Flow Chemistry

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Intermolecular Carbonyl–olefin Metathesis with Vinyl Ethers Catalyzed by Homogeneous and Solid Acids in Flow

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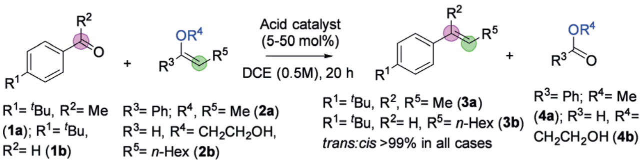
Abstract: *The carbonyl–olefin metathesis reaction has experienced significant advances in the last seven years with new catalysts and reaction protocols. However, most of these procedures involve soluble catalysts for intramolecular reactions in batch. Herein, we show that recoverable, inexpensive, easy to handle, non-toxic, and widely available simple solid acids, such as the aluminosilicate montmorillonite, can catalyze the intermolecular carbonyl–olefin metathesis of aromatic ketones and aldehydes with vinyl ethers in-flow, to give alkenes with complete trans stereoselectivity on multi-gram scale and high yields. Experimental and computational data support a mechanism based on a carbocation-induced Grob fragmentation. These results open the way for the industrial implementation of carbonyl–olefin metathesis over solid catalysts in continuous mode, which is still the origin and main application of the parent alkene–alkene cross-metathesis.*

The direct transformation of carbonyl compounds into alkenes is now moving from stoichiometric and waste-generating Wittig-type protocols to more efficient catalytic processes.[1] Among them, the carbonyl–olefin metathesis reaction stands out by the availability and low price of the starting materials, redox neutrality, and simplicity of retrosynthetic disconnections, akin to parent alkene cross-metathesis.[2] However, in contrast to the latter, only one solid precursor has apparently been reported for the carbonyl–olefin metathesis,[3,4] with just two substrates in 15–30 % yields.[5] The lack of solid catalysts for the carbonyl olefin metathesis comes from the extreme acidity required for the catalyst to increase the reaction rate towards the final carbonyl/alkene products, that is, the pK_a of soluble acids employed so far is well below 0, particularly those involving intermolecular reactions.[6,7] Thus, it is difficult to think of a conventional solid with the level of acidity required for the transformation which does not concomitantly triggers other, more favorable, acid catalyzed reactions such as the aldol, alkene, and Prins couplings.[8] To circumvent these drawbacks, we envisaged the use of vinyl ethers as alkene partners in the intermolecular carbonyl–olefin metathesis, since the generation of unreactive esters instead of competing aldehyde/ketone as by-products may shift the equilibrium towards the products, facilitate the catalytic action not only of metal salts, but also of simple solids acids, and enable an easy purification of the alkene products by column chromatography (Supporting Information, Figure S1).[9]

Table 1 shows selected catalytic results for the metathesis reaction between aromatic ketones and aldehydes **1a**,**b** with vinyl ethers **2a**,**b**, where different Lewis acids ($FeCl_3$, $BF_3{\cdot}OEt_2$) and Brönsted acids (HOTf) give significant yields of *trans* alkenes **3a**,**b** at room temperature (entries 1–7, no *cis* alkenes detected by gas chromatography, GC; see also Tables S1–S3 and Figures S2,S3 in the Supporting Information). Notice that these metal salts are well-known active

Table 1: Selected results of the catalyst screening for the carbonyl–olefin metathesis of ketones **1a** or aldehyde **1b** with vinyl ethers **2a**,**b** (1.5 equiv.) in batch (see complete screening in the Supporting Information). Yields reported for isolated products after complete consumption of **2a**,**b** or 20 h reaction time.



