Published in final edited form as:

Trends Chem. 2019 May ; 1(2): 272–273. doi:10.1016/j.trechm.2019.02.011.

Lewis acid-catalyzed carbonyl-olefin metathesis

Paul S. Riehl, Corinna S. Schindler*

University of Michigan, Department of Chemistry, Willard Henry Dow Laboratory, 930 North University Ave., Ann Arbor, MI 48109, US.

Online Abstract

Catalytic carbonyl-olefin metathesis reactions enable direct carbon-carbon bond formation between carbonyl and olefin substrates relying on carbonyl-activation with a suitable Lewis acid. Based on this reaction design principle, efficient protocols for intermolecular carbonyl-olefin metathesis, as well as ring-closing and ring-opening carbonyl-olefin metathesis have been developed.

Keywords

FeCl₃; carbonyl-olefin metathesis; Lewis acid catalysis; oxetane

Origin

Routine methodologies for alkene formation rely on direct elimination, stoichiometric carbonyl-olefination, and olefin-olefin metathesis. Carbonyl-olefin metathesis (COM) represents a new, catalytic alternative for direct alkene formation from carbonyl and olefin substrates upon activation with a Lewis acid.

Reaction Mechanism

Metathesis reactions describe chemical transformations involving an exchange of parts of two substrates. Specifically, in carbonyl-olefin metathesis reactions carbonyl and alkene substrates are interchanged directly to form new carbonyl and alkene products. The Lewis acid catalyst (FeCl₃ in Figure 2) binds to the carbonyl oxygen of the substrate (1) to enable formation of an oxetane intermediate (4) via a [2+2]-cycloaddition with the alkene substrate. This step proceeds in a concerted, yet asynchronous, fashion in which the carbon-carbon bond is formed to a greater extent than the carbon-oxygen bond in the transition state (3). Subsequent asynchronous, concerted retro-[2+2]-cycloaddition (via transition state 5) results in fragmentation of the oxetane intermediate and formation of the desired alkene as metathesis product (6) and the carbonyl component and byproduct (7). Several metal- and carbocation-based Lewis acids have been shown to catalyze carbonyl-olefin metathesis reactions, however, FeCl₃ proved particularly efficient resulting in high yields of up to 99% yield without competing isomerization of the desired alkene products. Based on this design

*Correspondence: corinnas@umich.edu (C. S. Schindler).

principle, reaction protocols for intermolecular, ring-opening and ring-closing carbonyl-olefin metathesis have been developed.

Currently accessible products include aryl cyclopentenes and –hexenes, polyaromatic hydrocarbons, nitrogen containing heterocycles, aliphatic cyclopentenes, as well as functionalized styrenes. Importantly, aryl and alkyl ketone substrates undergo the desired carbonyl-olefin metathesis via distinct reaction mechanisms. Compared to aryl ketones, their aliphatic analogs bind less strongly to the Lewis acid catalyst by ~ 1 kcal/mol and lack the transition state stabilization necessary for oxetane formation. Importantly, reactions of both aryl and alkyl ketones exhibit zero-order dependence in substrate, consistent with the catalyst resting state (2) being FeCl₃ bound to carbonyl. However, aryl ketones show first-order dependence in FeCl₃ whereas alkyl ketones show second-order dependence in Lewis acid which results in distinct activation modes for the two different substrate classes. When considering aryl ketones, the catalyst resting state in which monomeric FeCl₃ is bound to substrate is sufficiently activated to undergo carbonyl-olefin metathesis. In comparison, the activation barrier for alkyl ketones is higher and requires a second equivalent of FeCl₃ to bind to form an Fe(III) singly-bridged homodimer for the reaction to proceed. This homobimetallic association of a second equivalent of FeCl₃ generates a stronger Lewis acid that functions as a “superelectrophile” that is capable of lowering the energy of the transition state to provide sufficient activation for alkyl ketone substrates.

