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Organocatalytic Carbonyl-Olefin Metathesis

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Supporting Information

ABSTRACT: The development of a catalytic carbonyl-olefin metathesis strategy is reported, in the context of the ring-opening metathesis of cyclopropenes with aldehydes using a simple hydrazine catalyst. The key to this reaction is a conceptual blueprint for metathesis chemistry that forgoes the traditional reliance on [2 + 2] cycloaddition modes in favor of a [3 + 2] paradigm.

Chemical reactions that effect the metathesis of double-bonded functional groups have had a revolutionary impact on how chemists approach the synthesis of complex molecules. The most widely used representatives of this class of transformation include the Wittig olefination of aldehydes and ketones with phosphorus ylides,[1] and olefin metathesis with transition metal alkylidenes[2] (Figure 1). In contrast, to the best

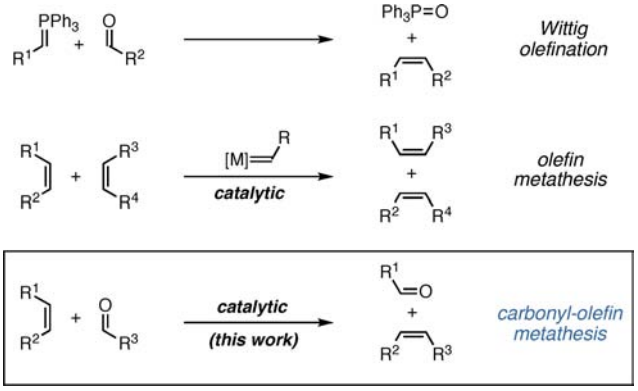

Figure 1. Double bond metathesis reactions, including the Wittig olefination, olefin metathesis, and carbonyl-olefin metathesis.

of our knowledge there currently exists no general catalytic strategy for the metathesis of olefins and carbonyls,[3] despite the extraordinary potential utility of such a process and significant efforts toward its development dating back many decades.[4−7] Toward this end, we report herein a catalytic platform for carbonyl-olefin metathesis that employs thermally allowed cycloaddition reactions and simple hydrazine-based catalysts.

While there have been isolated reports of carbonyl-olefin metathesis by various strategies, these reactions have required photochemical promotion, stoichiometric amounts of transition metal reagents, or substrates prone to cationic cyclization. Attempts to extend established metal-mediated carbonyl-olefin metathesis strategies to the development of a catalytic process have been unsuccessful due to the difficulties in achieving turnover of what are typically strong metal-oxo bonds.[4] Alternative strategies have been envisioned involving the direct metathesis of carbonyl and olefin partners, although here again success has been limited.[5] Thus while [2 + 2] cycloadditions between carbonyls and olefins (Paterno−Büchi reaction) are well-known,[8] these symmetry-forbidden reactions are typically only achievable photochemically, which thus limits the generality and practicality of this approach. Finally, there have been isolated reports of Brønsted[6] and Lewis acid[7] promoted carbonyl-olefin metathesis, but only with substrates that are predisposed to undergo stepwise [2 + 2] cycloadditions/cycloreversions. Thus the identification of a carbonyl-olefin metathesis strategy that is general, operationally simple, and catalytically mediated by a structurally well-defined and tunable catalyst remains a prominent goal.[9]

In this regard, we have devised a strategy to achieve carbonyl-olefin metathesis that relies on an orthogonal mechanistic paradigm for metathesis chemistry. Specifically, we recognized that rather than relying on the [2 + 2] cycloaddition/cycloreversion strategy upon which established double bond metathesis chemistries are based (Figure 2A),[10] a [3 + 2] manifold could instead be employed (Figure 2B), given a few basic requirements. Thus such a process would require simply that (1) there exist a facile pathway for the conversion of one of the double bonded components to and from a reactive partner for the [3 + 2] cycloaddition and (2) the intermediate cycloadducts possess sufficient pseudosymmetry such that an orthogonal cycloreversion[11]—that is to form metathesis products rather than starting materials—would be feasible. Importantly, such a process would rely on thermally allowed pericyclic reactions rather than highly strained and symmetry-forbidden [2 + 2] manifolds. With this conceptual blueprint in mind, we hypothesized that these design requirements could be readily met by application of the azomethine imine 1,3-dipolar cycloaddition reaction.[12,13]

