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Carbocation catalysed ring closing aldehyde–olefin metathesis†

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A highly efficient aldehyde–olefin metathesis catalysed by the carbocation, 4-phenylphenyl-diphenylmethylium ion, has been developed. This protocol is characterized by high yields, low catalyst loading (down to 2 mol%), good functional group compatibility and mild reaction conditions.

In contradiction to the well established transition metal catalysed alkene–alkene metathesis,[1] the direct catalytic carbonyl–olefin metathesis is vastly underdeveloped despite its great potential with respect to atom economy and substrate scope. In the forefront of current research, a series of successful iron(III)-catalysed ring closing ketone–olefin metathesis strategies have been reported.[2–6] However, the catalytic aldehyde–olefin metathesis still remains elusive.[7] As one of the few exceptions, Lambert *et al.* reported the first aldehyde–olefin metathesis, where they showed that a bicyclic hydrazine derivate could catalyse the ring opening metathesis of cyclopropene derivatives and aldehydes (Scheme 1, equiv. (a)).[8] Unfortunately, this work was limited to cyclopropene derivatives as the olefinic component. Our group reported intermolecular aldehyde–olefin metathesis by carbocation catalysis as an extension of the earlier report by Bickelhaupt (Scheme 1, equiv. (b)).[9–11] Although an important proof of concept, from the synthetic point of view, this protocol suffered from high catalyst loading and a rather limited substrate scope. The main problem associated with aldehyde–olefin metathesis is mainly due to the decomposition of both the starting materials and the products in the presence of the Lewis acid catalysts required for the reaction. Schindler *et al.* reported a few specific examples of intramolecular aldehyde–olefin metathesis in the formation of highly stable polycyclic aromatic compounds (Scheme 1, equiv. (c)).[3b]

Here we show that 4-phenylphenyl-diphenylmethylium tetra-fluoroborate efficiently catalyses the intramolecular aldehyde–olefin metathesis of enals under mild reaction conditions and

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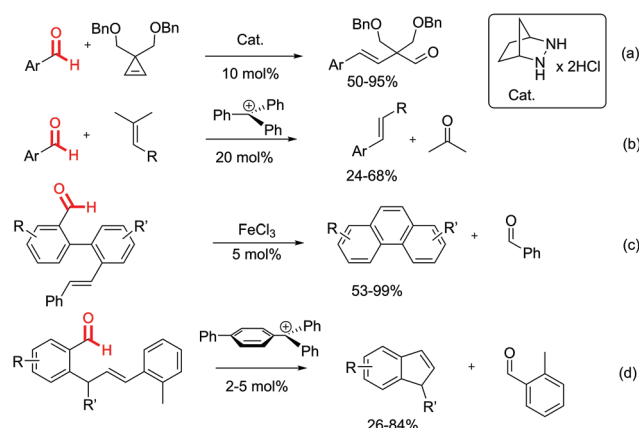
Scheme 1 Strategies toward aldehyde–olefin metathesis.

low catalyst loading with high yields (Scheme 1, equiv. (d)). It is shown that the substituents on the olefin moiety as well as the carbocation Lewis acidity are of crucial importance for minimizing starting material and product decomposition.

The general mechanism for the Lewis acid mediated metathesis is proposed to involve Lewis acid (LA) induced LUMO activation of enal **A** through initial formation of oxonium ion **B** (Scheme 2). The latter is now activated toward nucleophilic attack from the pendant alkene moiety resulting in the formation of oxetane **C**. The formation of oxetane **C** can occur either through a stepwise [2+2] mechanism involving a carbocationic
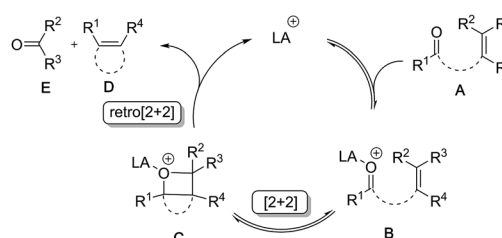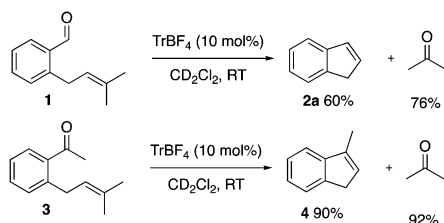

Scheme 2 Overview of the Lewis acid catalysed ring-closing metathesis.

