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Ruthenium-Catalyzed Hydroaroylation of Styrenes in Water through Directed C–H Bond Activation

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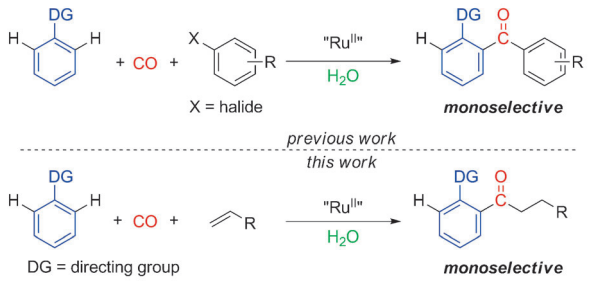
Selective C–H bond-functionalization reactions of arenes offer the potential for a more benign synthesis of fine chemicals and organic building blocks for the life science industries. In this respect, direct carbonylative coupling reactions of (hetero)arenes allow for the straightforward synthesis of (hetero)aromatic ketones and related derivatives. Herein, we present an efficient ruthenium(II)-catalyzed carbonylative hydroarylation of alkenes through directed C–H functionalization. More specifically, the carbonylative hydroarylation of styrenes with 2-aryl-(heteroaryl)pyridines and related derivatives proceeds selectively and with 100% atom efficiency in water as the solvent.



Scheme 1. Carbonylative three-component C–C coupling reactions.

On the basis of the development of organometallic coupling reactions, the transition-metal-catalyzed construction of C–C and C–heteroatom bonds of aryl halides and related substrates is nowadays routinely applied for all kinds of organic syntheses. Without doubt, these methodologies provide an efficient tool box for both basic research as well as for the industrial production of fine chemicals on the ton scale.[1] However, the inherent problem of salt-waste formation as well as the necessity for additional prefunctionalization steps generates interest to develop more straightforward and greener processes. Thus, in the last decade several novel coupling reactions making use of the direct functionalization of C–H bonds have been disclosed.[2] As catalysts, ruthenium complexes exhibit a unique activation mechanism for these processes and have enabled significant progress in cross-coupling reactions including C(sp^2)–H bond activation.[3] Although interesting ruthenium-catalyzed hydroarylations were initially developed,[4,5] related hydroaroylations leading to ketones by additionally incorporating a molecule of carbon monoxide have been studied less. In general, for the latter reactions harsh reaction conditions are required (up to 180 °C), and known protocols are basically limited to the functionalization of imidazole derivatives or to the use of (a large excess amount of) ethylene as the coupling partner.[6,7]

On the basis of our interest in carbonylation reactions[8] and the recent development of selective Ru-catalyzed aroylations of (hetero)arenes,[9] herein we report a general and selective three-component coupling of alkenes, carbon monoxide, and (hetero)arenes bearing *ortho*-directing groups to give the corresponding alkyl aryl ketones (Scheme 1).

Notably, such ketones can also be obtained through intermolecular hydroacylation reactions;[10] however, presynthesis of the corresponding aldehydes is required. In addition, cross-dehydrogenative-coupling provides alternative access to these products. In this latter case, the requirement of (over)stoichiometric amounts of an oxidant is a drawback.[11] Finally, it is worth mentioning that classical three-component carbonylative processes in the presence of (over)stoichiometric amounts of organometallic coupling reagents also allow for the synthesis of similar ketones.[12]

Our initial catalytic experiments were performed with 2-phenylpyridine and styrene as model substrates in the presence of [Ru(cod)Cl_2] (5 mol%, cod = 1,5-cyclooctadiene) polymer at a medium pressure (3 MPa) of carbon monoxide. The testing of different solvents showed their crucial influence on this reaction. Employing common polar and nonpolar organic solvents such as DMSO, DMF, *N*-methylpyrrolidone (NMP), toluene, MeCN, and 1-propanol did not result in any conversion of the starting material (Table 1, entries 1–7). However, changing the solvent to water induced a significant increase in reactivity, which is in agreement with other Ru-catalyzed coupling reactions.[13] Gratifyingly, the desired 3-phenyl-1-[2-(pyridin-2-yl)-phenyl]propan-1-one was obtained in water in 73% yield (Table 1, entry 7). The reaction proceeded highly selective towards the mono-hydroaroylation product and no trace amounts of the direct hydroarylation product or the double hydroarylation product were observed. Nevertheless, trace amounts of side products derived from the hydroformylation and reduction of styrene were observed.

