ACS Catalysis

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Catalytic Ester Metathesis Reaction and Its Application to Transfer Hydrogenation of Esters

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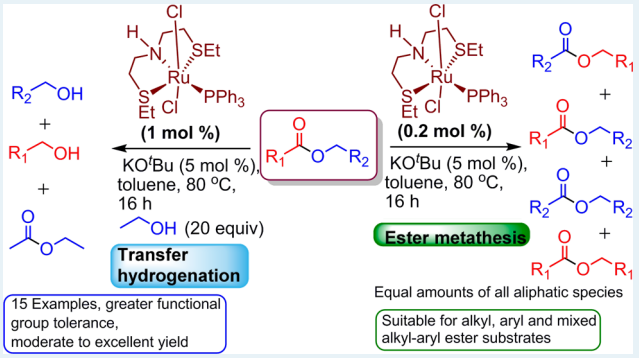
Supporting Information

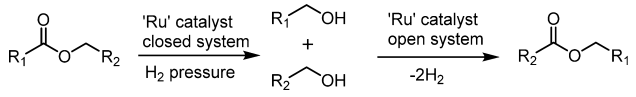
ABSTRACT: We report a Ru-complex-catalyzed ester metathesis reaction where an unsymmetrical ester such as ethyl hexanoate can be transformed to a mixture of starting material, hexyl ethanoate, ethyl acetate, and hexyl hexanoate in equal proportions, as expected from a classical metathesis reaction with 0.2 mol % catalyst. A 20× excess of low boiling alcohol, such as ethanol, allows for the transfer of an acyl moiety to the sacrificial low boiling ethyl acetate product, while significantly increasing the functional group tolerance and substrate scope; yields of alcohols can reach 90%, which represents an attractive alternative to current high H_2 pressure hydrogenation protocols for Ru-based ester reduction chemistry. Both reactions have not been reported previously in the field of Ru-catalyzed transformations of the ester functionality.



KEYWORDS: *metathesis, esters, pincer complex, transfer hydrogenation, homogeneous catalysis, ruthenium*

The efficient, Ru-pincer-complex-catalyzed alcohol coupling reaction to form esters with the concurrent release of H_2 gas was first reported in 2005;[1] the reverse reaction, or hydrogenation of esters to form alcohols, was published soon afterward (Scheme 1).[2] Today, both reactions are well-established processes of increasing industrial relevance.[3,4] Oxidative alcohol coupling is attractive as it represents an atom-economical, green-chemistry alternative to previous synthetic routes, with H_2 being the only byproduct that leaves as gas during the reaction. Likewise, reduction of esters to alcohols normally requires stoichiometric reagents such as lithium aluminum hydride; however, reduction with H_2, despite the high pressures (often 50 bar) and specialized equipment required, offers an atom economical way of obtaining the desired alcohol. Some of the applications of this attractive chemistry include reducing triglycerides into important component alcohols[5] as well as decomposing polyesters to alcohol components.[6]

Scheme 1. Alcohol Coupling Reaction To Form Esters and Ester Hydrogenation under H_2 Pressure



We summarize some of the complexes relevant to ester reactivity, along with the date and application in Figure 1.[1,7−14] It can be seen that last-generation Ru catalysts are notable for their low catalyst loadings. However, the full reactivity scope for both the forward and reverse reaction is still absent as ester hydrogenation under H_2 pressure is reported in preference to the alcohol coupling reaction; this may be because the latter reaction is unselective unless a primary and secondary (or benzylic/aliphatic) alcohol are used or the homocoupling of one alcohol is the desired outcome.

Since most of the catalysts are capable of promoting both ester hydrogenation and alcohol coupling, we decided to see if we could observe the simultaneous reduction and oxidation of different parts of the ester molecule in one pot. According to Scheme 1, the overall reaction should be accomplished with hydrogen gas as a cocatalyst. However, only high pressures of H_2 had been reported so far for ester hydrogenation, and under these conditions alcohols should be obtained as the exclusive product.

