huang and co-workers in 2004. In this case, the corresponding dihydronaphthalene derivatives **47** were obtained in moderate yields (Scheme 12).[29,30] Substituents on MCPs **1** have significant

SCHEME 13. $Mn(OAc)_3$-Mediated Reactions of MCPs **1** with 1,3-Diketones



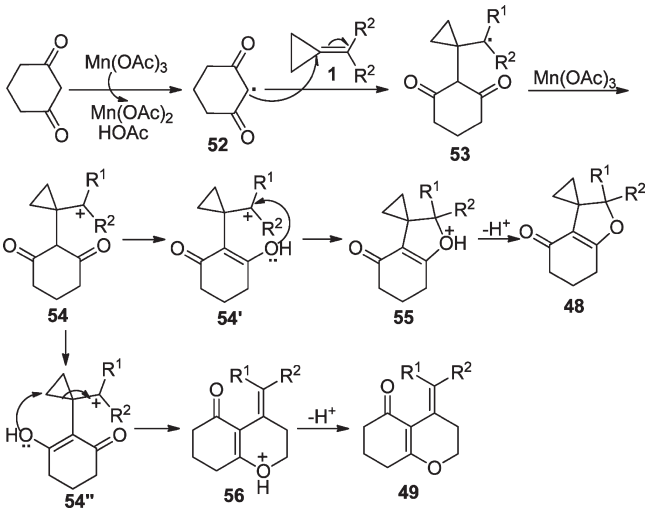
effect on these reactions. That is, the reactions of MCPs **1** bearing electron-rich or -neutral aromatic groups (Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, etc.) are faster than those with moderately electron-poor aromatic groups (4-ClC_6H_4, 4-BrC_6H_4). MCPs **1** with a strongly electron-withdrawing group (MCP **1l**: R^1 = 4-$NO_2C_6H_4$, R^2 = H) resulted in no desired product even in a prolonged reaction time.

The formation of products **47** can be rationalized as below: The reaction of malonic acid diethyl ester with $Mn(OAc)_3$ can give radical **44**,[31] which adds to the C2 position of MCPs **1** with high regioselectivity to give intermediate **45**.[32] A β-scission of the C2−C3 (or -C4) bond in the cyclopropyl ring in intermediate **45** affords another intermediate **46**,[33] in which the radical carbon attacks the aromatic ring intramolecularly to give the cyclized products **47** along with the release of a proton in the presence of $Mn(OAc)_3$ (Scheme 12).

Soon after, we reported that if 1,3-diketones were used instead of malonic acid diethyl ester for the above reactions, 4,5-dihydrofuran derivatives **48** or **50** as the [3 + 2] annulation products were obtained in good yields under similar conditions (Scheme 13).[34]

A plausible mechanism for the formation of products **48** and **49** is depicted below: Similarly, the reaction of cyclohexane-1,3-dione with $Mn(OAc)_3$ can give radical **52**, which adds to MCPs **1** to afford radical intermediate **53**. Intermediate **53** is further oxidized by another molecule of $Mn(OAc)_3$ to give cationic intermediate **54**. Enolization of intermediate **54** can give enols **54′** and **54″**. Intramolecular attack of the oxygen atom in intermediate **54′** gives the oxonium cation **55**. Deprotonation of **55** furnishes the corresponding [3 + 2] annulation products **48**. Alternatively, intramolecular attack of the oxygen atom in intermediate **54″** to the cyclopropyl ring can give pyran oxonium cation **56**. Finally, deprotonation of **56** gives the corresponding products **49** (Scheme 14). As can be seen from these results, it is clear that the finding between Huang's group and ours is slightly different from

SCHEME 14. A Plausible Mechanism for the $Mn(OAc)_3$-Mediated Reactions of MCPs **1** with Cyclohexane-1,3-dione



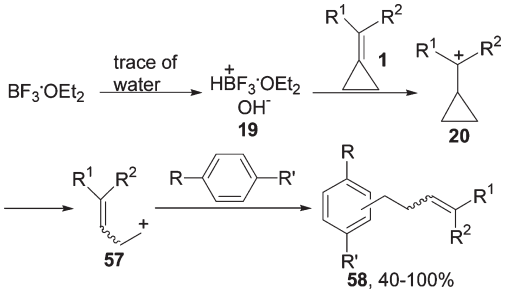
each other, presumably due to the enolizability of the two different intermediates such as **45** and **54** since **54** is more labile to undergo enolization to give intermediates **54′** and **54″**, which are the key intermediates for the formation of products **48** and **49**.

