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Atom Economic Ruthenium-Catalyzed Synthesis of Bulky β-Oxo Esters

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Dedicated to Professor Dr. Klaus Banert on the occasion of his 60th birthday.

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Abstract: Ruthenium complexes with the formulae $Ru(CO)_2(PR_3)_2(O_2CPh)_2$ [**6a–h**; R = *n*-Bu, *p*-MeO-C_6H_4, *p*-Me-C_6H_4, Ph, *p*-Cl-C_6H_4, *m*-Cl-C_6H_4, *p*-CF_3-C_6H_4, *m*,*m*′-$(CF_3)_2C_6H_3$] were prepared by treatment of triruthenium dodecacarbonyl [$Ru_3(CO)_{12}$] with the respective phosphine and benzoic acid or by the conversion of $Ru(CO)_3(PR_3)_2$ (**8e–h**) with benzoic acid. During the preparation of **8**, ruthenium hydride complexes of type $Ru(CO)(PR_3)_3(H)_2$ (**9g**, **h**) could be isolated as side products. The molecular structures of the newly synthesized complexes in the solid state are discussed. Compounds **6a–h** were found to be highly effective catalysts in the addition of carboxylic acids to propargylic alcohols to give valuable β-oxo esters. The catalyst screening revealed a considerably influence of the phosphine′s electronic nature on the resulting activities. The best performances were obtained with complexes **6g** and **6h**, featuring electron-withdrawing phosphine ligands. Additionally, catalyst **6g** is very active in the conversion of sterically demanding substrates, leading to a broad substrate scope. The catalytic preparation of simple as well as challenging substrates succeeds with catalyst **6g** in yields that often exceed those of established literature systems. Furthermore, the reactions can be carried out with catalyst loadings down to 0.1 mol% and reaction temperatures down to 50 °C.

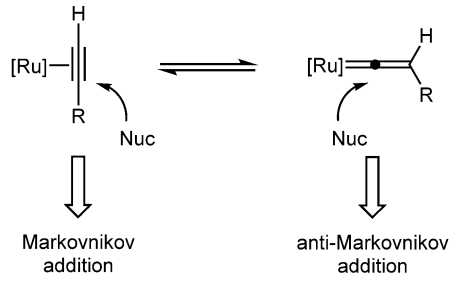
Keywords: homogeneous catalysis; phosphines; propargylic alcohols; ruthenium; solid state structure

Introduction

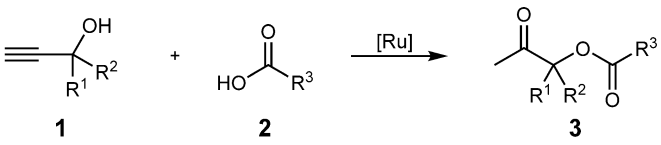
Designing effective catalysts for reactions with high atom economy and high selectivity is still a fundamental goal for the chemical industry, as it faces rising costs of waste disposal.[1,2] In this context, ruthenium catalysts obtain increasing interest because of their ability to catalyze a variety of selective carbon-carbon and carbon-heteroatom bond formations.[3,4]

Ruthenium catalysts are known to activate alkynes towards nucleophilic attack by coordination of the triple bond to the electrophilic metal center.[5,6] Depending on the tautomerization between η^2-alkyne and vinylidene binding modes the ruthenium complexes promote either the Markovnikov addition or afford the anti-Markovnikov products by nucleophilic attack at the α-carbon of the vinylidene analogues (Scheme 1).[7–9]

The nucleophilic addition of carboxylic acids to terminal alkynes is an elegant method to produce enol esters.[10] The addition to propargylic alcohols leads to β-oxo esters (Scheme 2),[11] which are useful intermediates in the synthesis of natural products and pharmaceuticals.[12] For example, β-oxo esters can be



Scheme 1. Tautomerization of alkyne/vinylidene complexes and their different reactivity towards nucleophilic attack.[7]



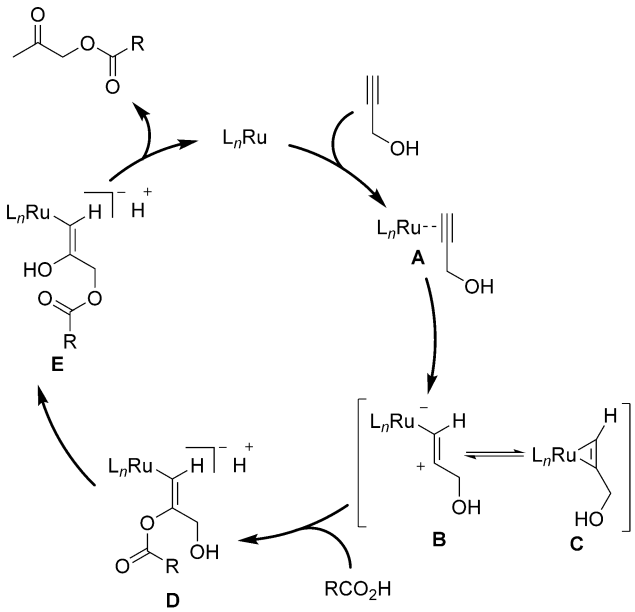
Scheme 2. Formation of β-oxopropyl esters by the Ru-catalyzed addition of carboxylic acids to propargylic alcohols.

easily transformed into the corresponding α-hydroxy ketones,[13] which are key building blocks in many natural products.[12b,14] As activated esters they are efficient acylating reagents which give access to amides and peptides.[15,16] It has been shown that they can also be used as antibacterial compounds[17] and photolabile protecting groups for carboxylic acids.[18] In addition, they are intermediates in the synthesis of furanones[19] and imidazoles.[20]

In comparison to other known synthetic methodologies for the preparation of β-oxo esters, e.g., the two-step hydration/esterification of propargylic alcohols,[21] the carboxylation of α-halo ketones,[18a] the copper-catalyzed insertion of α-diazo ketones into the O–H bond of carboxylic acids,[22] the Wacker oxidation of allyl carboxylates[23] or the oxidation of ketones with metal acetate complexes,[24] the direct ruthenium-catalyzed addition is the most straightforward and atom-economical route. Moreover, the reaction conditions are relatively mild (60 to 120 °C) and the substrates are simple and commercially available.[25]

The proposed mechanism for the ruthenium-catalyzed formation of β-oxo esters starts with the nucleophilic attack of the carboxylic acid to the η^2-alkyne ruthenium complex **A** giving Markovnikov addition. To explain the regioselectivity of the nucleophilic attack at the C-2 position of the alkyne, the species **B** and **C** have been postulated as reactive intermediates.[4,16,26] The resulting enol ester **D** undergoes an intramolecular transesterification to the alkenyl derivative **E**, which after keto-enol tautomerization and protonation releases the β-oxo ester and regenerates the catalytically active ruthenium species (Scheme 3).[27–29]

The first catalytic system which was able to generate β-oxo esters was described by Mitsudo and Watanabe.[30] They employed a mixture composed of bis(η^5-cyclooctadienyl)ruthenium, $P(n\text{-}Bu)_3$ and maleic anhydride. To date, the best results in terms of productivity and selectivity have been achieved with mononuclear arene-Ru(II) derivatives $[Ru(\eta^6\text{-arene})(PR_3)Cl_2]$ [arene = *p*-cymene, C_6H_6, C_6Me_6; $PR_3 = PPh_3$, PMe_3, phosphoramidite, $P(cyclo\text{-}C_4H_3O)_2(C{\equiv}CFc)$], the mononuclear bis(allyl)ruthenium(IV) complex *trans*-$[Ru(\eta^3{:}\eta^3\text{-}C_{10}H_{16})(PPh_3)Cl_2]$ and the dimeric complex $[Ru_2(CO)_4(PPh_3)_2(\mu^2\text{-}O_2CH)_2]$.[11,27–29,31,32] In addition, Cadierno and co-workers have shown that ruthenium(II) complexes containing hydrosoluble phosphine ligands enable the formation of β-oxo esters in aqueous medium.[27]



