Ruthenium-catalyzed Addition of Carboxylic Acids to Propargylic Alcohols

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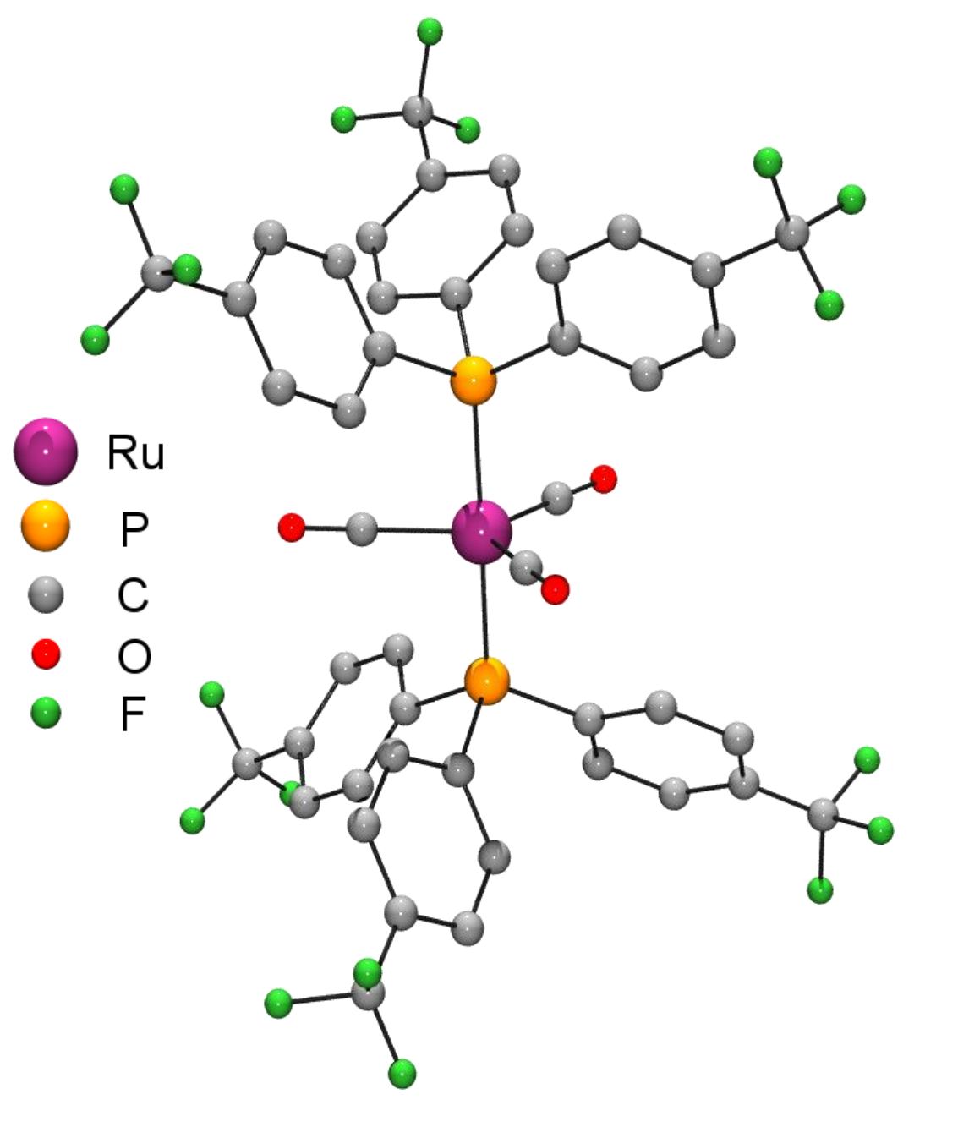
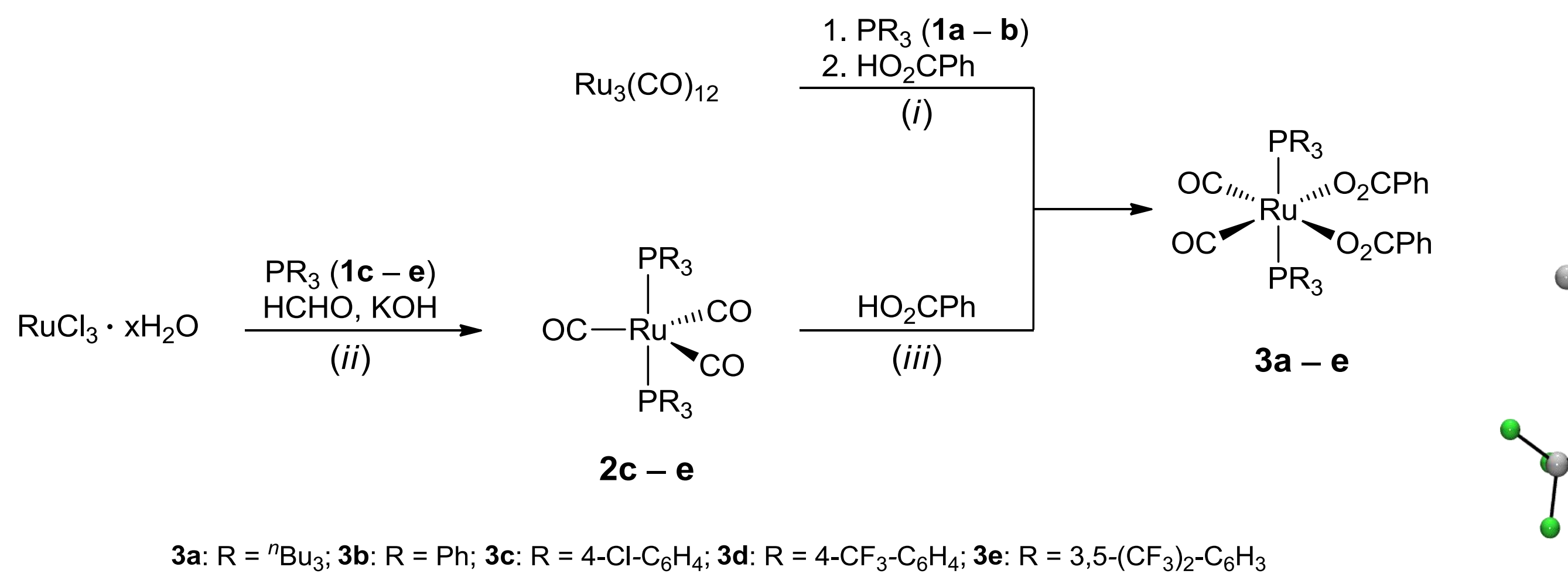
Introduction

