Metathesis

International Edition: DOI: 10.1002/anie.201604349
German Edition: DOI: 10.1002/ange.201604349

# $FeCl_3$-Catalyzed Ring-Closing Carbonyl–Olefin Metathesis

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***Abstract:*** *Exploiting catalytic carbonyl–olefin metathesis is an ongoing challenge in organic synthesis. Reported herein is an $FeCl_3$-catalyzed ring-closing carbonyl–olefin metathesis. The protocol allows access to a range of carbo-/heterocyclic alkenes with good efficiency and excellent trans diastereoselectivity. The methodology presents one of the rare examples of catalytic ring-closing carbonyl–olefin metathesis. This process is proposed to take place by $FeCl_3$-catalyzed oxetane formation followed by retro-ring-opening to deliver metathesis products.*

Ring-closing metathesis (RCM) of two carbon–carbon double bonds is one of the most significant reactions for the synthesis of various-sized rings (Figure 1 a).[1] The impact of RCM can be appreciated from its use in the synthesis of materials, drugs, natural products, etc. Inspired by the power of RCM, chemists are also interested in developing ring-closing carbonyl–olefin metathesis (RCCOM) of carbonyl-enes to synthesize ring compounds (Figure 1 b).[2] First, the carbonyl group in carbonyl-enes are either readily available or easily prepared, while di-alkenes for RCM need more steps to be synthesized. Second, carbonyl–olefin metathesis is a powerful means to synthesize highly substituted and otherwise difficult-to-obtain alkenes. However, the reported RCCOM is realized by using a stoichiometric amount of an RCM catalyst, such as titanium, molybdenum, or rhuthenium catalysts.[3] The mechanism of these reported RCCOM reactions involve the formation of the M=O reagent. Generation of this M=O reagent precludes the development of a catalytic version of RCCOM, as it would dramatically increase the cost of synthesis because of the high prices of the molybdenum and ruthenium reagents. To circumvent this shortcoming, chemists developed the photochemical [2+2]/retro[2+2] cycloaddition to facilitate the RCCOM.[4] Stoichiometric Lewis-acid-promoted reactions of RCCOM have also been disclosed, but only a few of carbocycles could be achieved.[5] Importantly, organocatalyzed ring-opening metathesis (ROM) of cyclopropenes with aldehydes was first realized by the group of Lambert.[6] In 2015, the group of Franzén reported the trityl-catalyzed metathesis of aromatic aldehydes and alkenes.[7] Very recently, Schindler and co-workers reported an iron-catalyzed carbonyl–olefin metathesis for the construction of functionalized carbocycles and the method demonstrated a broader range of substrates, thus representing a breakthrough in this area.[8] Considering the limited success in the past and the urgent development of green synthetic methodologies, developing a catalytic RCCOM is challenging but worthy of further exploration.

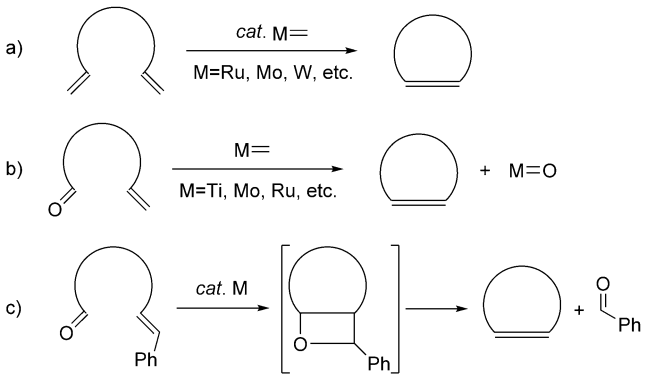


***Figure 1.*** Overview of ring-closing double-bond metathesis.

It was envisioned that if the olefin bears an aryl group and is exposed to a Lewis acid, it could give an oxetane intermediate, which then undergoes retro [2+2], and thus a RCCOM reaction can be realized (Figure 1 c). Toward this end, we report an approach for the catalytic RCCOM reaction using an earth-abundant and inexpensive iron catalyst.[9]

We commenced our investigation by studying the carbonyl–olefin metathesis of **1a** to give the cyclopentene **2a** (Table 1). Efforts to address a catalytic RCCOM centered on suitable catalysts. With extensive screening of a variety of Lewis acids and Brønsted acids, to our delight, the desired cyclopentene product **2a** was obtained in 73 % yield by using $FeCl_3$ as the catalyst in DCE (1,2-dichloroethane; entry 1), while other Lewis acids and Brønsted acids either failed to deliver **2a** (entries 2–7) or showed lower efficiency (entries 8 and 9). Carrying out the reaction in a dilute solution resulted in 87 % yield of **2a** (entry 10). Interestingly, DCM (dichloromethane) and PhCl are also applicable solvents for the reaction (entries 11 and 12). However, **2a** was not observed in THF or acetonitrile (entries 13 and 14). Notably, only the *trans*-product **2a** was obtained in the reactions shown in entries 1 and 10–12. We hypothesized that the steric bulk of the phenyl and benzoyl group play a key role in the formation of the oxabicyclo[3.2.0]heptane derivative, which is proposed as an intermediate of this reaction.

