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Organometallic Chemistry: A New Metathesis

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Abstract

Carbonyls and alkenes, two of the most common functional groups in organic chemistry, generally do not react with one another. Now, a simple Lewis acid has been shown to catalyse metathesis between alkenes and ketones in a new carbonyl olefination reaction.

Students in introductory chemistry courses are taught that two of the most important reactions in organic chemistry are the addition of nucleophiles to carbonyl compounds and the addition of electrophiles to alkenes. Yet those students would almost certainly be marked off if they proposed an addition of an alkene to an aldehyde or ketone: they should know that alkenes are simply not nucleophilic enough to add to a typical carbonyl. Indeed, many natural and unnatural compounds possess both functional groups, and some very important reactions — such as hydroformylations, Diels-Alder reactions, and radical polymerizations — involve transformations of alkenes in the presence of carbonyl compounds. All of which makes a recent report by Schindler and co-workers¹ particularly intriguing, as it describes the facile reaction between alkenes and ketones catalysed by a mild and inexpensive Lewis acid. This surprising result challenges our understanding of the interactions between these most fundamental of functional groups, and suggests there is potential for other new reactions to be discovered.

It must be noted that there are a small number of well-known transformations, including the Prins² and carbonyl-ene³ reactions, and photochemical [2+2] cycloadditions⁴, in which alkenes do react directly with carbonyl compounds. However, these reactions generally require strong activation of the carbonyl partner via chemical or physical means. Now, Schindler and the team show that the simple metal chloride salt FeCl₃ catalyses an intramolecular carbonyl-olefin metathesis reaction, in which a ketone and an alkene residing within the same molecule undergo an exchange to form a new cyclic alkene and a new ketone. This transformation is highly reminiscent of the well-known olefin metathesis reaction, which involves exchange of two alkenes and, in fact, traditional metal alkylidene olefin metathesis catalysts have been known to promote carbonyl-olefin metathesis⁵; however, the metal-oxo generated upon fragmentation of the metallacycle intermediate is observed to be a thermodynamic sink, preventing catalyst turnover (Figure 1, Path A).

To avoid this problem Schindler and co-workers took a new approach to metal-catalysed metathesis that invokes the formation of an oxetane rather than a metallacycle intermediate. While oxetanes can be generated from carbonyls and alkenes via photochemical methods⁴ (Figure 1, Path B), the authors sought catalysts that can promote both oxetane formation and fragmentation in a single reaction sequence (Figure 1, Path C). Given the reactivity

paradigms for alkenes and ketones, one could easily expect such an approach would not be viable. Indeed, a number of the acids screened resulted in no reaction (e.g. FeCl_2 , ZnCl_2 , HCl), olefin hydrochlorination (e.g. AlCl_3), or alkylation products (e.g. SnCl_4 , TiCl_4). But the very common Lewis acids FeCl_3 , ScOTf_3 and $\text{BF}_3 \cdot \text{OEt}_2$ were found to catalyse the metathesis pathway with impressive efficiency. It appears that a fine balance between Lewis acidity and oxophilicity is required in order to induce ketone activation without engaging in deleterious side reactions.

Isolated prior examples of Lewis and Brønsted acids promoting the alkenylation of aldehydes⁶ and ketones⁷ do exist. These systems, however, are limited in scope and require either exotic acids or super-stoichiometric quantities of the promoter. In contrast, the FeCl_3 -catalyzed reaction displays remarkable breadth and practicality. The FeCl_3 -catalyzed reactions are generally carried out at room temperature with 5 mol% of FeCl_3 to afford products in good-to-excellent yields. The transformation is applicable to the synthesis of both five- and six-membered rings with a variety of substitution patterns and functional groups. While the carbonyl component is currently limited to aryl ketones, both electron-rich and electron-poor aryl ketones can be successfully reacted.

Schindler and co-workers advance two limiting mechanisms for the reaction, each of which proceeds through an FeCl_3 -bound oxetane intermediate. The first option features stepwise addition of alkene to the Lewis acid-bound ketone via a carbocationic intermediate, and finds analogy in the mechanistic scenarios offered in previous reports of aldehyde and ketone olefination^{6,7}. The second option involves a $[2 + 2]$ cycloaddition followed by a $[2 + 2]$ cycloreversion, and bears closer resemblance to the classical olefin metathesis mechanism. A combination of substrate probes and computations led the authors to favour the $[2 + 2]$ mechanism⁸. The proposed concerted mechanism accounts for the impressive chemoselectivity observed in the reaction; cationic intermediates could give rise to a wealth of side products via elimination or rearrangement pathways — which were not observed.

Orbital symmetry rules dictate that thermal, concerted $[2 + 2]$ cycloadditions are forbidden unless they proceed in an antarafacial manner⁹. While precedent exists for Fe-catalysed $[2 + 2]$ cycloadditions¹⁰, both an Fe(I/III) redox-cycle and a redox-active ligand have been invoked to account for this reactivity. Continued investigation into the details of the carbonyl-olefin metathesis reaction will be worthwhile, especially if it broadens our understanding of cycloaddition mechanisms.

The work of Schindler and co-workers raises several questions on the synthetic side as well. Will this transformation be amenable to an intermolecular analog? Can the catalyst be modified such that the activation of aliphatic ketones is possible, thus extending the range of products beyond styrenyl derivatives? Regardless, as the first widely applicable and operationally simple catalytic method for the conversion of an unsaturated ketone to a new cyclic alkene, this work is an important advance in carbonyl-olefin metathesis chemistry. More broadly, it expands our fundamental notions of the reactivity and compatibility of ketones with alkenes.

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Figure 1.

Approaches for the carbonyl-olefin metathesis reaction. Path A depicts an intermolecular reaction between an aldehyde and olefin using stoichiometric amounts of an olefin metathesis catalyst. Path B depicts an intermolecular, two-step reaction sequence. First, a [2 + 2] photocycloaddition to generate an oxetane intermediate, followed by an acid promoted thermolysis. Path C outlines a Lewis-acid catalysed ring closing metathesis reaction, which proceeds through an in situ generated oxetane intermediate.