β-Oxopropyl esters are important substrates in the pharmaceutical chemistry as the acetonyl ester motif can be found in many biologically active steroids like ulipristal acetate, which is an active component for emergency contraception or treatment of uterine fibroids.[1] Furthermore, β-oxo esters can be easily transformed into the corresponding α-hydroxy ketones,[2] which are key building blocks in many natural products.[3] As activated esters they are efficient acylating reagents which give access to amides and peptides.[4] In contrast to other known methodologies for the synthesis of β-oxo esters, e.g., the two-step hydration and esterification of propargylic alcohols,[5] the direct ruthenium-catalyzed addition, which was first described by Mitsudo and Watanabe[6] in 1987, is the most straightforward and atom-economical approach.[7] Up to date, the mononuclear Ru(II) derivatives [Ru(η^6-arene)(PR_3)Cl_2] (arene = *p*-cymene, C_6H_6; R = Ph, Me), and the dinuclear species [$Ru_2(CO)_4(PPh_3)_2(\mu^2\text{-}O_2CH)_2$] have shown the best productivities for this reaction.[8] Herein, we present new air stable ruthenium complexes for the effective catalytic conversion of even challenging substrates like 1,1-diphenyl-2-propyn-1-ol or demanding steroid ethisterone to *β*-oxopropyl esters under mild reaction conditions.

