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Brønsted Acid-Catalyzed Carbonyl-Olefin Metathesis inside a Self-Assembled Supramolecular Host

Lorenzo Catti[a] and Konrad Tiefenbacher*[a,b]

Abstract: Carbonyl-olefin metathesis represents a powerful, yet underdeveloped, method for the formation of carbon-carbon bonds. So far, no Brønsted acid-based protocol for the catalytic carbonyl-olefin metathesis has been described in the literature. Herein, a cocatalytic system based on a simple Brønsted acid (HCl) and a self-assembled supramolecular host is presented. The developed system compares well with the current benchmark catalyst for carbonyl-olefin metathesis in terms of substrate scope and isolated product yield. The control experiments performed provide strong evidence that the reaction proceeds inside the cavity of the supramolecular host. A mechanistic probe indicates that a stepwise reaction mechanism is likely.

Catalytic *olefin* metathesis is regarded as one of the most powerful methods of carbon-carbon bond formation and has led to significant advances in both academic and industrial synthesis.[1] The related *carbonyl-olefin* metathesis has received significantly less attention, despite its undisputable potential, mainly due to the difficulty to establish a catalytic process. Although olefin metathesis catalysts can also promote the carbonyl-olefin metathesis,[2] turnover is prevented by the formation of a kinetically inert metal-oxo complex during the cycloreversion step (Figure 1a). Most protocols described depend on stoichiometric amounts of Lewis acid.[3] In 2012, the Lambert group disclosed an organocatalyzed ring-opening carbonyl-olefin metathesis.[4] Although being a significant contribution, the method is limited to cyclopropene derivatives as olefinic components. In addition, a Lewis acid-catalyzed intermolecular carbonyl-olefin metathesis was reported by Franzén *et al.* using 20 mol% of trityl tetrafluoroborate.[5] The reaction requires, however, a fivefold excess of the carbonyl component and is restricted in terms of substrate scope. Finally, in 2016, a breakthrough in carbonyl-olefin metathesis was accomplished by Schindler and coworkers utilizing catalytic amounts of FeCl₃.[6] The developed method displays a relatively broad substrate scope, mild reaction conditions and operational simplicity.[6-7] Shortly after, a similar approach was described by the Li group for the construction of carbo- and heterocyclic alkenes.[8] Both methods proceed via a [2+2] cycloreversion of an *in situ* formed

oxetane intermediate (Figure 1b). It is noteworthy that the Schindler group performed a systematic study to exclude that the reaction is catalyzed by HCl-traces, which might be formed by hydrolysis of FeCl₃. Even with 100 mol% of HCl, no conversion of the employed substrate was observed.[9]

Figure 1. Carbonyl-olefin metathesis. a) Stoichiometric in transition metal. b) Catalyzed by FeCl₃. c) This work: catalyzed by HCl in the presence of a supramolecular host.
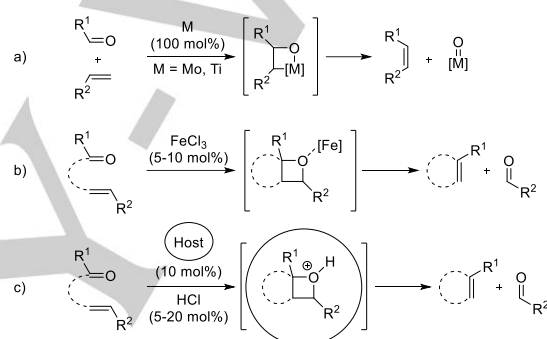

