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Iron(III)-Catalyzed Ring-Closing Carbonyl–Olefin Metathesis

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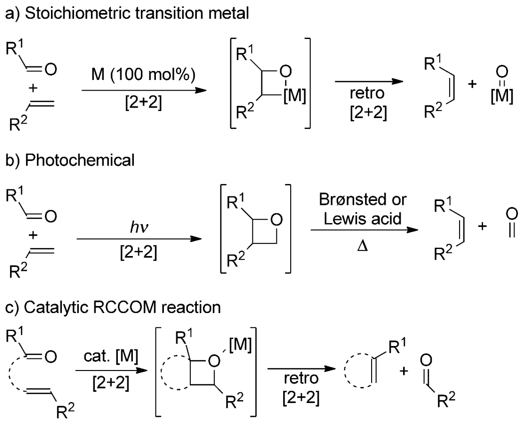
Compared to the universal recognition of catalytic olefin–olefin metathesis (e.g., ring-closing metathesis, cross-metathesis) as one of the most powerful carbon–carbon bond-forming reactions,[1] carbonyl–olefin metathesis has received hardly any attention from the chemical community. The requirement of stoichiometric amounts of transition metals with the concurrent formation of kinetically inert metal oxo species, which preclude the regeneration of the active metal catalyst, has probably been the main reason for the obscurity of the carbonyl–olefin metathesis reaction (Scheme 1 a).[2] An alternative approach, namely a photoinduced [2+2] cycloaddition, the so-called Paterno–Büchi reaction,[3] followed by a [2+2] cycloreversion, is underused owing to the relatively harsh reaction conditions needed and because of the competing polymerization reactions of the reaction partners (Scheme 1 b). Achieving mild catalytic conditions to perform carbonyl–olefin metathesis thus constitutes a significant challenge. Herein, recent efforts to develop a mild Lewis acid catalyzed ring-closing carbonyl–olefin metathesis (RCCOM) process are highlighted (Scheme 1 c).[4]



Scheme 1. Stoichiometric and catalytic carbonyl–olefin metathesis.

To address the challenge of developing an efficient catalytic RCCOM process, Schindler and co-workers envisioned the in situ formation of oxetanes as reactive intermediates (Scheme 1 c).[4] They hypothesized that metallic Lewis acids could activate the carbonyl partner to react with the olefin to form the oxetane intermediate,[5] as in a metallo-Paterno–Büchi-type reaction.[6] The corresponding oxetane intermediates are known to undergo fragmentation to the desired carbonyl–olefin metathesis products,[5] thus enabling catalyst turnover in contrast to the kinetically inert metal oxo complexes formed during stoichiometric carbonyl–olefin metathesis. An extensive search for a Lewis acid finally led to iron(III) chloride, containing an environmentally benign transition metal, as the optimal catalyst.

Aromatic β-ketoesters bearing a pendant isoprenyl group were the initial substrates used for optimizing the RCCOM reaction. Schindler and co-workers found that under the optimized mild conditions, with 5 mol% of $FeCl_3$ in DCE (0.01 M) at room temperature, aromatic β-ketoesters bearing electron-donating or electron-withdrawing substituents on any position of the ring gave rise to the corresponding carbonyl–olefin metathesis products in good to excellent yields (Scheme 2). The scope of the reaction was further analyzed by including different β-substitution patterns and functional groups, and with substrates lacking Lewis basic substituents in the β-position, substrates bearing quaternary carbon centers in the α-position in linear or cyclic motifs, and also substrates with elongated homoisoprenyl subunits (Scheme 2). In all cases, the RCCOM products were obtained in good to excellent yields.

The reaction was much more sensible to the steric (and electronic?) nature of the pendant olefin moiety. Whereas isoprenyl units afforded the corresponding cyclized products in nearly quantitative yields, substrates bearing phenyl-substituted isoprenyl units or a phenyl moiety instead of one methyl group at the terminal carbon atom as well as tetrasubstituted olefins and *trans*- and *cis*-β-substituted styrenes gave the corresponding RCCOM products in moderate to good yields (Scheme 2, not all shown).