Entry	Catalyst (mol %)	T [°C]	Carbonyl/vinyl ether	Product (% yield)
1[a]	$FeCl_3$ (50)	25	**1a/2a**	**3a** (51)
2		25	**1b/2b**	**3b** (24)
3		60	**1b/2b**	**3b** (25)
4	$BF_3{\cdot}OEt_2$ (50)	25	**1a/2a**	**3a** (56)
5		25	**1b/2b**	**3b** (64)
6	HOTf (50)	25	**1a/2a**	**3a** (45)
7	HOTf (10)	25	**1b/2b**	**3b** (56)
8	Nafion™ (50)	60	**1b/2b**	**3b** (58)
9	Amberlyst A15 (50)	60	**1b/2b**	**3b** (38)
10	Zeolite HUSY (50)	60	**1b/2b**	**3b** (6)
11		100	**1b/2b**	**3b** (38)
12	MCM-41 (50)	60	**1b/2b**	**3b** (16)
13	Montmorillonite K10 (50)	60	**1b/2b**	**3b** (45)
14		100	**1b/2b**	**3b** (65)
15[b]	Montmorillonite K10 (5)	100	**1b/2b**	**3b** (87)

[a] No reaction with anhydrous $FeCl_3$. [b] In-flow reaction: **1b** in toluene 0.5 M, 0.01 mL min^{-1} over 8 h at 120 °C (see Figure 1 for a 40 h reaction time experiment).

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catalysts for intramolecular carbonyl olefin metathesis but not for intermolecular reactions.[10]

A freshly open sample of anhydrous $FeCl_3$, used in a glovebox, did not catalyze the metathesis reaction. However, when 50 mol% of water were added, the metathesis reaction started. Addition of a proton quencher such as di-*tert*-butyl pyridine to the reaction medium (50 mol%) stops not only the metathesis but also any other parasite reaction (aldol, hydrolysis of the vinyl ether, etc.), for all the soluble catalysts tested. These results indicate that in situ formed protons are also the catalytically active species during the metal salt-catalyzed intermolecular carbonyl–olefin metathesis, and with this in mind and the positive results obtained for soluble Brönsted acids, a variety of commercially-available solid acids (entries 8–15) were tested as catalysts for the metathesis (Supporting Information, Table S4).[11] The results in Table 1 show that all the solid Brönsted acid catalysts tested gave similar product yields and selectivity to the soluble acids for alkene product **3b**, including the widely available, inexpensive, and non-toxic pillared clay montmorillonite K10 (< 10 euros kg^{-1}, entries 14–15). The ester by-products **4a**,**b** are completely unreactive under the present reaction conditions for any catalyst, according to control experiments, and the purification of the final alkene products by column chromatography becomes easier in the absence of additional alkene/aldehydes/ketones in the mixture. These results support our starting hypothesis that vinyl ethers are suitable alkene partners for the intermolecular carbonyl–olefin metathesis.

A convenient and productive way to circumvent side reactions during the intermolecular metathesis could be to perform the reaction in flow over a fixed-bed reactor with a solid catalyst, in order to rapidly separate the acid catalyst from the reaction mixture after the metathesis reaction. Gratifyingly, a consistent good yield of **3b** (70–95%, GC) over 8 h in-flow reaction time was obtained with fixed-bed montmorillonite K10 (entry 15 in Table 1). Figure 1 (top) shows that the procedure with montmorillonite K10 in continuous mode is also suitable to prepare a variety of *trans* alkenes in high yields after just 1 h on stream time (condition A), generally in better yields than with soluble $BF_3{\cdot}OEt_2$ catalyst in batch (condition B). The main side reaction corresponds to vinyl ether hydrolysis, which explains the better reactivity of the in situ generated vinyl ethers from acetals **2a**–**g** (see also Figure S4 in the Supporting Information).[12] Good to moderate yields are generally obtained, and some functional groups are shown to be tolerated, including halides (compounds **3g**, **3i**–**l**), aromatic ethers (**3g**), esters (**3n**), amides (**3t**), thioethers (**3v**), and other alkenes (**3x**).

Figure 1 (bottom) shows that montmorillonite K10 is still active after 40 h in-flow, which gives a turnover number (TON) of 150, which is significantly higher than homogeneous catalysts.[3] This backs up the robustness of the solid catalyst to give access to multi-gram amounts of alkene **3b**. Furthermore, the selectivity towards the alkene product is consistently higher than 90%, highlighting the benefits of performing the reactions in flow with a solid catalyst (see also Table S5 in the Supporting Information).