Under optimal reaction conditions, we initially examined the scope of the $FeCl_3$-catalyzed ring-closing carbonyl–olefin metathesis for the formation of five-membered carbocycles (Table 2). The 1,3-dicarbonyl-derived substrates **1a–g** afforded the corresponding metathesis products **2a–g** in 62–84 % yields. In these cases, only the *trans*-configured products

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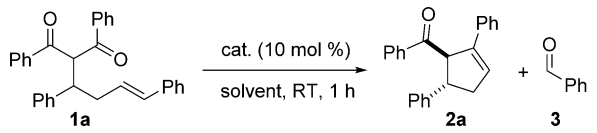
Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201604349.

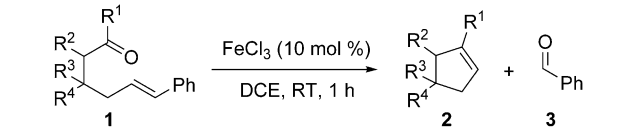
***Table 1:*** Optimization of reaction conditions.[a]

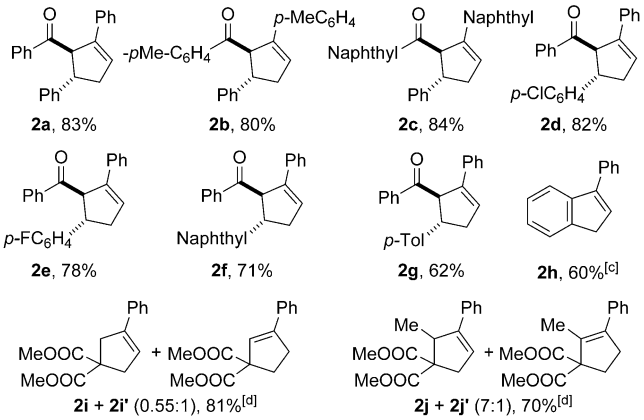



| Entry | Catalyst | Solvent | Yield [%][b] 2a | 3 |
|---|---|---|---|---|
| 1 | $FeCl_3$ | DCE | 73 | 60 |
| 2 | $FeCl_2$ | DCE | – | – |
| 3 | $[Fe(acac)_3]$ | DCE | – | – |
| 4 | $CuCl_2$ | DCE | – | – |
| 5 | $CoCl_2$ | DCE | – | – |
| 6 | $ZnCl_2$ | DCE | – | – |
| 7 | $AlCl_3$ | DCE | – | – |
| 8 | $BF_3{\cdot}Et_2O$ | DCE | 30 | 18 |
| 9 | TfOH | DCE | 15 | 7 |
| 10[c] | $FeCl_3$ | DCE | 87 | 65 |
| 11[c] | $FeCl_3$ | DCM | 86 | 64 |
| 12[c] | $FeCl_3$ | PhCl | 85 | 60 |
| 13[c] | $FeCl_3$ | THF | – | – |
| 14[c] | $FeCl_3$ | MeCN | – | – |

[a] Reaction conditions: **1a** (0.1 mmol), cat. (0.01 mmol), solvent (1.0 mL), RT, 1 h, unless otherwise noted. [b] Yields were determined by $^1$H NMR spectroscopy using an internal standard. [c] Solvent (3.0 mL). acac = acetylacetonate, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran.