Gratifyingly, when exploring the reactivity of an unsymmetrical ester, ethyl hexanoate **10**, with commercially available catalysts **2**−**4**, we found that upon the addition of activating base, the catalyst was capable of reacting and rearranging the ester without the need of any addition of hydrogen cocatalyst. After 16 h of heating at 80 °C in the presence of 1 mol % of catalyst **2** (Table 1), ^{1}HNMR in C_6D_6 (Supporting Information (SI), Figures S1 and S2) confirmed complete scrambling of the starting materials to a statistical equilibrium of products

Received: March 22, 2016
Revised: April 25, 2016

DOI: 10.1021/acscatal.6b00827
ACS Catal. 2016, 6, 3998−4002

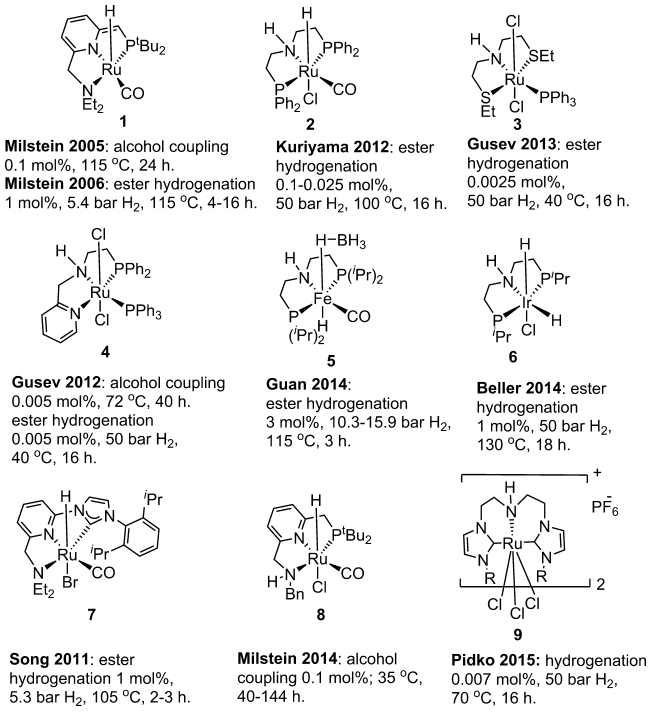
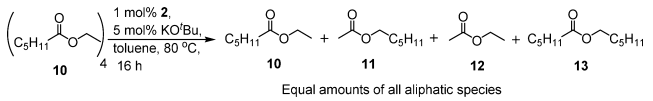


Figure 1. A brief overview of pincer catalysts and their application.

(Scheme 2), meaning that true metathesis had occurred. Organometallic mediated metathesis has previously been observed with alkenes,[15] alkynes,[16] and alkanes,[17,18] but not with esters.

Scheme 2. Metathesis Reaction with Ethyl Hexanoate 10



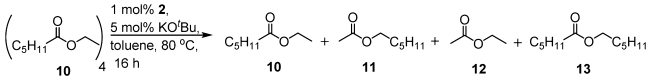
Although all the products are obtained as a statistical mixture, the boiling point differences do make isolation of a particular desired product a possibility. The reaction may also find applicability in the flavoring industry where changing an ester composition results in different scent, and a mixture of simple esters can now react not only via transesterification but also via metathesis scrambling. To the best of our knowledge, the transformation is unique; thus, the full scope of its practicality may become more apparent in the future.

Screening of the catalysts **2**−**4** for the ester metathesis identified **3** as the most effective (Table 1, entry 6). Catalyst **2** was also effective but gave slightly poorer yields (Table 1, entries, 1−3), whereas catalyst **4** failed to give a metathesis product. A short screening showed that toluene/benzene was the only solvent appropriate for the reaction, as THF and CH_3CN gave no conversion and reactions in hexane performed poorly, likely due to solubility of the catalyst. Other activating bases, such as KHMDS, had no effect on outcomes.

With the optimal conditions in hand (Table 1, entry 6), we decided to investigate the applicability of the reaction to various esters that contained benzylic, olefin, halogen, and ether moieties. Currently, functional groups or compounds that can form a conjugated, stabilized double bond with the acyl moiety are not tolerated with the catalysts we tested. Importantly, however, alkyl (Table 1), aryl (Table 2, entry 5), and mixed alkyl-aryl (Table 2, entries 3−4) esters were all scrambled equally well during the reaction at 0.2 mol % catalyst loadings. Control reactions without either the activating base, or catalyst, gave no conversion. Metathesis efficiency was determined by the difference between unsymmetrical products (i.e., **10** and **11** for Table 1; see GC traces in the SI for each entry).

