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Iron Catalysis

Iron(III)-Catalyzed Cycloisomerizations of Acetal–Vinylidenecyclopropanes: An Efficient Synthetic Route to 1,2-Disubstituted Cyclobutenes

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Abstract: A novel iron(III)-catalyzed intramolecular cycloisomerization of acetal–vinylidenecyclopropanes to afford a series of halogenated 1,2-disubstituted cyclobutenes tethered with a tetrahydropyrrole has been developed. The reaction is thought to proceed through a formal iron-catalyzed Prins cyclization followed by a ring-enlarging rearrangement of the methylenecyclopropane carbocation. The present protocol provides an alternative route to functionalized disubstituted cyclobutenes and the corresponding products could be successfully transformed into eight-membered oxacyclic products.

Vinylidenecyclopropanes (VDCPs), bearing an allene moiety connected to a highly strained cyclopropane ring, serve as fascinating building blocks in organic synthesis and have attracted great attention from organic chemists. In the past few years, numerous useful and unique transformations of VDCPs have been discovered by our group and other research groups.[1] As one of the most important structural motifs, cyclobutene moieties are present in a great number of natural products and pharmacological compounds with diverse biological properties (Figure 1).[2] Despite the many applications of cyclobutenes, methods for their synthesis are limited. Among the approaches to access cyclobutenes, cycloaddition of alkynes and alkenes[3] and ring-expansions of cyclopropane derivatives,[4] including alkylidenecyclopropanes,[5] allenylcyclopropanes[6] and α-diazo cyclopropanes,[7] are the most effective synthetic strategies. In 2006, Pt^{II}- and Pd^{II}-catalyzed ring expansions of alkylidenecyclopropanes (ACP) into monosubstituted cyclobutene derivatives have been disclosed by Fürstner and Aïssa[5f] and our group,[5g] respectively (Scheme 1 A). More recently, we also developed a Rh^{I}-catalyzed intramolecular [2+2] cycloaddition of the yne–VDCPs to build tetrasubstituted cyclobutenes.[1k]

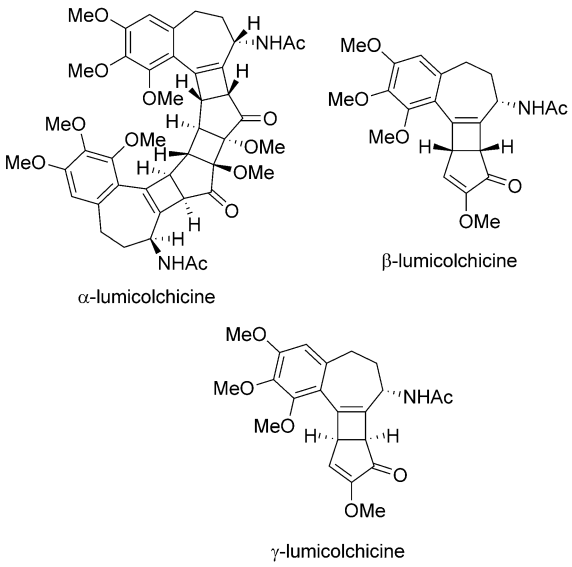
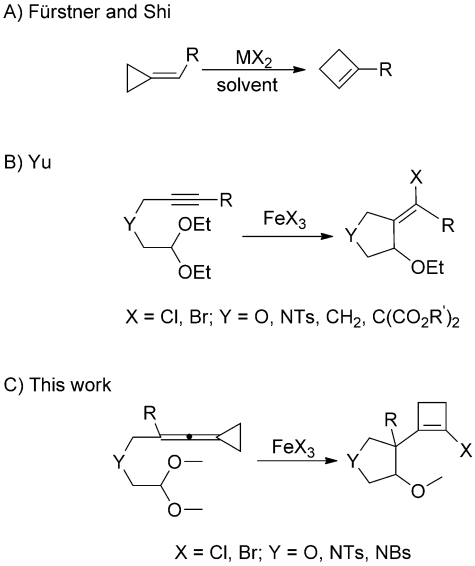


Figure 1. Representative biologically active natural products containing a cyclobutene core.



Scheme 1. Syntheses of cyclobutene: A) ring-expansion of MCP; B) FeX_3-promoted cyclization of alkynyl acetals; C) current work.