Scheme 3 Comparison of aldehyde–olefin and ketone–olefin metatheses.

intermediate, or through a concerted [2+2] cycloaddition. Recent mechanistic studies by Schindler *et al.* for FeCl$_3$ catalysed ketone–olefin metathesis show strong support for a Lewis acid induced concerted, asynchronous [2+2]-cycloaddition.[3c] A subsequent fragmentation of oxetane **C**, either a stepwise or concerted retro-[2+2] cycloaddition, leads to the formation of the cycloalkene adduct **D** and the carbonyl by-product **E**.

In line with our previous work[9,11a–e] and inspired by the elegant work of Schindler[3] and Li,[4] we sought to overcome the difficulties associated with the catalytic aldehyde–olefin metathesis and turned our attention towards the trityl ion catalysed ring closing metathesis of enal **1**. After extensive optimization, the best yield of indene **2a** was 60% after full conversion of **1a** in only 5 minutes (Scheme 3). This indicates that enal **1** decomposes or undergoes side reactions in the presence of TrBF$_4$. Furthermore, as outlined in the mechanistic proposal of the carbonyl–olefin metathesis (see Scheme 2), the metathesis adduct **D** and a new carbonyl compound **E** are formed in a 1 : 1 ratio. Thus, a comparison of the yield of **2a** with the yield of the formed acetone (60% and 76%, respectively) indicates that product **2a** decomposes under these reaction conditions, most likely through Lewis acid initiated polymerization. In comparison, the metathesis of the corresponding ketone **3** under the same reaction conditions gave a very high yield, almost the same as that of **4** and acetone, indicating minor decomposition/side reactions of starting material **1b** and negligible trityl ion induced decomposition of methyl-indene **4** (Scheme 3).

Inspired by Li's work[4] we instead investigated the trityl ion catalysed ring closing metathesis of enals. Gratifyingly, indene **2a** and benzaldehyde **6a** were obtained in 71% and 86% yields, respectively (Table 1, entry 1). Surprisingly, FeCl$_3$, which was successfully used for intramolecular ketone–olefin metathesis both by Schindler and Li,[3,4] rapidly consumed enal **5** without any observable formation of indene **2a** (Table 1, entry 2). However, the formation of benzaldehyde **6a** in 74% yield shows that the metathesis do occur although indene **2a** rapidly decomposes in the presence of FeCl$_3$. The same outcome was observed for InCl$_3$, BF$_3$·Et$_2$O and HBF$_4$·Et$_2$O that gave benzaldehyde **6a** in high yields and with low or no observable formation of indene **2a** (Table 1, entries 3–5). AlCl$_3$ was the least efficient catalyst with only 36% conversion and 3% yield (Table 1, entry 6).[12]

In order to gain further insight into the metathesis process, in terms of reactivity and Lewis acid induced decomposition, we turned our attention to the styryl moiety. Decreasing the electron density/nucleophilicity through an electron withdrawing *para*-nitro group (enal **7**) completely stopped both enal

Table 1 Optimization of Lewis acid catalysed aldehyde–olefin ring closing metathesis[a]

		Yield[b] (%)		
Entry	Catalyst	**5**	**2a**	**6a**
1	TrBF$_4$	0	71	86
2	FeCl$_3$	0	0	74
3	InCl$_3$	0	14	78
4	BF$_3$·Et$_2$O	0	20	100
5	HBF$_4$·Et$_2$O	0	0	83
6	AlCl$_3$	64	3	17

[a] Reaction conditions: TrBF$_4$ was added to **5a** in DCM (0.01 M) for 4 hours at room temperature. [b] Yields were determined by ^{1}H NMR spectroscopy.

Table 2 Evaluation of the influence of olefin substitution and carbocation Lewis acidity on aldehyde–olefin metathesis[a]

					Yield[b] (%)		
Entry	S. M.	R	Catalyst	t (h)	S. M.	**2a**	**6**
1	**7**	*p*-NO$_2$	TrBF$_4$	2.5	100	0	0
2	**8**	*p*-MeO	TrBF$_4$	5 min	0	22	26
3	*9a*	*o*-Me	*TrBF$_4$*	*40 min*	*0*	*75*	*84*
4	**10**	*p*-Me	TrBF$_4$	15 min	0	60	74
5	**9a**	*o*-Me	**Cat A**	29	8	17	78
6	**9a**	*o*-Me	**Cat B**	4	0	76	85
7	**9a**	*o*-Me	**Cat C**	3	0	80	86
8^c	*9a*	*o*-Me	*Cat C*	*8*	*0*	*80*	*86*

