Ruthenium-catalyzed Addition of Carboxylic Acids to Propargylic Alcohols

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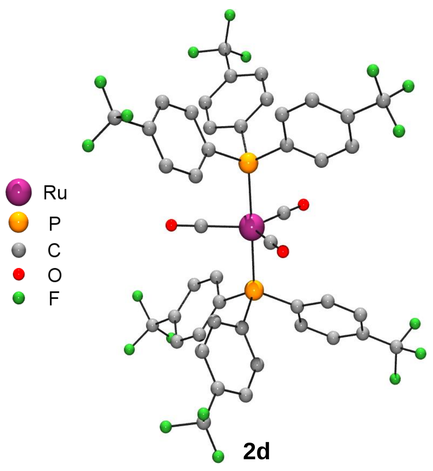
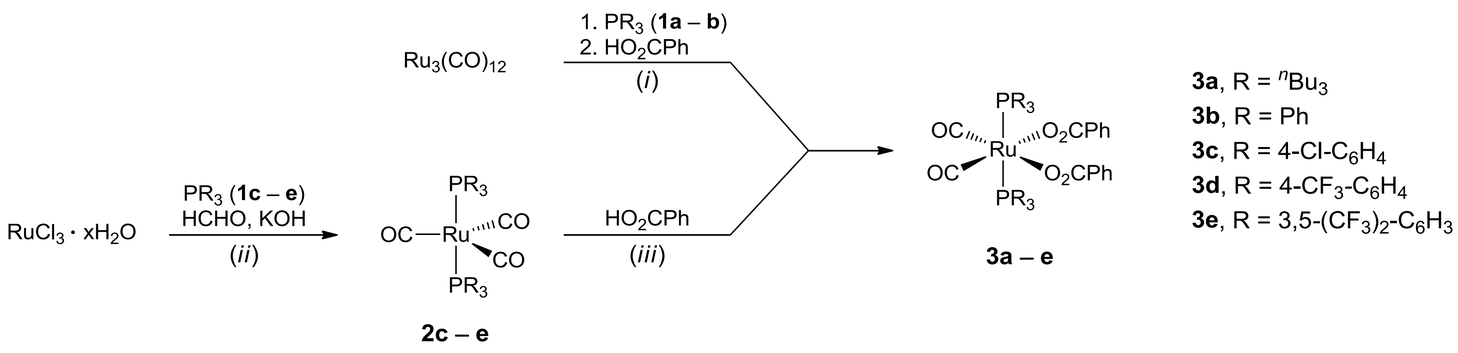
Introduction

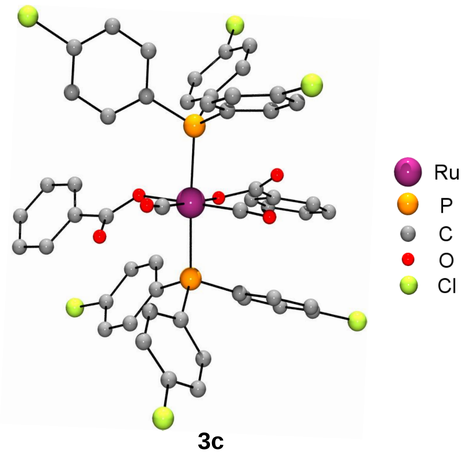
Ruthenium complexes catalyze a variety of atom economical carbon-carbon and carbon-heteroatom bond formations.[1] In this context, the addition of carboxylic acids to propargylic alcohols is an elegant access to β-oxopropyl esters,[2] which can be applied in the synthesis of natural products and pharmaceuticals.[3] The proposed mechanism for this reaction involves the initial Markovnikov addition of the carboxylic acid to the Ru(η^2-alkyne) complex, followed by an intramolecular transesterification step.[4] Recently, we could show that electron-withdrawing ligands at the metal fragment accelerate the formation of β-oxo esters.[5] Herein, we present new effective and air stable ruthenium complexes for the catalytic formation of β-oxopropyl esters under mild reaction conditions. The electronic influence of different phosphine ligands on the reactivity of the catalytic system was systematically investigated. Furthermore, a correlation of the Hammett value and the reaction rate for a series of *para*-substituted benzoic acids as well as the substrate generality of the propargylic alcohol was examined.

Synthesis and Characterization



2d





3c

Scheme 1. Synthesis of ruthenium complexes **2c** – **e** and **3a** – **e**. (*i*) 4-Methylpentan-2-one, ΔT, 16 h; (*ii*) 2-methoxyethanol, ΔT, 8–16 h; (*iii*) 4-methylpentan-2-one, 100 °C, 1 h.