To improve the carbonylative coupling process further, we investigated the effect of different additives. Recently, Ackermann and co-workers demonstrated that the addition of catalytic amounts of carboxylates enhanced the reactivity of Ru

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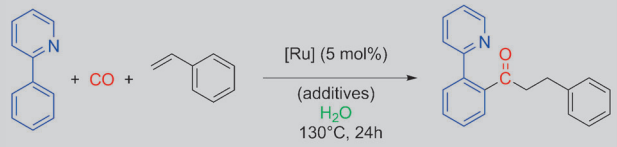
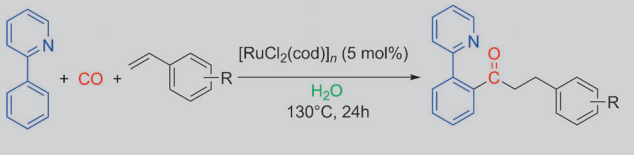
Table 1. Ruthenium-catalyzed carbonylative C–H activation of 2-phenylpyridine: Variation of the reaction conditions.[a]

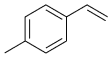
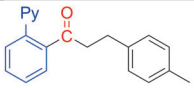
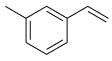
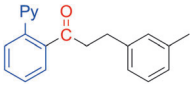
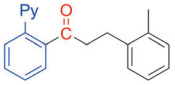
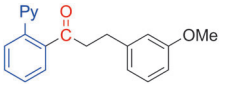
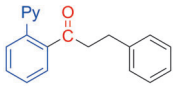
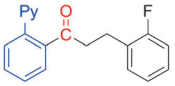
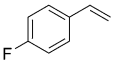
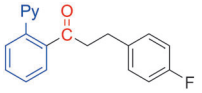
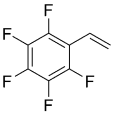
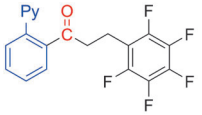
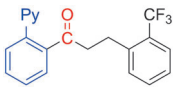
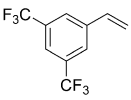
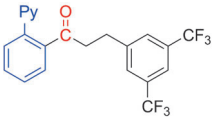
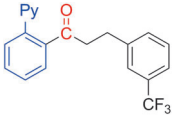


Entry	Solvent (1 mL)	[Ru] (5 mol%)	Additive (0.2 equiv.)	Yield[b] [%]
1	DMSO	$[RuCl_2(cod)]_n$	–	0
2	DMF	$[RuCl_2(cod)]_n$	–	0
3	NMP	$[RuCl_2(cod)]_n$	–	0
4	PhMe	$[RuCl_2(cod)]_n$	–	0
5	MeCN	$[RuCl_2(cod)]_n$	–	0
6	1-propanol	$[RuCl_2(cod)]_n$	–	0
7	H_2O	$[RuCl_2(cod)]_n$	–	73 (64)[c]
8	H_2O	$[RuCl_2(cod)]_n$	KOAc	52
9	H_2O	$[RuCl_2(cod)]_n$	HOAc	44
10	H_2O	$[RuCl_2(cod)]_n$	CHOONa	24
11	H_2O	$[RuCl_2(cod)]_n$	$AgSbF_6$[d]	18
12	H_2O	$[RuCl_2(p\text{-cymene})]_2$	–	67
13	H_2O	$CpRuCl(PPh_3)_2$	–	0
14	H_2O	$Ru(acac)_3$	–	13
15	H_2O	$[RuCl_2(cod)]_n$	–	41,[e] 63[f]
16	H_2O	–	–	0

[a] Reactions were performed with styrene (5 mmol), 2-phenylpyridine (0.5 mmol), ruthenium complex (5 mol%), and additive (0.2 equiv.) under carbon monoxide pressure (3 MPa) at 130 °C for 24 h unless otherwise noted; Cp = cyclopentadienyl. [b] Calibrated yield was obtained by GC by using hexadecane as an internal standard; average of two runs. [c] Yield of isolated product is given in parentheses. [d] $AgSbF_6$ (10 mol%) was used. [e] Reaction was performed at 120 °C. [f] Reaction was performed with CO (2 MPa).