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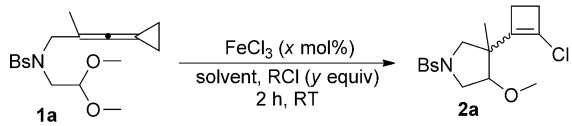
During the last few decades, iron catalysis has emerged as a promising and environmentally benign alternative to traditional transition metal catalysis for a wide range of organic transformations, due to its many advantages, such as low cost, nontoxicity, good stability, and easy handling.[8] Compared with traditional transition metal catalysis, iron takes part in various biological systems as a key essential element, for example, in metalloproteins for the transport or metabolism of small molecules (e.g., oxygen, nitrogen, methane) and electron-transfer reactions.[9] The principal use of iron in organic catalysis is related to oxo and hydride transfer reactions, as well as related transformations of carbenes, nitrenes, and carbanions.[10] Another important use of iron as a catalyst profits from its Lewis acidic character, which allows its participation in a broad range of synthetic transformations, such as Diels–Alder reactions,[11] 1,3-dipolar cyclizations,[12] Friedel–Crafts reactions,[13] or Mannich reactions.[14] In addition, FeX_3 and other Lewis acid-promoted carbon–carbon bond-forming cyclizations of alkenyl and allenyl acetals have been frequently reported.[15] In 2009, Yu and co-workers[15d,e] discovered that intramolecular alkynyl acetal derivatives could be transformed into various cyclopentanes, tetrahydropyrans, and tetrahydropyrroles in the presence of FeX_3 (Scheme 1B). Intrigued by the versatile interactions of Lewis acids with acetals, we envisaged that a highly strained methylenecyclopropane (MCP) carbocation might be generated from a Prins cyclization of acetal–VDCPs catalyzed by Fe^{III}. The MCP carbocation would then undergo an intramolecular rearrangement with the ring-opening of the cyclopropane to give the corresponding cyclobutene derivatives. Herein we report the iron-catalyzed intramolecular cycloisomerization of acetal–vinylidenecyclopropanes to afford a series of disubstituted cyclobutenes tethered with a tetrahydropyrrole (Scheme 1C; X = Cl or Br).

To test the feasibility of our hypothesis, acetal–vinylidenecyclopropane **1a** was selected as the substrate, in which the acetal and vinylidenecyclopropane moieties are connected by a "BsN" anchor (Bs = 4-bromobenzenesulfonyl). To our delight, the desired reaction proceeded smoothly in the presence of $FeCl_3$ in 1,2-dichloroethane (DCE) at room temperature, affording the chlorinated cyclobutene tethered by a tetrahydropyrrole, product **2a**, in 69% yield (Table 1, entry 1). The structure of *syn*-**2a** was unambiguously assigned by X-ray diffraction (see the Supporting Information).[16] Notably, product **2a** was formed as a pair of diastereoisomers with a 1:1 ratio. Encouraged by this preliminary result, we attempted to improve the reaction performance by screening various conditions. First of all, acetyl chloride (1.0 equiv) was found to be a better chloride source, so that only a catalytic amount of $FeCl_3$ (e.g., 5 mol%) was required to afford the desired product **2a** in 75% yield (Table 1, entry 2). When N-chlorosuccinimide (NCS) and tetrabutylammonium chloride (TBACl) were utilized as chloride sources, only traces of **2a** could be detected by thin-layer chromatography (TLC) monitoring (Table 1, entries 3 and 4). Trimethylsilyl chloride (TMSCl) and benzoyl chloride showed similar reactivities to that of acetyl chloride to give **2a** in 70% and 72% yield, respectively (Table 1, entries 5 and 6). The reaction was less efficient when carried out in toluene or CH_2Cl_2, and no identifiable product was formed in THF or CH_3CN (Table 1, entries 7–10). Without $FeCl_3$, the reaction gave **2a** in less than 5% yield and the addition of 4 Å molecular sieves did not improve the yield of **2a** (Table 1, entries 11 and 12). Gratifyingly, an improvement was achieved by increasing the employed amount of acetyl chloride to 1.5 equivalents, giving **2a** in 85% yield (Table 1, entry 13). We finally identified that carrying out the reaction in DCE at room temperature for 2 h using 5 mol% $FeCl_3$ as the catalyst with MeCOCl as a halogen source as the best reaction conditions.

Table 1. Screening conditions for cycloisomerization of **1a**.