[a] Reaction conditions: TrBF$_4$ (10 mol%) was added to **7–10** in DCM (0.01 M) for the indicated time at room temperature. [b] Yields were determined by ^{1}H NMR spectroscopy. [c] 5 mol% of **Cat C** was used.

decomposition and metathesis and only starting materials could be recovered (Table 2, entry 1). In contrast, increasing the electron density/nucleophilicity of the alkene by introducing an electron donating *para*-methoxy-group greatly accelerated the decomposition of enal **8** in the presence of TrBF$_4$, enabling full conversion in only 5 minutes with a low yield of indene **2a** (Table 2, entry 2). Additional tuning of the electronic properties of the alkene moiety revealed that the weak electron donating groups *o*-methyl **9a** and *p*-methyl **10** shorten the reaction time, leading to a somewhat reduced product decomposition and only a minor increased enal decomposition (Table 2, entries 3 and 4). Among the latter, *o*-methyl substituted enal **9a** was the most efficient, affording indene **2a** in 75% yield (Table 2, entry 3).[13]
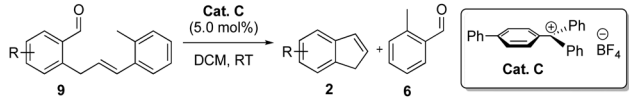
After identifying the *o*-tolyl-group in enal **9a** as the best alkene-leaving group, we investigated the influence of carbocation Lewis acidity on the aldehyde–olefin metathesis. The trityl

ion constitutes a rather unique mode of carbon-centered Lewis acidity with extensive possibilities for relatively easy tuning through variation of the electronic properties of the surrounding aromatic groups.[11a–e,14] The trityl ions **Cat A–C** were screened as catalysts for the metathesis of enal **9a**. The mono-methoxy substituted trityl ion, **Cat A**, is the least Lewis acidic carbocation screened, due to the strong electron donating properties of the *p*-methoxy-phenyl group to the carbocationic center. Unfortunately, the lower Lewis acidity of **Cat A** resulted in a drastically prolonged reaction time and low yield of indene **2a** and did not prevent starting material/product decomposition (Table 2, entry 5). The mono-methyl substituted trityl ion, **Cat B**, is a considerably stronger Lewis acid compared to **Cat A** although it is less Lewis acidic compared to TrBF$_4$ and gave full conversion after 4 h (Table 2, entry 6). Interestingly, despite the increased reaction time, the yield was virtually the same as for TrBF$_4$, indicating that product decomposition was considerably slower with **Cat B** (Table 2, entry 6). However, after extensive screening, we found that with the mono-*p*-phenyl substituted trityl ion, **Cat C**, the yield of indene **2a** could be increased up to 80% within 3 h (Table 2, entry 7). Notably, reducing the catalyst loading to only 5 mol% prolonged the reaction time to 8 h without any loss in the yield (Table 2, entry 8). Thus, the *p*-phenyl substituted trityl ion, **Cat C**, almost completely diminished product decomposition, giving essentially the same yields of metathesis adduct **2a** and 2-methylbenzaldehyde **6**.

With these optimal conditions in hand (**Cat C** (5 mol%), DCM, RT), the aldehyde–olefin metathesis of enal **9a** gave indene **2a** in 81% isolated yield (Table 3, entry 1). Introducing a methyl-substituent in the 5-position of enal **9b** gave the corresponding 7-methyl-indene **2b** in 71% yield (Table 3, entry 2). In contrast, the 3-methyl-group in enal **9c** greatly accelerated the metathesis and afforded 7-methyl-indene **2c** in 78% yield within 30 minutes of reaction time (Table 3, entry 3). The increased reactivity is most likely a result of 1,3-allylic strain induced by the 3-methyl-group that locks the conformation with the olefin side chain in closer proximity to the aldehyde moiety.