Our proposed organocatalytic carbonyl-olefin metathesis design entails the use of a symmetric 1,2-dialkylhydrazine[14] catalyst **1**, which can readily engage an aldehyde **2** via condensation to form an azomethine imine **3** reactive intermediate (Figure 2C). Cycloaddition of **3** with an olefin substrate **4** would produce a pyrazolidine cycloadduct **5** possessing the pseudosymmetry called for by our mechanistic design. Upon orthogonal cycloreversion of cycloadduct **5**, product olefin **6** and a new azomethine imine **7** would be produced.[15] Hydrolysis of **7** would then liberate the product aldehyde **8** and regenerate the hydrazine catalyst **1**.

To test the validity of this proposal, we selected readily available cyclopropene substrate **9**, which we reasoned would

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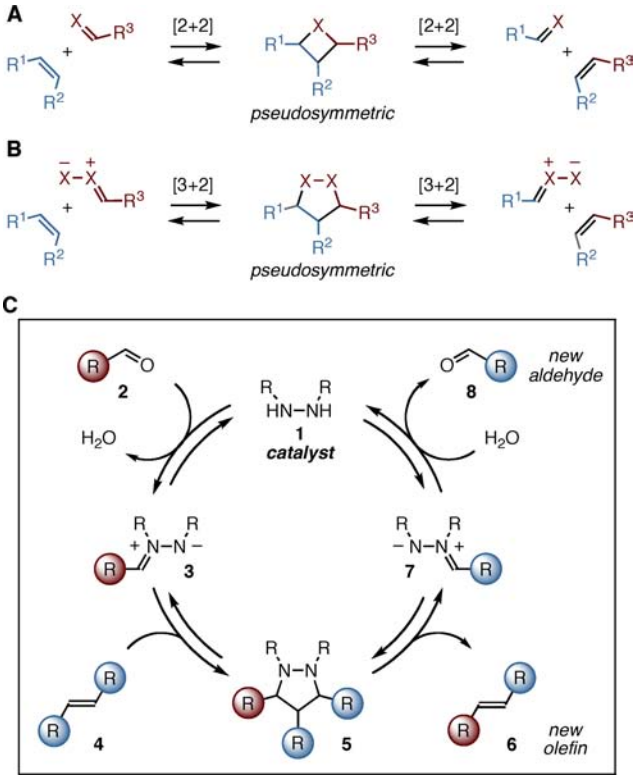
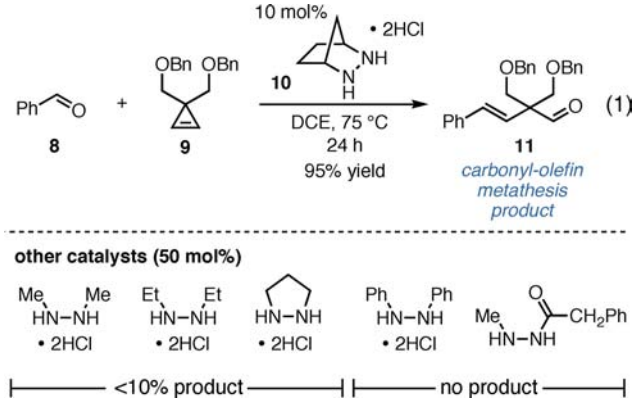


Figure 2. (A) Traditional [2 + 2] metathesis paradigm. (B) [3 + 2] metathesis paradigm. (C) Catalytic design of a hydrazine catalyzed carbonyl-olefin metathesis reaction based on azomethine imine 1,3-dipolar cycloadditions.