2.6. Lewis Acid-Catalyzed Intermolecular Friedel–Crafts Reactions of MCPs. MCPs **1** can react with various arenes efficiently to give the intermolecular Friedel–Crafts reaction products **58** in good to excellent yields in the presence of Lewis acid $BF_3 \cdot OEt_2$, providing the advantages of direct C–C coupling reaction of MCPs **1** with arenes under mild conditions.[35] Substituents on MCPs **1** also have significant effect on the reactions. For instance, MCPs **1** bearing moderately electron-poor or -donating bis-aryl or bis-alkyl groups showed good reactivity to give the corresponding products in good to high yields, while when MCP **1g** ($R^1 = R^2 =$ 4-$MeOC_6H_4$) was used as the substrate, almost no desired product was achieved. We believed that the 4-methoxyphenyl groups on MCP **1g** are also good Friedel–Crafts reaction electrophiles, which may result in self Friedel–Crafts reaction on the 4-methoxyphenyl ring or other related side reactions.

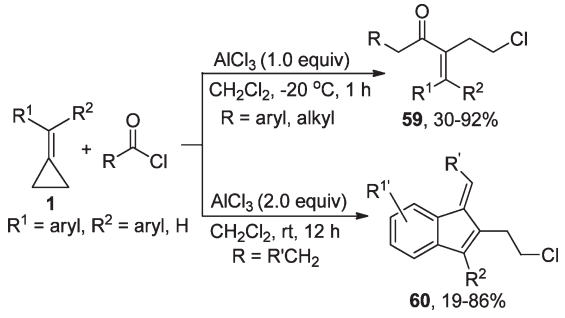
Similar to that shown in Scheme 5, MCPs **1** are first protonated by the Lewis acid $BF_3 \cdot OEt_2$ and trace adventitious water to give the cationic intermediate **20**, which immediately rearranges to the corresponding homoallylic carbocation **57** (the corresponding counterion of $BF_3 \cdot OEt_2$, that is HO^-, has been omitted for convenience). Subsequent electrophilic addition of **57** to arenes with release of a proton furnishes the final products **58** (Scheme 15).

2.7. Lewis Acid-Mediated Acylation Reactions of MCPs. The acylation of MCPs **1** is also an attractive task for organic

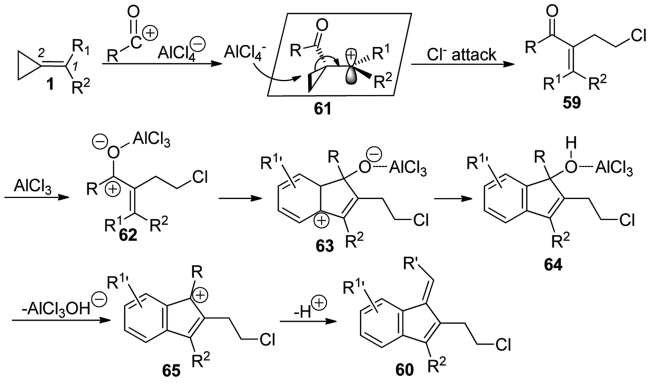
SCHEME 15. $BF_3 \cdot OEt_2$-Mediated Intermolecular Friedel–Crafts Reactions of MCPs **1** with Arenes



SCHEME 16. Lewis Acid $AlCl_3$-Mediated Acylation Reactions of MCPs **1**



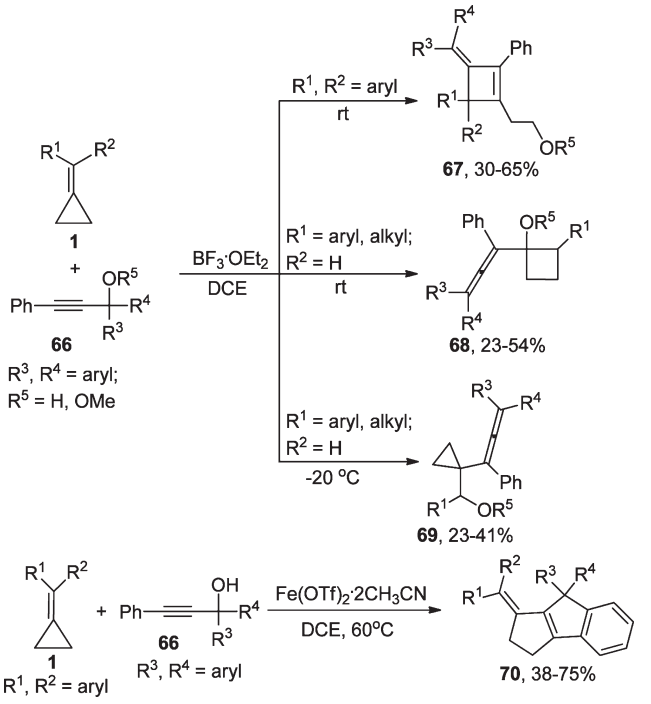
SCHEME 17. A Plausible Mechanism for the Formation of Products **59** and **60**