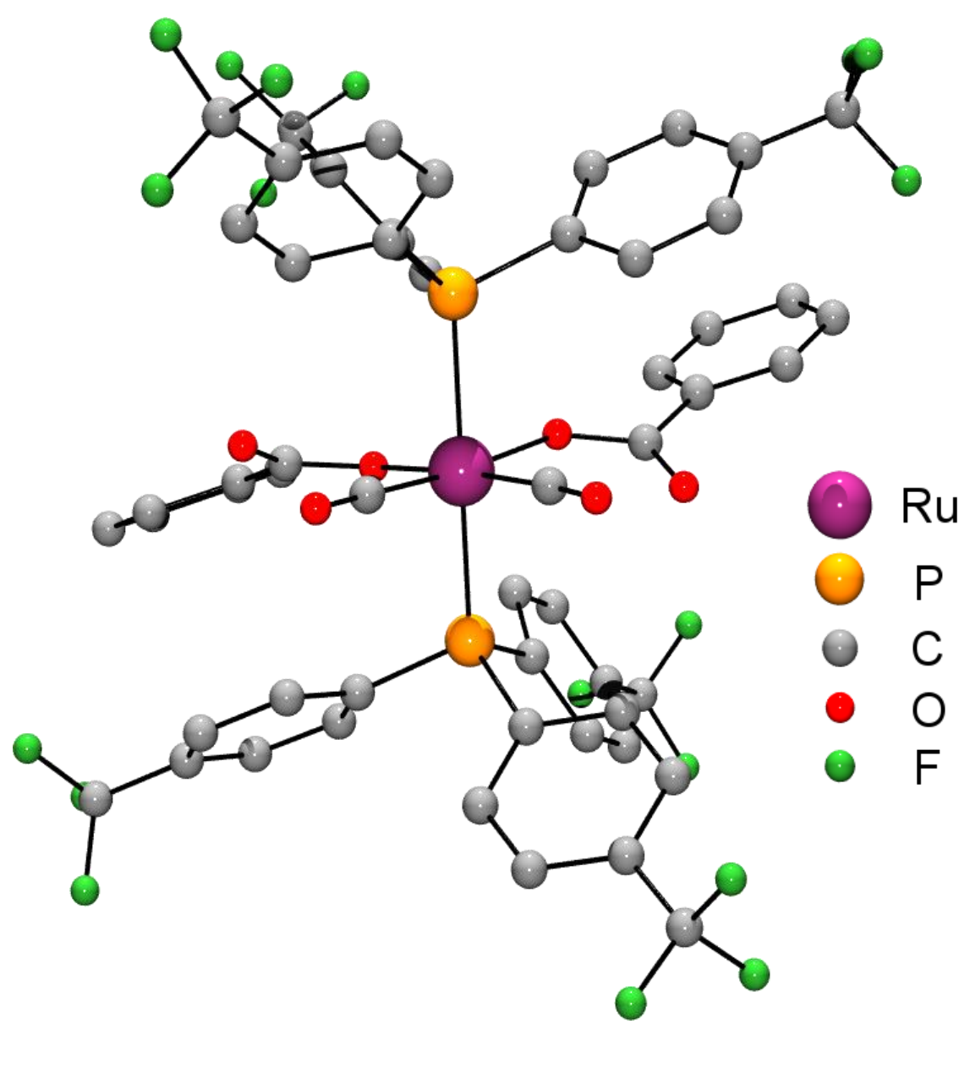
Synthesis and Characterization



2d

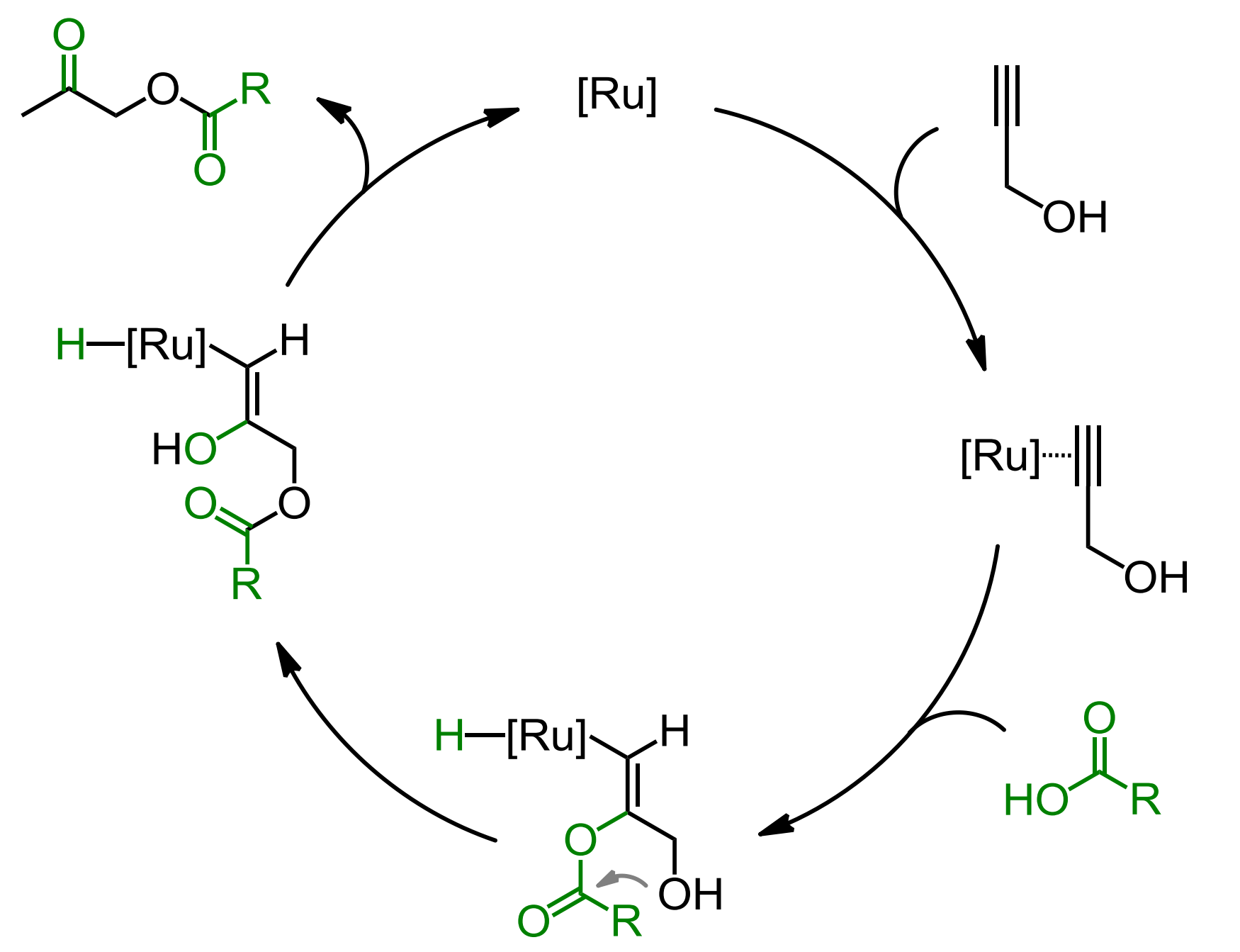


Scheme 1. Synthesis of ruthenium complexes **2c – e** and **3a – e**. (*i*) MIBK, ΔT, 16 h; (*ii*) 2-methoxyethanol, ΔT, 8–16 h; (*iii*) MIBK, 100 °C, 1 h.