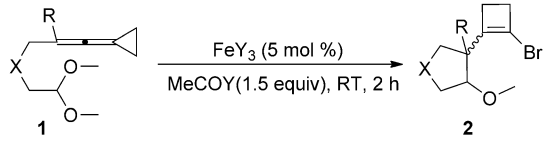
Entry[a]	x	Solvent	R	y	Yield [%][b,c]
1	100	DCE	–	–	69
2	5	DCE	Ac	1.0	75
3[d]	5	DCE	–	1.0	< 5
4[e]	5	DCE	–	1.0	< 5
5	5	DCE	TMS	1.0	70
6	5	DCE	Bz	1.0	72
7	5	CH_3CN	Ac	1.0	< 5
8	5	THF	Ac	1.0	< 5
9	5	toluene	Ac	1.0	51
10	5	CH_2Cl_2	Ac	1.0	61
11	–	DCE	Ac	1.0	< 5
12[f]	5	DCE	Ac	1.0	67
13	**5**	**DCE**	**Ac**	**1.5**	**85**

[a] Substrate **1a** (0.2 mmol), $FeCl_3$ (*x* mol%), RCl (*y* equiv) and the corresponding solvent (2 mL); [b] yield of isolated product; [c] product **2a** consists of a pair of diastereoisomers and the ratio is 1:1; [d] $nBu_4N^+Cl^-$ was employed; [e] *N*-chlorosuccinimide (NCS) was employed; [f] 4 Å molecular sieves were added.

Having optimzed the reaction conditions, we next examined the scope and limitations of this $FeCl_3$-catalyzed cycloisomerization (Table 2). With acetal–VDCPs **1b–i** as the substrates (R = primary or secondary alkyl groups; X = TsN or BsN anchor), the desired products **2b–i** were obtained in moderate to good yields (46–81%; Table 2, entries 2–9). When acetal–VDCP **1j** was employed as substrate, in which R was benzyl (Bn) group, the corresponding product **2j** could also be afforded in 71% yield (Table 2, entry 10). However, when acetal–VDCP **1k** (X = O, R = Me) or **1l** (X = CH_2, R = Me), with O or CH_2 as anchors, was used as substrate, the reaction gave the desired product **2k** in 25% yield or a complex product mixture, respectively (Table 2, entries 11 and 12).

To further investigate the scope of this reaction, other halogen sources were surveyed as well. When acetyl bromide was used as halogen source and $FeBr_3$ (5 mol%) was used as the catalyst, the corresponding brominated product **3a** was obtained in 71% yield (Table 2, entry 13). However, when benzoyl fluoride and other halogen sources, such as KF and NaI, were used, none of the corresponding halogenated products could be detected. Thus, the reactions of acetyl bromide and $FeBr_3$ with other acetal–VDCPs **1** were then carried out to define the

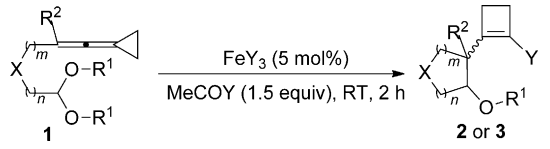
Table 2. Fe^{III}-catalyzed cycloisomerization of **1**.



Entry[a]	X/Y	Substrate R		Yield [%][b] 2 or 3	d.r.[c]
1	BsN/Cl	Me	**1a**	**2a**, 85	1.1:1
2	TsN/Cl	Me	**1b**	**2b**, 80	1:1.3
3	BsN/Cl	Et	**1c**	**2c**, 72	1:1.1
4	TsN/Cl	Et	**1d**	**2d**, 71	1.2:1
5	BsN/Cl	*i*Pr	**1e**	**2e**, 74	1:1.5
6	BsN/Cl	*n*Bu	**1f**	**2f**, 73	1:1.2
7	TsN/Cl	*n*Bu	**1g**	**2g**,81	1:1.1
8	BsN/Cl	3-butenyl	**1h**	**2h**, 60	1.2:1
9	TsN/Cl	3-butenyl	**1i**	**2i**, 46	1:1.0
10	BsN/Cl	Bn	**1j**	**2j**, 71	1:1.0
11	O/Cl	Me	**1k**	**2k**, 25	1:1.0
12	CH_2/Cl	Me	**1l**	complex mixture	
13	BsN/Br	Me	**1a**	**3a**, 71	1:1.1
14	TsN/Br	Me	**1b**	**3b**, 66	1:1.1
15	BsN/Br	Et	**1c**	**3c**, 65	1:1.4
16	TsN/Br	Et	**1d**	**3d**, 65	1:1.1
17	BsN/Br	*i*Pr	**1e**	**3e**, 65	1:1.5
18	BsN/Br	*n*Bu	**1f**	**3f**, 66	1:1.2
19	TsN/Br	*n*Bu	**1g**	**3g**, 68	1:1.3
20	BsN/Br	3-butenyl	**1h**	**3g**, 50	1.2:1
21	TsN/Br	3-butenyl	**1i**	**3i**, 57	1:1.0
22	BsN/Br	Bn	**1j**	**3j**, 63	1:1.2