Methyl ester **14** is not active in the reactions (Table 2, entry 1−2), which may be due to catalyst inactivation by carbonyls formed in situ from the methanol. After long reaction times, benzyl acetate **19** (entry 4) is selective for transformation to

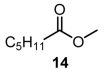
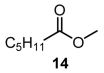
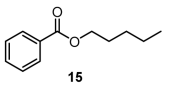
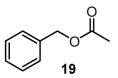
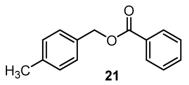
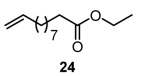
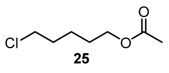
Table 1. Optimization of Ester Metathesis[a]



entry	catalyst (*X* mol %)	efficiency
1	**2** (1 mol %)	94%
2	**2** (0.5 mol %)	74%
3	**2** (0.2 mol %)	89%
4	**3** (1.0 mol %)	99%
5	**3** (0.5 mol %)	99%
6	**3** (0.2 mol %)	99%
7	**3** (0.1 mol %)	91%
8	**4** (1.0 mol %)	trace

[a]Amounts based on 1 mg of catalyst in 3 mL of toluene in an 11 mL closed container.

Table 2. Esters Tested in Metathesis and Products[a]

Entry	Catalyst (X mol%)	Substrate	Efficiency	Products
1	**3** (1 mol%)	 **14**	0%	No Reaction
2	**4** (1 mol%)	 **14**	0%	No Reaction
3	**3** (0.2 mol%)	 **15**	99%	Pentyl benzoate (**15**) Benzyl pentanoate (**16**) Pentyl pentanoate (**17**) Benzyl benzoate (**18**)
4	**3** (0.2 mol%)	 **19**	99%	Benzyl benzoate (**18**) Benzyl acetate (**19**) Ethyl Benzoate (**20**)
5	**3** (0.2 mol%)	 **21**	99%	4-Methylbenzyl benzoate (**21**) Benzyl-4-methylbenzoate (**22**) 4-Methylbenzyl-4-methylbenzoate (**23**) Benzyl benzoate (**18**)
6	**3** (0.2 mol%)	 **24**	0%	No Reaction
7	**3** (0.2 mol%)	 **25**	0%	No Reaction

[a]Amounts based on 1 mg of catalyst in 3 mL of toluene in an 11 mL closed container.

DOI: 10.1021/acscatal.6b00827
ACS Catal. 2016, 6, 3998−4002

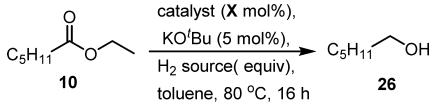
ethyl benzoate **20**, reflecting the greater thermodynamic stability of an ester with an acyl group in the benzylic position. From NMR experiments, it was found that the reaction will proceed at temperatures as low as 50 °C with **19**; however, a temperature of 80 °C and a 16 h heating period were used as general conditions. We determined efficiency to be at ∼99% when the starting material was at ≤25% of the initial amount, and the product was correspondingly ≥25%. The amounts may not exactly end up at 25% if the product is more thermodynamically stable than the starting material.

In light of the excellent results obtained with the metathesis reaction, we decided to see if it can be applied to make a single product selectively. There are a number of reports on transfer hydrogenation of ketones, aldehydes, alkynes, olefins, and imines.[19] We are only aware of one report from the Nikonov group in 2015, where transfer hydrogenation of esters is reported with a Ru half-sandwich complex and isopropanol as the sacrificial hydrogen donor.[20] Good activity (∼20 TON) is obtained only with secondary trifluoroacetate esters.

Transfer hydrogenation should be possible if an excess of primary alcohol, such as ethanol is introduced together with the ester. The advantages of ethanol and the ethyl acetate byproduct include low boiling points and cost due to them being common solvents and biofuels. Formally, the reaction would be ester metathesis, but technically transfer dehydrogenation (TH) of an ester would have occurred because products can be isolated after removing solvent (toluene and ethanol) and byproducts (ethyl acetate) under vacuum. By avoiding high pressures of H_2 gas, TH of esters has the advantages of safety and ease of operation.

