

Review

Iron-Catalyzed Carbonyl–Alkyne and Carbonyl–Olefin Metathesis Reactions

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Abstract: Construction of carbon–carbon bonds is one of the most important tools for the synthesis of complex organic molecules. Among multiple possibilities are the carbonyl–alkyne and carbonyl–olefin metathesis reactions, which are used to form new carbon–carbon bonds between carbonyl derivatives and unsaturated organic compounds. As many different approaches have already been established and offer reliable access to C=C bond formation via carbonyl–alkyne and carbonyl–olefin metathesis, focus is now shifting towards cost efficiency, sustainability and environmentally friendly metal catalysts. Iron, which is earth-abundant and considered as an eco-friendly and inexpensive option in comparison to traditional metal catalysts, fulfils these requirements. Hence, the focus of this review is on recent advances in the iron-catalyzed carbonyl–alkyne, carbonyl–olefin and related C–O/C–O metathesis reactions. The still large research potential for ecologically and economically attractive and sustainable iron-based catalysts is demonstrated.

Keywords: iron catalysts; carbonyl-olefin metathesis; carbonyl-alkyne metathesis; C=C bond formations

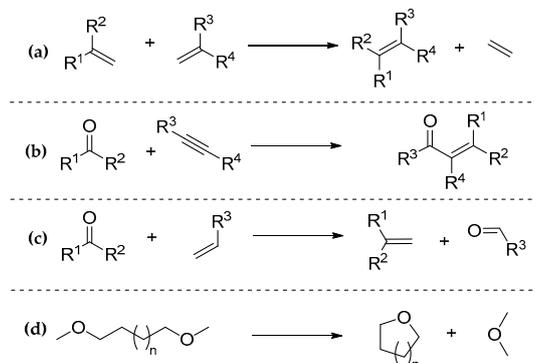
1. Introduction

The formation of carbon–carbon bonds is one of the most important goals in chemistry [1]. For fast, efficient and selective coupling, catalysis via metal salts or metal complexes is an elegant option with versatile applications in academic research or industry [2–4]. Among known efficient C–C bond formation methods are metal-catalyzed cycloadditions, which provide attractive alternatives to photochemical [5], radical [6] or thermal [7,8] cyclization reactions, as they do not require expensive photosensitizers and mostly work under mild conditions. One of the most important methodologies is the metal-catalyzed olefin–olefin metathesis reaction (Scheme 1a), which is a powerful tool for the formation of carbon–carbon double bonds with a wide range of applications [9–12]. It provides access to unsaturated compounds which are otherwise impossible to prepare, pharmaceuticals in particular [13].

In addition to the olefin metathesis reaction, carbonyl–alkyne and carbonyl–olefin metathesis reactions offer an alternative possibility to generate carbon–carbon bonds. In contrast to olefin–olefin metathesis (as shown in Scheme 1a), carbonyl–alkyne (Scheme 1b) and carbonyl–olefin metathesis (Scheme 1c) do not follow the Chauvin mechanism, even though the reaction proceeds via a formal [2 + 2] cycloaddition with an oxetene or oxetane as the intermediate [14,15]. As the reaction mechanism differs from olefin metathesis, use of a different type of catalyst is required. Most common metal catalysts for these reactions are Lewis acids, which activate both the carbonyl and the oxetene/oxetane species during the reaction [16,17].

A special case is the C–O/C–O metathesis reaction (as depicted in Scheme 1d), which forms a new C–O bond resulting in cyclic ether derivatives. Even though the reaction does not form a new C–C bond, the reaction can be considered as a ring-closing C–O/C–O metathesis of aliphatic ethers [18].

While many catalytic systems have already been reported, mainly employing organic Lewis acids [19] or metal-based Lewis acids [20], the development of new sustainable, cost-saving, earth-abundant metal-containing catalysts is highly desirable in today's chemistry [21,22]. Recently, FeCl_3 , which fulfills the abovementioned requirements, has been established for carbonyl-olefin and carbonyl-alkyne metathesis as a reliable catalyst. Therefore, the current review summarizes all recent developments in this field of research and related Fe-catalyzed C–O/C–O metathesis reaction.

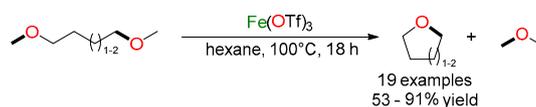


Scheme 1. Selected metathesis reactions: (a) olefin–olefin metathesis, (b) carbonyl–alkyne metathesis, (c) carbonyl–olefin metathesis and (d) ring-closing C–O/C–O metathesis.