[a] **1** (0.2 mmol), FeY_3 (5 mol%), MeCOY (1.5 equiv), (Y = Cl or Br), and DCE (2.0 mL). [b] yield of isolated product; [c] diastereoisomeric ratio, *syn/anti*.

Table 3. Further exploration of Fe^{III}-catalyzed cycloisomerizations of **1**.



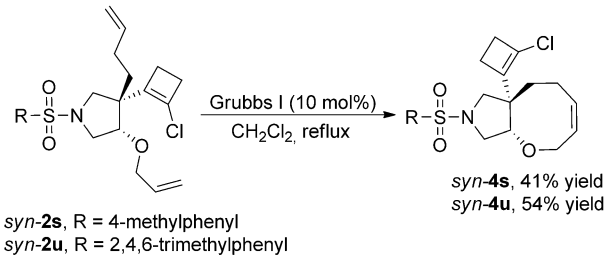
Entry[a]	X/Y	R^1	R^2	*m*/*n*		Yield [%][b] 2 or 3	d.r.[c]
1	BsN/Cl	Me	Me	2/1	**1m**	**2m**, 64	1:1.4
2	BsN/Br	Me	Me	2/1	**1m**	**3m**, 56	1:1.8
3	BsN/Cl	Me	Me	3/1	**1n**	complex mixture	
4	TsN/Cl	Et	Me	1/2	**1o**	**2o**, 61	>10:1
5	TsN/Br	Et	Me	1/2	**1o**	**3o**, 63	>10:1
6	TsN/Cl	OCH_2CH_2O	Me	1/1	**1p**	complex mixture	
7	TsN/Cl	2-propenyl	Me	1/1	**1q**	**2q**, 86	1.2:1
8	TsN/Br	2-propenyl	Me	1/1	**1q**	**3q**, 67	1:1.1
9	BsN/Br	2-propenyl	Me	1/1	**1r**	**3r**, 68	1:1.1
10					**1s**	**2s**, 44	1:1.0
11					**1t**	**3t**, 48	1.1:1
12					**1u**	**2u**, 45	1:1.2

[a] **1** (0.2 mmol), FeY_3 (5 mol%), MeCOY (1.5 equiv), (Y = Cl or Br), and DCE (2.0 mL). [b] yield of isolated product; [c] diastereoisomeric ratio, *syn/anti*.

generality of this protocol. Similarly, when using acetal–VDCPs **1b–j** as the substrates, the desired brominated products **3b–j** were obtained in moderate to good yields (50–68%; Table 2, entries 14–22).

Next, the carbon chain length of acetal–VDCPs was extended and different acetals were synthesized to expand the substrate scope and conduct further transformation of the products (Table 3). Interestingly, when acetal–VDCP **1m**, which contains a $(CH_2)_2$ carbon chain to connect the anchor with the VDCP moiety, was used as substrate, the desired cycloisomerization products **2m** and **3m** could also be produced in moderate yields under the optimal conditions (Table 3, entries 1 and 2). However, when acetal–VDCP **1n**, bearing a $(CH_2)_3$ carbon chain to the VDCP moiety, was used as substrate, the reaction afforded a complex product mixture (Table 3, entry 3). Extending the carbon chain to the acetal moiety with a $(CH_2)_2$ tether, the desired products **2o** and **3o** were obtained in 61 and 63% yields, respectively (Table 3, entries 4 and 5). It should be noted that products **2o** and **3o** were formed with better diastereoselectivities than **2m** and **3m**, presumably due to the increased steric flexibility. Next, ethylene glycol acetal–VDCP **1p** and diallyl acetal–VDCPs **1q–u** were synthesized, because their corresponding products are suitable for further transformations. Upon examination, we found that **1p** decomposed when $FeCl_3$ was employed as the catalyst (Table 3, entry 6). However, when **1q–u** were used as substrates, the corresponding reactions took place smoothly, affording the desired products in moderate to good yields under the optimal conditions (44–86%; Table 3, entries 7–12).