As we had expected, using ethanol is a viable strategy for the hydrogenation of esters via our procedure. However, the catalyst loading has to be increased to 1 mol % in order to get acceptable yields as reactivity with ethanol lowers the rate of useful reactions with the ester substrate (Table 3). At 20 equiv

Table 3. Optimization of Transfer Hydrogenation of Esters[a]



entry	catalyst (*X* mol %)	H_2 source (equiv)	yield (%)
1	**2** (1 mol %)	ethanol (5 equiv)	57
2	**2** (1 mol %)	ethanol (10 equiv)	65
3	**2** (1 mol %)	ethanol (20 equiv)	71
4	**3** (0.2 mol %)	ethanol (20 equiv)	60
5	**3** (1 mol %)	ethanol (20 equiv)	89
6	**4** (1 mol %)	ethanol (20 equiv)	70
7	**3** (1 mol %)	benzyl alcohol (10 equiv)	20
8	**3** (1 mol %)	benzyl alcohol (20 equiv)	18
9	**3** (1 mol %)	*iso*-propanol (20 equiv)	43

[a]Amounts based on 1 mg of catalyst in 3 mL of toluene in an 11 mL closed container.

of ethanol to substrate, ethyl hexanoate is converted to hexanol at 89% yield (Table 3, entry 5) after 16 h at 80 °C. Fewer equivalents of ethanol led to lower conversions after 16 h of reaction time. Interestingly, catalyst **4**, which was very poorly active in metathesis, gave alcohol product, albeit to a lesser extent than **3**. The lower reactivity in entries 7−8 is likely the result of product inhibition as aromatic benzylic alcohol and esters outcompete the aliphatic ester for binding to the catalyst.

The reaction with isopropanol as the sacrificial H_2 donor resulted in 43% yield of hexanol (40TON; Table 3, entry 9), which is less than our maximum yields obtained with ethanol. In the case of a secondary alcohol, ester metathesis with isopropanol cannot take place, and the cost of making acetone may be greater than the energy gained by making primary alcohols from an ester.

Interestingly, other substrates that were not active in ester metathesis are also converted to alcohols, often in good yields (Table 4, entry 1, 5, 11, 14−16).

Our protocol was also applicable in the hydrogenation of triglycirides, hydrogenations of which with H_2 pressure have recently been reported.[5] The long-chain alcohols obtained from these natural products are of commercial interest and are normally obtained by stoichiometric reduction; milder alternatives involving H_2 or transfer hydrogenation are highly desired. Along with the alcohol product (∼57% for tripalmitin), a significant amount of the intermediate ethyl ester of palmitate is also observed. The yield of the alcohol here is limited by the solubility of the starting triglyceride in the toluene solvent. Attempts to use other solvents or perform a neat reaction gave worse outcomes.

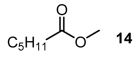
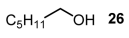
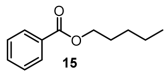
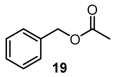
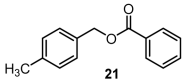
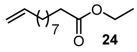
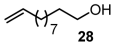
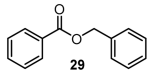
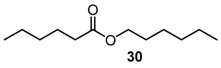
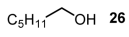
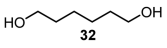
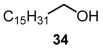
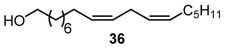
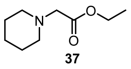
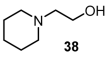
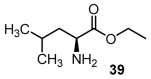
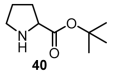
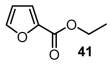
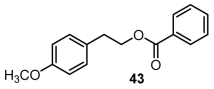
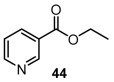
We show our working mechanistic hypotheses for this reaction in Figure 2. The metathesis reaction of benzyl acetate **19** was followed by ^{1}HNMR, confirming the formation of the three products. We observed that the rate of appearance of symmetrical metathesis products, which form at an equal rate to each other, is more rapid than the formation of the more thermodynamically stable, unsymmetrical ethyl benzoate **20** (SI, Figures S7−S16). According to pathway I, symmetrical products are formed initially, and the unsymmetrical product can be generated when the catalyst subsequently reacts with these symmetrical products, or by the trans-esterification (TE) reaction active in the presence of base (TE is slower than metathesis and is discussed in more detail in the SI). An acyl Ru species that is suggested by the mechanism also helps explain the rapid deactivation of the catalyst when methyl esters are involved; it is unlikely that this type of organometallic species (RCO-Ru) would be tolerant of other functional groups as well. Acyl-Ru species have been isolated and characterized for monometallic Ru complexes.[21]