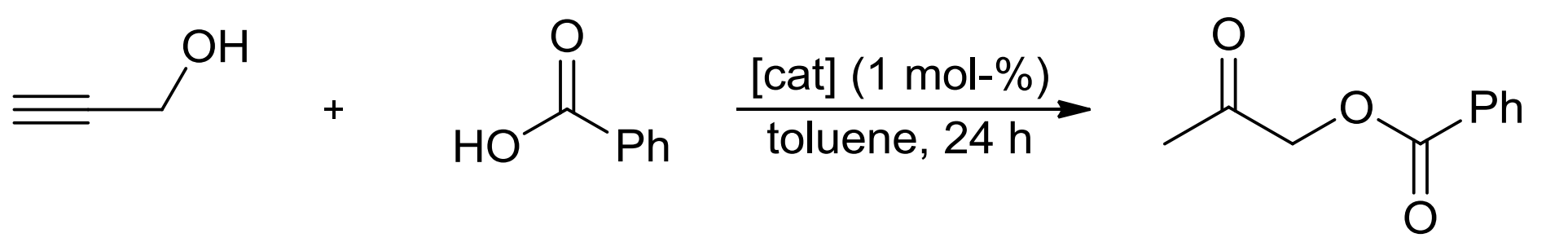


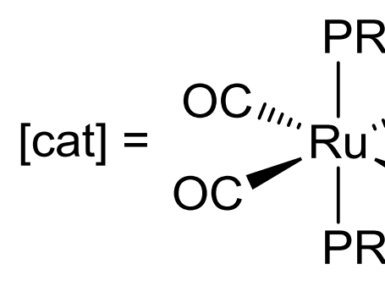
3d

Proposed Mechanism



Influence of Phosphine Ligands in the *β*-Oxo Ester Synthesis





[cat] =

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

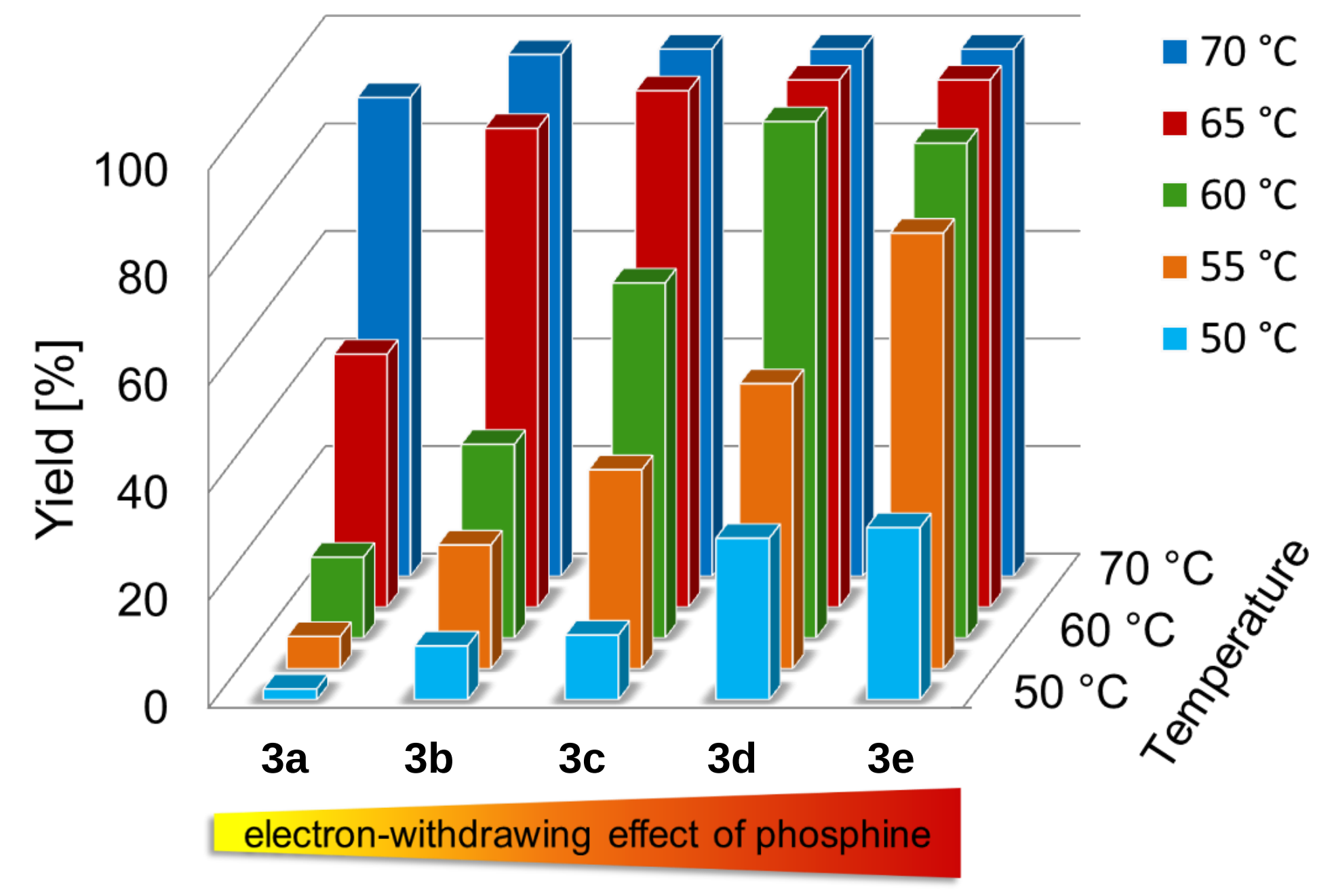


Figure 1. Screening of complexes [$Ru(CO)_2(PR_3)_2(O_2CPh)_2$] (**3a**, R = ^{n}Bu; **3b**, R = Ph; **3c**, R = 4-Cl-C_6H_4; **3d**, R = 4-CF_3-C_6H_4; **3e**, R = 3,5-$(CF_3)_2$-C_6H_3) on their productivity in the addition of benzoic acid to propargylic alcohol at varying temperatures.