Figure 2 shows that the activation enthalpy values for the metathesis reaction between **1b** and **2b** with different Brönsted acids, correlate well with the pK_a of the catalyst for the homogeneous acids and also for montmorillonite K10, and deviate towards higher values for other solid acids (see also Figure S5, and Figure S6 in the Supporting Information for entropy correlation).[11b] Kinetic experiments at different stirring rates show that the reaction is controlled by diffusion for all solid catalysts except for montmorillonite K10,[13] which strongly supports the assumption that the reaction enthalpy is directly related to proton strength.

Figure 3 (top) shows experimental and computational evidences about the mechanism of the reaction (see also Figure S7 and Table S6 in the Supporting Information). A Hammett plot with different *para*-substituted acetophenones (Supporting Information, Figure S8) gives $\rho = -2.7$, which

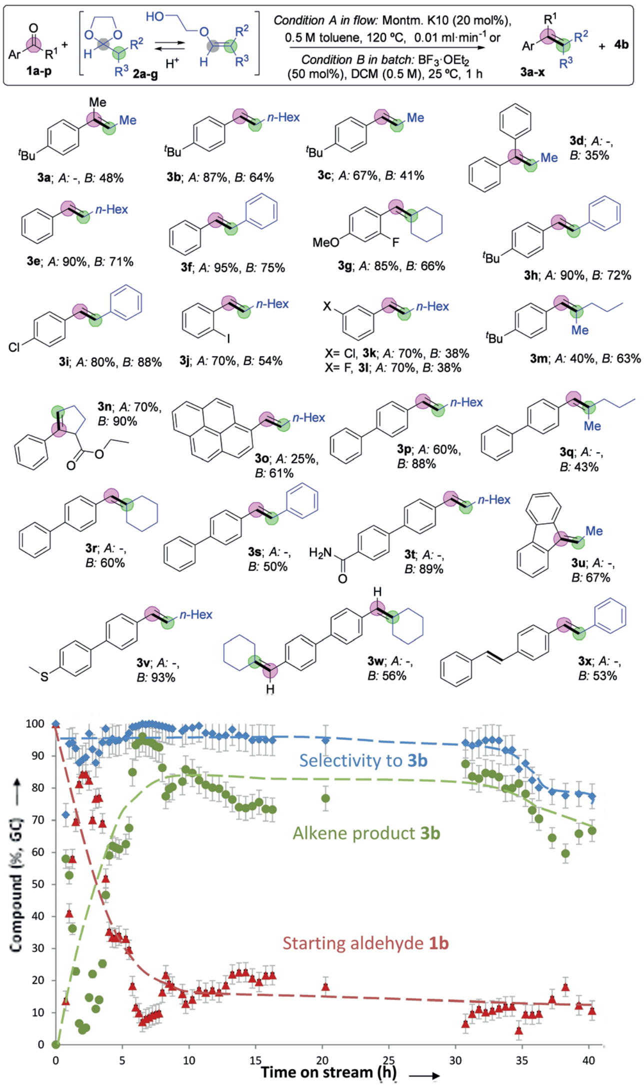

Figure 1. Top: Carbonyl olefin metathesis reactions of aryl aldehydes **1b**,**d**–**i** with in situ formed vinyl ether **2d**–**g** catalyzed by montmorillonite K10 (A) or $BF_3{\cdot}OEt_2$ (B) under the indicated reaction conditions. Bottom: Kinetic profile for the metathesis reaction between **1b** and **2d** in a fixed-bed tubular reactor with montmorillonite K10 catalyst (0.5 M toluene, 0.01 $mL\,min^{-1}$ over 40 h at 120 °C). Color Scheme: starting aldehyde **1b** in red, alkene product **3b** in green, selectivity in blue. Error bars account for a 5% uncertainty.