Pathway II may be active in TH with ethanol, where free H_2 from excess alcohol in the closed reaction system opens up an opportunity for Ru dihydride complex formation *in situ*. The activity of some substrates in hydrogenation that proved to be inactive in metathesis, as well the dramatic improvement in the activity of catalyst **4** (Table 4, entry 5), suggests that both pathways I and II can be active in transfer hydrogenation of esters, and it is likely that only pathway I is active in one-component ester metathesis. In-situ transfer hydrogenation in a reaction between a primary ester and a secondary alcohol has been hinted at by an earlier Milstein report where trace ketone byproducts were obtained; however, the authors focused on generating secondary alcohol esters, and because only symmetrical primary esters were used as reactants, metathesis could also not be observed.[22] Presumably, this reaction proceeded via pathway II (Figure 2), but acyl group reduction could not be obtained due to the absence of sacrificial primary alcohols.

The current work shows that it is possible to think of the ester functionality as an easily modifiable moiety where metathesis can occur under the right catalysis conditions. Until now, this was thought of as a two-pot reaction that required different conditions and instrumental setups for each

DOI: 10.1021/acscatal.6b00827
ACS Catal. 2016, 6, 3998−4002

Table 4. Substrates Tested for Transfer Hydrogenation and Yields of Alcohol[e]

Entry	Ester	Product	Yield (%)
1	 14	 26	90
2	 15	 27	90
3	 19	 27	84[a]
4	 21	 27	89
5	 24	 28	90[b]
6	 29	 27	74[c]
7	 30	 26	87[c]
8	 31	 32	58
9	Tripalmitin (**33**)	 34	57
10	Glyceryl Trilinoleate (**35**)	 36	16[d]
11	 37	 38	>95
12	 39	No Reaction	-------
13	 40	No Reaction	-------
14	 41	 42	95
15	 43	 27	15
16	 44	 45	72

[a]Only substrate given with alcohol part of ester as product; presence of metathesis isomers confirmed as side-products. [b]Catalyst **4** was used; conversion factor used to calculate yield based on hexanol*2; products and remaining material were a mix of compounds where the double bond isomerizes to the 2,3, and 4 positions of the chain. [c]Yield calculated based on alcohol obtained/2. [d]Mixture of olefin isomers. [e]Amounts based on 1 mg of catalyst in 3 mL of toluene in an 11 mL closed container; 20 equiv of ethanol except for entries 9 and 10 (30 equiv of ethanol).

step. The ability to carry out this reaction rapidly and efficiently leads to some interesting applications such as an efficient ester transfer hydrogenation reaction with ethanol acting as the sacrificial substrate. We hope that this report spurs further interest and research in the reduction of esters via Ru-catalyzed ester scrambling as well as investigation of new catalysts[23] that display a wider functional group tolerance.

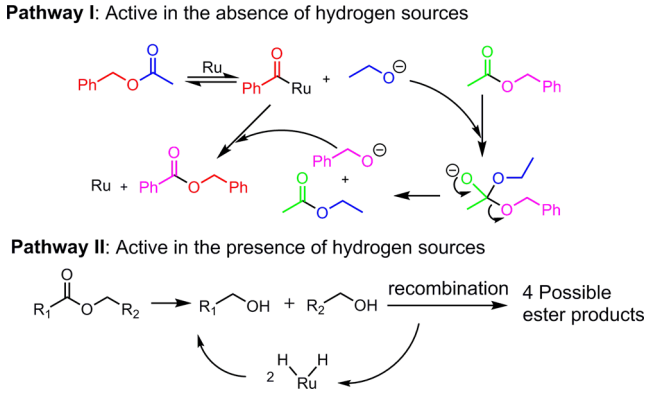


Figure 2. Working mechanistic hypotheses.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.6b00827.

Stoichiometric/kinetic NMR experiments, mechanistic discussion, GC/FID traces, and DFT calculations (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors wish to acknowledge the Okinawa Institute of Science and Technology for full funding of the project.

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