chemists with regard to the nucleophilicity of the double bond in MCPs **1** and the similarity between the cyclopropyl ring and the olefinic double bond. In 2007, Huang and coworkers reported that in the reactions of MCPs **1** with acyl chlorides, products **59** and **60** can be obtained, respectively, according to the used amount of the Lewis acid $AlCl_3$ and the substituents on the acyl chlorides (Scheme 16).[36]

Possible pathway for the formation of products **59** and **60** is shown in Scheme 17. First, an acyl cation formed from Lewis acid-coordinating acyl chloride adds to the C2 position of MCPs **1** regioselectively to afford the cationic

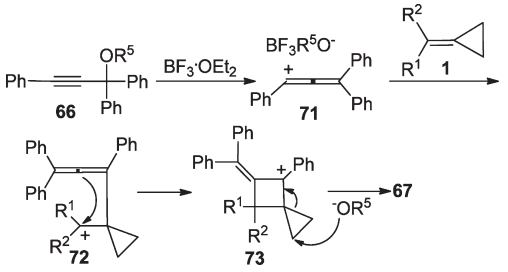
SCHEME 18. Lewis Acid Catalyzed Reactions of MCPs **1** with 1,1,3-Triarylprop-2-yn-1-ols or Their Methyl Ethers **66**



intermediate **61**. Subsequent nucleophilic attack of the chlorine anion (or $AlCl_4^-$) to intermediate **61** furnishes products **59**. In the case of presence of excessive Lewis acid, the carbonyl group of **59** is coordinated by $AlCl_3$ again to give the corresponding intermediate **62**. The intramolecular Friedel–Crafts reaction of **62** produces the bicyclic intermediate **63**. Proton migration in intermediate **63** gives intermediate **64**, and subsequent elimination of water from intermediate **64** furnishes the final products **60**.

2.8. Lewis Acid-Mediated Reactions of MCPs with 1,1,3-Triarylprop-2-yn-1-ols or Their Methyl Ethers. The Lewis acid-mediated reactions between MCPs **1** and 1,1,3-triarylprop-2-yn-1-ols or their methyl ethers **66** were also investigated in this laboratory. We found that in these cases, the employed Lewis acids, the substituents on MCPs **1**, and the temperature dramatically affect the reaction patterns. For instance, the Lewis acid $BF_3 \cdot OEt_2$-mediated reactions of diaryl-substituted MCPs **1** (R^1, R^2 = aryl) with 1,1,3-triarylprop-2-yn-1-ols **66** can afford methylenecyclobutenes **67** exclusively at room temperature; while with monoaryl-substituted MCPs **1** (R^1 = aryl, alkyl, R^2 = H) as the substrates in this case, cyclobutanes **68** and cyclopropanes **69** can be obtained at room temperature and −20 °C, respectively;[37] using $Fe(OTf)_2 \cdot 2CH_3CN$ as the Lewis acid, tetrahydrocyclopenta[*a*]indenes **70** were formed exclusively in moderate yields at 60 °C in DCE (Scheme 18).[38]

SCHEME 19. A Plausible Mechanism for the Formation of Products **67**



A plausible mechanism for the formation of products **67** is shown in Scheme 19. In the presence of Lewis acid $BF_3 \cdot OEt_2$, **66** produces cationic intermediate **71** via a Meyer–Schuster rearrangement,[39] which reacts with MCPs **1** to give intermediate **72** stabilized by two aromatic rings and one cyclopropyl group. Intramolecular cyclization of intermediate **72** affords intermediate **73**, which undergoes nucleophilic attack by R^5O^- to provide products **67**.

