



Merger of Johnson–Claisen rearrangement and alkoxy carbonylation for atom efficient diester synthesis



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ABSTRACT

The orthoester Johnson–Claisen rearrangement of allyl alcohol with triethyl orthoacetate for the synthesis of ethyl 4-pentenoate has been optimized, in order to allow for a selective and efficient subsequent alkoxy carbonylation using formates in an atom efficient manner. Diethyl adipate was successfully yielded in up to 89% applying very low orthoester excess, formic acid and mild reaction conditions in an innovative, one-pot procedure.

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Since its initial discovery in 1912,¹ the Claisen rearrangement and the numerous developed versions related to this concept have emerged as powerful tools for the construction of γ,δ -unsaturated carbon scaffolds in many examples from allylic starting materials.^{2,3} All of these have a [3,3] sigmatropic rearrangement of a pre-formed ‘allyl-vinyl-ether-type’ intermediate in common, and hence, are in principle highly atom-economic. However, the formation of the central intermediate undergoing the [3,3] sigmatropic rearrangement is typically accompanied by the formation of large amounts of coproducts. Additionally, usually high excess of co-reagents for the formation of the central intermediates from the allylic starting material is used. As a result, the overall atom-economy of such a protocol for the formation of, for example, γ,δ -unsaturated esters by orthoester Johnson–Claisen rearrangement (JCR)^{4,5} is low (Scheme 1).

In our ongoing interest in the intensification and merger of existing reactions and the development of new and innovative reaction concepts,⁶ we were interested in the incorporation of orthoester Johnson–Claisen rearrangements in tandem reactions.

The γ,δ -unsaturated esters resulting from JCR offer the potential for further functionalization of the double bond to furnish bifunctional compounds. Transition metal catalyzed reactions showed to be particularly effective and atom economic in this regard.^{7,8}

Among them, alkoxy carbonylation of olefins and unsaturated esters has recently attracted many investigations,⁹ and especially one catalytic systems comprising of a palladium precursor, the ligand 1,2-DTBPMB (Fig. 1) in combination with a sulfonic acid as co-catalyst, has shown general usability.^{10,11} Besides terminal alkenes, also internal alkenes can be transformed into the respective linear esters by tandem isomerizing alkoxy carbonylation.^{12–20}

Like in other carbonylative transformations, carbon monoxide is usually applied as C₁-building block, but its inherent toxicity and non-ease handling on a laboratory scale has led to the development of alternative substrates for alkoxy carbonylation, such as formates.^{21–23} However, to the best of our knowledge, the merger of orthoester Johnson–Claisen rearrangement with an atom-economic functionalization of the resulting γ,δ -unsaturated esters by transition metal catalysis has not been reported so far. Even though numerous combinations yielding differently substituted bifunctional carbon scaffolds from readily available starting materials are potentially feasible.

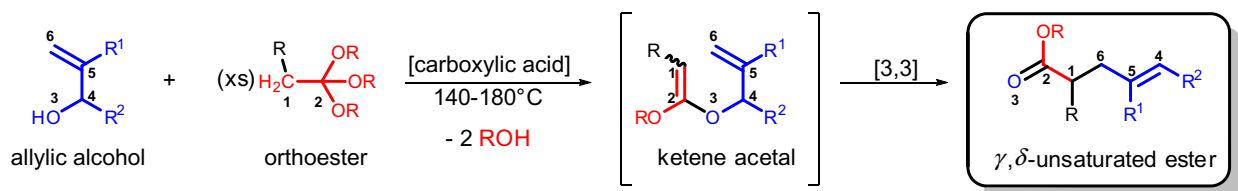
Taking all of the aforementioned aspects into account, the demonstration of the general feasibility of such a reaction combination is the goal of this study. We envisioned the JCR of allyl alcohol (1) with triethyl orthoacetate (2) as a model reaction with subsequent Pd-catalyzed formate alkoxy carbonylation. The product ethyl 4-pentenoate (4) from JCR can be transformed into a linear adipate diester (6) by the alkoxy carbonylation with formates (5), preferable in a one-pot or tandem reaction sequence (Scheme 2). Adipic acid and its ester derivatives constitute an

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Scheme 1. General orthoester Johnson–Claisen rearrangement for the synthesis of γ,δ -unsaturated esters from allylic alcohols.

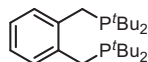


Figure 1. Ligand used in several alkoxyacylations: 1,2-DTBPMB (1,2-bis((di-*tert*-butylphosphino)methyl)benzene).

important class of compounds, for example, in the synthesis of polycondensates and plasticizers.²⁴

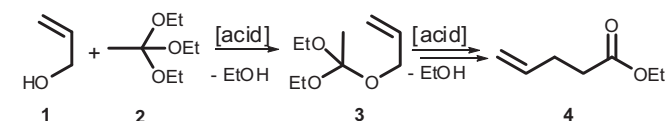
To address resource efficiency and to determine reaction conditions suitable for both reaction parts (Johnson–Claisen rearrangement and alkoxyacylation), each reaction was optimized separately in preliminary investigations.