2. Results

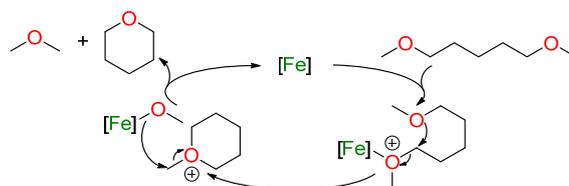
2.1. Iron-Catalyzed C–O/C–O Ring-Closing Metathesis

As the first example of a related metathesis reaction we chose the $\text{C}(\text{sp}^3)\text{--O}/\text{C}(\text{sp}^3)\text{--O}$ ring-closing reaction reported by Morandi and co-workers [18]. This single bond “metathesis” reaction is a Lewis acid-catalyzed ring closing, which transforms linear diethers into five- or six-membered cyclic ethers (Scheme 2).



Scheme 2. General equation of the reaction developed by Morandi and co-workers.

Different substitution patterns, including benzyl groups with electron donating and electron withdrawing groups as well as methyl groups and heteroatoms in the chain, are tolerated in the reaction system. To investigate if the generation of dimethyl-ether is the driving force of the reaction, experiments were performed with 1,5-pentandiol etherified with different alcohols (MeOH, PrOH and ButOH). As the yield of the cycloether was identical, it could be concluded that dimethyl-ether formation is not the key driving force of the reaction. Additional investigations showed also that generation of the cyclic ether is irreversible. In conclusion the authors suggest a bimolecular mechanism, which was supported by a crossover experiment with methyl- and propyl-ether derivatives. The proposed mechanism is depicted in Scheme 3:



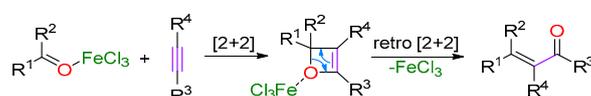
Scheme 3. Proposed mechanism for the C–O/C–O metathesis reaction.

The reaction also works with different Lewis acids, such as e.g., AlCl_3 or $\text{Sc}(\text{OTf})_3$, stressing the role of iron in the proposed mechanism. Although the mechanism is bimolecular and yields cross-products, the metal catalyst only activates the oxygen and therefore strongly deviates from the Chauvin mechanism. In conclusion, the iron-catalyzed C–O/C–O ring-closing reaction is the first of its kind which gives access to cyclic ethers, even though it cannot be considered a classical metathesis reaction.

2.2. Iron-Catalyzed Carbonyl-Alkyne Metathesis

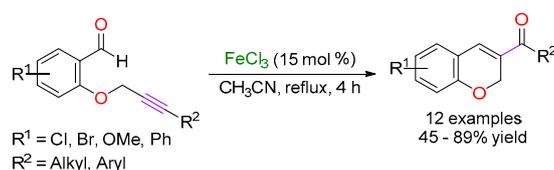
The carbonyl–alkyne metathesis (oxygen transfer from carbonyl to carbon–carbon triple bond) is an atom-efficient reaction which had its rush time in the early 2000s as a gold-catalyzed reaction [23]. In contrast to stabilized Wittig reagents, the carbonyl–alkyne metathesis reaction offers a favorable alternative as it possesses full atom efficiency for the synthesis of highly functionalized alkene derivatives. The discovery of the reaction being catalyzed by AgSbF_5 led the focus to less expensive Lewis acids [24]. Even though the reaction has also been described to occur with other Lewis acids, iron-based Lewis acids have been found to be one of the most favorable, which can be explained by the HSAB theory: [25] Fe^{III} can be considered as a “harder” Lewis acid than e.g., In^{III} , as it has a smaller ionic radius and, therefore, a more concentrated charge, which can be beneficial for interaction, resulting in better catalytic performance [26].

It is important to notice here that iron(III)chloride is only used to activate the aldehyde and the oxetene inside the—concerted, albeit non-synchronous—[2 + 2] cycloaddition, as depicted in Scheme 4. Iron d-orbitals do not take part in the cycloaddition step. Consequently, the reaction does not follow the Chauvin mechanism, as the metal is not included in the cycle formed in the transition structure. In general, the reaction itself is better described as an economical catalytic alternative to the Wittig reaction [27]. Nevertheless, carbonyl–alkyne metathesis consists of formal [2 + 2] and retro [2 + 2] cycloadditions and enables access to multiple heterocycles similar to olefin–metathesis and will be discussed in the following part.



Scheme 4. Reaction mechanism of carbonyl–alkyne metathesis.

The first example of carbonyl–alkyne metathesis catalyzed by iron was described by Jana and co-workers in 2011 (Scheme 5) [17].