Scheme 3. Proposed mechanism for the Ru-catalyzed formation of β-oxopropyl esters.[27–29]

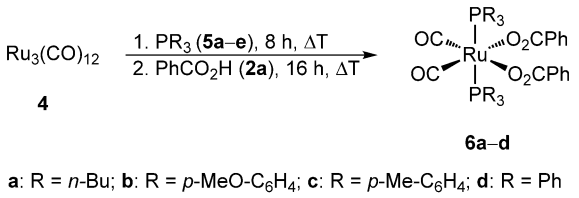
Recently, we could show for the first time that mononuclear ruthenium compounds of the type $[Ru(CO)_2(PPh_3)_2(O_2CR)_2]$ ($R = CH_2OCH_3$, *i*-Pr, *t*-Bu, 2-*cyclo*-C_4H_3O, Ph) are efficient catalysts for the addition of carboxylic acids to propargylic alcohols, even when challenging substrates were applied.[33] The varying carboxylate ligands did not have an influence on the productivities, because the carboxylates exchange rapidly during the reaction, as it was proven by $^{31}P\{^1H\}$ NMR spectroscopic studies.[33]

In continuation of our investigations and since the tautomerization between the η^2-alkyne and vinylidene binding mode (Scheme 1) should be affected by electrophilicity of the metal fragment,[7–9,34] we explored the electronic influence of different phosphine ligands on the reactivity of the catalytic system. Accordingly, we synthesized a series of novel mononuclear Ru(II) complexes of type $[Ru(CO)_2(PR_3)_2(O_2CPh)_2]$ [R = *n*-Bu, *p*-MeO-C_6H_4, *p*-Me-C_6H_4, Ph, *p*-Cl-C_6H_4, *m*-Cl-C_6H_4, *p*-CF_3-C_6H_4, *m*,*m*′-$(CF_3)_2C_6H_3$] with modified phosphine ligands. These ruthenium complexes were successfully applied in the catalytic formation of β-oxo esters under mild reaction conditions. Furthermore, experiments to better understand the mechanism of the reaction, like a correlation of the Hammett value and the reaction rate for a series of *para*-substituted benzoic acids, were performed.

Results and Discussion

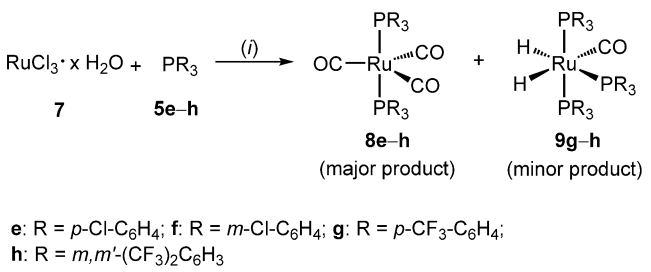
Synthesis and Characterization of Novel Ruthenium-Carboxylate Complexes

The ruthenium complexes $[Ru(CO)_2(PR_3)_2(O_2CPh)_2]$ with basic phosphine ligands (**6a**, R = *n*-Bu; **6b**, R = *p*-MeO-C_6H_4; **6c**, R = *p*-Me-C_6H_4; **6d**, R = Ph) were prepared starting from $Ru_3(CO)_{12}$ (**4**) by a single step conversion with the respective phosphine **5** and benzoic acid (**2a**) analogously to a procedure described by Bianchi[35] (Scheme 4).



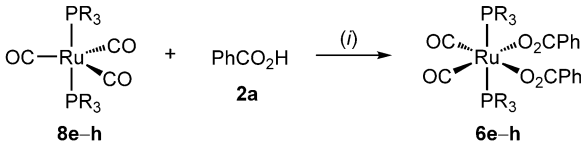
Scheme 4. Synthesis of ruthenium complexes **6a–d**.

For ruthenium complexes **6e–h** featuring electron-withdrawing phosphine ligands the above described synthesis procedure led, however, to poor yields and purities of the obtained products. Therefore, we chose another preparation strategy using $Ru(CO)_3(PR_3)_2$ [**8e**, R = *p*-Cl-C_6H_4; **8f**, R = *m*-Cl-C_6H_4; **8g**, R = *p*-CF_3-C_6H_4; **8h**, R = *m,m'*-$(CF_3)_2C_6H_3$] as starting material. Complexes **8e–h** could be obtained by slightly modified literature procedures.[36] To a boiling solution of $RuCl_3 \cdot x H_2O$ (**7**), the phosphine **5** and KOH dissolved in 2-methoxyethanol an aqueous formaldehyde solution was added (Scheme 5). The less basic the phosphine, the longer the solution had to be refluxed (2 to 18 h) after which time the product precipitated as yellow microcrystals. For the success of this reaction, particularly for the preparation of **8g** and **8h**, an adequate amount of solvent is essential to avoid precipitation of sparingly soluble intermediates, which then may fail to react further. As such intermediates we could isolate ruthenium hydride complexes of type $Ru(CO)(PR_3)_3(H)_2$ [**9g**, R = *p*-CF_3-C_6H_4; **9h**, R = *m,m'*-$(CF_3)_2C_6H_3$]. The isostructural complex $Ru(CO)(PPh_3)_3(H)_2$ is known since 1968[37] and has become an important and widely used catalyst especially in hydrogen transfer reactions.[38]



Scheme 5. Synthesis of ruthenium complexes **8e–h** and **9g**, **h**. (*i*) 2-Methoxyethanol, HCHO, KOH, Δ*T*, 2–18 h.

The ruthenium complexes **8e–h** were subsequently converted with benzoic acid to novel ruthenium carboxylates $[Ru(CO)_2(PR_3)_2(O_2CPh)_2]$ [**6e**, R = *p*-Cl-C_6H_4; **6f**, R = *m*-Cl-C_6H_4-Cl; **6g**, R = *p*-CF_3-C_6H_4; **6h**, R = *m,m'*-$(CF_3)_2C_6H_3$] (Scheme 6).[39] As solvent for this conversion 4-methylpentan-2-one was chosen, as it prevents the formation of dinuclear ruthenium side products.[33] For complexes **6b–d** a preparation methodology starting from $Ru(CO)_3(PR_3)_2$ (**8b–d**) is also possible.



Scheme 6. Synthesis of ruthenium complexes **6e–h**. (*i*) 4-Methylpentan-2-one, 100 °C, 1 h.

The identity of all compounds was confirmed by elemental analysis, IR and NMR (^1H, $^{13}C\{^1H\}$, $^{31}P\{^1H\}$) spectroscopy and ESI mass spectrometry (see the Supporting Information). In addition, the structures of **6a–c**, **6e–h**, **8e–h** and **9g** in the solid state were determined by single-crystal X-ray structure analysis.

The $^{31}P\{^1H\}$ NMR spectra of **6a–h** and **8b–h** each exhibit one singlet for the phosphine ligands in a range from 17.6 to 35.9 ppm for **6a–h** and from 49.8 to 63.5 ppm for **8b–h** (Table 1). When compared to the free phosphines **5a–h**, all resonance signals of the as-prepared ruthenium complexes are shifted downfield, indicating the coordination to the transition metal.[40]

Table 1. Comparison of $^{31}P\{^1H\}$ NMR δ values of complexes **6a–h** and **8b–h** with free phosphines **5a–h**.

δ PR_3[a] [ppm]		δ PR_3[a] [ppm]		δ free PR_3[a] [ppm]	
6a	17.6			**5a**	−30.9
6b	28.3	**8b**	49.8	**5b**	−10.1
6c	29.8	**8c**	52.5	**5c**	−7.9
6d	31.2	**8d**	55.4	**5d**	−5.4
6e	30.7	**8e**	54.4	**5e**	−8.4
6f	32.4	**8f**	58.4	**5f**	−4.5
6g	32.8	**8g**	57.6	**5g**	−6.0
6h	35.9[b]	**8h**	63.5[b]	**5h**	−4.3

[a] Solvent: $CDCl_3$.
[b] Solvent: acetone-d_6.

The ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of **6a–h** and **8b–h** are in accordance with the proposed structures. Some of the signals in the $^{13}C\{^{1}H\}$ NMR spectra are split into triplets. This is a common phenomenon for complexes containing *trans*-phosphine ligands, which was observed for this kind of complexes before.[33] Furthermore, this finding is confirmed by calculations of Metzinger[41] and Harris.[42]

The ^{1}H NMR spectrum of complex **9g** exhibits hydride signals ranging from −8.8 to −7.1 ppm with a characteristic splitting pattern of a triplet of doublets of doublets (tdd) for the hydride *cis* to P_{eq} and a doublet of triplets of doublets (dtd) for the hydride *trans* to P_{eq} (Figure 1a). The $^{31}P\{^{1}H\}$ NMR spectrum of **9g** shows two signals of which the equatorial phosphine P_{eq} reveals a triplet at 46.1 ppm and the axial phosphine groups P_{ax} a doublet at 57.6 ppm (Figure 1b).

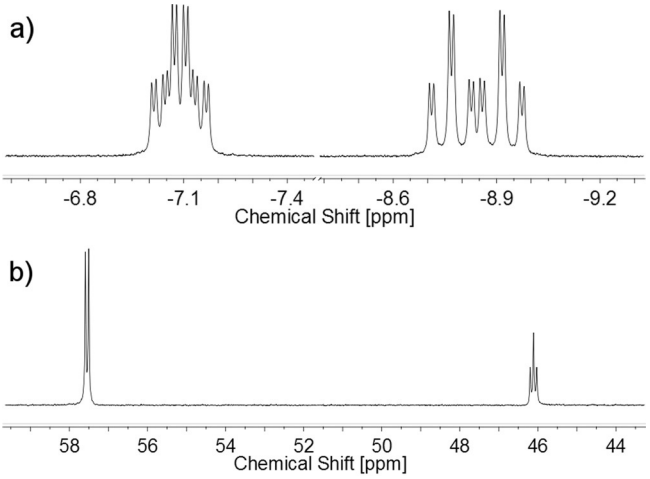


Figure 1. a) ^{1}H NMR spectrum of **9g** in $CDCl_3$ (hydride region); b) $^{31}P\{^{1}H\}$ NMR spectrum of **9g** in $CDCl_3$.

The IR spectra of ruthenium complexes **6a–h** distinguish themselves by two intensive absorptions for the stretching vibrations of the terminal carbonyl groups between 1966 and 2059 cm^{-1} and by the characteristic bands for the asymmetric ($\tilde{\nu}_{asym}$) and symmetric ($\tilde{\nu}_{sym}$) carboxylate stretching vibrations. From the number of the CO vibrations one can conclude that the carbonyl groups have to adopt a *cis*-arrangement in the octahedral coordination sphere of the Ru(II) ion, as for a *trans* isomer only one strong carbonyl stretching is expected.[39b] The increasing frequency of the carbonyl stretching vibrations for complexes **6a–h** as well as **8b–h** indicates a decreased back-bonding in electron-poor complexes (Table 2). Furthermore, the separation $\Delta\tilde{\nu}_{CO_2}$ ($\Delta\tilde{\nu}_{CO_2} = \tilde{\nu}_{asym} - \tilde{\nu}_{sym}$) between the C–O stretching frequencies can be used to estimate the nature of carboxylate coordination as described by Deacon and Phillips.[43] The large values of $\Delta\tilde{\nu}$ ranging from 252 to 284 cm^{-1} indicate a monodentate coordination of the carboxylate groups (Table 2), which was confirmed by single-crystal X-ray structure determination (see below).

Table 2. IR stretching frequencies of carbonyl and carboxylate groups of complexes **6a–h**.

Complex	$\tilde{\nu}_{CO}$ [cm^{-1}]	$\Delta\tilde{\nu}_{CO_2}$ [a] [cm^{-1}]
6a	2036 (vs), 1970 (vs)	264
6b	2030 (s), 1966 (s)	254
6c	2045 (s), 1983 (s)	252
6d	2047 (vs), 1986 (vs)	270
6e	2035 (vs), 1972 (vs)	269
6f	2044 (vs), 1982 (vs)	275
6g	2051 (s), 1991 (s)	284
6h	2059 (m), 2007 (m)	277

[a] $\Delta\tilde{\nu}_{CO_2} = \Delta\tilde{\nu}_{asym} - \Delta\tilde{\nu}_{sym}$.

The ruthenium carboxylates **6a–c**, **6e–h**, the tricarbonyl containing **8b**, **e**, **g** and ruthenium hydrides **9g**, **h** were characterized by single-crystal X-ray diffraction analysis. One example of each type of ruthenium complexes is shown in Figure 2, Figure 3 and Figure 4, respectively. Remaining structures, the explanation of the crystal growth as well as further details pertaining to the crystal and structure refinement data are summarized in the Supporting Information.

The title compounds crystallize in the triclinic space group *P*-1 (**6f**, **g**, **8e**, **g**), in the monoclinic space

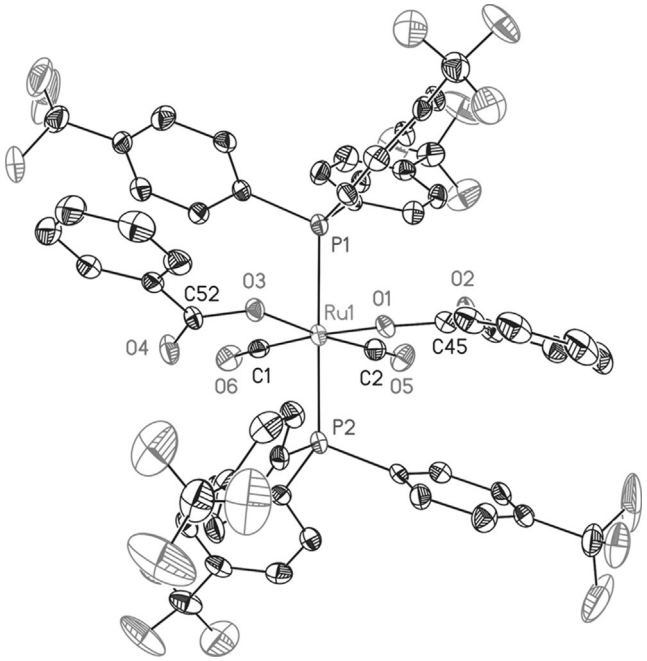


Figure 2. ORTEP diagram (50% probability level) of the molecular structure of **6g** with the selected atom numbering scheme. Hydrogen atoms and packing solvent (CH_2Cl_2) have been omitted for clarity.

groups *C*2/*c* (**6a**, **c**), $P2_1/c$ (**6b**, **9g**), $P2_1/n$ (**6e**, **8b**, **9h**) and $P2_1/a$ (**6h**) with one crystallographically independent molecule in the asymmetric unit, except for **6h** with two and **6a** with one half of the compound and a mirror plane through the Ru atom. Some crystals contain packing solvent (see the Supporting Information). Most of the CF_3 substituents and disordered phenyl rings have been refined using rigid models (AFIX, DFIX and DANG instructions).