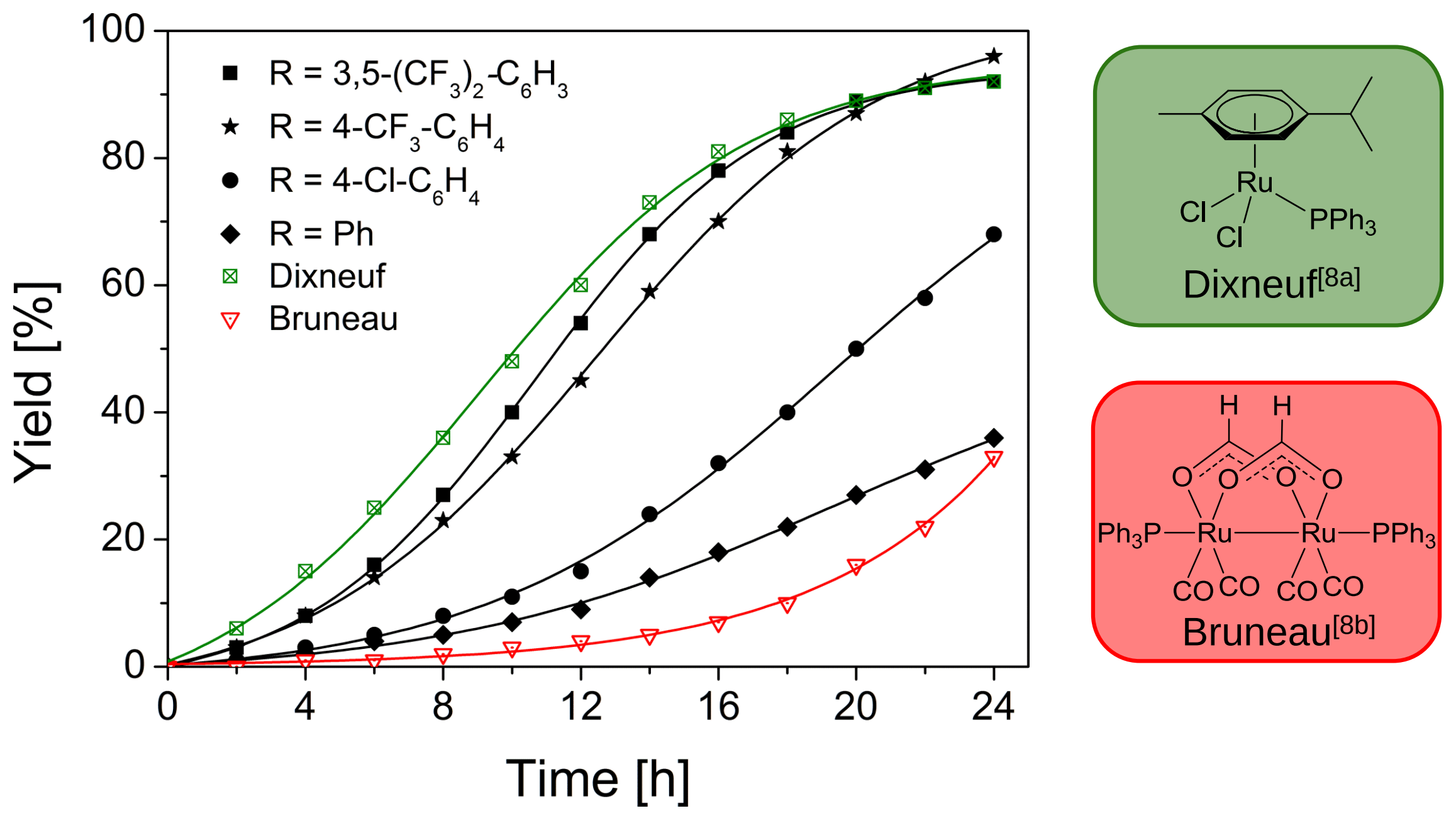
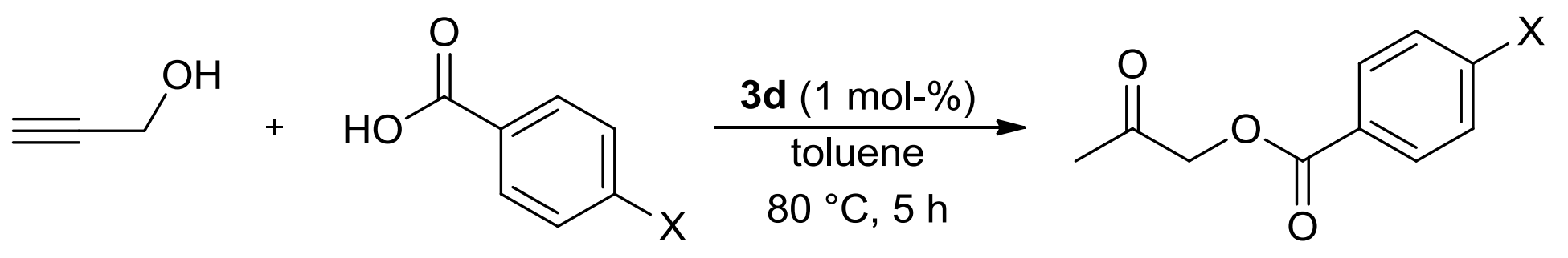
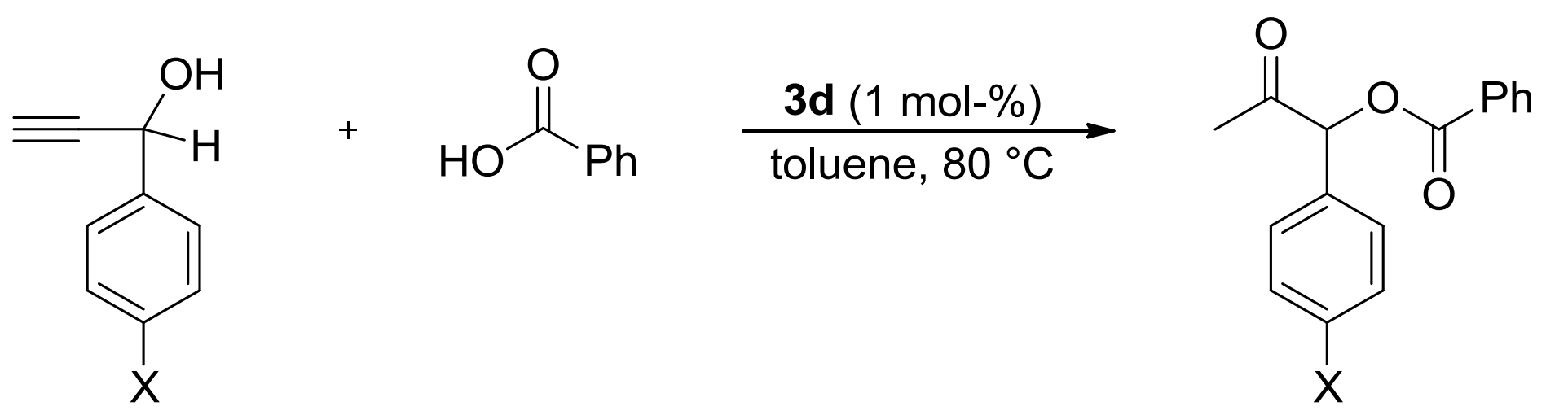