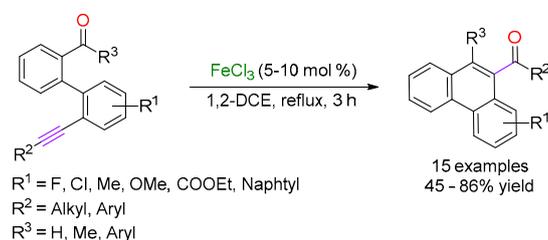


Scheme 5. FeCl_3 -catalyzed carbonyl–alkyne metathesis reaction towards 2H-chromenes.

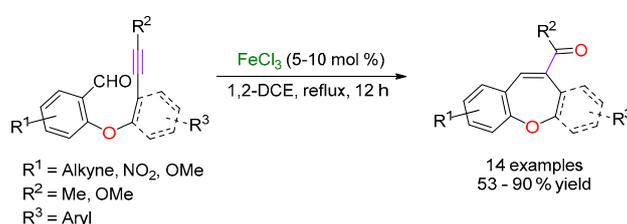
Similar reactions yielding 2H-chromene derivatives were described with different catalysts before, e.g., Ru- [28] and Au-based [29] catalysts. While former methodologies suffer from their usage of an expensive metal catalyst, the new method employing iron as Lewis acid decreases the costs of the reaction drastically. One year later, the research group of Jana published a novel procedure towards phenanthrene derivatives (Scheme 6).

In this case the metathesis reaction is exploited to directly yield completely conjugated ring systems. In addition to the straightforward synthesis of precursors (two steps, palladium cross-coupling reactions), the method possesses a good tolerance with respect to functional groups, including methoxy, methyl, fluorine, chloride and ester moieties.

An additional approach for the carbonyl–alkyne metathesis was reported by Bera et al. in 2013 (Scheme 7). By applying 2,2' functionalized diarylesters it was possible to synthesize dibenzo[*b,f*]oxepine and benzo[*b*]oxepine core structures, which possess many applications in medicinal chemistry. Additionally, these ring systems represent the first examples of artificially synthesized seven-membered heterocycles reported in the literature to this date.

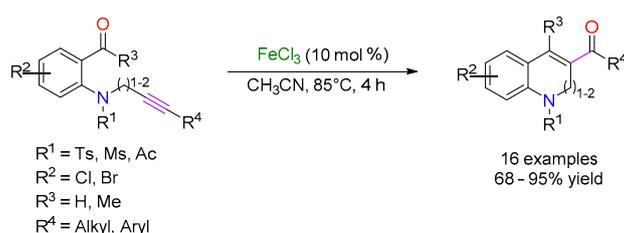


Scheme 6. Iron(III)-catalyzed carbonyl–alkyne metathesis reaction towards phenanthrenes.



Scheme 7. Synthesis of dibenzo[*b,f*]oxepine and benzo[*b*]oxepine compounds.

In 2014, the research group of Jana further expanded the applicability of iron-catalyzed carbonyl–alkyne metathesis by synthesizing precursors inspired by their work published in 2011 (Scheme 5). By replacement of oxygen by nitrogen and variation of the chain length of the alkyl bridge to the alkyne moiety, a new library of six- or seven-membered nitrogen-containing heterocycles was reported (Scheme 8). Again, these classes of compounds were already well established in pharmacological applications and may lead to novel bioactive compounds.



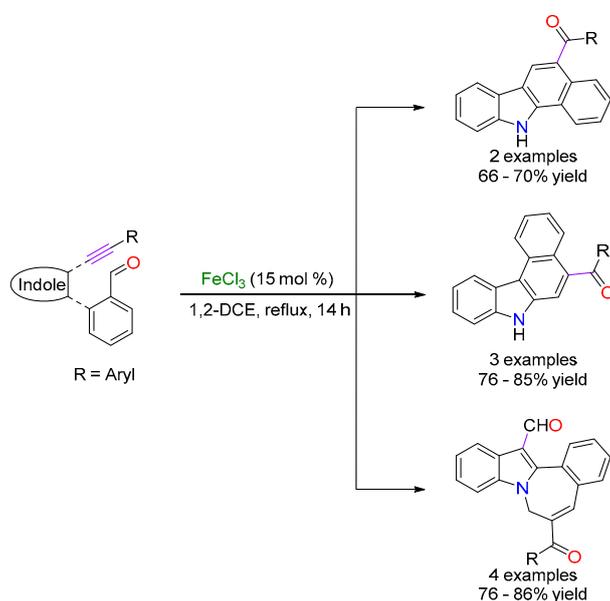
Scheme 8. Carbonyl–alkyne metathesis reaction towards dihydroquinolines, quinolines and dihydrobenzo[*b*]azepines.