The octahedral ruthenium carboxylates **6a–c** and **6e–h** (Figure 2, Supporting Information, Figures S1–S6) consist of two axial *trans*-positioned phosphines and two *cis*-carbonyl and benzoate ligands in the equatorial plane, with the phosphines bent towards the carboxylates with P–Ru–P angles of 166.75(4)–175.47(3)°. The carbonyl oxygens of the carboxylates are directed to the carbonyls avoiding electronic interactions. Thus, the steric demand affects the O–Ru–C angle, which is increased to 94.51(6)–96.80(8)°, whereas the O–Ru–O [79.06(8)–82.74(10)°] and C–Ru–C [84.45(18)–88.96(10)°] angles are decreased. Within the carboxylate moieties a clear distinction between a C–O single bond, with 1.287(3)–1.303(6) Å, bonded to the Ru atom, and a C=O double bond of 1.225(6)–1.235(3) Å is possible, which verifies the results of the IR measurements (Table 2).

Furthermore, the carboxylate plane is almost coplanar with the phenyl ring [5.7(2)–23.2(4)°] and the central C_2O_2Ru plane [19.7(3)–32.82(11)°].[44] The torsions of the carbonyl atoms of the carboxylates in each complex are always directed *anti*, above and below the central plane.

Tricarbonyl containing compounds **8b**, **8e** and **8g** (Figure 3, Supporting Information, Figures S7 and S8) exhibit a trigonal bipyramidal coordination environment with both phosphines in the axial position. The higher symmetry results in more linear P–Ru–P angles [174.46(2)–178.95(7)°] compared to the carboxylates **6**. Dihydrido complexes **9g**, **h** (Figure 4, Supporting Information, Figure S9) exhibit a strong distorted octahedral coordination environment, bearing two phosphine ligands in the axial, and one in the equatorial position with the remaining carbonyl ligand and both hydrogens arranged *cis* towards each other. The steric demand of the equatorial phosphine diminishes the P–Ru–P angle to 143.81(11) (**9g**) and 148.87(6)° (**9h**) bending towards both hydrogens, and thus, increases the angles between the phosphines in equatorial and axial position to 99.54(5)–109.57(10)°. The positions of the hydrogen atoms and their Ru–H distances were refined based on residual electron density in **9h** [1.63(6) and 1.55(5) Å] or fixed to 1.80(2) Å for **9g**, due to strongly deviating values for known crystal structures.[45]

The C≡O bond of the carbonyls is neither affected by the electronically different phosphines, nor by different substitution patterns at the Ru atom. Furthermore, an influence of the phosphines is also not present for the Ru–P bonds, which are comparable for the carboxylates **6** and **8b** [2.3496(13)–2.4297(6) Å]. However, the tricarbonyl compounds **8e**, **g** exhibit significantly shorter bond lengths of 2.3264(16)–2.3311(9) Å, due to their electron withdrawing *para* substituents. In the dihydrido complexes **9g**, **h** a differentiation between the axial phosphines, whose Ru–P bonds are shortened to 2.304(3)–2.3199(15) Å and those in the equatorial plane with longer distances of 2.366(3)–2.3698(16) Å is possible (Supporting Information, Table S12).

The torsion of the *p*-methoxy substituents in **6b** and **8b** remains coplanar between 0.1(4) and 15.1(4)°.

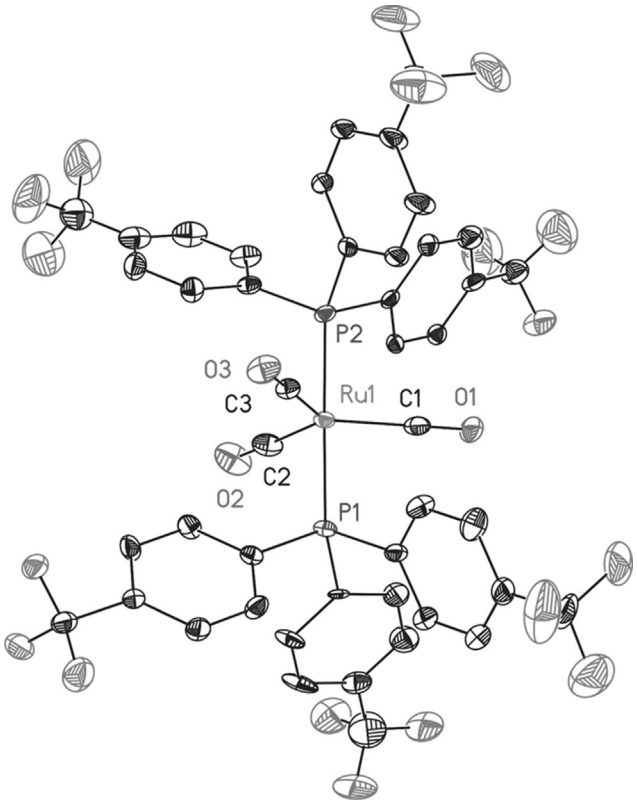


Figure 3. ORTEP diagram (30% probability level) of the molecular structure of **8g** with the selected atom numbering scheme. Hydrogen atoms, disordered parts and packing solvent (CH_2Cl_2) have been omitted for clarity.

Catalytic Experiments

As in our previous catalytic investigations we chose the conversion of benzoic acid and propargylic alcohol in toluene as model reaction.[33] The reactions were performed under relatively mild conditions and no special precautions against air or moisture in the handling of the complexes were needed. In a typical experiment, benzoic acid (1.0 mmol), propargylic

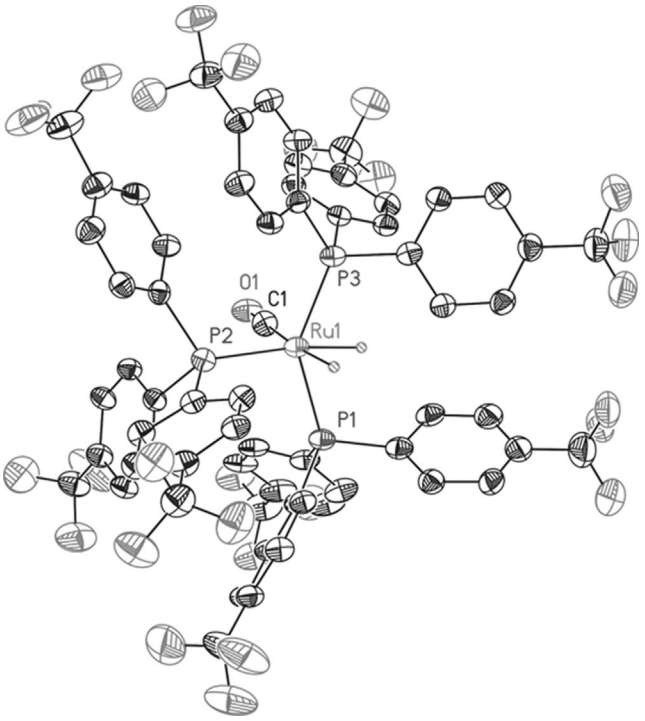


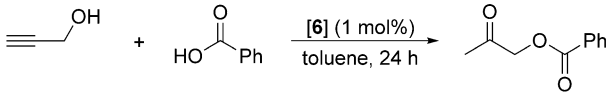
Figure 4. ORTEP diagram (50% probability level) of the molecular structure of **9g** with the selected atom numbering scheme. Aromatic hydrogen atoms, disordered parts and packing solvent (3 toluene) have been omitted for clarity.

alcohol (2.0 mmol), the catalyst **6** (0.01 mmol) and acenaphthene (0.5 mmol) as internal standard were dissolved in toluene (1 mL) and reacted for 24 h at 60 °C. The products have all been characterized spectroscopically, and the efficiencies of the reactions have been determined by ^{1}H NMR spectroscopy (for optimization studies and reaction profiles) or by isolation (substrate screening).

It was already shown that the carboxylates bound to the ruthenium in **6** do not influence the productivities of the reactions, because they exchange rapidly in solution for the carboxylic acids applied during the reaction.[33] For this reason we decided just to prepare and apply the respective benzoate complexes of **6**, as in our model reaction and most other reactions benzoic acid was converted.