Influence of Phosphine Ligands in the β-Oxo Ester Synthesis

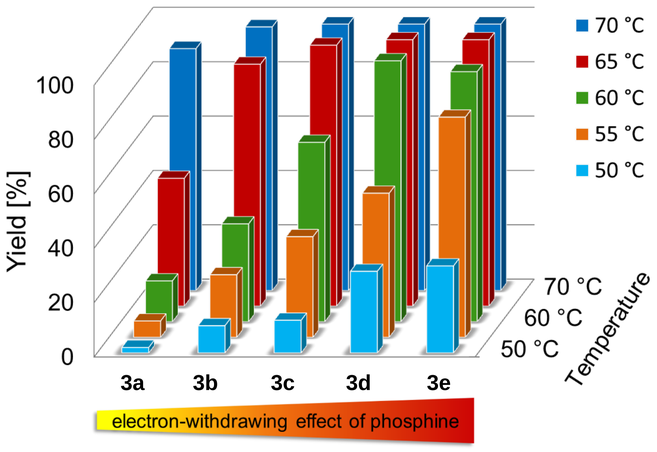


Figure 1. Screening of complexes $[Ru(CO)_2(PR_3)_2(O_2CPh)_2]$ (**3a**, R = ^{n}Bu; **3b**, R = Ph; **3c**, R = 4-Cl-C_6H_4; **3d**, R = 4-CF_3-C_6H_4; **3e**, R = 3,5-$(CF_3)_2$-C_6H_3) on their productivity in the addition of benzoic acid to propargylic alcohol at varying temperatures.

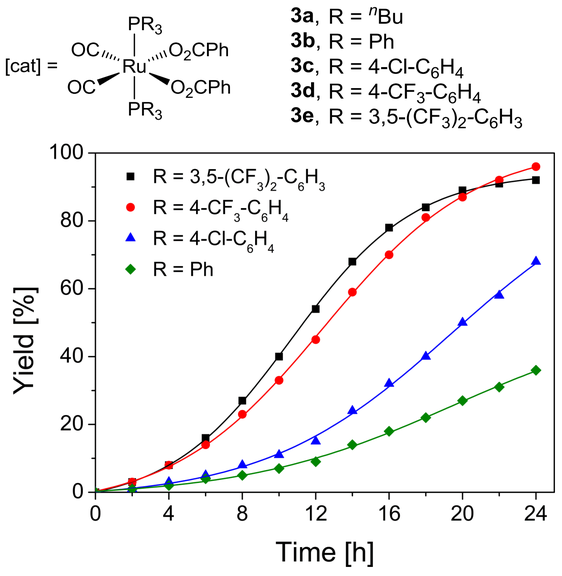
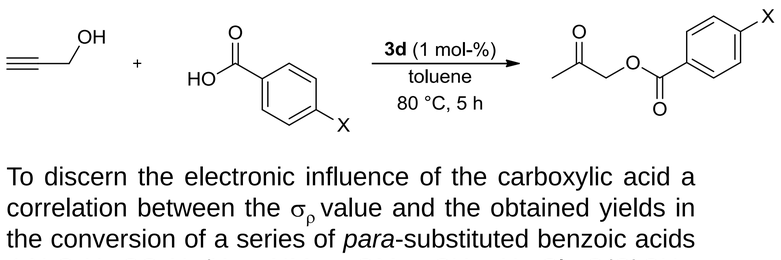


Figure 2. Reaction profiles for the addition of benzoic acid to propargylic alcohol at 60 °C applying different catalysts $[Ru(CO)_2(PR_3)_2(O_2CPh)_2]$ (**3b**, R = Ph; **3c**, R = 4-Cl-C_6H_4; **3d**, R = 4-CF_3-C_6H_4; **3e**, R = 3,5-$(CF_3)_2$-C_6H_3).

The screening of ruthenium complexes **3a** – **e** with varying phosphine ligands reveals a considerably influence of the phosphine´s electronic nature on the productivity in the addition of benzoic acid to propargylic alcohol to give β-oxopropyl benzoate (Fig. 1). When ruthenium complexes with electron-withdrawing phosphine ligands (**3c** – **e**) are applied, the reaction proceeds with higher activity than with more basic ruthenium complexes **3a** – **b** (Fig. 2). This finding can be explained with a facilitated coordination of the electron-rich triple bond of the propargylic alcohol to an electrophilic ruthenium center, which is most likely the rate determining step.

Electronic Influence of the Carboxylic Acid



To discern the electronic influence of the carboxylic acid a correlation between the σ_ρ value and the obtained yields in the conversion of a series of *para*-substituted benzoic acids 4-X-C_6H_4-CO_2H (X = NMe_2, OMe, CH_3, H, Cl, C(O)CH_3, CF_3, NO_2) with propargylic alcohol was examined.
The positive ρ value in Figure 3 reveals electron-withdrawing groups on the benzoic acids to modestly increase the productivity. This result indicates the cleavage of the O–H bond through deprotonation or oxidative addition of the acid to the Ru catalyst instead of nucleophilic addition to be rate-limiting.