The last work concerning alkyne–olefin metathesis was reported by Jalal et al. in 2017. In this publication, the focus was laid on the conversion of indole-derived compounds towards benzocarbazole and azepinoindole core structures as depicted in Scheme 9. As these are known to exhibit antitumor [30] and antiestrogenic [31] properties, the expansion of the scope towards novel compounds is highly desirable. By varying conformation of aldehyde and alkyne function, the carbonyl–alkyne metathesis gave facile access to the desired core structures, which were only accessible via expensive synthetic routes or toxic reagents before.

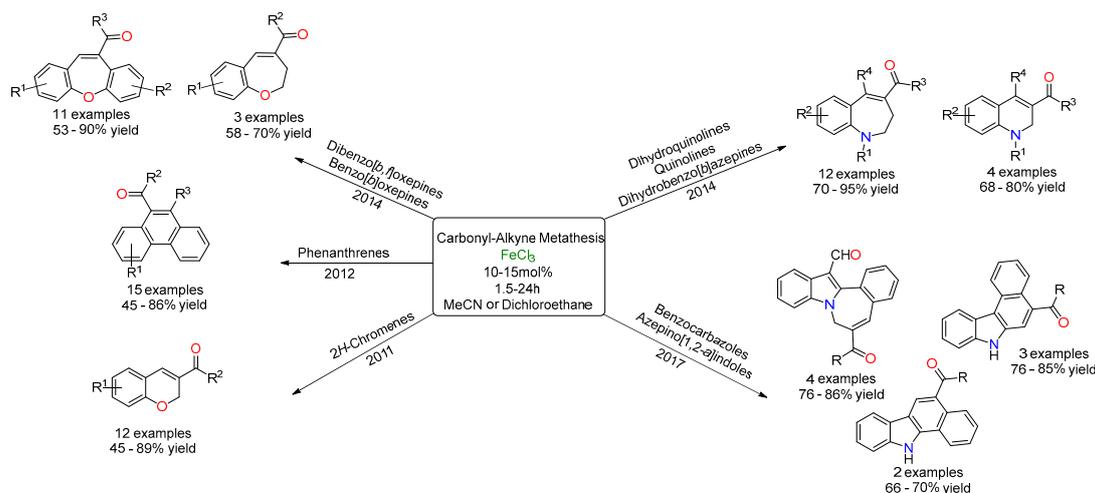
An additional advantage of this methodology is the straightforward precursor synthesis, which consists of only two steps.

In summary, the carbonyl–olefin metathesis reaction is a useful tool for the synthesis of novel, uncommon heterocyclic compounds or for straightforward synthesis of phenanthrene aldehydes. As synthesis of precursors involves simple reaction steps and the metathesis catalyst is non-toxic and

cheap, this methodology might be useful for the discovery or development of novel pharmaceutically active compounds. An overview of all reported reactions and that of resulting derivatives is depicted in Scheme 10.



Scheme 9. FeCl₃-catalyzed reaction towards benzocarbazoles and azeptino[1,2-*a*]indoles.



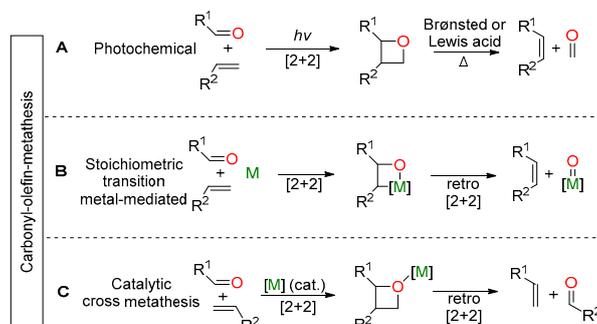
Scheme 10. Overview of the reported carbonyl-alkyne metathesis reactions.

2.3. Iron-Catalyzed Carbonyl-Olefin Metathesis

Similar to carbonyl-alkyne metathesis and olefin-olefin metathesis, carbonyl-olefin metathesis is a powerful tool for C=C bond formation [16]. The early carbonyl-olefin metathesis protocols required harsh conditions, like the first described example employing a two-step sequence including a photoinduced [2 + 2] cycloaddition, known as the Paternò-Büchi reaction [32,33], and an acidic or thermal retro-cyclization to yield the desired products (Scheme 11A) [34]. Another possibility of yielding the desired metathesis products is the stoichiometric use of a metal catalyst (Scheme 11B), which is oxidized during the reaction, as was described by the research group of Grubbs in 1990 [35]. Since this process is not catalytic, it is not suitable for industry due to its low atom economy.