Table 3 shows the screening of ruthenium complexes **6a**–**h** in the addition of benzoic acid to propargylic alcohol to give 2-oxopropyl benzoate at varying temperatures. In general, it can be seen that the working temperature plays a crucial role. A decrease of the temperature by only 5 °C can lead to a productivity drop by half or even more. All catalysts, except for **6a**, reached nearly quantitative yields at 70 °C, whereas the conversion at 50 °C is for all tested complexes less than one third. The best conditions to compare the performances of the catalysts were found at 60 °C due to the wide range of the obtained yields. The

Table 3. Dependency of the productivity on the applied catalyst and temperature in the formation of 2-oxopropyl benzoate.[a]



Entry	Catalyst	Yield[b] [%] 50 °C	55 °C	60 °C	65 °C	70 °C
1	**6a**	2	6	15	47	89
2	**6b**	15	38	85	98	98
3	**6c**	14	31	64	98	98
4	**6d**	10	23	36	89	97
5	**6e**	12	37	66	96	98
6	**6f**	10	29	44	96	98
7	**6g**	30	53	96	98	98
8	**6h**	32	81	92	98	98

[a] *Reaction conditions:* benzoic acid (1.0 mmol), propargylic alcohol (2.0 mmol), catalyst **6** (0.01 mmol), acenaphthene (0.5 mmol), 24 h, toluene (1 mL).
[b] The yields were determined by ^{1}H NMR spectroscopy applying acenaphthene as internal standard.

screening of ruthenium complexes **6a**–**h** with varying phosphine ligands revealed a considerably influence of the phosphine′s nature on the productivity. At 60 °C the best yields of more than 90% were obtained with complexes **6g**, **h**, which possess the most electron-withdrawing phosphine ligands. Conversely, only 15% was reached with the most basic P(*n*-Bu)$_3$-substituted complex **6a**. This finding can be explained with a facilitated coordination of an electron-rich C≡C triple bond to the electrophilic ruthenium ion, which probably is the first and rate-determining step of the catalytic cycle. Additionally, electron-withdrawing ligands at the ruthenium do not favor the tautomerization of the η^2-alkyne to a vinylidene complex, which would lead to side reactions like anti-Markovnikov addition.[10k] However, the substituted triarylphosphine complexes **6b**, **c** with electron-donating triarylphosphine ligands give better yields than the isostructural PPh_3-substituted complex **6d**. A possible explanation for the increased yields can be found in a facilitated generation of the catalytic active species, which partly compensates electronic drawbacks during the actual catalytic cycle.

In contrast to our previous reported catalytic reactions with less active PPh_3-substituted ruthenium complexes,[33] we waived the addition of Na_2CO_3, as no enhancement was detected for the application with more active catalysts **6g**, **h**.

Besides the productivity, the catalytic activity was also studied. Therefore, the addition of benzoic acid to propargylic alcohol was followed over time for selected catalysts. The yield-time plots are depicted in Figure 5. The overall productivity is mainly deter-

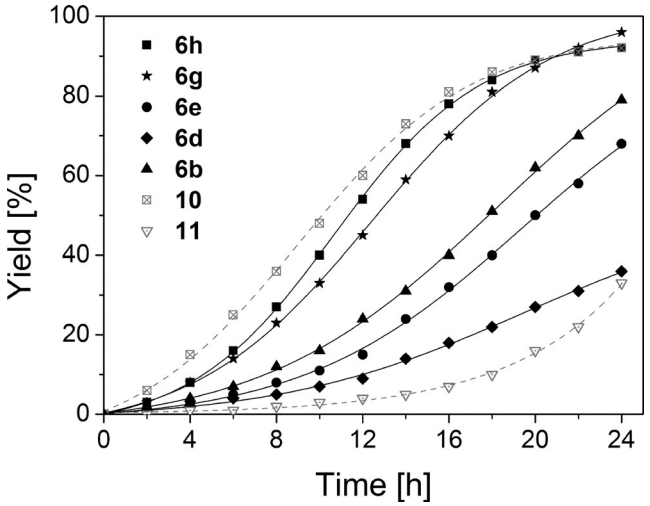


Figure 5. Kinetic investigation for catalysts **6b**, **d**, **e**, **g**, **h**, **10** and **11** in the reaction of benzoic acid with propargylic alcohol to give 2-oxopropyl benzoate (1.0 mol% based on [Ru], 60 °C) followed over time by ^{1}H NMR spectroscopy; for reaction conditions see Table 3.

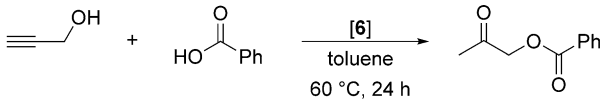
mined by the length of activation time at the beginning of the conversion, whereas the activity of investigated complexes **6b**, **d**, **e**, **g**, **h** is well comparable after the generation of the catalytic active species. Furthermore, we did compare the activity of our complexes with literature known catalysts. As typical examples we chose the mononuclear Ru(*p*-cymene)PPh_3Cl_2 (**10**)[11] and the dinuclear $Ru_2(CO)_4(PPh_3)_2(O_2CH)_2$ (**11**)[31] species. When equal ruthenium loadings are applied, the performances of our catalysts are significantly better than that of dinuclear complex **11**, due to the increased activation time of **11**. Compared to the mononuclear compound **10** the activity and productivity is very similar to that of **6g** and **6h**.

For further testing and optimization reactions complexes **6g**, **h** were chosen, as they showed the highest activities and productivities. First of all, we wanted to find out if the ruthenium loading can be further reduced. Therefore, the yields that could be obtained after 24 h at 60 °C with ruthenium loadings between 0.1 and 1.0 mol% were determined (Table 4). Yields of more than 80% could be reached with 0.5 mol% of **6g** or down to 0.25 mol% of **6h**. With loadings of only 0.1 mol% both catalysts still achieved yields between 34–45%. Nearly no drop of productivity was observed for **6h** going from 1.0 mol% down to 0.5 mol%, which can be explained with its incomplete solubility at higher loadings.

As in literature loadings of 1.0 mol% have been usually applied,[6,11,29,31,33,46] we decided to use this amount in further substrate screenings for reasons of comparability, too.

Applying the optimized reaction conditions (60 °C, 1.0 mol%) somewhat more challenging propargylic alcohols were converted with catalysts **6g**, **h** and literature known **10** to explore their substrate generality (Table 5). Whereas the productivity of the catalysts is comparable, when applying the simplest propargylic alcohol **1a**, significant differences in the obtained yields were observed when sterically more demanding substrates like 2-methyl-3-butyn-2-ol (**1g**) or 1-ethynylcyclohexanol (**1l**) were reacted with benzoic acid at 60 °C. The performance of literature known catalyst **10** is strongly dependent on the steric hindrance of

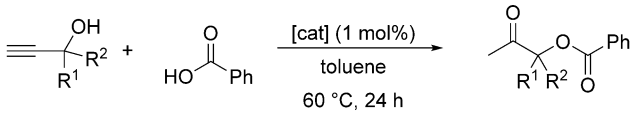
Table 4. Dependency of the productivity on the ruthenium loading in 2-oxopropyl benzoate formation.[a]

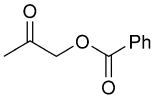
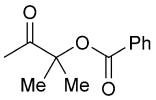
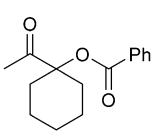


	Yield[b] [%]				
Catalyst (mol%)	0.1	0.25	0.5	0.75	1.0
6g	34	60	82	88	96
6h	45	86	91	91	92

[a] *Reaction conditions:* benzoic acid (1.0 mmol), propargylic alcohol (2.0 mmol), acenaphthene (0.5 mmol), 24 h at 60 °C in toluene (1 mL).
[b] The yields were determined by ^{1}H NMR spectroscopy applying acenaphthene as internal standard.