Importance

The mechanism for Lewis acid-catalyzed carbonyl-olefin metathesis fundamentally differs from the previously established state of the art reaction protocol. Rather than requiring a full equivalent of air-sensitive molybdenum alkylidene, it is instead based on the *in-situ* formation of oxetanes as reactive intermediates via [2+2]-cycloaddition of a carbonyl and olefin upon activation with a Lewis acid catalyst. This distinct intermediate no longer limits the process to metal alkylidenes as reagents, and enables catalytic turnover relying on cheap and environmentally benign Lewis acids. As a result, this method can be applied to the scalable synthesis of various classes of useful molecular scaffolds.

Literature

- 1). Ludwig JR; Zimmerman PM; Gianino JB; Schindler CS * Iron(III)-catalyzed carbonyl-olefin metathesis. *Nature* 2016, 533, 374–379. 10.1038/nature17432 [PubMed: 27120158]
- 2). Ma L; Li W; Xi H; Bai X; Ma E; Yan X; Li Z FeCl₃-Catalyzed Ring-Closing Carbonyl–Olefin Metathesis. *Angew. Chem. Int. Ed* 2016, 55, 10410–10413. 10.1002/anie.201604349
- 3). Naidu VR; Bah J; Franzén J Direct Organocatalytic Oxo-Metathesis, a trans-Selective Carbocation-Catalyzed Olefination of Aldehydes. *Eur. J. Org. Chem* 2015, 8, 1834–1839. 10.1002/ejoc.201403651
- 4). Ludwig JR; Phan S; McAtee CC; Zimmerman PM; Devery JJ III; Schindler CS * Mechanistic Investigations of the Iron(III)-Catalyzed Carbonyl-Olefin Metathesis Reaction. *J. Am. Chem. Soc* 2017, 139, 10832–10842 10.1021/jacs.7b05641 [PubMed: 28753008]
- 5). McAtee CC; Riehl PS; Schindler CS * Polycyclic Aromatic Hydrocarbons via Iron(III)-Catalyzed Carbonyl-Olefin Metathesis. *J. Am. Chem. Soc* 2017, 139, 2960–2963. 10.1021/jacs.7b01114 [PubMed: 28221039]
- 6). Albright H; Riehl PS; McAtee CC; Reid JP; Ludwig JR; Karp L; Zimmerman PM; Sigman MS Schindler CS * Catalytic Carbonyl-Olefin Metathesis of Aliphatic Ketones: Iron(III) Homo-

Dimers as Lewis Acidic Superelectrophiles. J. Am. Chem. Soc. Just Accepted Manuscript
10.1021/jacs.8b11840

- 7). Groso EJ; Golonka AN; Harding RA; Alexander B; Sodano TM; Schindler CS * 3-Aryl-2,5-Dihydropyrroles via Catalytic Carbonyl-Olefin Metathesis. ACS Catalysis 2018, 8, 2006–2011. 10.1021/acscatal.7b03769 [PubMed: 30276008]
- 8). Albright HR; Alexander BW; Vonesh H; Schindler CS * GaCl₃-Catalyzed Ring-Opening Carbonyl-Olefin Metathesis. Org. Lett 2018, 20, 4954–4958 10.1021/acs.orglett.8b02086 [PubMed: 30052456]
- 9). Becker MR; Rykaczewski K; Ludwig JR; Schindler CS * Carbonyl-Olefin Metathesis for the Synthesis of Cyclic Olefins. Org. Synth 2018, 95, 472 10.15227/orgsyn.095.0472
- 10). Fu GC; Grubbs RH Synthesis of cycloalkenes via alkylidene-mediated olefin metathesis and carbonyl olefination. J. Am. Chem. Soc 1993, 115, 3800–3801. 10.1021/ja00062a066

Figure 1.

Figure 2.

Accessible Products

aryl cyclopentenes and -hexenes

polyaromatic hydrocarbons (PAHs)

nitrogen-containing heterocycles

aliphatic cyclopentenes

functionalized styrenes

ring-opening and intermolecular COM