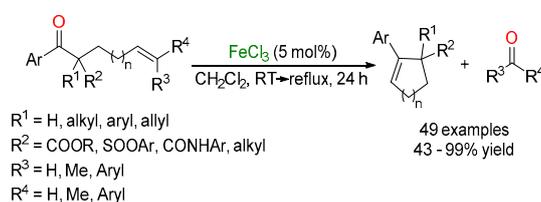
In 1983, Schopov and co-workers reported the first catalytic procedure employing tungsten chloride for the synthesis of polyconjugated polymers [36]. Even though this was the first catalytic approach, the reaction has a strong limitation as it requires a conjugated C=C and C=O bond. Only one year later, Snider and co-workers published a modified version of the oxetane-forming reaction of

an aldehyde and an olefin - employing SnCl_4 as catalyst (Scheme 11C) [37,38]. The modified version used a 1:2 ratio of $\text{Me}_2\text{AlCl}:\text{MeAlCl}_2$ yielding the desired diene in 30% yield. Further experiments with different ratios of the catalytic mixture already gave evidence that the catalytic activity is connected to the strength of the Lewis acid. In the following years different approaches with Lewis acids, for example with EZP-10 (solid Lewis acid catalyst) or $\text{BF}_3\cdot\text{OEt}_2$ were published [19,39]. As already described in the previous section for the carbonyl–alkyne metathesis reaction, the Lewis acid activates the oxygen of the carbonyl and also in the transition structure inducing the retro-[2 + 2]-addition [40].



Scheme 11. Types of carbonyl-olefin metathesis: (A) photochemical; (B) stoichiometric transition metal-mediated; (C) catalytic cross metathesis.

The first catalytic carbonyl–olefin metathesis approach employing the Lewis acid FeCl_3 as an environmentally friendly catalyst in a ring-closing reaction was published by the research group of Schindler, which presented a wide scope of almost 50 examples with moderate-to-excellent yields under mild reaction conditions (Scheme 12): [40]



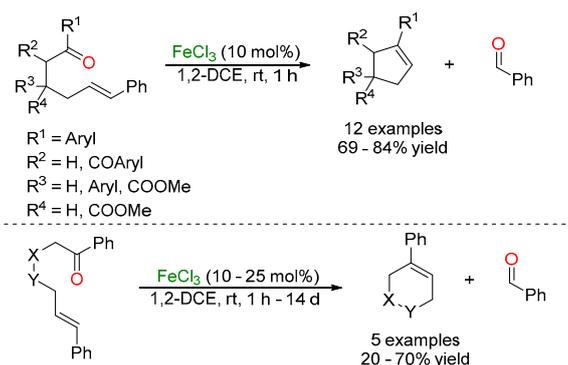
Scheme 12. General equation of the reaction reported by Schindler.

In a small review, Saá highlighted the most important features of the new approach: the reaction tolerates various aromatic substituents, while bulky olefin moieties decrease product formation. Moreover, metal enolates were not necessary to yield the desired products, as moieties bearing quaternary carbons in α -position are viable towards the reaction [41]. Nevertheless, compared to olefin metathesis, the versatility of the reaction is still poor, as the already existing metathesis catalyst pool makes the design of suitable reaction conditions for almost every substitution pattern possible.

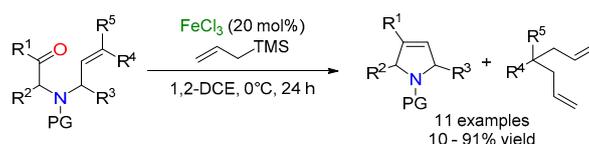
In the same year further applications of iron-catalyzed carbonyl–olefin metathesis were demonstrated by Li and co-workers, published in 2016, providing access to highly substituted five-membered carbocycles and six-membered heterocycles (Scheme 13) [42].

As the authors hypothesized that bulky benzoyl and phenyl groups play a key role in the formation of the transition structure, mainly these were chosen for R^1 , R^2 and R^3 . Extending the previous scope, modification of the conditions was also employed to provide five-membered nitrogen heterocycles in poor to excellent yields. The reaction temperature was lowered to 0° and allyltrimethylsilane was used as an additive (5 eq.), as the reaction did not proceed by only using iron(III)chloride (Scheme 14).

The role of allyltrimethylsilane could not be clarified in the studies, but it is suggested that both functional groups, the trimethylsilyl and allyl group, are required for the transformation. The authors further suggested two possible roles of the additive: first, it might promote coordination of the catalyst and therefore the formation and ring opening of the oxetane intermediate, and second, it may support the separation of the aldehyde, as the bisallylated product was found as the by-product.