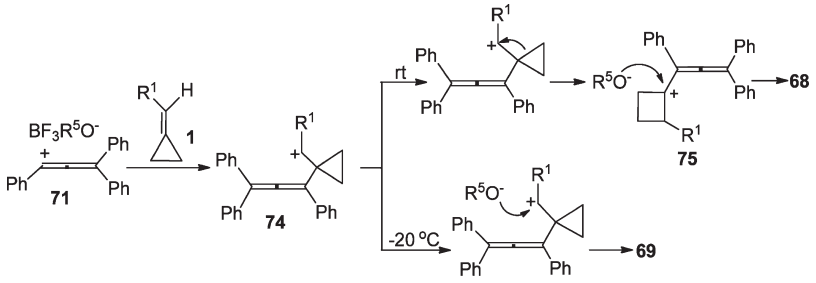
A plausible mechanism for the formation of products **68** and **69** is outlined in Scheme 20. The addition of intermediate **71** to monoaryl-substituted MCPs **1** produces intermediate **74**, which undergoes ring expansion to give intermediate **75** at higher temperature (room temperature), presumably due to the higher temperature facilitating the ring-expansion process. The nucleophilic attack by R^5O^- provides products **68**. On the other hand, at lower temperature (−20 °C), nucleophilic attack by R^5O^- at intermediate **74** takes place to provide products **69** directly.

In the case of $Fe(OTf)_2 \cdot 2CH_3CN$ as the Lewis acid, similarly, intermediate **76** will be first formed. Subsequently, the [3 + 2] cycloaddition of intermediate **76** with MCPs **1** occurred exclusively to afford intermediate **77**, which will result in the final products **70** via intramolecular Friedel–Crafts reaction, presumably because the soft Lewis acid $Fe(OTf)_2 \cdot 2CH_3CN$ favors such [3 + 2] cycloaddition (Scheme 21).

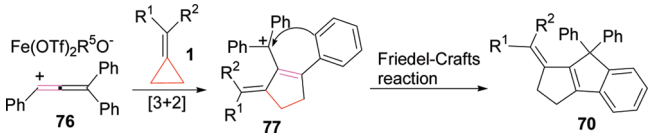
3. Reaction Patterns of MCPs and the Mechanistic Investigation

3.1. Summary of the Reaction Patterns in the Lewis or Brønsted Acid Mediated Chemistry of MCPs. As shown above, substituents on MCPs **1** can significantly affect the reactivity and the regioselectivity. MCPs **1** with at least one substituent (usually one aromatic group) at the olefinic moiety (without substituents at the cyclopropyl ring in this case) or with electron-withdrawing group(s) on the cyclopropyl ring normally show high reactivity in the presence of Lewis or Brønsted acid; however, MCPs with aliphatic

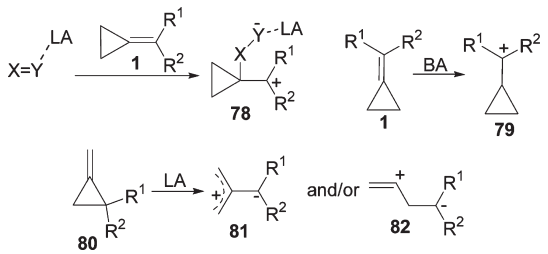
SCHEME 20. A Plausible Mechanism for the Formation of Products **68** and **69**



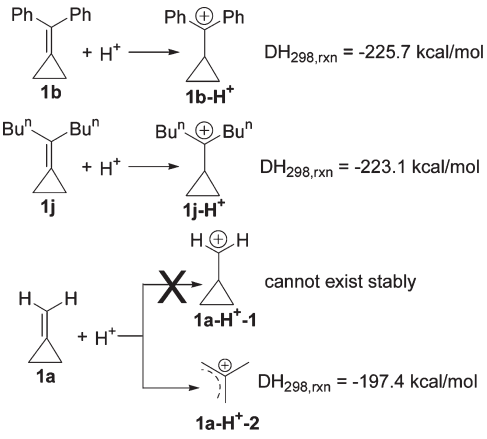
SCHEME 21. A Plausible Mechanism for the Formation of Products **70**