Supramolecular host systems are increasingly investigated regarding their ability to facilitate reactions difficult to perform in bulk solution.[10] The resorcin[4]arene hexamer **I** represents one of the most investigated supramolecular host systems (Figure 2).[11] It spontaneously self-assembles via hydrogen bonding in apolar solvents like chloroform from eight water molecules and six resorcin[4]arene units **1**,[12] which are easily prepared in multigram scale in a single step. Hexamer **I** is believed to be capable of stabilizing cationic transition states via cation-π interactions with the aromatic cavity walls.[12f] Recently we demonstrated that host **I** forms a cocatalytic system with the Brønsted acid HCl to catalyze the tail-to-head terpene cyclization,[13] a reaction that is difficult to perform in bulk solution.[14] In addition, Scarso and Strukul demonstrated that hexamer **I** and HBF₄ work in a synergistic fashion to catalyze the hydration of aryl alkynes.[15] The ability of hexamer **I** to facilitate challenging reactions involving Brønsted acids prompted us to investigate the catalytic activity of the hexamer **I**/HCl system in the carbonyl-olefin metathesis.

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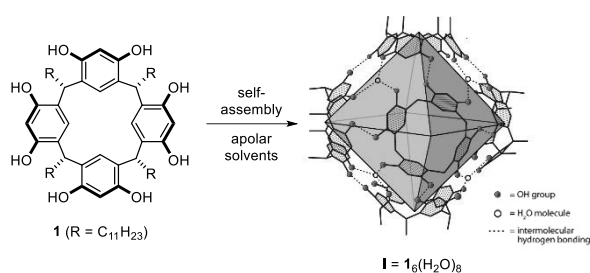
Figure 2. Self-assembly of building block **1** into hexameric host **I**.

As a model reaction, the carbonyl-olefin metathesis of β-ketoester **2** (Table 1) was investigated, based on previous studies by Schindler and coworkers.[6] In initial experiments, substrate **2** was treated with 10 mol% of hexamer **I** and 10 mol% of HCl in chloroform at 50 °C. GC analysis indicated complete conversion of the starting material after 2 days. Subsequent isolation of product species **3** confirmed the capability of the hexamer **I**/HCl system to catalyze the carbonyl-olefin metathesis. Importantly, successful conversion was only observed in the presence of both catalytic components (see below). Based on an optimization of the HCl content (Supporting Information (SI) chapter 5), a combination of 10 mol% of hexamer **I** and 5 mol% of HCl (Table 1, entry 1) was chosen as the standard condition for the subsequent investigations. In the absence of HCl, no conversion of substrate **2** was observed under otherwise identical conditions (Table 1, entry 2). Furthermore, no conversion of substrate **2** was observed in the absence of hexamer **I** (Table 1, entry 3). This demonstrates that a synergistic interplay between the supramolecular host and the Brønsted acid is required for catalytic activity.

Next, a series of control experiments were performed, which confirmed that the reaction only takes place inside the cavity of hexamer **I** (SI chapter 8). For example, when the cavity was blocked by addition of a strong binding ammonium guest, the conversion of substrate **2** dropped to 6% after 4 days. Additionally, when a mixture of differently sized β-ketoesters was subjected to the reaction conditions, a significantly faster conversion of the smaller substrate was detected, due to its more efficient encapsulation. In contrast, when the same experiment was performed with FeCl$_3$, no size selectivity was observed.