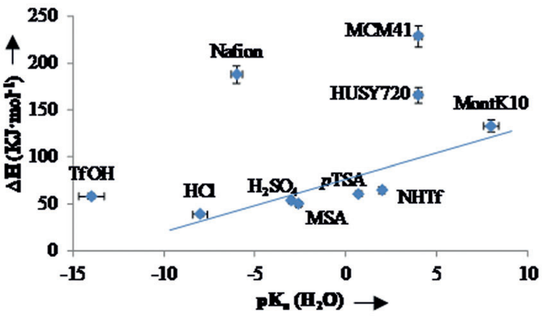

Figure 2. Activation enthalpy ($KJ\,mol^{-1}$) for the carbonyl–olefin metathesis of **1b** with **2b** with different acids. Aluminosilicates were dried under vacuum at 250 °C for 3 h before reaction. Linear regression, $R^2 = 0.88$. Error bars account for a 5 % uncertainty.

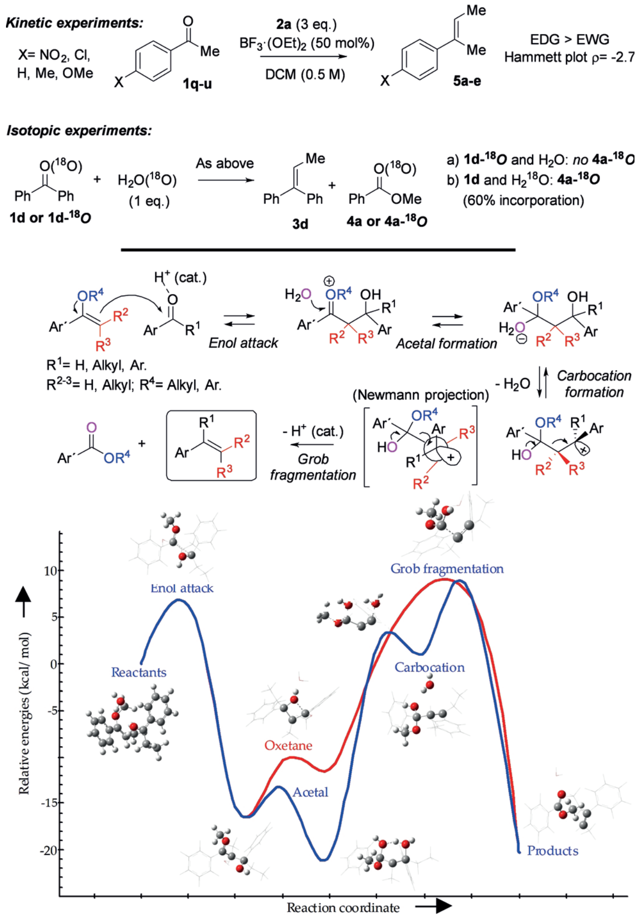

Figure 3. Experimental evidences (top) and plausible reaction mechanism (middle) for the acid-catalyzed metathesis reaction between aromatic aldehydes/ketones and vinyl ethers. Computed energy profile (bottom) for the proton-catalyzed metathesis of **1b** and **2a**. Color Scheme for atoms: carbon in grey, oxygen in red, and hydrogen in white. Blue and red curves stand for the reaction through the acetal and oxetane intermediates, respectively.

indicates building of positive charge on the carbonyl group in the rate-determining step of the reaction. No traces of oxetane could be detected during the reaction, and the preparation of the postulated oxetane intermediate was elusive when using the most accepted photochemical methods, in accordance with the lack of efficient reported methods for α-hydroxyoxetanes.[14] These results point to the formation of a cationic intermediate during the metathesis reaction. Indeed, the activation entropy for homogeneous acids is negative (the expected value for an associative transition state) but positive for solids, including montmorillonite K10, which is consistent with an extra-stabilized carbocation transition state within the anionic aluminosilicate framework (Supporting Information, Figure S6).[11b]

Figure 3 also shows that the isotopically labelled ketone **1d-^{18}O**[15] gives an ester by-product that does not contain any labelled oxygen atom, while the addition of one equivalent of $H_2{}^{18}O$ in the reaction medium generates a significant amount of isotopically labelled ester. Control experiments without **2a** confirm that no *O* atom exchange occurs in the absence of the vinyl ether (Supporting Information, Figure S9). These results unveil that the alkene product actually comes from a water-mediated carbonyl–olefin metathesis and not from a direct transferring of the carbonyl oxygen atom, which seems to be accepted in the literature as a formal carbonyl–olefin metathesis reaction[7c] (see also Figure S10 and Table S7 in the Supporting Information).[16] These results strongly support the participation of external alcohol or water molecules as nucleophiles during reaction.