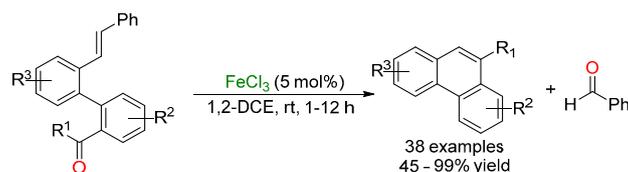


Scheme 13. General equations of the published reactions by Li.



Scheme 14. General reaction equation of published reactions employing allyltrimethylsilane.

Another example of carbonyl–olefin metathesis was reported by Schindler and co-workers in 2017, expanding the scope of FeCl_3 catalysis to polycyclic aromatic compounds (Scheme 15) [43]. This work also included the isolation of an oxetane intermediate as evidence for the cycloaddition reaction step.



Scheme 15. General equation for the synthesis of polycycles.

To get deeper insights into the reaction mechanism of the carbonyl–olefin ring-closing reaction depicted in Scheme 12, Zimmerman and Schindler cooperated to investigate by computational, kinetic and synthetic analysis the nature of the Lewis acid-catalyzed reaction (Figure 1) [44]. For the computations, ZStruct, a DFT-based program which is able to detect reaction pathways by generating a range of intermediates and calculate their thermodynamic availability, independent from bond forming and breaking, was used [45]. In the synthetic analysis, it was possible to identify acetone as a by-product in reactions with $\text{R}_3 = \text{R}_4 = \text{methyl}$ via NMR spectroscopy, which lends further support to the proposed mechanism.

To identify the role of the Lewis acid, especially Fe^{III} , to differentiate between a stepwise, cationic reaction mechanism and a concerted, non-synchronous mechanism in the formation and dissociation of the oxetane and for the determination of the turnover-limiting step, experiments like cation trapping, EPR measurements, determination of the secondary kinetic isotope effect and ZStruct calculations were carried out.

The results were summarized as follows (Figure 1): concerning Fe^{III} as catalyst, the efficiency is related to the Lewis acidity of the catalyst used, and the best results were obtained for iron(III)chloride, which binds to the carbonyls without an electron transfer event, while small impurities or usage of iron(III)chloride hydrate did not affect the yield of the metathesis reaction. It was also possible to exclude the influence of possible HCl formation on the reaction rate.

Concerning turnover limitation: the transition state, governing the turnover of the cycle, is highly ordered and displays high levels of bond reorganization energy, and *B*-SKIE analysis indicated oxetane formation as the turnover-limiting step. In this step, the π system of the aryl group stabilizes the HOMO through electron delocalization. The activation barriers of the rate-limiting step of the two

suggested mechanisms were found to be almost identical, but as cation-trapping experiments were not successful, a stepwise reaction was excluded.

Concerning dissociation mechanism: experiments gave different yield results vs. conversion for benzyl- and alkyl-substituted olefins, indicating that both mechanisms are possible, depending on the substitution pattern. Styrenyl-derived substrates seem to prefer the cationic-stepwise reaction, as they are able to delocalize the positive charge via mesomerism. In conclusion, Fe^{III} as catalyst in carbonyl–olefin metathesis provides a simple and straightforward road to versatile compounds via ring-closing metathesis.