We next set out to compare the performance of this supramolecular catalytic system with the current benchmark catalyst FeCl$_3$ in terms of substrate scope and product yield (Table 2). The α-methylstyryl substrate **4** was converted in good yield, although at a slower reaction rate. We next investigated β-ketoamide **5**, which gave cyclopentene **6** in 87% yield after 43 hours. It is noteworthy that amide **5** required stoichiometric amounts of FeCl$_3$ for full conversion, due to its increased Lewis basicity. Conversion of β-ketoesters with electron-rich arene subunits (**7**, **9**, **11**) gave the corresponding cyclopentene derivatives (**8**, **10**, **12**) in good to excellent yields. However, in the case of an electron-donating substituent in the *para*-position, protonation of the formed double bond was favored, resulting in a mixture of alkene isomers. Isomerization of the newly formed double bond was also occasionally observed by Schindler and coworkers in their studies utilizing FeCl$_3$.[6] In accordance with the literature, the corresponding electron-poor chloroarene **13** proved reluctant to undergo the metathesis reaction and additional HCl was required to achieve a reasonable reaction time. The δ,ε-unsaturated ketones **15**, **17** and **19** were converted cleanly to the corresponding cyclopentenes (entries 8-10). Interestingly, the obtained yields marked a significant improvement over the values reported in the literature. Also, more rigid substrates like **21** and **23** were accommodated readily inside the large cavity of hexamer **I**, yielding the corresponding polycyclic aromatic hydrocarbons **22** and **24** in good to excellent yields. The successful conversion of substrate **25** furthermore demonstrated that, as previously observed with substrate **15**, bis-substitution in the α-position is tolerated well by the catalytic system and that the method is suitable to access structurally more complex motifs like spirolactone **26**. Additionally, substrate **27** proved that the cocatalytic system also provides access to cyclohexenes like **28**. Although FeCl$_3$ performs better with some of the substrates, Table 2 clearly demonstrates that the cocatalytic system provides a valuable alternative for the majority of the investigated substrates. Unfortunately, preliminary attempts to catalyze the *inter*molecular carbonyl-olefin metathesis between benzaldehyde and acyclic alkenes remained unsuccessful.

Table 1. Control experiments using the optimized conditions.

Entry	Hexamer **I** (mol%)	HCl (mol%)	MeOH (mol%)	nBu$_4$N$^+$Br$^-$ (mol%)	Conversion (4 d, 50 °C)
1	10	5	-	-	100
2	10	-	-	-	0[a]
3	-	5	-	-	0
4	10	5	-	15	6
5	10	5	9000	-	0

[a] After 3.5 d

Table 2. Scope of the hexamer **I**/HCl-catalyzed carbonyl-olefin metathesis.[a]

Entry	Substrate	Product	Ratio of DB isomers[b]	Yield[c]
1	**2** (R^1= OEt; R^2= Me)	**3** (R^1= OEt)	1:0	91% (FeCl$_3$: 99%)
2	**4** (R^1= OEt; R^2= Ph)	**3** (R^1= OEt)	8.9:1	71% (FeCl$_3$: 49%)
3	**5** (R^1 = NHPh; R^2 = Me)	**6** (R^1 = NHPh)	1:0	87% (FeCl$_3$: 57%)
4	**7**	**8**	1:0	91% (FeCl$_3$: 64%)
5	**9** (R^1= H; R^2=R^3= OMe)	**10** (R^1= H; R^2=R^3= OMe)	1.2:1 (2:1)	87% (FeCl$_3$: 99%)
6	**11** (R^1=R^2= OMe; R^3= OEt)	**12** (R^1=R^2= OMe; R^3= OEt)	3.4:1	76% (FeCl$_3$: 66%)
7	**13** (R^1= Cl; R^2= H; R^3= OEt)	**14** (R^1= Cl; R^2= H, R^3= OEt)	1:0	40% (FeCl$_3$: 52%)
8	**15**	**16**	1:0	90% (FeCl$_3$: 44%)
9	**17** (R= H)	**18** (R= H)	7.5:1	78% (FeCl$_3$: 43%)
10	**19** (R= OMe)	**20** (R= OMe)	0:1	79% (FeCl$_3$: 59%)
11	**21** (R= Me)	**22** (R= Me)	1:0	98% (FeCl$_3$: 99%)
12	**23** (R= H)	**24** (R= H)	1:0	71% (FeCl$_3$: 75%)
13	**25**	**26**	1:0	95% (FeCl$_3$: 87%)
14	**27**	**28**	2.2:1 (2.5:1)	62% (FeCl$_3$: 71%)

[a] Reaction conditions: substrate (100 mol%), hexamer **I** (10 mol%), HCl (5 mol%), CHCl$_3$, 50 °C, 1-8 d (exceptions: **4**: 10 mol% HCl, 17 d; **13**: 20 mol% HCl, 15 d); [b] GC/NMR-based ratio between the depicted double bond (DB) isomer and the tetrasubstituted (trisubstituted for **27**) double bond isomer (values in brackets refer to the FeCl$_3$ experiment)[7-8]; [c] Yield of the isolated product (values in brackets refer to the FeCl$_3$ experiment).[7-8]