The main features of this novel transformation are that 1) various aromatic substituents are tolerated, 2) sterically encumbered olefin moieties hamper product formation,

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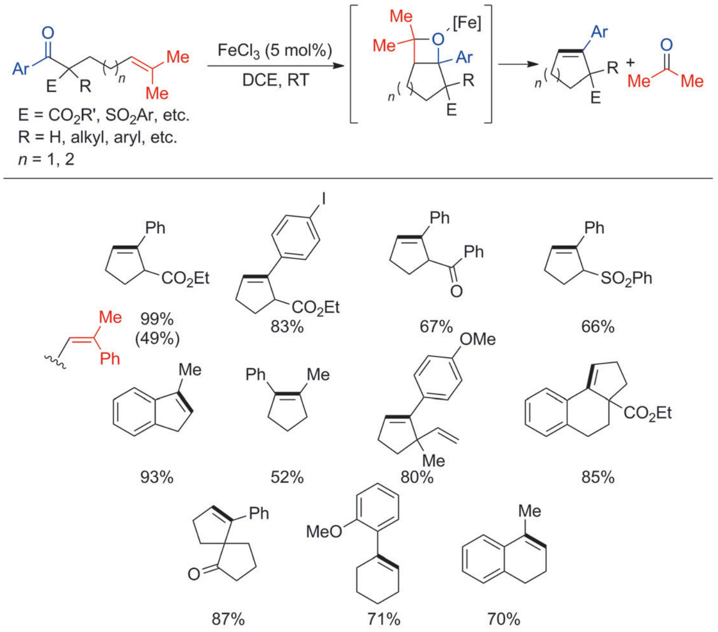
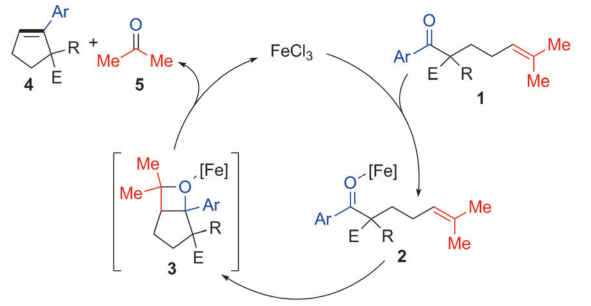


Scheme 2. Scope of the iron(III)-catalyzed RCCOM. DCE = 1,2-dichloroethane.



Scheme 3. Proposed mechanism for the iron(III)-catalyzed RCCOM.

3) metal enolates are not required to yield the products as substrates with quaternary centers are completely viable, and 4) acetone is formed as the carbonyl byproduct (observed by ^{1}H NMR spectroscopy), which supports the formation of the key oxetane intermediate.

The carbonyl–olefin metathesis reaction was proposed to be initiated by coordination of keto-olefin **1** to iron(III) chloride to form adduct **2**, which triggers two concerted events, namely [2+2] cycloaddition to give oxetane intermediate **3** followed by [2+2] cycloreversion, to give carbonyl–olefin metathesis product **4** and carbonyl byproduct **5** (Scheme 3). Negative nucleophilic trapping experiments with alcohols (MeOH, *i*PrOH) and acetic or benzoic acid seem to exclude an alternative pathway via a carbocation intermediate. The proposed concerted mechanism was further validated by computational analysis with the ZStruct method,[7] which provided accurate predictions for the activation barriers and energies of all reaction steps. Calculating the barriers of iron(III) decoordination from **5** and recoordination to aryl keto-olefin **1** might be very useful to understand the overall process.

The Lewis acid catalyzed RCCOM discovered by Schindler and co-workers constitutes a new synthetic method to access various important cycloalkenes from simple keto-olefins. We expect that this process will soon be extended to intermolecular carbonyl–olefin cross-metathesis and the synthesis of valuable heterocyclic structures and also be explored in industrial settings.

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