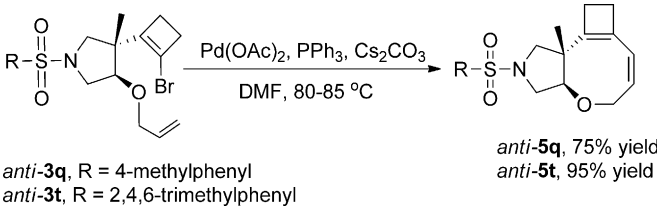
Ruthenium-catalyzed intramolecular ring-closing olefin metathesis has become a powerful strategy to construct five-, six-, and seven-membered cyclic compounds and has been used as a crucial step in total synthesis of many natural products.[17] The construction of eight-membered rings, especially those containing one heteroatom, by ring-closing olefin metathesis is thought to be relatively difficult, due to unfavorable entropy loss. Therefore, the synthesis of eight-membered oxacyclic compounds remains a challenge.[18] We further explored the transformations of products **2** and **3** in order to illustrate their



Scheme 2. Transformation of products *syn*-**2s** and *syn*-**2u** into *syn*-**4s** and *syn*-**4u**.

synthetic utility. Products *syn*-**2s** and *syn*-**2u** could be easily transformed to compounds *syn*-**4s** and *syn*-**4u** in moderate yields by intramolecular ring-closing olefin metathesis using Grubbs I catalyst (Scheme 2). The structures of *syn*-**2u** and *syn*-**4u** were determined by NMR spectroscopic investigations, including COSY, HSQC, HMBC, and NOESY (see the Supporting Information). Compounds *syn*-**4s** and *syn*-**4u** both contain an eight-membered oxacyclic core, which is frequently found in natural products, a fused pyrrolidine ring, and a cyclobutene side chain.[19]

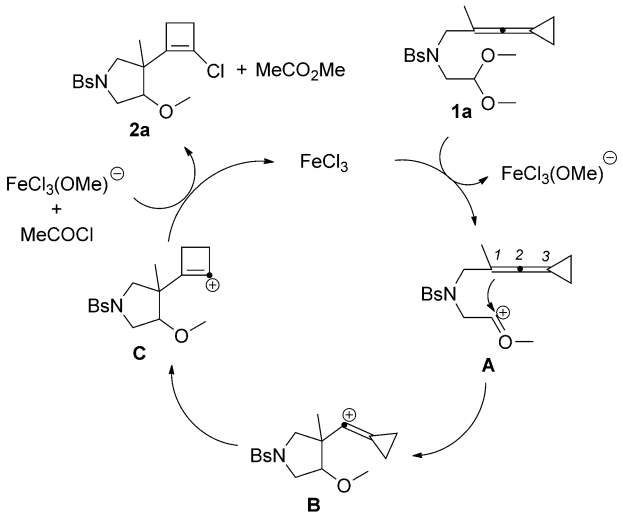
Intramolecular palladium-catalyzed oxidative cyclization is another powerful method for the construction of heterocycles.[20] Products *anti*-**3q** and *anti*-**3t** could be successfully converted into the tricyclic compounds *anti*-**5q** and *anti*-**5t** bearing an eight-membered oxacyclic diene core in good to excellent yields in the presence of 10 mol% of $Pd(OAc)_2$ (Scheme 3).



Scheme 3. Transformation of products *anti*-**3q** and *anti*-**3t** into *anti*-**5q** and *anti*-**5t**. Reagents and conditions: a) Cs_2CO_3 (1.0 equiv), $Pd(OAc)_2$ (10 mol%), PPh_3 (0.25 equiv), DMF, 80–85 °C, 10 h.

The structure of *anti*-**5t** was also confirmed by NMR spectroscopy (COSY, HSQC, HMBC, and NOESY; see the Supporting Information).

A reaction mechanism is proposed in Scheme 4, using **1a** as a model substrate for the cycloisomerization on the basis of previous reports.[21] Initially, $FeCl_3$ abstracts a methoxy group from **1a** to form a $[FeCl_3(OMe)]^-$ anionic species and an oxocarbenium intermediate **A**. Then, a Prins-type cyclization takes place to give the cationic MCP intermediate **B** in a 5-*exo*-trig manner. The ring-enlarging rearrangement of MCP in intermediate **B** occurs to afford intermediate **C**, followed by nucleophilic attack of the chloride anion from MeCOCl to yield the desired product **2a** along with the regeneration of $FeCl_3$ for the catalytic cycle.