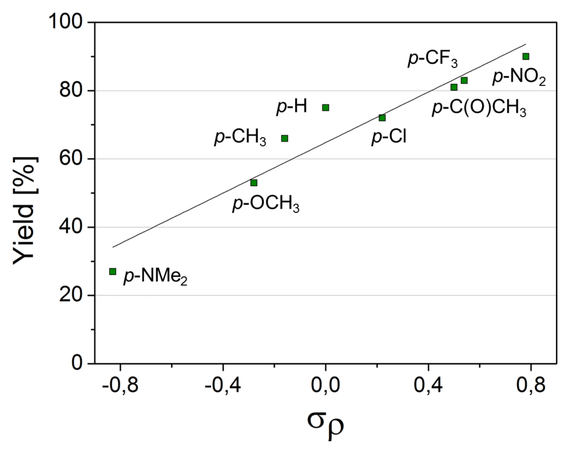
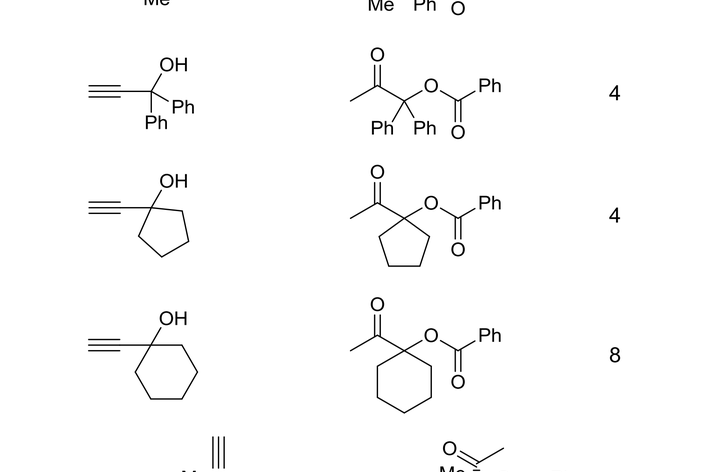
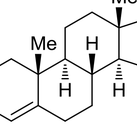
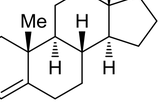
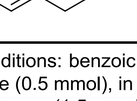
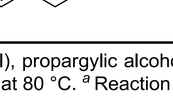
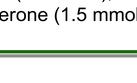
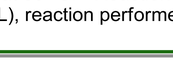
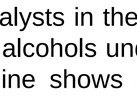
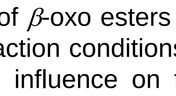
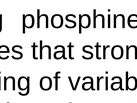
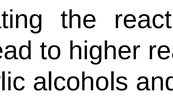
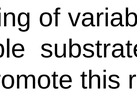
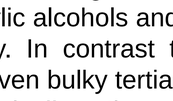
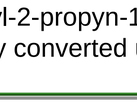
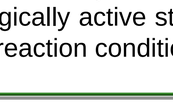


Figure 3. Hammett plot of the coupling reaction of *para*-substituted benzoic acids 4-X-C_6H_4-CO_2H with propargylic alcohol. Linear regression: y = 37x + 64.8; R^2 = 0.91.

Variation of the Propargylic Alcohol

Table 1. Ruthenium-catalyzed synthesis of β-oxo esters with varying propargylic alcohols under optimized reaction conditions.



Entry	Alkyne	Product	Time[a] [h]	Yield[b] [%]
1			5	99
2			6	88
3			2	78
4			6	89
5			6	86
6			4	74
7			4	100
8			8	84
9[c]			16	63

Reaction conditions: benzoic acid (1.0 mmol), propargylic alcohol (2.0 mmol), **3d** (0.01 mmol), acenaphthene (0.5 mmol), in toluene (1 mL) at 80 °C. [a] Reaction times are optimized. [b] Isolated yield. [c] Ethisterone (1.5 mmol), toluene (5 mL), reaction performed at 100 °C.

References and Acknowledgement

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Conclusion

We could show for the first time that ruthenium complexes **3a** – **e** are efficient catalysts in the synthesis of β-oxo esters from carboxylic acids and propargylic alcohols under mild reaction conditions. The electronic nature of the phosphine shows an obvious influence on the activity with electron-withdrawing phosphines accelerating the reaction. The Hammett study demonstrates that stronger acids lead to higher reaction rates.
The screening of variable propargylic alcohols and carboxylic acids revealed a remarkable substrate generality. In contrast to other catalyst systems known to promote this reaction[4,6] even bulky tertiary propargylic alcohols like 1,1-diphenyl-2-propyn-1-ol or biologically active steroid ethisterone could be successfully converted under mild reaction conditions.