

Brønsted and Lewis Acid Mediated Carbonyl Metathesis Reactions

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INTRODUCTION

Olefin metathesis reactions are some of the most powerful carbon-carbon bonding forming reactions available to chemists. Since their discovery they have garnered significant attention due to their atom efficiency, reliability, and their ability to enable unique disconnections in synthesis planning. Although less well-studied, carbonyl-olefin metathesis reactions are potentially equally empowering. Despite using more abundant and shelf-stable catalysts and easily accessible carbonyl compounds, these metathesis reactions have been underdeveloped to date.

Carbonyl-olefin metathesis (COM) reactions can follow four basic mechanisms: Paterno-Büchi type, organocatalytic, transition metal-mediated, and Lewis acid-catalyzed COM. This seminar will focus on the most well-studied method, Lewis and Brønsted acid-catalyzed carbonyl metathesis reactions.

First discovered serendipitously by Borer in 1971, oxetane intermediates could be accessed by a SnCl_4 -mediated intramolecular (2+2) cycloaddition reaction between a trisubstituted olefin and a ketone.¹ Following this work, Snider showed that the metathesis product could be obtained in 30% yield using a mixture of MeAlCl_2 and Me_2AlCl .² Since the initial discovery over forty years ago, several advances have been made to apply carbonyl metathesis reactions to more complex systems and investigate the mechanism of these reactions.

Ring Closing Carbonyl Olefin Metathesis

The Schindler group at the University of Michigan has pioneered the development of COM in modern methodology. Using iron trichloride, her group synthesized a number of different ring systems.³

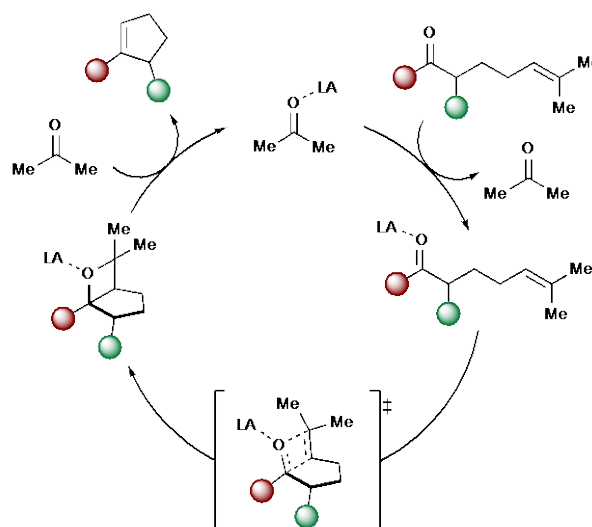


Figure 1: Mechanism of Carbonyl-Olefin Metathesis

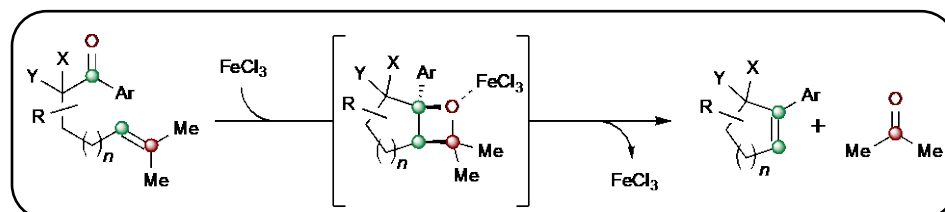


Figure 2. General Scheme for FeCl_3 Catalyzed Carbon-Olefin Metathesis

Their preliminary work relies on aryl ketones to stabilize the partial positive charge formed during the concerted, asynchronous (2+2) cycloaddition. The Schindler group also showed that alkyl ketones were competent in this reaction using Fe(III) homodimer “superelectrophiles”.⁴ Other Lewis acids like BF₃•OEt₂, tropylium or trityl tetrafluoroborate, and heterometallic electrophiles are able to affect the same transformation, although often with more restricted substrate scope and increased catalyst loadings.

Carbonyl-Olefin Cross-Metathesis

COM reactions have also been extended to cross-metathesis reactions to generate more substituted olefins from simple aldehydes and olefins. These use the same Lewis acids as the ring-closing COM, but in many cases require long reaction times or activating additives.⁵ Remarkably, all catalytic systems provided the (*E*)-isomer as the exclusive product.

Interrupted Carbonyl Olefin Metathesis

Although experiments using tethered nucleophiles to trap a plausible carbocation intermediate in FeCl₃ catalyzed COM reactions failed, indicating that the reaction goes through a concerted cycloaddition and cycloreversion, using tethered nucleophiles in TfOH-catalyzed COM systems provided the trapped product, generating substituted tetrahydrofluorenes in a single step.⁶

Summary and Outlook

Carbonyl metathesis reactions are still an underdeveloped area of chemistry, often relying on use of strong Lewis acid catalysts and aryl ketones or aldehydes. Due to these constraints, many functional groups are not tolerated under the reaction conditions, and the products generated are often not synthetically useful. However, the potential advantages of using cheap, earth-abundant metals and readily available ketones or aldehydes as starting materials justifies more investigation into expanding these reaction manifolds to more complex settings. In the future, heterometallic Lewis acid pairs will likely further expand the scope of these reactions to less-activated ketones and aldehydes and better control over Lewis acid strength may allow for the incorporation of previously incompatible functional groups.

References

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