SCHEME 22. Summary for Lewis or Brφnsted Acid Mediated Reactions of MCPs



SCHEME 23. Reaction Enthalpies for MCPs **1-H**$^+$

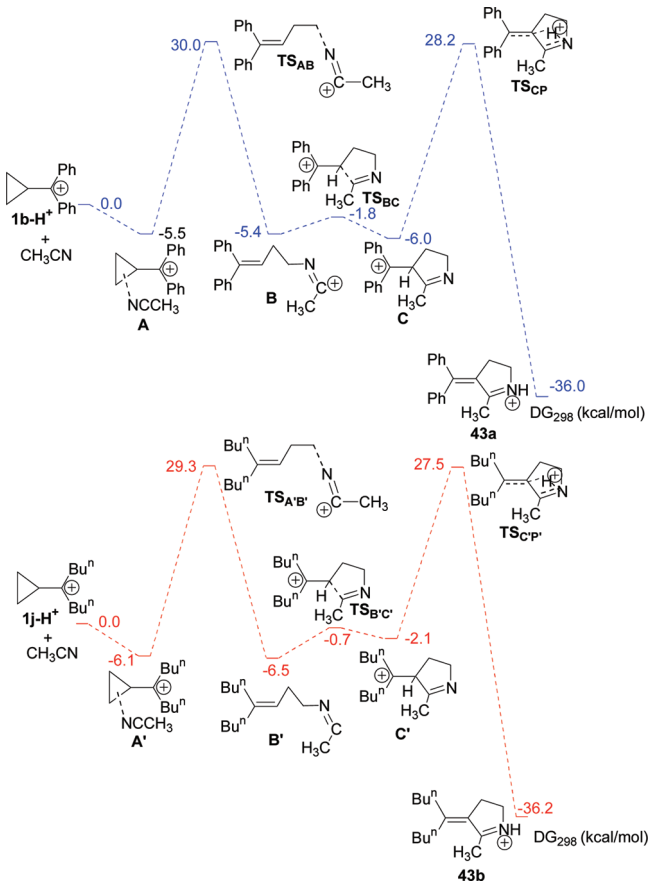


substituents at the olefinic moiety often provided mixture of many unidentified products. As summarized in Scheme 22, the two key intermediates such as **78** and **79** may be generated in the Lewis or Brønsted acid mediated reactions of MCPs, in which two substituents (R^1 and R^2) with at least one aromatic group or other type of substituent are always required to stabilize these two key intermediates. For the case of no substituent at the olefinic moiety of MCPs **80**, intermediates **81**, **82**, or both are usually formed in the presence of Lewis or Brønsted acid for further transformations. In this case, with R^1 or R^2 or both being an electron-withdrawing group, the cyclopropyl ring of MCPs **1** might be further activated to undergo a ring-opening reaction, and the formed zwitterionic intermediates **81** and **82** are well-stabilized to proceed to further transformations.

3.2. Computational Studies on the Substituent Effects of MCPs with [3 + 2] Cycloaddition of MCPs 1 with Acetonitrile as the Model. The geometries of all systems have been optimized at the B98/6-31G(d) level of theory. The subsequent frequency calculations on the stationary points were carried out at the same level of theory to ascertain the nature of the stationary points as minima or first-order saddle points on the respective potential energy surfaces. All transition states were characterized by one and only one imaginary frequency pertaining to the desired reaction coordinate. The intrinsic reaction coordinate (IRC) calculations were carried out at the same level of theory to further authenticate the transition states. The conformational space of flexible systems has been carefully searched manually. Thermochemical corrections to 298.15 K have been calculated for all minima from unscaled vibrational frequencies obtained at this same level. The thermochemical corrections have been combined with single-point energies calculated at MP2(FC)/6-31+G(2d,p)//B98/6-31G(d) level to yield enthalpies H_{298} and free energies G_{298} at 298.15 K. For conformationally flexible systems, the energies of the best conformers are used to generate the reaction profiles shown in Scheme 23. All quantum mechanical calculations have been performed with Gaussian 03.[40]

The theoretical studies were carried out to investigate the reactivity differences between MCPs with aromatic substituents and aliphatic substituents, with the Brønsted acid TfOH-mediated [3 + 2] cycloaddition of MCPs with acetonitrile as the model reaction.[27] We initially chose MCPs **1b**

SCHEME 24. Reaction Pathways for the Brφnsted Acid Mediated Reactions of MCPs **1b** or **1j** with Acetonitrile