***Table 2:*** Examples for five-membered carbocycles.[a,b]



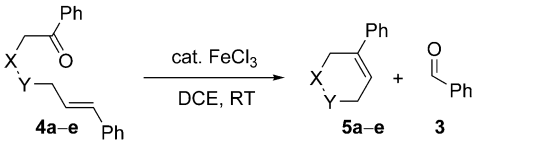



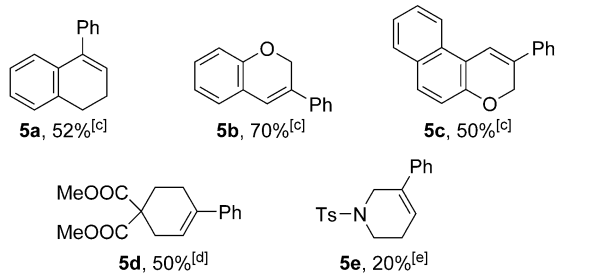

[a] Reaction conditions: **1** (0.1 mmol), $FeCl_3$ (0.01 mmol), DCE (3.0 mL), RT, 1 h, unless otherwise noted. [b] Yield of isolated product. [c] 12 h. [d] $FeCl_3$ (0.025 mmol).

were obtained. The benzene-linked substrate **1h** gave the desired indene **2h** in 60% yield. In the case of malonate-ester-derived substrates, the reactions yielded a mixture of the normal metathesis products **2i** and **2j** and the double-bond isomerization products **2i′** and **2j′**.

Next, we extensively investigated the scope of the $FeCl_3$-catalyzed ring-closing carbonyl–olefin metathesis for the formation of six-membered cycles and heterocycles (Tables 3–5). The efficiency of the method is lower for the formation of six-membered rings (Table 3). The benzene-linked substrate **4a** gave the dihydronaphthalene **5a** in 52% yield. The oxygen-linked substrates **4b** and **4c** yielded the pyran derivatives **5b** and **5c**, respectively, in reasonable yields. The reaction of the malonate ester-derived substrate **4d** was very slow, and it needed 14 days to afford **5d** in 50% yield; 30% of **4d** was recovered. The metathesis of the nitrogen-linked substrate **4e** was much more difficult, and a stoichiometric amount of $FeCl_3$ was needed, thus delivering the tetrahydropyridine **5e** in 20% yield upon isolation.

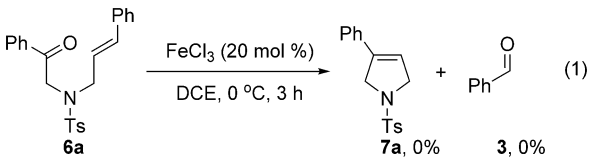
***Table 3:*** Examples for six-membered cycles.[a,b]




[a] Reaction conditions: **4** (0.1 mmol), DCE (3.0 mL), RT. [b] Yield of isolated product. [c] $FeCl_3$ (0.025 mmol), 1 h. [d] $FeCl_3$ (0.01 mmol), 14 d. [e] $FeCl_3$ (0.1 mmol), 1 h.

Considering that five-membered nitrogen heterocycles are ubiquitously found in an array of natural products and serve as useful precursors for the synthesis of biologically active compounds, we screened various reaction conditions to deliver a 2,5-dihydropyrrole skeleton[1,10] by a ring-closing carbonyl–olefin metathesis. Although the 2,5-dihydropyrrole product was not observed by using $FeCl_3$ itself [Eq. (1); Ts = 4-toluenesulfonyl], ring-closing carbonyl–olefin metathesis of **6a** led to the desired 2,5-dihydropyrrole **7a** in 91% yield when allyltrimethylsilane was added as an additive [Eq. (2);



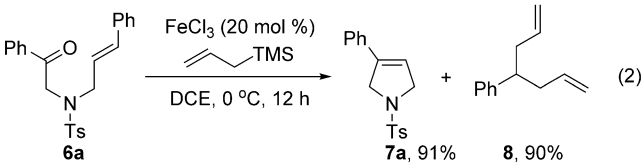
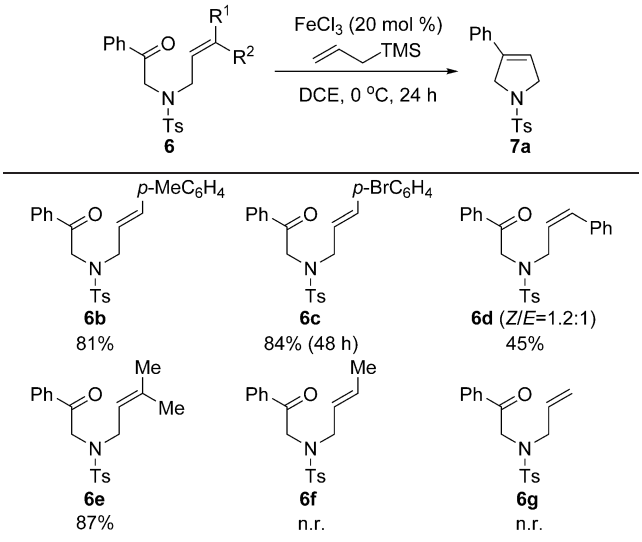