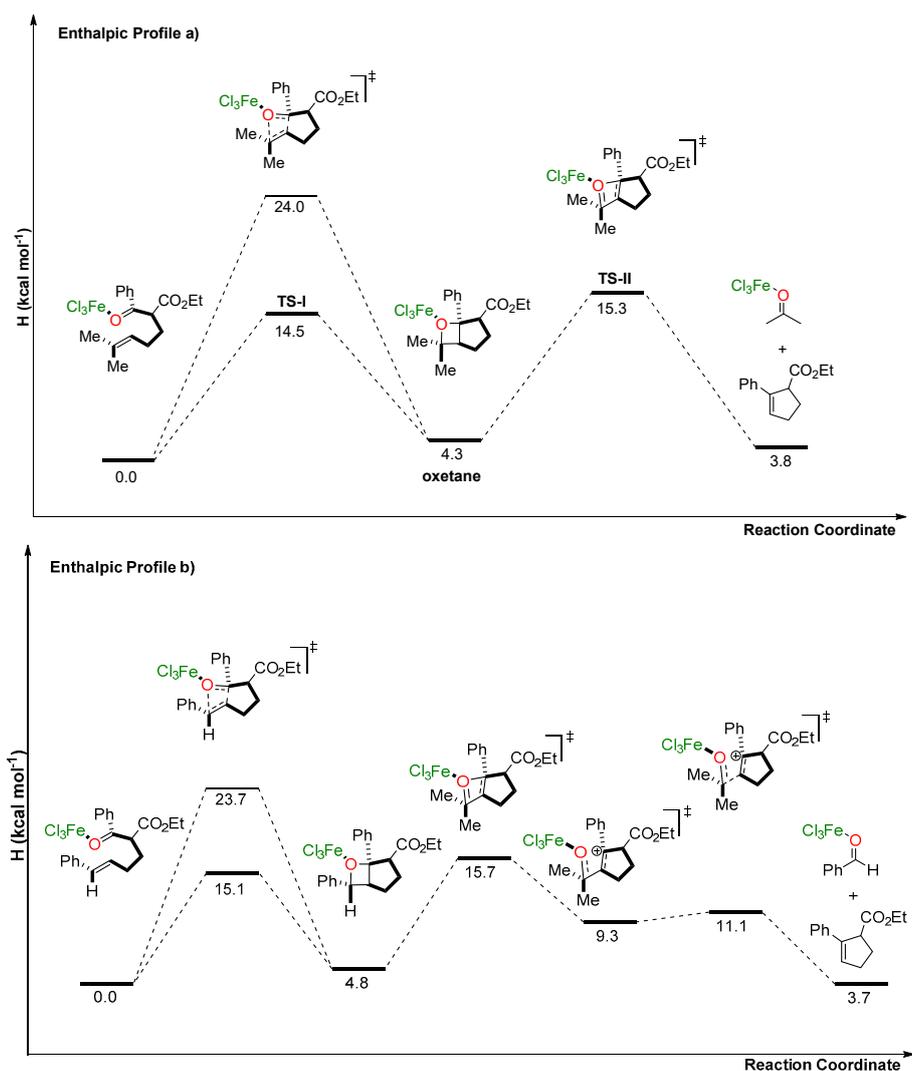
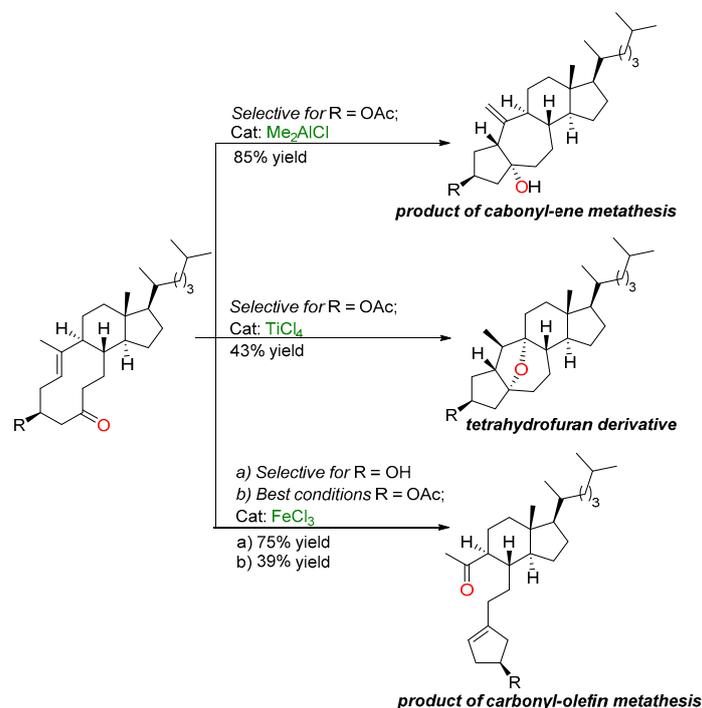


Figure 1. Reaction profiles of the two possible reaction pathways calculated by the research group of Zimmermann.

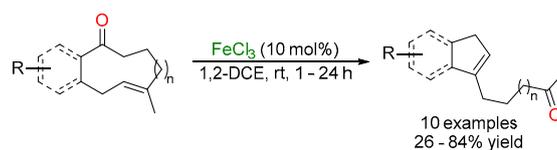
In 2019, Schindler and co-workers reported an additional type of carbonyl–olefin synthesis, which allows the manipulation of functionalized decalin derivatives [46]. These compounds can be synthesized by three-step modification of naturally occurring steroids. In contrast to previously reported carbonyl–olefin metathesis reactions, two additional side-paths occur during the reaction, which may result in carbonyl–ene metathesis product or tetrahydrofuran compounds instead of the desired product (Scheme 16), which are also interesting in their similarity to biologically active molecules. Interestingly, by changing the catalyzing Lewis acid, a selectivity towards the desired molecules can be achieved. Fe^{III} turned out to work best for the desired carbonyl–olefin metathesis

product, albeit it was not possible to suppress the formation of tetrahydrofuran derivative formation. Total selectivity can be achieved by using alcohol as R in the decalin derivatives instead of acetate.