Orthoester Johnson–Claisen rearrangement

First, JCR of **1** with **2** was investigated towards potential acid catalysts. Propionic acid usually is used in catalytic amounts to initiate the ketene acetal formation via the mixed allyl orthoester **3**. However, other carboxylic acids are rarely applied, and sulfonic acids are not known to catalyze JCR. Usually, sulfonic acids are applied in alkoxyacylations, such as methanesulfonic acid (MSA) or *p*-toluenesulfonic acid (*p*-TSA), and hence, we tested these among different carboxylic acids in the JCR to potentially use these acids in the ongoing alkoxyacylation (Table 1).

The JCR of allyl alcohol (**1**) with triethyl orthoacetate (**2**) was successful with each applied acid with good to excellent yields. Surprisingly, we found that sulfonic acids are superior compared to carboxylic acids, with MSA furnishing highest yields of the desired unsaturated ester **4** of 97% (entry 1.4, Table 1). However, besides the expected product **4**, intermediate **3** and ethanol as condensation product, we detected the corresponding ethyl ester of each catalyst acid (acid-OEt) and ethyl acetate in the GC-FID traces of Table 1. Non-catalytic esterification by the applied orthoester

Table 1
Variation of acid in JCR of **1** with **2**



Entry	Acid	Conversion (1) [%]	Yield (3) [%]	Yield (4) [%]	Selectivity ^a (4) [%]	Yield (acid-OEt) ^b [%]
1.1	Pivalic acid	82	3	79	96	76
1.2	Propionic acid	75	3	72	96	72
1.3	<i>p</i> -TSA	86	5	81	94	99
1.4	MSA	99	2	97	98	99
1.5	Benzoic acid	72	2	70	96	78
1.6	Formic acid	94	2	92	97	80

Conditions: $n_1 = 1.6$ mmol, 3.5 eq. **2**, acid = 10 mol %, solvent = 1.15 mL Toluol, $T = 150$ °C, $t = 15$ h, 12 mL pressure tubes. Yields and conversion determined with GC-FID and *n*-dodecane as internal standard.

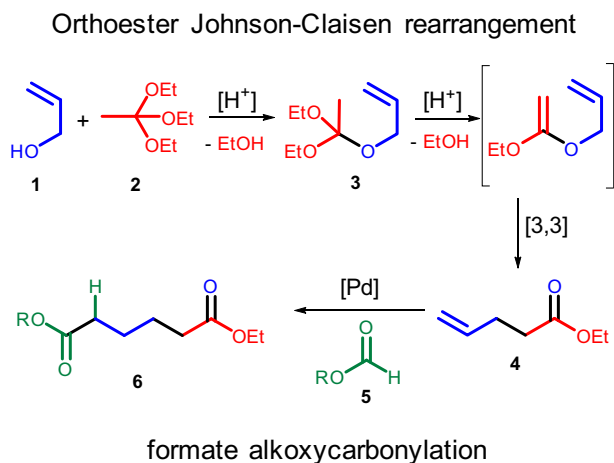
^a Selectivity (**4**) = yield (**4**)/conversion (**1**)⁻¹.

^b Acid-OEt corresponds to the ethyl ester of the respective acid catalyst applied.

presumably leads to the formation of the acid esters with ethyl acetate being the coproduct (Scheme 3, lower path). Sulfonic acids seem more prone to esterification under these conditions, as already described earlier in the literature.²⁵ Nevertheless, considering a further function of the acid in the ongoing alkoxyacylation, an in situ esterification is not tolerable.

However, to make a virtue out of that necessity, we envisioned the JCR applying formic acid as catalyst yielding 92% of the desired unsaturated ester **4** at a conversion of 94% with high selectivity (entry 1.6, Table 1). Ethyl formate (**5**) is then the corresponding catalyst acid ethyl ester (acid-OEt), which potentially can be used in the formate alkoxyacylation of **4** to yield **6** (Scheme 3). Moreover, ethanol as the coproduct of JCR is the solvent in formate alkoxyacylation together with the formate esters.²² Hence, formic acid would be the ideal catalyst acid for the combination of JCR with formate alkoxyacylation in terms of leveraging resource efficiency and linking these two reactions.

In systematic investigations of the JCR of **1** and **2** with formic acid as catalyst, the amount of acid and the orthoester excess were minimized (Fig. 2). The scale of the reaction was doubled, thereby enabling the reaction to be set-up without additional solvent. Formic acid proved to be an effective catalyst for the solvent-free JCR already at moderate catalyst concentrations of 30 mol %, with



Scheme 2. Orthoester Johnson–Claisen rearrangement of allyl alcohol (**1**) with triethyl orthoacetate (**2**) for the formation of ethyl 4-pentenoate (**4**) via the mixed allyl orthoester **3**. Subsequent alkoxyacylation applying formates (**5**) yields adipate diester (**6**).

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