The 5-methoxy-substituted enal **9d** also had an accelerating effect on the metathesis and gave 5-methoxy-indene **2d** in 68% isolated yield (Table 3, entry 4). In contrast, the 4-methyl-group in enal **9e** and the 2-benzyloxy-group in **9f** gave the corresponding indenes **2e** and **2f** in low yields (Table 3, entries 5 and 6). This is most likely due to the increased product decomposition as a result of the higher reactivity of 6-methyl-indene **2e** and 4-benzyloxy-indene **2f** caused by the electron donating properties of the methyl- and benzyloxy-groups in the *para*- and *ortho*-positions, respectively, to the indene double bond. Different halogenated enals were also screened and fluorinated enals **9g–i** gave indenes **2g–i** in good yields. However, the 5-chloro-substituent in enal **9j** had a negative effect on the metathesis and 5-chloro-indene **2j** was isolated in 45% yield.

We next evaluated functionalization at the benzylic position of enals **11** that would allow for easy access to 1-functionalized indenes **12** (Table 4). To our delight, functionalization at this position had a remarkable effect on the reactivity and for the **Cat C** catalysed metathesis of enals **11a–h**, the catalyst loading could be reduced down to 2.0 mol% without any loss in the efficiency. Under these conditions, the corresponding products **12a–h** were isolated in 78–84% yields within less then one hour. This drastic increase in the reactivity is most likely due to the Thorpe–Ingold effect favouring cyclization. However, the 3-benzyloxypropyl functionalized enal **11i** reacted considerably slower and required 5 mol% catalyst loading to give indene **12i** in 80% yield. The terminal alkene moiety in enal **11j** had a negative influence on the metathesis with an increased reaction time and side reactions to give **12j** in only 37% yield.

In conclusion, we have developed a direct organocatalytic aldehyde–olefin ring closing metathesis. The reaction is operationally simple and enables direct coupling of aldehydes and pendant olefins in the presence of the easily available 4-phenyl-phenyl-diphenylmethylium ion as the Lewis acid catalyst. The catalyst loadings can be reduced as low as 2 mol% and the

Table 3 Substrate scope of carbocation catalysed aldehyde–olefin ring closing metathesis[a]

Entry	S. M.	R	Product	*t* (h)	Yield[b] (%)
1	**9a**	H	**2a**	8	81
2	**9b**	5-Methyl	**2b**	4	71
3	**9c**	3-Methyl	**2c**	0.5	78
4	**9d**	5-Methoxyl	**2d**	0.75	68
5	**9e**	4-Methyl	**2e**	6	40
6	**9f**	2-BnO	**2f**	1.75	26
7	**9g**	4-Fluro	**2g**	4	80
8	**9h**	6-Fluro	**2h**	0.5	60
9	**9i**	4,5-Difluro	**2i**	4	73
10	**9j**	5-Chloro	**2j**	5	45

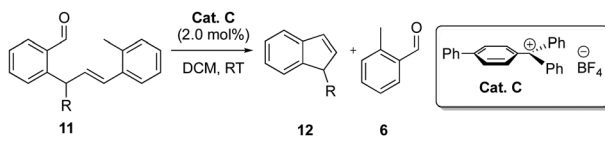[a] Reaction conditions: **Cat C** (5 mol%) was added to **9** in DCM (0.01 M) for the indicated time at room temperature. [b] Isolated yield.

Table 4 Substrate scope of carbocation catalysed aldehyde–olefin ring closing metathesis[a]

Entry	S. M.	R	Product	*t* (h)	Yield[b] (%)
1	**11a**	Me	**12a**	0.5	78
2	**11b**	*n*-Butyl	**12b**	1	83
3	**11c**	Cyclopentyl	**12c**	0.5	84
4	**11d**	Phenylethyl	**12d**	1	84
5	**11e**	Phenylpropyl	**12e**	0.75	80
6	**11f**	3-Chlorophenylethyl	**12f**	1	83
7	**11g**	2-Fluorophenylethyl	**12g**	1	81
8	**11h**	4-Methylphenylethyl	**12h**	1	81
9[c]	**11i**	3-Benzyloxypropyl	**12i**	1	80
10[c]	**11j**	3-Butenyl	**12j**	4	37

[a] Reaction conditions: **Cat C** (2 mol%) was added to **11** in DCM (0.01 M) for the indicated time at RT. [b] Isolated yield. [c] 5 mol% catalyst loading was used.

products are isolated in good yields, often in a very clean and selective manner. With the developed procedure, a variety of functionalized indene derivatives could be easily prepared. This protocol represents a rare example of a catalytic aldehyde–olefin metathesis and efforts to extend this process to a broader array of substrates are currently on going in our laboratory. These results will be reported in due course.

Conflicts of interest

The authors confirm the absence of conflicts of interest.

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