help to favor the forward reaction and increase the rate of the cycloreversion step due to relief of ring strain[16,17] (eq 1). In the



event, we identified the bicyclic hydrazine[18] **10**•2HCl as a productive catalyst for this transformation. As shown, **10**•2HCl readily effects carbonyl-olefin metathesis of cyclopropene **9** with benzaldehyde (**8**), delivering the desired product **11** in 95% yield (^{1}H NMR analysis, 80% yield of corresponding alcohol after $NaBH_4$ reduction)[19] over 24 h at 75 °C in DCE as a single observable olefin isomer. Importantly, benzaldehyde (**8**) and cyclopropene **9** do not undergo any reaction in the absence of catalyst **10** or in the presence of only HCl or trialkylammonium chlorides.

Notably, the bis HCl salt of hydrazine **10** was significantly more effective than either the mono salt or the free base. For example, in the reaction of cyclopropene **9** with benzaldehyde (**8**) using 50 mol % catalyst, **10**•2HCl produced the product **11** in 60% yield after 6 h, while **10**•HCl and **10** (free base) produced only 35% and 15% yields respectively.[20] The role of the acid cocatalyst is not known at this time.

As opposed to the high efficiency of the catalyst **10**•2HCl, we found that the use of 50 mol % of 1,2-dimethylhydrazine, 1,2-diethylhydrazine, or pyrazolidine dihydrochlorides resulted in the generation of less than 10% of aldehyde **11** under the optimized conditions (eq 1). Neither 1,2-diphenylhydrazine dihydrochloride nor *N*′-methyl phenylacetic hydrazide effected this transformation to any observable extent. Clearly the bicyclic structure of **10** plays a key role in the high performance of this hydrazine catalyst.

Our substrate scope studies for this protocol have revealed a tolerance of a variety of aryl aldehydes and other functionality (Table 1). In addition to benzaldehyde (entry 1), we have demonstrated that **10**•2HCl catalyzes carbonyl-olefin metathesis of cyclopropene **9** with a range of other substrates, including alkyl- (entries 2 and 3) and oxygen-substituted (entry 4) benzaldehydes. In general, there appears to be an inverse correlation between the electron-rich character of the aldehyde and the yield of isolated metathesis product, which we believe is due to the sensitivity of the electron-rich styrenyl products to decomposition. Substrates bearing electron-withdrawing functionality such as *p*-nitro (entry 5) and *m*-bromo (entry 6) substituents are also viable. The rate of conversion with these substrates is noticeably slower than with less electron-deficient substrates, which is consistent with the idea that the HOMO of the azomethine imine fragment is engaged in typical electron demand 1,3-dipolar cycloadditions.[13] Products derived from naphthaldehydes (entries 7 and 8) and heteroaryl aldehydes such as furfural (entry 9) are also readily accommodated in this process. Notably, the use of thiophenecarboxyaldehyde resulted in clean production of the corresponding metathesis product (entry 10), although the yield was only modest due to the sensitive nature of the vinylthiophene functionality. In addition to aryl aldehydes, we found that carbonyl-olefin metathesis with an aliphatic aldehyde such as hydrocinnamaldehyde could be observed as well (entry 11); however the desired product was accompanied by significant amounts of unidentified side products. Given the propensity for aliphatic aldehydes to participate in a variety of amine-catalyzed transformations, this finding is not surprising.

In terms of variation of the cyclopropene reaction partner, we have found that other useful *O*-linkages including acetoxy and *tert*-butyldiphenylsiloxy groups are well tolerated (entries 12 and 13). Soft heteroatom substituents such as thioethers, which can be problematic with certain metal-based metathesis catalysts due to catalyst poisoning,[21] were also found to be compatible with this organocatalytic reaction (entry 14).