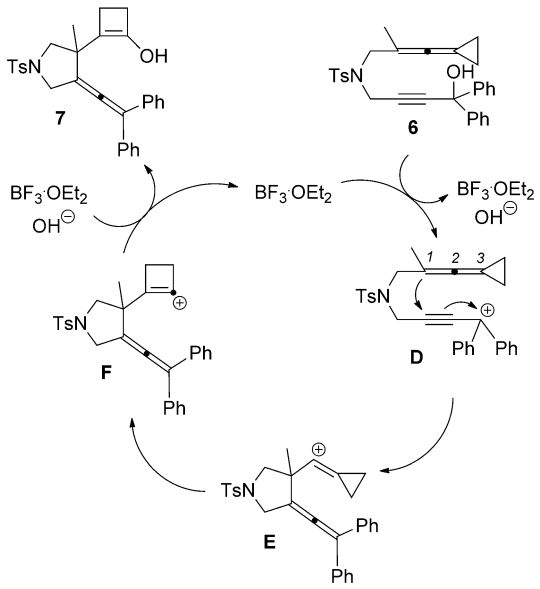


Scheme 4. Proposed mechanism for the formation of **2a**.

In our previous work, we reported that the reaction of VDCPs with 1,1,3-triarylprop-2-yn-1-ols or their methyl ethers selectively produced 4-dihydro-1*H*-cyclopenta[*b*]naphthalene derivatives or 1,2,3,8-tetrahydrocyclopenta[*a*]indene derivatives in the presence of Lewis acid, depending on the substituents at the cyclopropane.[22] However, the intramolecular reaction of VDCPs with propargyl alcohol has not been explored to date. On the basis of the above investigation, we synthesized a new propynol–VDCP **6** to investigate its reactivity in the presence of various Lewis acids, and the results are summarized in Supporting Information (Table S1). The reaction proceeded smoothly in DCE to afford product **7** in 51% yield within 1 h at 60 °C in the presence of $BF_3{\cdot}OEt_2$ (10 mol%) and 4 Å molecular sieves (50 mg; Scheme 5). The structure of **7** was unambiguously assigned by X-ray diffraction (see the Supporting Information).[16] This product is slightly labile during purification with silica gel column chromatography.

Scheme 5. Cycloisomerization of propynol–VDCP **6** in the presence of $BF_3{\cdot}OEt_2$.

A plausible mechanism for $BF_3{\cdot}OEt_2$ promoted cycloisomerization of **6** is proposed in Scheme 6, which is quite similar to the cycloisomerization of **1a** indicated in Scheme 4. At first, $BF_3{\cdot}OEt_2$ activates the hydroxyl group in **6** to give a propargyl carbocation species **D**, which cyclizes with the C-1 carbon in the tethered VDCP to give the corresponding cationic MCP intermediate **E** in a 5-*exo*-dig manner. Then, the intermediate **E** gives intermediate **F** via a ring-enlarging rearrangement, fol-



Scheme 6. Proposed reaction mechanism for the formation of **7**.

lowed by nucleophilic attack of hydroxyl anion to give the desired product **7** along with the regeneration of $BF_3{\cdot}OEt_2$. Notably, the key step, which is the ring-enlargement of the cationic MCP intermediate, is identical in these two kinds of reactions.

In conclusion, we have developed a novel Fe^{III}-catalyzed intramolecular cycloisomerization of acetal–VDCPs, which can be used to efficiently synthesize halogenated 1,2-disubstituted cyclobutenes tethered with a tetrahydropyrrole in moderate to good yields under mild conditions. The further transformation of these products into functionalized eight-membered heterocycles can be easily realized by Ru-catalyzed ring-closing olefin metathesis or palladium-catalyzed oxidative cyclization. Moreover, propynol–VDCP can be converted into a novel cyclobut-1-enol tethered with an allenic tetrahydropyrrole in moderate yield in the presence of $BF_3{\cdot}OEt_2$. Further work will be devoted to applying this new methodology to synthesize biologically active products.

Acknowledgements

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Keywords: cycloisomerization · homogeneous catalysis · iron · ring expansion · small ring systems

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