Figure 2. Comparison of the reaction profiles for mononuclear Ru-complexes **3b – e** with literature known catalyst [Ru(*p*-cymene)(PPh_3)Cl_2], firstly applied by Dixneuf *et al.*, and the dimeric complex [$Ru_2(CO)_4(PPh_3)_2(O_2CH)_2$], established by Bruneau *et al.,* in the addition of benzoic acid to propargylic alcohol at 60 °C.

Electronic Influence of the Carboxylic Acid and the Propargylic Alcohol





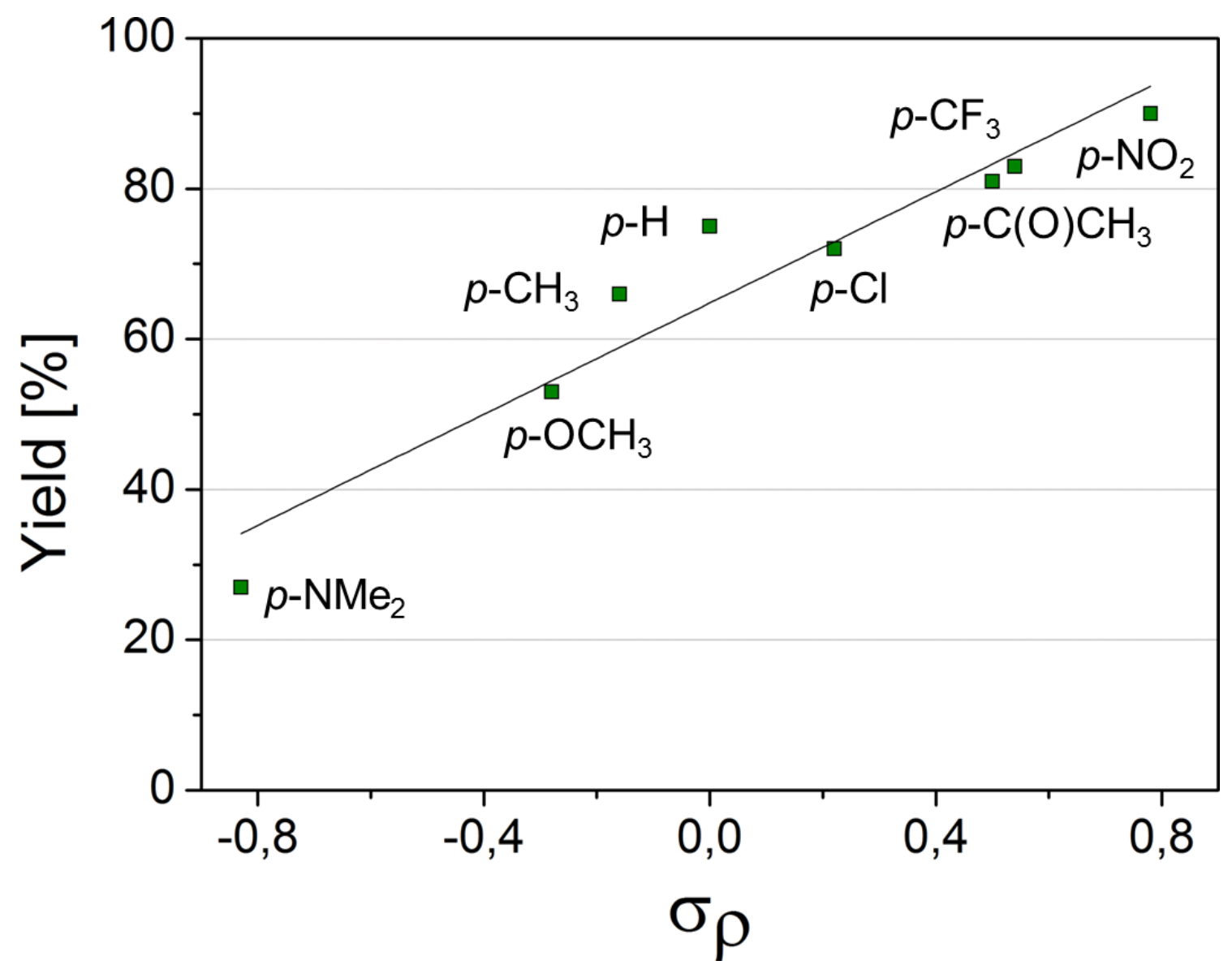


Figure 3. Hammett plot of the coupling reaction of *para*-substituted benzoic acids 4-X-C_6H_4-CO_2H with propargylic alcohol.

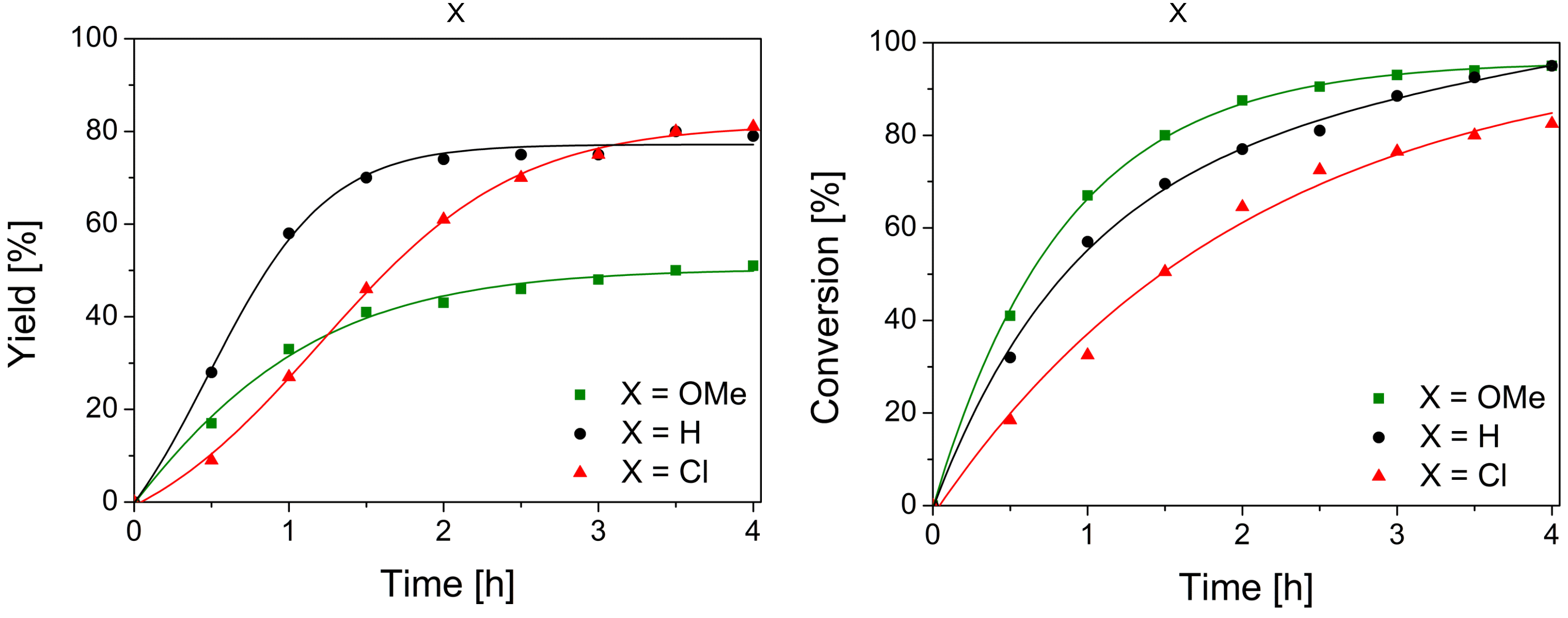
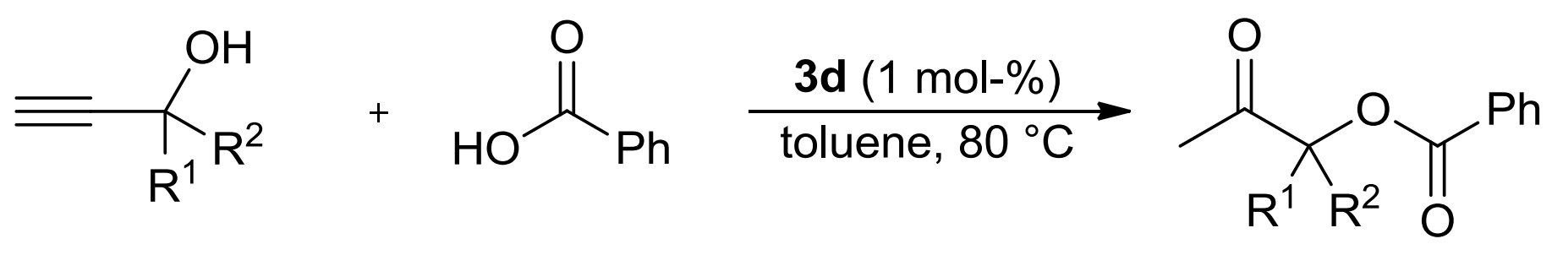
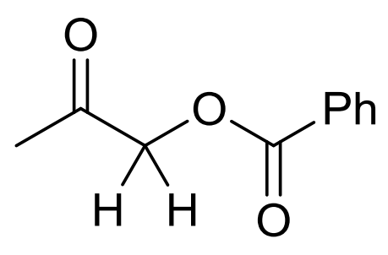
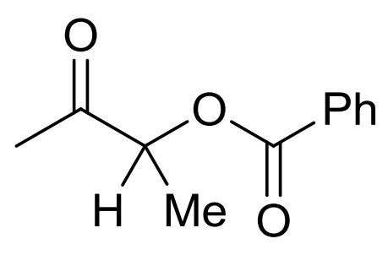
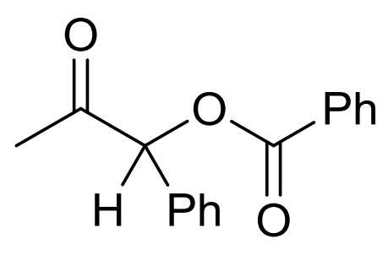
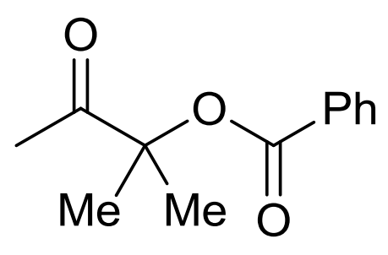