Table 5. Screening of varying propargylic alcohols in the formation of β-oxopropyl esters for catalysts **6g**, **6h** and **10** at 60 °C.[a]



Entry	Product		Yield[b] [%]		
			6g	**6h**	**10**
1	**3a**		96	92	92
2	**3g**		75	24	47
3	**3l**		53	19	15

[a] *Reaction conditions:* benzoic acid (1.0 mmol), propargylic alcohol (2.0 mmol), acenaphthene (0.5 mmol), 24 h at 60 °C in toluene (1 mL).
[b] The yields were determined by ^{1}H NMR spectroscopy applying acenaphthene as internal standard.

the substrate. This fact was already reported to be true for the applied carboxylic acids.[11] It is also interesting to note that with complex **6h** only about one third of the yields compared to that of compound **6g** were achieved. These reduced yields are presumably caused by steric hindrance of the CF_3 groups in the *meta*-position of the triarylphosphine ligands. As catalyst **6g** shows the highest productivities, even when sterically more demanding substrates are converted, this complex was chosen for all further substrate screening reactions.

As it becomes evident from Table 5, even with the most productive catalyst **6g** reaction times of at least 24 h are necessary to reach full conversions of the benzoic acid at a working temperature of 60 °C. This prompted us to study the temperature dependent reaction profiles (Figure 6). As it was already presented in Figure 5, a nearly quantitative yield in the addition of benzoic acid to propargylic alcohol was achieved after 24 h at 60 °C. When raising the temperature by 10 °C the same yield is reached after only 9 h. By a further increase of 10 °C the reaction time could even be reduced down to 5 h.

For final substrate screening we decided to perform the reactions with 1.0 mol% of catalyst **6g** at 80 °C, which allowed us to reduce the reaction times down to approximately one quarter when compared to a reaction temperature of 60 °C.

To assess the substrate scope of the reaction diverse propargylic alcohols were treated with benzoic acid under the optimized reaction conditions. Scheme 7 shows that next to the primary propargylic alcohol prop-2-yn-1-ol (**1a**) also secondary (**1b–f**) and tertiary propargylic alcohols (**1g–l**) can be successfully converted into the corresponding β-oxopropyl esters with good to excellent isolated yields. In comparison to our previously reported studies on β-oxo ester synthesis[33] we were not only able to obtain higher yields but also to significantly reduce the reaction temperature and time.

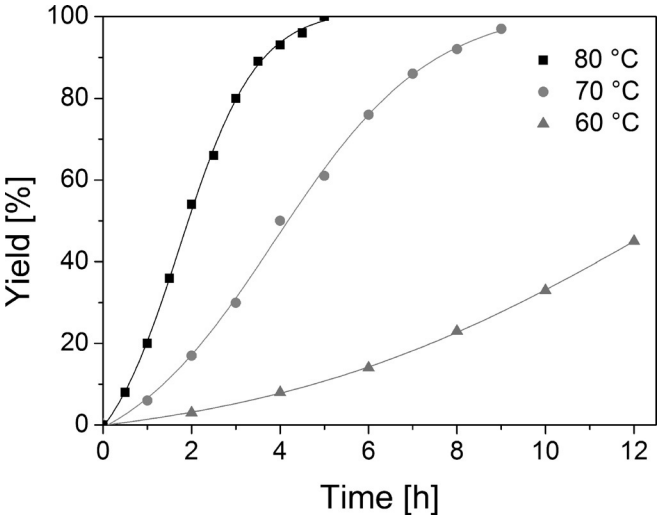
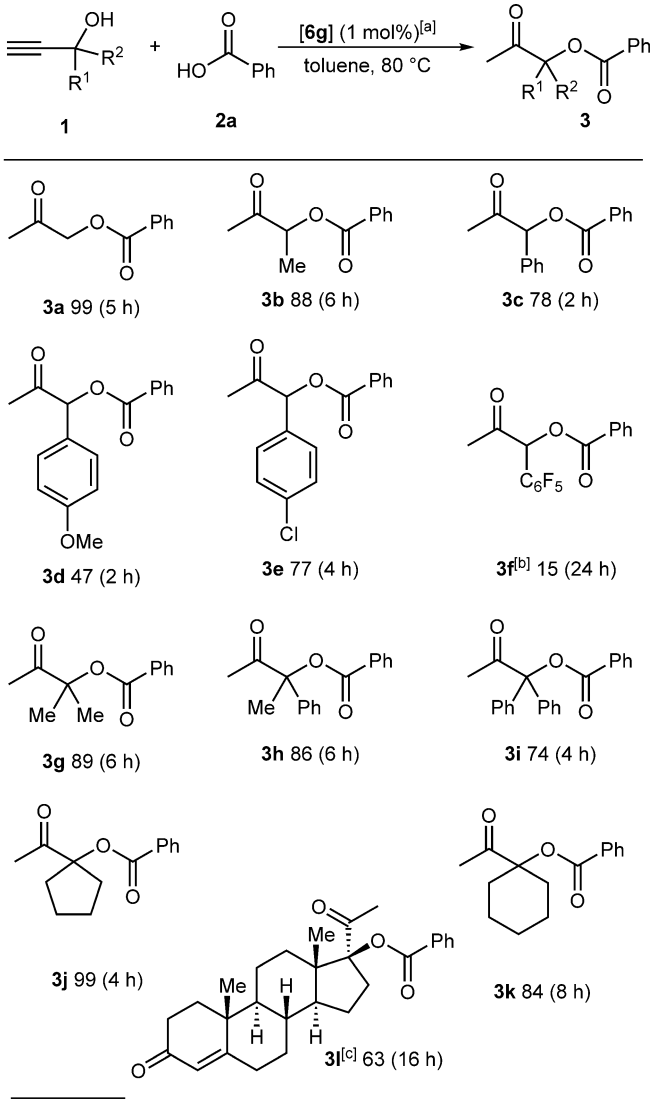


Figure 6. Temperature dependent reaction profiles for the addition of benzoic acid to propargylic alcohol catalyzed by **6g**.



[a] *Reaction conditions:* benzoic acid (1.0 mmol), propargylic alcohol (2.0 mmol), **6g** (0.01 mmol), 80 °C, toluene (1.0 mL). Isolated yields. Optimized reaction times are given in brackets.
[b] Yield determined by ^{1}H NMR spectroscopy.
[c] Ethisterone (1.5 mmol), toluene (5.0 mL), the reaction was performed at 100 °C.

Scheme 7. Scope of the propargylic alcohol in the formation of β-oxopropyl esters.

The catalyst **6g** exhibits productivities, for both simple and challenging substrates, that often match or even exceed those of other complexes known to promote this reaction. The hydrosoluble catalytic systems $\{RuCl_2(\eta^6\text{-}C_6H_6)[PPh_2(m\text{-}C_6H_4\text{-}SO_3Na)]\}$ (**12**)[27] and *trans*-$[RuCl_2(\eta^3{:}\eta^3\text{-}C_{10}H_{16})(PPh_3)]$ (**13**)[47] of Cadierno

et al. show high productivities and tolerate a broad range of functional groups at the substrates. But these systems suffer from limitations in the use of bulky tertiary alkynols.[27] So far, just with complex [$RuCl_2$(*p*-cymene){(*R*)}-BINOL-*N*,*N*-dibenzyl-phosphoramidite}] (**14**) reported by Bauer et al. acceptable yields in the conversion of 1,1-diphenylprop-2-yn-1-ol (**1i**) to benzoic acid 2-oxo-1,1-diphenylpropyl ester (**3i**) were obtained.[28] All other systems failed in this conversion as they could only detect trace amounts of the desired product.[27,46] By applying catalyst **6g** we could now isolate 74% of product **3i** in 4 h at 80 °C, whereas with complex **14** just 68% after 5 h at 90 °C were achieved. The group of Lynam succeeded with their ruthenium-carboxylate complex [$Ru(PPh_3)_2(OAc)_2$] (**15**) in the conversion of the bulky steroid ethisterone. They were able to isolate 53% of product **3l** after 16 h at 120 °C.[46] Compared to that, we could isolate 63% by performing the reaction only at 100 °C.

