Angewandte Highlights

Synthetic Methods

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Organocatalyzed Carbonyl–Olefin Metathesis

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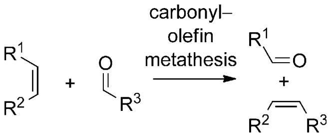
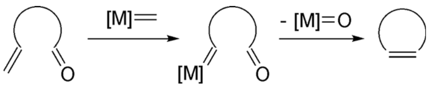
The metathesis of double-bond functional groups has long been utilized by chemists for the synthesis of complex molecules. For example, the Wittig olefination between aldehydes/ketones and phosphorus ylides,[1] as well as alkene metathesis,[2] are well known and representative classes. In contrast, metathesis between an alkene and a carbonyl group (Scheme 1) has so far been a less general strategy for synthesis.[3] This lack of generality and utility is due to the fact that for decades, methods for carbonyl–olefin metathesis mainly required either photochemical promotion,[4] stoichiometric amounts of transition-metal reagents,[5] or substrates prone to cationic cyclization.[6] For example, two decades ago, Fu and Grubbs elegantly showed that sequential olefin metathesis/carbonyl olefination via molybdenum alkylidenes can effect an overall carbonyl–olefin metathesis, but the reaction requires stoichiometric amounts of the molybdenum reagent because of the typically strong metal–oxo bonds (Scheme 2).[7] Currently, transition-metal approaches are still stoichiometric in nature. Thus, a big breakthrough in the field would be the development of a catalytic, thermally allowed (versus photochemical), and operationally simple method, which could be more widely adopted by the synthetic community.

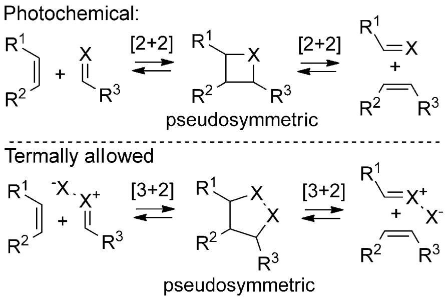


Scheme 1. Carbonyl–olefin metathesis.

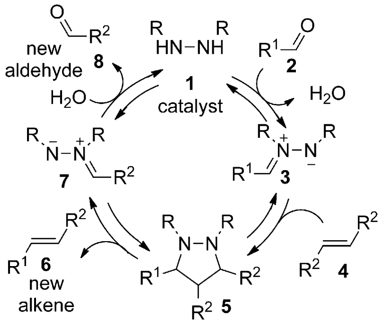


Scheme 2. Transition-metal approach.

This highlight describes an important contribution made by Lambert et al. on a catalytic and operationally simple carbonyl–olefin metathesis.[8] The Lambert group elegantly achieved this by moving away from the traditional and symmetry-forbidden [2+2] cycloaddition/cycloreversion strategy,[9] towards a thermally allowed [3+2] pathway (Scheme 3). Their strategy, using azomethine imine 1,3-dipolar cycloadditions,[10] utilizes the hydrazine **1**[11] as a catalyst to form the azomethine imine **3** (Scheme 4). [3+2] cycloaddition with the olefin substrate **4** should produce cycloadduct **5** which gives the new olefin **6** upon cycloreversion, and final hydrolysis of **7** produces the new aldehyde **8** as well as regeneration of **1**.



Scheme 3. The [2+2] versus [3+2] strategies.



Scheme 4. Catalytic design of hydrazine catalyzed carbonyl–olefin metathesis.

As a proof-of-concept, the cyclopropenes[12] **9** were chosen as the alkene substrate, as it was reasoned that the relief of ring strain would favor the forward reaction (Scheme 5). After screening a range of hydrazines, the bicyclic hydrazine HCl salt **10**[13] was found to be by far the most active catalyst. The authors note that both the bicyclic structure and the HCl salt are necessary for the high performance of **10**. Thus, using