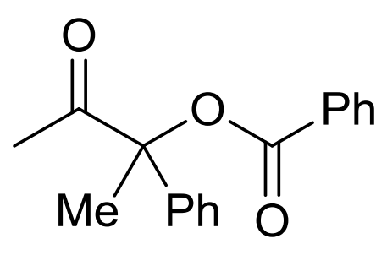
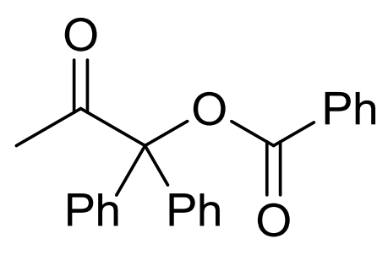
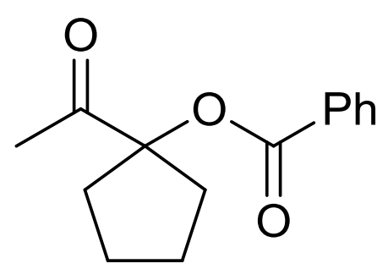
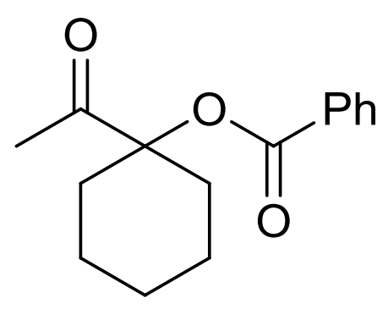
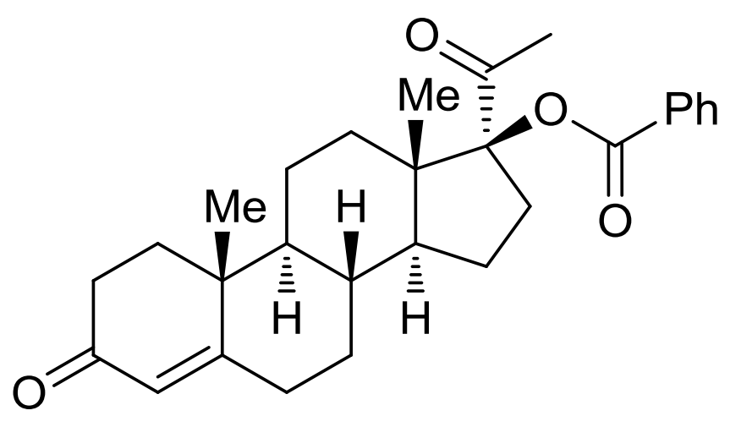


Figure 4. Comparison of the Yield-Time plots (left) and the Conversion-Time plots (right) for the reaction of varying *para*-substituted 1-phenylprop-2-yn-1-ols with benzoic acid at 80 °C in toluene.

Scope of the Propargylic Alcohol

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



Entry	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.

Conclusion, References and Acknowledgement

Ruthenium complexes **3a – e** are efficient catalysts in the synthesis of *β*-oxo esters from carboxylic acids and propargylic alcohols. We could show that the phosphine´s electronic nature has a considerably influence on the productivity. When ruthenium complexes with electron-withdrawing phosphine ligands (**3c – e**) are applied, the reaction proceeds with higher activity. The Hammett study demonstrates that electron-withdrawing groups at the benzoic acids modestly increase the productivity. The conversion of *para*-substituted 1-phenylprop-2-yn-1-ols (X = OMe, H, Cl) reveals electron-rich substituents at the propargylic alcohol not only to accelerate the desired reaction but also side reactions like Meyer-Schuster and Rupe rearrangements.[9] 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[8,10] even challenging substrates like bulky tertiary propargylic alcohol 1,1-diphenyl-2-propyn-1-ol or biologically active steroid ethisterone could be successfully converted under mild reaction conditions.

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