However, when alkynols with varying electronic features (**1c**–**f**) were investigated, significant differences in the obtained yields of **3c**–**f** were observed. Cadierno et al. also evaluated the productivities when applying aromatic propargylic alcohols with diverse electronic properties. They came to the conclusion that propargylic alcohols with electron-withdrawing groups show higher reactivities when compared to substrates with electron-donating functionalities.[27] One could come to the same conclusion, when just our results for products **3c**–**e** were considered. Taking also into account the low yield for the formation of **3f**, this finding needs some additional explanation. For this reason we followed the reactions to form **3c**–**e** over time. The respective yield-time and conversion-time plots are depicted in Figure 7.

From the yield-time plot it can be seen that the reaction of benzoic acid with 1-(4-methoxyphenyl)prop-2-yn-1-ol (**1d**) at 80 °C is already finished after 2 h. However, yields of only approximately 50% are reached. On the contrary, when substrates with electron-withdrawing groups like 1-(4-chlorophenyl)prop-2-yn-1-ol (**1e**) are used, the initial rate is lower, but higher yields can be obtained. The observation of different initial reaction rates becomes even more apparent, when the conversions of the various propargylic alcohols are followed over time. Figure 7 shows that the more electron-donating the functionalities are, the higher is the conversion of the respective alkynol. This fact can be explained by a facilitated activation of the electron-rich C≡C triple bond by coordination of the propargylic alcohol to the electrophilic ruthenium atom. However, the low yields obtained with electron-rich substrates suggest that not only the formation of the β-oxo esters is accelerated, but also that undesired side reactions take place. For this reason the crude reaction mixtures were analyzed by GC-MS. Thereby, olefinic side products resulting from the

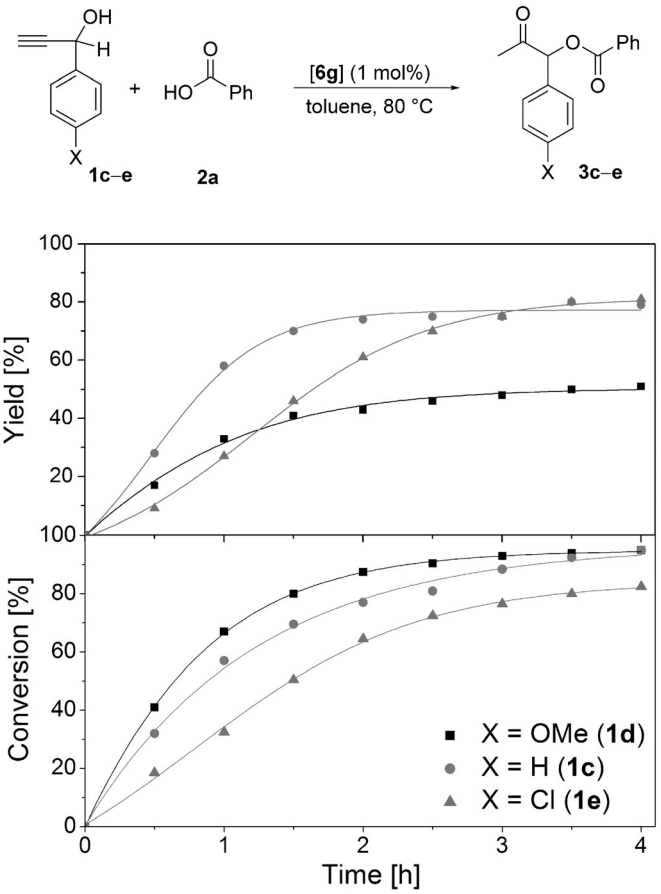


Figure 7. Comparison of the yield-time plots (*top*) and the conversion-time plots (*bottom*) for the reaction of varying *para*-substituted 1-phenylprop-2-yn-1-ols **1c**–**e** with benzoic acid at 80 °C in toluene. The conversion was determined by measuring the amount of the propargylic alcohol.

cleavage of the C≡C bond[27,28,47] or α,β-unsaturated vinyl aldehydes arising from a Meyer–Schuster-type rearrangement[46,48] of the propargylic alcohol were observed. Both reaction pathways have already been reported to occur in the ruthenium-catalyzed addition of carboxylic acids to propargylic alcohols.

To complete our studies on different electronic influences of the catalyst ligands and substrates in the ruthenium-catalyzed β-oxo ester formation, we finally studied the impact of the carboxylic acid. Therefore, a correlation of the Hammett value σ_p and the obtained yields in the conversion of a series of *para*-substituted benzoic acids *p*-X-C_6H_4-CO_2H (X = NMe_2, OMe, CH_3, H, Cl, $C(O)CH_3$, CF_3, NO_2) was established (Figure 8). The positive ρ value in Figure 8 reveals electron-withdrawing groups on the benzoic acid to modestly increase the productivity. This result indicates that not the nucleophilic attack of the acid is rate-limiting, but the cleavage of the O–H bond through deprotonation or oxidative addition of the acid to the Ru catalyst. Unfortunately, we were not able to clarify which of the latter paths takes place, as

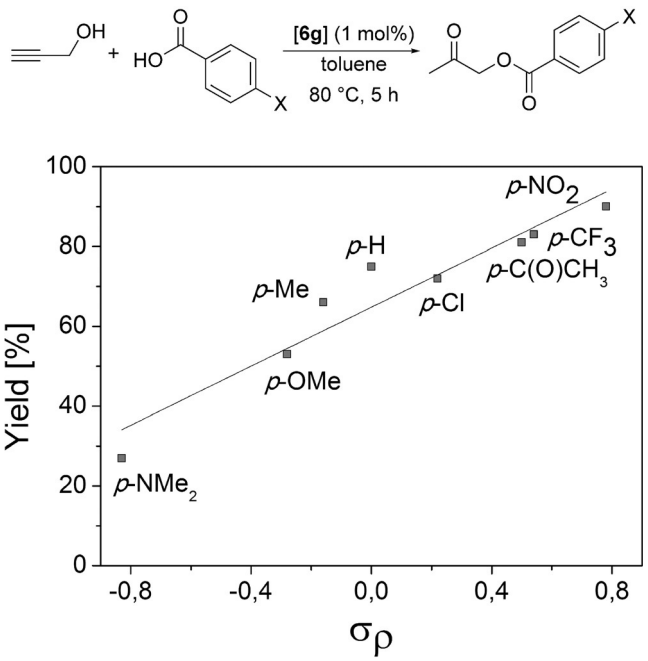


Figure 8. Hammett plot of the coupling reaction of *para*-substituted benzoic acids *p*-X-C_6H_4-CO_2H with propargylic alcohol. Linear regression: $y = 37x + 64.8$; $R^2 = 0.91$.

the complexes **6a**–**h** remained nearly unaffected after the reaction and the concentration of the real catalytic species was too low to be detected by *in situ* IR or NMR spectroscopic studies. Additionally, the coordination of the propargylic alcohol to the ruthenium complex seems to be the rate-determining step, as indicated by the strong impact of the nature of alkynol, which is why no possible ruthenium-hydride intermediate suggesting an oxidative addition could be detected.

It is also interesting to note that the carboxylate groups bound to the initial catalyst complex are converted, too, as confirmed by ^{1}H NMR spectroscopy. This means that in our case, by applying a catalyst loading of 1.0 mol%, the yields are limited to 98% when acids distinct from benzoic acid are converted.