($R^1 = R^2 =$ Ph), **1j** ($R^1 = R^2 = {}^n$Bu), and **1a** ($R^1 = R^2 =$ H) as model systems to investigate the stabilities of their corresponding carbocations.[41] The reaction enthalpies for the formation of carbocations as **1b-H**$^+$, **1j-H**$^+$, and **1a-H**$^+$ shown in Scheme 23 were calculated at the MP2(FC)/6-31+G(2d,p)//B98/6-31G(d) level of theory. As can be seen from Scheme 23, the reaction enthalpy for the formation of carbocation **1b-H**$^+$ is lower than that of **1j-H**$^+$ by 2.6 kcal/mol, indicating that the carbocation **1b-H**$^+$ is more stable than **1j-H**$^+$; however, this is not a big energy difference. In the case of MCP **1a**, instead of forming carbocation **1a-H**$^+$**-1**, the ring-opening carbocation **1a-H**$^+$**-2** is formed. The carbocation **1a-H**$^+$**-2** is much less stable than **1b-H**$^+$ and **1j-H**$^+$ by 26 kcal/mol or so. Based on these results, we may generally conclude that MCPs without substituents at the olefinic moiety, which cannot form more stable carbocations after protonation, may not undergo the following reactions smoothly.

We then investigated the whole reaction pathway for this cycloaddition reaction starting from CH_3CN with **1b-H**$^+$ and **1j-H**$^+$ at the MP2(FC)/6-31+G(2d,p)//B98/6-31G(d) level of theory (Scheme 24). The carbocation **1b-H**$^+$ is initially combined with CH_3CN to form a reactant complex **A**. Along the reaction pathway, CH_3CN leads to the ring opening of MCP via transition state **TS$_{AB}$** to generate the intermediate **B**. The subsequent intramolecular electrophilic attack takes place and passes through transition state **TS$_{BC}$** to give intermediate **C**, which undergoes a proton transfer step to afford the protonated product **43a**. For MCP **1j** with two *n*-butyl groups, the reaction pathway is similar to that of MCP **1b** at the first ring-opening step and the last proton transfer step. However, it is noticed that the energy barrier of the intramolecular electrophilic attack step involving MCP **1b** is 3.6 kcal/mol, which is lower than that of the step involving MCP **1j** (5.8 kcal/mol). This result indicated that the intramolecular electrophilic attack step involving MCP **1b** with two phenyl groups should take place faster than the step involving MCP **1j** with two *n*-butyl groups. Meanwhile, we found that the intermediate **C** is thermodynamically more stable than the intermediate **B** by 0.6 kcal/mol; in contrast, the intermediate **C**′ is thermodynamically less stable than the intermediate **B**′ by 4.4 kcal/mol. This observation implied that the intramolecular electrophilic attack step involving MCP **1j** is thermodynamically disfavored, which may lead to the intermediate **B**′ taking part in other side reactions at this stage. The higher energy barrier for the intramolecular electrophilic attack step and the less stable intermediate **C**′ may account for the previous experimental observations[27] showing that the reaction using MCP **1j** as the substrate was sluggish and many unidentified side products were formed. Generally, we may conclude that the substituent effects on the Lewis or Brønsted acid mediated reactions of MCPs do not show at the initial ring-opening step; however, they may affect the following reaction step or the stabilities of other intermediates during the reaction.

4. Conclusion

In summary, the importance of MCPs has long been realized by synthetic organic chemists. The tendency to ring-opening and cycloaddition reactions of MCPs has made them useful synthons in organic chemistry. Besides transition metal-catalyzed chemistry of MCPs, Lewis or Brønsted acid mediated reactions of MCPs have made great progress in the past decade. As shown in this Account, using commercially available Lewis or Brønsted acid catalysts, a variety of synthetically useful compounds, such as cyclobutanones, tetrahydrofurans, indenes, tetrahydroquinolines, and pyrrolidines, can be obtained from easily available MCPs in a straightforward protocol. In a word, the Lewis or Brønsted

acid mediated chemistry of MCPs opens new and exciting opportunities for organic synthesis in the rapid generation of molecular complexity, which also brings up a strong guarantee for the abundant future of the Lewis or Brønsted acid mediated chemistry of MCPs.

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Supporting Information. Fe(II)-catalyzed reaction of MCP **1b** with compound **66a**, full author names of ref 40, X-ray data of compound **70a** and DFT calculation details. This information is available free of charge via the Internet at http://pubs.acs.org.

BIOGRAPHICAL INFORMATION

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FOOTNOTES

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