Figure 3 (middle) shows a reaction mechanism consistent with all the experimental data described above. The first step is the nucleophilic attack of the vinyl ether on the proton-activated carbonyl group, which, after hemiacetal formation and acid- catalyzed dehydration, generates a suitable anti-α hydroxyl carbocation to undergo a Grob fragmentation[17] and give the final *trans* alkene.[18] Density functional theory (DFT) calculations were then conducted for the proton-catalyzed metathesis reaction between **1b** and **2a**, without imposing any geometrical restriction to reactants, products, and transition states, and with vibrational calculations to confirm the nature of the located minima in the potential energy surface, including solvent effects.[19] Figure 3 (bottom) shows that the most favorable mechanism, highlighted in blue, consists of the proton-catalyzed nucleophilic attack of **2a** to **1b** through a barrier of 6.3 $kcal\,mol^{-1}$ to give the thermodynamically favorable aldol-like adduct, 15.4 $kcal\,mol^{-1}$ more stable than the parent reactants and in equilibrium with the corresponding hemi-acetal (only differing in 2.0 $kcal\,mol^{-1}$), which then triggers a proton transfer to the vicinal hydroxyl group to give the carbocation. The latter reaction is the limiting step of the process, with an energetic barrier of 22.4 $kcal\,mol^{-1}$, after which the Grob fragmentation proceeds with a barrier of 5.9 $kcal\,mol^{-1}$ to give the final *trans* alkene product (20.5 $kcal\,mol^{-1}$ more stable than **1b** and **2a**). The alternative mechanism through the oxetane, highlighted in red, is kinetically impeded by 5.1 $kcal\,mol^{-1}$ compared to acetal formation, and with a reversion energy barrier of only 1 $kcal\,mol^{-1}$ from the oxetane to the aldol adduct. All accumulated experimental and theoretical evidences strongly support carbocation formation and later Grob fragmentation as plausible mechanism for this metathesis reaction.[6a,7c]

In conclusion, the intermolecular carbonyl–olefin metathesis of aromatic aldehydes and ketones with vinyl ethers catalyzed by fixed-bed Brönsted solid acids or, alternatively, by metal salts or conventional Brönsted acids in solution, has been accomplished. Mild solid acids, particularly the aluminosilicate montmorillonite K10, catalyze the intermolecular reaction with vinyl ethers by shifting the equilibrium towards the alkene products and by stabilizing intermediate carbocations formed during the reaction. These results enable the synthesis of *trans* alkenes in continuous flow by intermolecular carbonyl–olefin metathesis, with potential applications as simple building blocks in chemical industry.[20]

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Conflict of interest

The authors declare no conflict of interest.

Keywords: carbonyl–olefin metathesis · heterogeneous catalysis · in-flow reactions · montmorillonite K10 · vinyl ethers

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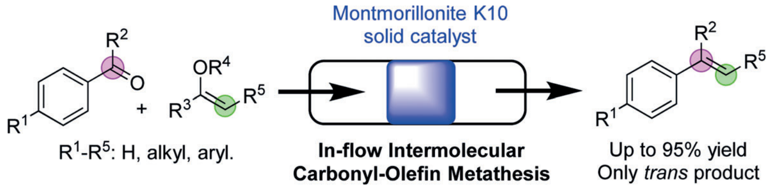

The intermolecular carbonyl–olefin metathesis between aromatic ketones/aldehydes and vinyl ethers is accomplished with not only simple soluble but also solid acid catalysts to give *trans* alkenes in high yields, multi-gram amounts, and in-flow.