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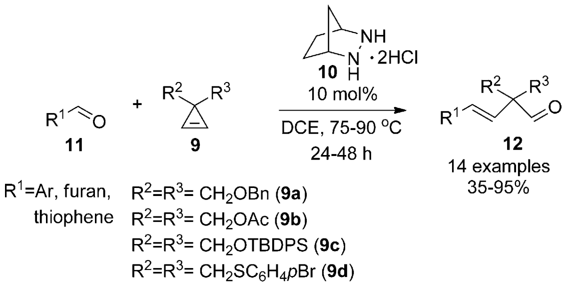
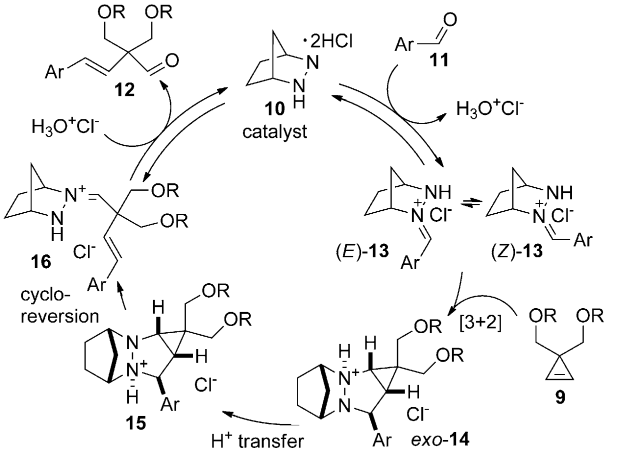


Scheme 5. Substrate scope of carbonyl–olefin metathesis using the hydrazine **10**. TBDPS = *tert*-butyldiphenylsilyl.



Scheme 6. Proposed mechanism.

the simple hydrazine catalyst **10**, the carbonyl–olefin metathesis was demonstrated for a range of aryl and heterocyclic aldehydes (**11**) in generally good to excellent yields (Scheme 5).

An inverse correlation between the electron-rich character of **11** and the yields of the isolated products was reported, and was presumed to be due to the sensitivity of the electron-rich products to decomposition. In contrast, electron-poor aldehydes (**11**) work well but are noticeably slower, which is consistent with the electron demand in 1,3-dipolar cycloadditions.[10] Aliphatic aldehydes do not work as well in the carbonyl–olefin metathesis, producing many unidentified side products. In terms of the cyclopropene scope, symmetrical substrates with O linkages (**9a**–**9c**) and S linkage (**9d**) were reported to react well. It is not clear if the heteroatom linkages facilitate the reaction as no other substituents were reported. Nevertheless, there appears to be plenty of potential regarding the scope with respect to the cyclopropene, for example, if $R^2 \neq R^3$ in **9**, then there is the possibility of asymmetric desymmetrization to form all-carbon quaternary centers.

The proposed mechanism for the organocatalyzed carbonyl–olefin metathesis is shown in Scheme 6. Catalyst **10** reacts with **11** to give the hydrazonium ion **13**, which is thought to undergo [3+2] cycloaddition to give *exo*-**14**. Proton transfer followed by ring-strain-relieving cycloreversion produces **16**, which upon hydrolysis furnishes the product **12** with concomitant regeneration of **10**. It is thought that the excellent *E* selectivity of the products **12** originates from the cycloaddition of (*E*)-**13** via an *exo* transition state (versus (*Z*)-**13** via an *exo* transition state), which is favored by 3,3-disubstituted cyclopropenes because of the minimization of steric congestion.

In support of their mechanistic rationale, the stable perchlorate salt version of the putative intermediate **13**[14] was prepared and reacted with **9a**. Not only was the expected carbonyl–olefin metathesis product **12** formed, the perchlorate version of hydrozonium intermediate **16** was also observed by ^{1}H NMR analysis, thus lending further support to the proposed mechanism.

In conclusion, a catalytic carbonyl–olefin metathesis, using thermally allowed, classic pericyclic reactions is described. The reaction is operationally simple and utilizes the simple organocatalyst **10**. It thus constitutes an important development in a field which previously predominantly relied on stoichiometric transition-metal or photochemical strategies. However, as with all proof-of-concept work, more work needs to be carried out before the methodology can be considered general. The biggest limitation at the moment is the generality of the olefin substrate: only highly strained cyclopropenes have been used. Thus, additional developments on the scope with respect to the alkene substrate of this elegant proof-of-concept study are highly anticipated, as it will truly demonstrate the potential of carbonyl–olefin metathesis as a useful synthetic tool. The seminal contribution by Lambert et al. highlighted herein will surely be a starting point for new developments in this field.

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