Conclusions

The ruthenium complexes of the type $Ru(CO)_2(PR_3)_2(O_2CPh)_2$ [**6a**, R = *n*-Bu; **6b**, R = *p*-MeO-C_6H_4; **6c**, R = *p*-Me-C_6H_4; **6d**, R = Ph; **6e**, R = *p*-Cl-C_6H_4; **6f**, R = *m*-Cl-C_6H_4; **6g**, R = *p*-CF_3-C_6H_4; **6h**, R = *m*,*m*′-$(CF_3)_2C_6H_3$] were found to be highly effective catalysts in the addition of carboxylic acids to propargylic alcohols to give valuable β-oxo esters. In comparison to our previously reported catalytic studies, we were able to improve the productivities by simultaneous reduction of the reaction time and temperature.[33] We could also show that the reactions can still be effectively carried out at catalyst loadings down to 0.1 mol% or reaction temperatures down to 50 °C. The screening of the electronic nature of the phosphine ligands revealed a considerably influence on the activities of the resulting catalysts. All substituted triarylphoshine complexes gave better yields than PPh_3 complex **6d**. But no general correlation between the basicity of the phosphine ligand and the catalytic performance could be established. Of all tested catalysts, complex **6g** with electron-withdrawing CF_3 groups, was found to be the most active and productive. This catalyst effectively promotes the conversion of a broad range of simple as well as challenging substrates in yields that often match or even exceed those of established literature systems. Additionally, we did examine the electronic impact of the substrates. The Hammett study demonstrated that electron-withdrawing benzoic acids modestly increase the productivity. In contrast to that, the electronic influence of the alkynol was much more decisive, which is why we consider the activation of the propargylic alcohol by the ruthenium to be the rate-determining step. Furthermore, we found that alkynols with electron-donating functionalities do not only accelerate the desired reaction, but also support side reactions like the cleavage of the C≡C bond or Meyer–Schuster-type rearrangements. For this reason propargylic alcohols with electron-withdrawing substituents need longer reaction times, but can under certain circumstances lead to higher yields.

Experimental Section

General Information

Compounds **1d**–**f**,[49,50] **5b**, **c**[51] and **5e**–**h**[51] were prepared in a modified reaction protocol according to published procedures. Toluene was dried by a solvent-purification system (MB SPS-800, MBraun). All other chemicals were purchased from commercial suppliers and were used as received. If necessary, solvents were deoxygenated by standard procedures. For column chromatography silica with a particle size of 40–60 μm (230–400 mesh (ASTM), Fa. Macherey–Nagel) was used.

Instruments

NMR spectra were recorded with a Bruker Advance III 500 spectrometer operating at 500.3 MHz for ^{1}H, 125.7 MHz for $^{13}C\{^1H\}$ and 202.5 MHz for $^{31}P\{^1H\}$ spectra in the Fourier transform mode at 298 K. Chemical shifts are reported in δ (ppm) downfield from tetramethylsilane with the solvent as reference signal (^{1}H NMR, $CHCl_3$ $\delta = 7.26$, acetone-d_6 $\delta = 2.05$; $^{13}C\{^1H\}$ NMR, $CDCl_3$ $\delta = 77.16$, acetone-d_6 $\delta = 206.26$; $^{31}P\{^1H\}$ NMR, standard external relative to 85% H_3PO_4 $\delta = 0.0$). FT-IR spectra were recorded using a FT Nicolet IR 200 instrument. The melting points were determined using a Gallenkamp MFB 595 010M melting point apparatus. Ele-

mental analyses were measured with a Thermo FlashAE 1112 instrument. High-resolution mass spectra were recorded on a Bruker Daltonite micrOTOF-QII spectrometer using electro-spray ionization (ESI).

Single-Crystal X-ray Diffraction Analysis

Diffraction data were collected with an Oxford Gemini S diffractometer at ≤ 110 K with graphite-monochromated Mo Kα radiation ($\lambda = 0.71073$ Å) (**6a**, **b**, **e**–**h**, **8b**, **e**, **g**, **9h**) and Cu Kα radiation ($\lambda = 1.54184$ Å) (**6c**, **9g**) using oil-coated shock-cooled crystals. The structures were solved by direct methods and refined by full-matrix least-squares procedures on F^2.[52,53] All non-hydrogen atoms were refined anisotropically, and a riding model was employed in the treatment of the hydrogen atom positions. Graphics of the molecular structures have been created by using SHELXTL[53] and ORTEP.[54]

CCDC 1413142 (**6a**), CCDC 1413143 (**6b**), CCDC 1413144 (**6c**), CCDC 1413145 (**6e**), CCDC 1413146 (**6f**), CCDC 1413147 (**6g**), CCDC 1413148 (**6h**), CCDC 1413149 (**8b**), CCDC 1413150 (**8e**), CCDC 1413151 (**8g**), CCDC 1413152 (**9g**) and CCDC 1413153 (**9h**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

General Preparation Procedure for $Ru(CO)_3(PR_3)_2$ (8b–h)

The complexes **8b**–**h** were prepared by modified literature procedures.[36] To a hot solution of $RuCl_3 \cdot x H_2O$ (390 mg, 1.49 mmol), the respective phosphine (9.0 mmol) and KOH (600 mg, 10.7 mmol) dissolved in 2-methoxyethanol (100–250 mL) was added aqueous formaldehyde (30 mL, 37% wt) in a single portion. The solution was refluxed for 2 to 18 h after which time the product precipitated as yellow microcrystals. The product was filtered off, washed with ethanol (1×10 mL), water (1×10 mL), ethanol (2×10 mL) and *n*-hexane (1×10 mL) and dried under vacuum. During the preparation of **8g**, **h** the dihydrido complexes **9g**, **h** could be obtained in minor yields as side products, especially when low solvent volumes (<150 mL) were applied.

General Preparation Procedure for $Ru(CO)_2(PR_3)_2(O_2CPh)_2$ – Method A

A solution of $Ru_3(CO)_{12}$ (200 mg, 313 μmol) and the respective phosphine (2.50 mmol) in 4-methylpentan-2-one (18 mL) was refluxed for 8 h. Benzoic acid (306 mg, 2.50 mmol) was added and the solution refluxed for further 16 h. After solvent removal under reduced pressure, the residue was washed with *n*-hexane and diethyl ether to give a colorless solid, which was dried under vacuum.

General Preparation Procedure for $Ru(CO)_2(PR_3)_2(O_2CPh)_2$ – Method B

A suspension of $Ru(CO)_3(PR_3)_2$ (**8e**–**h**) (400 mg) and benzoic acid (4 equiv.) in 4-methylpentan-2-one (10 mL) was stirred for 1 h at 100 °C. The solvent of the obtained clear yellow solution was removed under reduced pressure and the obtained residue was suspended in *n*-hexane (10 mL). The precipitate was collected by filtration, washed with diethyl ether (2×5 mL) and dried under vacuum.

Typical Procedure for β-Oxopropyl Ester Synthesis

In a screw-capped vial, benzoic acid (122 mg, 1.0 mmol), propargylic alcohol (112 mg, 2.0 mmol), acenaphthene (77 mg, 0.5 mmol) and the catalyst (0.01 mmol) were dissolved in toluene (1 mL). The sealed vial was immersed in a heating mantle preheated to 60 °C. After 24 h all volatiles were evaporated under reduced pressure. The yields of the optimization experiments were determined by ^{1}H NMR spectroscopy applying acenaphthene as internal standard. However, analytically pure products were isolated by column chromatography on silica gel. All catalytic results have been verified by at least two independent experiments.

Supporting Information

Detailed experimental procedures, characterization data, crystal data and structure refinement for all ruthenium complexes **6a**–**h**, **8b**–**h** and **9g**, **h**, as well as characterization data, ^{1}H and ^{13}C NMR spectra of catalysis products **3a**–**l** can be found in the Supporting Information.

Acknowledgements

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