A detailed mechanistic rationale for this metathesis process is depicted in Figure 3. Given that catalyst **10** is used as its dihydrochloride salt, we assume that the reaction proceeds via hydrazonium ion **12**, the protonated form of the putative azomethine imine.[14,22] We propose that cycloaddition of **12** with cyclopropene **9** produces pyrazolidinium salt **13**[23] although such intermediates have not been observed. It is plausible that cycloaddition and not cycloreversion is the rate-determining step in this transformation due to the high strain of the three-membered ring. Conversion of **13** to **14** by proton transfer would then facilitate strain-relieving cycloreversion to produce hydrazonium ion **15**. Upon hydrolysis of **15**, the metathesis aldehyde **11** would be produced with concomitant regeneration of hydrazine catalyst **10**.

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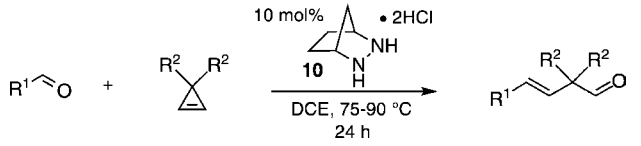
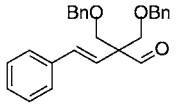
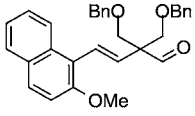
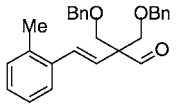
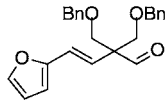
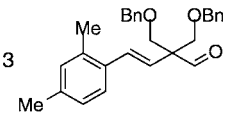
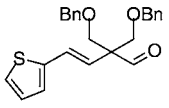
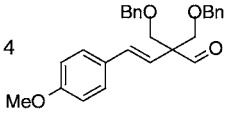
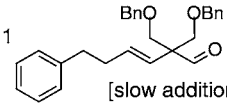
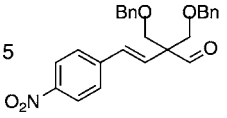
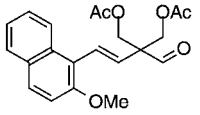
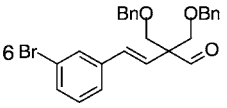
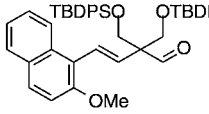
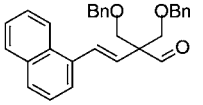
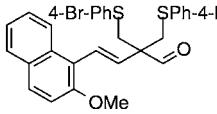
Table 1. Survey of the Substrate Scope for Ring Opening Carbonyl-Olefin Metathesis of Cyclopropenes with Aldehydes Catalyzed by Hydrazine 10•2HCl[a]



entry	product	% yield	entry	product	% yield
1		95 (80)	8		68 [6 h]
2		85	9		80
3		66	10		35
4		50	11		35 [slow addition 48 h]
5		60 [48 h]	12		68
6		75 (60) [48 h]	13		79
7		67	14		50

[a]Percent yields are based on isolated and purified material, except entries 1, 6, and 11, in which yields were determined by ^{1}H NMR versus mesitylene as an internal standard. The numbers in parentheses are yields of the corresponding alcohol products obtained after reduction with $NaBH_4$.

The complete (*E*)-olefin selectivity observed in these reactions can be rationalized by invoking cycloaddition of hydrazonium (*E*)-**12** via an *exo* transition state, which is known to be favored for 3,3-disubstituted cyclopropenes due to the minimization of steric congestion.[24] Although hydrazonium (*Z*)-**12** is the thermodynamically favored isomer (see below), geometric isomerization of this functional group is known to occur readily.[25] The alternative cycloaddition of (*Z*)-**12** (via the *exo* transition state) to produce *epi*-**13** is expected to be disfavored due to a significant destabilizing interaction between the phenyl substituent and a benzyloxymethyl group on the cyclopropene **9**. In addition, assuming the cycloreversion step is concerted, this alternative pathway would lead to formation of the product (*Z*)-**11**, which has not been observed.