Intrigued by the seemingly contradictory reports on the mechanism of the oxetane formation by the groups of Schindler and Li,[8-9] we decided to investigate the mechanism that applies to the hexamer **I**/HCl system, by employing the mechanistic probe

29 (Scheme 1) (SI chapter 7). It was expected that, in the case of a stepwise mechanism, the formation of a six-membered cyclic ether should be kinetically favored over the oxetane formation. Indeed, when probe **29** was subjected to the standard reaction conditions, heterocycle **31** was isolated as the sole reaction product, providing strong evidence for a stepwise oxetane formation, also favored by Li and coworkers. It is noteworthy that the strong evidence for a concerted, asynchronous oxetane formation, provided by the Schindler group, was based on studies with 1,3-dicarbonyl compounds. In contrast, the herein presented evidence and the evidence by the Li group were obtained from δ,ε-unsaturated aryl ketones. It appears likely that the mechanism of the oxetane formation depends on the employed substrate type. The reported influence of the olefin substitution pattern on the mechanism of the oxetane fragmentation step further corroborates this hypothesis.[9] This assumption might also explain the improved yields for substrates **15**, **17** and **19** with hexamer **I**/HCl, as the aromatic cavity has been demonstrated to provide an excellent medium for cationic cascade reactions.[13-14, 16]
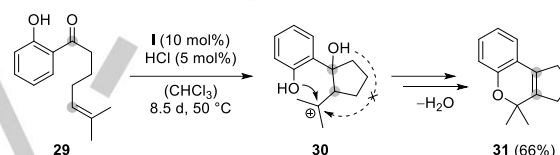
Scheme 1. Evidence for a stepwise oxetane formation.

In summary, it has been demonstrated that the presence of a supramolecular host enables for the first time a general protocol for Brønsted acid-catalyzed carbonyl-olefin metathesis. The control experiments performed clearly show that the supramolecular host and the Brønsted acid work in a synergistic fashion to catalyze the metathesis reaction and that the reaction proceeds inside the cavity of the host structure. The developed catalytic system provides comparable or even better yields than the current Lewis acid benchmark catalyst. Superior performance is especially observed with substrates bearing Lewis basic functionalities and δ,ε-unsaturated aryl ketones. Additionally, a mechanistic probe was shown to undergo stepwise oxetane formation under the optimized conditions. These results further highlight the increasing applicability of supramolecular catalysts for challenging organic transformations.

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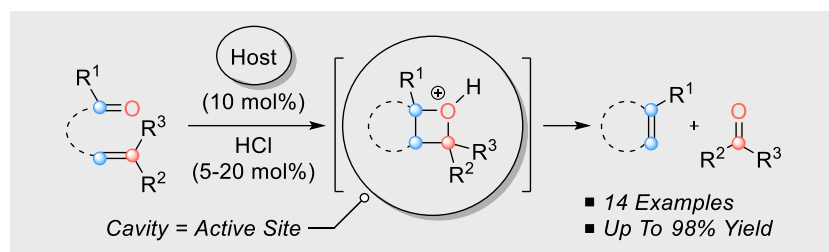
Lorenzo Catti and Konrad Tiefenbacher*

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Brønsted Acid-Catalyzed Carbonyl-Olefin Metathesis inside a Self-Assembled Supramolecular Host

■ *14 Examples*
■ *Up To 98% Yield*

Metathesis inside a host: A supramolecular host enables a general protocol for Brønsted acid-catalyzed carbonyl-olefin metathesis for the first time. A synergistic interplay between the host and the Brønsted acid is required for catalytic activity. The developed system provides comparable or even better yields than the current Lewis acid benchmark catalyst. A mechanistic study furthermore indicates a stepwise oxetane formation for some of the employed substrates.