Scheme 16. Overview of possible outcomes for the conversion of chosen decalin derivative.

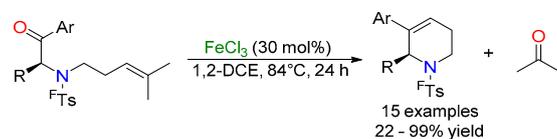
With the optimized conditions in hand, the scope of reaction was performed, which resulted in yields up to 84%; the general equation is depicted in Scheme 17. For this purpose, cyclodecenones were synthesized starting from the readily available steroids cholesterol, stigmasterol, dehydroepiandrosterone and pregnenolone.



Scheme 17. General equation for the transannular carbonyl-olefin metathesis.

Additional to experimental investigations of the mechanism, computational investigations were performed. In summary, the results suggest that the mechanism differs from the already established types: after activation of carbonyl-oxygen, two reversible transformations are possible. While the kinetic pathway yields the carbonyl-ene product (which can also be isolated at lower temperatures under otherwise standard conditions), [2 + 2]-cycloaddition can lead to the tetrahydrofuran product via elimination or yield the desired product via retro-[2 + 2]-cycloaddition.

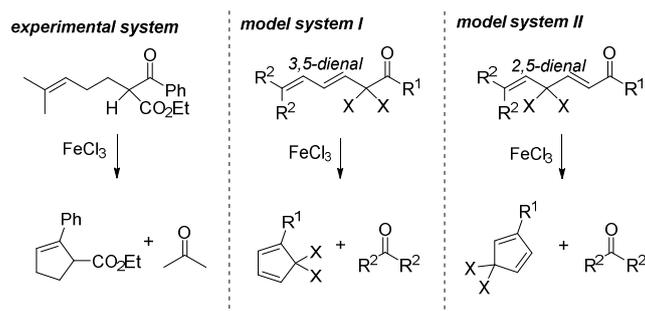
In their recent approach, the research group of Schindler focused on the synthesis of novel chiral tetrahydropyridine derivatives (Scheme 18). The precursors were synthesized via three steps, starting from commercially available amino acids.



Scheme 18. General equation for synthesis of tetrahydropyridine derivatives.

Further screening of the catalytic conditions and additional investigations indicated that the choice of the protecting group and the olefin subunit has a crucial influence on the reaction outcome. Furthermore, the deprotection of the synthesized products is straightforward: treatment with SmI_2 , H_2O and NEt_3 in THF grants facile access to the desired secondary amine. In conclusion, this method offers a simple route towards chiral tetrahydropyridines.

To expand the scope of Fe^{III} -catalyzed carbonyl–olefin reactions towards 2,5- and 3,5- hexadienals, analog to the Schindler's work (Scheme 19), Zhu and co-workers performed computational investigations to get information on how substitution patterns of those derivative may have beneficial influence on the outcome of the reaction [47].



Scheme 19. Carbonyl–olefin metathesis developed by Schindler and diene model systems investigated by Zhu and co-workers.

The results can be summarized as follows: first, electron density donating groups like methyl, as already reported in the example in Scheme 19, decrease energy of the cycloaddition barriers; second, cycloreversion barriers can be lowered by using substituents bearing an electron-donating, hyperconjugative effect (like $\text{X} = \text{SiH}_3$, Scheme 19). Additionally, the substitution for $\text{R}^1 = \text{Ar}$ is beneficial for the cycloreversion, even though it increases the cycloaddition barrier slightly (which is not considered as a major drawback by the authors). As 10 out of 33 designed systems were identified as promising candidates, this work gives strong evidence that carbonyl–olefin metathesis might be realized in future work.

3. Conclusions

Iron, one of the most abundant elements in the earth's crust, is the focus of extensive research in catalysis. Many applications employing iron in heterogeneous and homogeneous systems as a catalyst have already been realized. Among already established reactions are carbonyl–olefin and carbonyl–alkyne metathesis, which are catalyzed in solution by FeCl_3 , functioning as Lewis acid and providing a wide scope of reactions. The theoretical investigations of carbonyl–olefin metathesis reactions may give hints for the design of new procedures to even further expand the family of iron-catalyzed carbonyl–olefin metathesis reactions. By exploiting the described procedures, the synthesis of novel bioactive molecules or derivatives of already known drugs can be realized, which becomes more and more important in the light of increasing resistance towards already established pharmaceuticals.

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