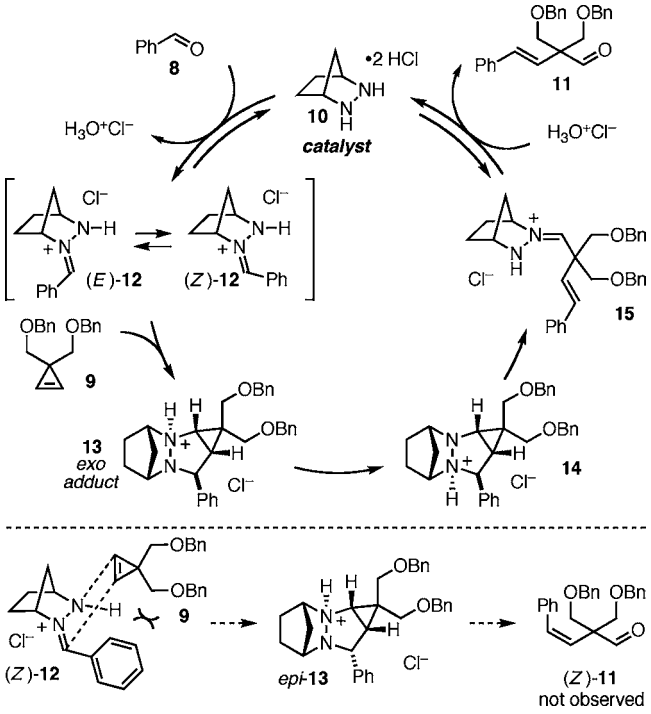
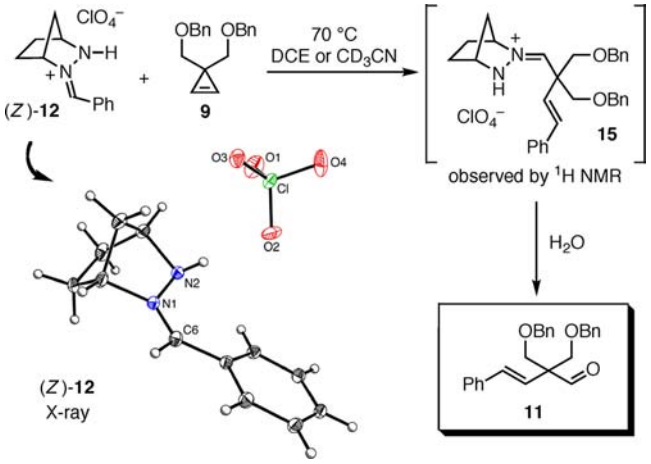


Figure 3. Mechanistic rationale for catalytic carbonyl-olefin metathesis using hydrazine **10**.

Scheme 1. Evidence in Support of Proposed Mechanism



In support of the proposed mechanism, we have prepared the known hydrazonium perchlorate (*Z*)-**12**,[22,26] a stable and crystalline solid, which corresponds to the putative intermediate of our catalytic reaction with benzaldehyde (Scheme 1). Heating equimolar amounts of hydrazonium **12** and cyclopropene **9** in DCE at 70 °C for 6 h resulted in the production, after aqueous workup, of the metathesis product **11** in 40% yield along with some oligomeric product. This stoichiometric process was also observed by ^{1}H NMR (CD_3CN), whereby peaks corresponding to the putative hydrazonium product **15** were identified. Furthermore, ^{1}H NMR observation of the catalytic reaction shown in Scheme 1 revealed the steady state presence (~5%) of hydrazonium **12**. Thus the fact that hydrazonium **12** effects the metathesis reaction and is demonstrably present during the catalytic reaction provides strong evidence that this process occurs in the manner we propose.

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In summary, a catalytic platform for carbonyl-olefin metathesis has been developed that utilizes simple organic catalysts and classic pericyclic reactions. With the current procedure, less-strained olefins such as norbornene or stilbene have not been observed to undergo methathesis. However, the development of catalysts that facilitate the cycloreversion step of this mechanistic design is expected to enable the extension of this process to a broader array of substrates. Such efforts are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and product characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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