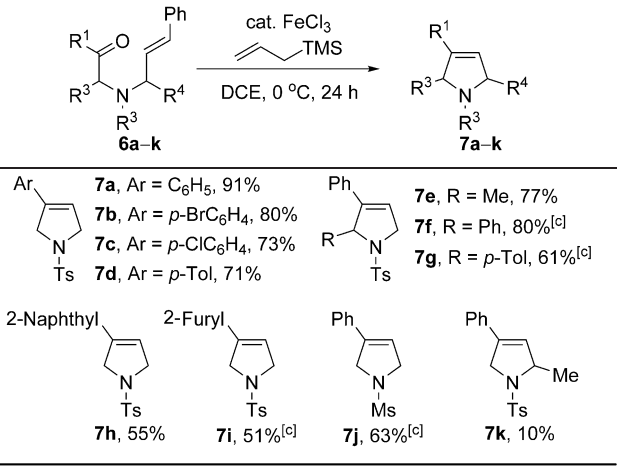

  

***Table 4:*** Effects of olefins.[a]




[a] Reaction conditions: **6** (0.1 mmol), $FeCl_3$ (0.02 mmol), allyltrimethylsilane (0.5 mmol), DCE (1.0 mL), 0 °C, 24 h. n.r. = no reaction.

***Table 5:*** Examples for 2,5-dihydropyrroles.[a,b]



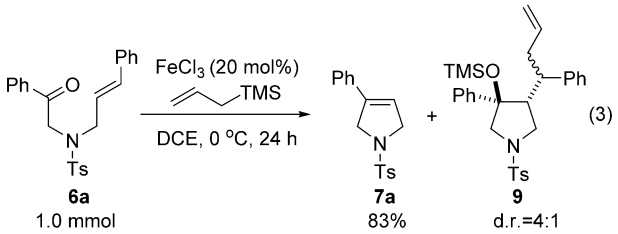

[a] Reaction conditions: **6** (0.1 mmol), $FeCl_3$ (0.02 mmol), allyltrimethylsilane (0.5 mmol), DCE (1.0 mL), 0 °C, 24 h. [b] Yield of isolated product. [c] $FeCl_3$ (0.05 mmol).

TMS = trimethylsilyl]. In this case, the bis(allyl)ation product **8** was formed instead of benzaldehyde (**3**). Further studies suggested that both the allyl group and TMS group are required for the transformation.[11] Although the exact role the of allyltrimethylsilane is not clear, we presume that it might play two functions here: one involves coordination to the iron catalyst to promote the formation/opening of the key oxetane intermediate, and the other is that allyltrimethylsilane serves as a scavenger to remove the generated benzaldehyde.

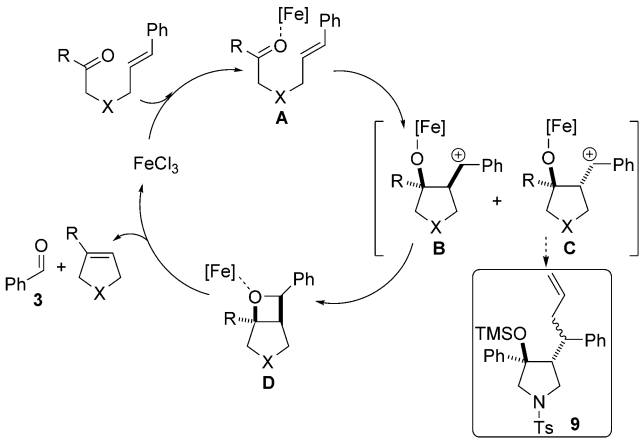
The influence of the substituents on olefin was subsequently examined (Table 4). Substrates with *trans*-aryl groups on the olefin afforded the desired dihydropyrrole **7a** in comparable yields, even though the bromophenyl-substituted substrate **6c** required a long reaction time. A substrate with a mixture of *Z*- and *E*-olefins afforded **7a** in 45% yield with 36% of the *Z*-olefin recovered. When the dimethyl-substituted olefin **6e** was employed, **7a** was formed in 87% yield. However, no product was detected when either the monomethyl-substituted olefin **6f** or simple allylamine **6g** was employed.

Under the optimal reaction conditions, we subsequently investigated the substrate scope of ring-closing carbonyl–olefin metathesis for 2,5-dihydropyrroles (Table 5). Substrates with methyl, chloro, and bromo substituents on the benzoyl groups afforded the corresponding dihydropyrroles **7b–d** in good yields. Substrates with substituents near the carbonyl group gave the trisubstituted dihydropyrroles **7e–g** smoothly. Naphthyl- and furyl-substituted substrates gave **7h** and **7i** in moderate yields. Beyond tosyl (Ts) as a protecting group on nitrogen atom, an *N*-methanesulfonyl (Ms) substrate was also transformed into the desired product **7j** in 63% yield. We next turned our attention to substrates with substituents near the double bond. The substrate **6k** afforded the corresponding dihydropyrroles **7k** in low yields (10%).

In addition, the $FeCl_3$-catalyzed ring-closing carbonyl–olefin metathesis could be scaled up, for example, an 83% yield of **7a** was achieved on a 1.0 mmol scale metathesis reaction [Eq. (3)]. Notably, the reaction allowed us to obtain a trace amount of the side-product **9**, which features a *trans*-configuration of pyrrolidine skeleton.




Oxetane is believed to be the key intermediate in the carbonyl–olefin metathesis. Formation of an oxetane can arise from either a concerted mechanism or a stepwise mechanism. Schindler and co-workers proposed a concerted mechanism based on calculations.[7] However, in our reaction, the formation of **9** supports a stepwise mechanism. Therefore a proposed mechanism for the $FeCl_3$-catalyzed ring-closing carbonyl–olefin metathesis is depicted in Scheme 1.[5a] $FeCl_3$ coordinates with the carbonyl group of the substrate to generate the intermediate **A**. Intramolecular electrophilic cyclization of **A** affords the zwitterionic intermediates **B** and **C**,[12] and **C** is a nonproductive intermediate. Subsequently, the fused oxetane intermediate **D** is formed from **B**. We rationalized that this stepwise process is reversible,[13] and this proposal is partially supported by the generation of **9** as depicted in Equation 3. Finally, concerted [2+2] cycloreversion[8] of **D** affords the metathesis product and releases the catalyst $FeCl_3$. In contrast, the metathesis product might be generated in a stepwise manner from **D**, and is an option which cannot be ruled out at this stage.[4,5,7,14]




***Scheme 1.*** Proposed mechanism for $FeCl_3$-catalyzed ring-closing carbonyl–olefin metathesis.

In summary, we have developed an $FeCl_3$-catalyzed ring-closing carbonyl–olefin metathesis. This method allows the synthesis of a range of carbo-/heterocyclic alkenes with good efficiency and excellent *trans* diastereoselectivity under mild reaction conditions. The present reaction was proposed to occur by $FeCl_3$-catalyzed stepwise oxetane formation followed by retro-ring-opening to deliver metathesis products. The methodology presents one of rare examples of catalytic ring-closing carbonyl–olefin metathesis using the inexpensive $FeCl_3$ catalyst. Efforts to understand the mechanism and expand on the synthesis of other heterocyclic scaffolds are ongoing and will be reported in due course.

## Acknowledgements

Financial support is acknowledged from the National Science Foundation of China (21272267), the State Key Laboratory of Heavy Oil Processing (SKLOP201401001), the Fundamental Research Funds for the Central Universities, the Research Funds of Renmin University of China (10XNL017), and Beijing National Laboratory for Molecular Sciences (BNLMS).

**Keywords:** alkenes · carbocycles · heterocycles · iron · metathesis

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[14] Discussions on possible reaction mechanisms are given in Schemes S1 and S2 of the Supporting Information.

Received: May 4, 2016
Revised: June 6, 2016
Published online: ■■ ■■, ■■■■

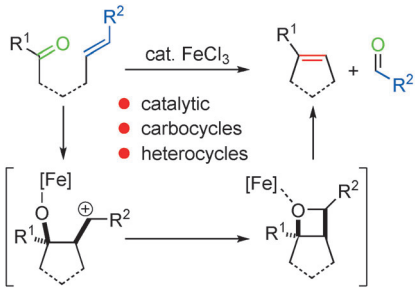
  

# Communications

## Metathesis

L. Ma, W. Li, H. Xi, X. Bai, E. Ma, X. Yan, Z. Li* ——— ■■■■–■■■■

FeCl$_3$-Catalyzed Ring-Closing Carbonyl–Olefin Metathesis




**Ironing it out**: The title reaction allows access to a range of carbo-/heterocyclic alkenes. The reaction is proposed to take place by FeCl$_3$-catalyzed oxetane formation followed by retro-ring-opening to deliver the metathesis products.