Table 2. Ruthenium-catalyzed hydroaroylation through C–H activation: Substrate scope with different aryl styrenes.[a]

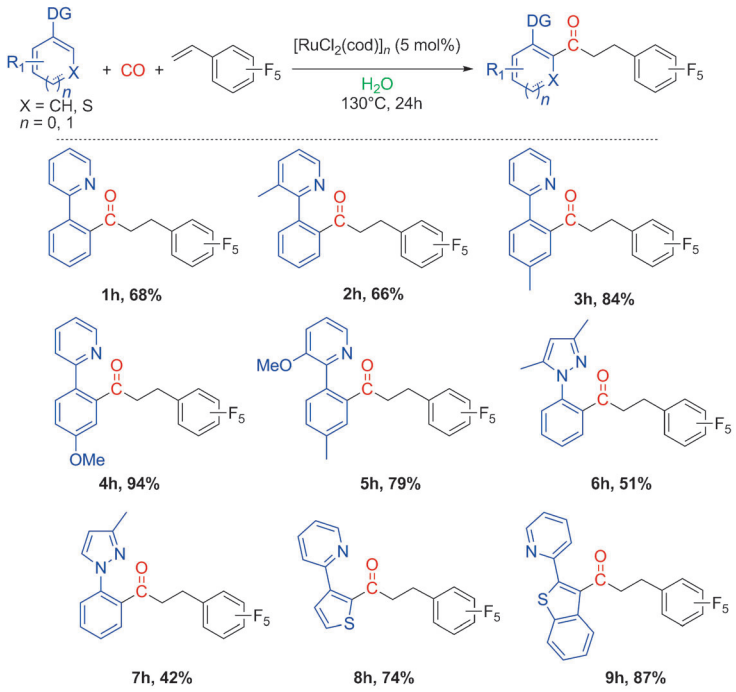


Entry	Styrene	Product		Yield[b] [%]
1			**1a**	65
2			**1b**	69
3			**1c**	52
4			**1d**	74
5			**1e**	64
6			**1f**	44
7			**1g**	64
8			**1h**	68
9			**1i**	38
10			**1j**	44
11			**1k**	78

[a] Reactions were performed with styrene (5 mmol), 2-phenylpyridine (0.5 mmol), and ruthenium complex (5 mol%) under carbon monoxide pressure (3 MPa) at 130 °C for 24 h. [b] Yield of isolated product.

catalysts in C–H functionalization reactions by facilitating the formation of the cyclometalated ruthenium intermediate.[5a] However, under our reaction conditions, the addition of potassium acetate (20 mol%) did not improve the reactivity or selectivity and even lowered the product yield (Table 1, entry 8). We assume that water could assist C–H bond cleavage and the subsequent formation of the cyclometalated ruthenium complex. The same trend was observed if the reaction was performed in the presence of acetic acid or sodium formate (Table 1, entries 9 and 10). Also, attempts to improve the reactivity by in situ formation of a cationic ruthenium complex through the addition of $AgSbF_6$ led to a poor product yield (Table 1, entry 11). Among the tested Ru complexes, the dichloro(*p*-cymene)ruthenium(II) dimer enabled a good yield of the desired product, although it was lower than that obtained withe the use of the $[Ru(cod)Cl_2]$ polymer (Table 1, entries 12–14; acac = acetylacetonate). Decreasing the carbon monoxide pressure to 2 MPa lowered the product yield slightly to 63%, whereas applying a lower temperature (120 °C) caused a stronger decrease in the formation of the product to 41% (Table 1, entry 15). No product formation was observed in a blank experiment (Table 1, entry 16).

With the optimized conditions in hand, we examined the carbonylation of 2-phenylpyridine with different styrenes by using $[RuCl_2(cod)]_n$ in H_2O (Table 2). Styrenes bearing either electron-donating (Table 2, entries 1–4) or electron-withdrawing groups (Table 2, entries 6–11) gave the corresponding ketone derivatives in moderate to very good yields (38–78%). No general trend was observed if the styrene was substituted in the *ortho*-, *meta*-, or *para* position. Interestingly, pentafluorostyrene led to the corresponding product **1h** in good yield (Table 2, entry 8). In general, excellent chemoselectivity with respect to phenylpyridine was observed. However, the use of an



Scheme 2. Ruthenium-catalyzed hydroaroylation through C–H activation: Substrate scope with different directing groups.[a,b] [a] Reactions were performed with styrene (5 mmol), aryl bearing a directing group (0.5 mmol), and the ruthenium complex (0.05 equiv.) under carbon monoxide pressure (3 MPa) at 130 °C for 24 h. [b] Yields of isolated products.

excess amount of the styrene derivative in some cases also led to olefin dimerization, especially for styrenes substituted with electron-withdrawing groups.

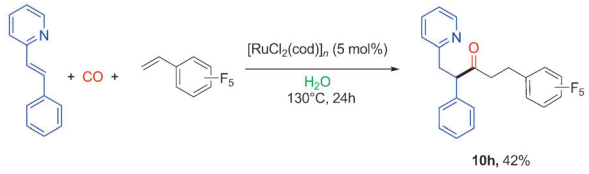
Next, we turned our attention to the variation of the heteroarene and the directing group (Scheme 2). Simple methyl- as well as methoxy-substituted phenylpyridines gave the corresponding ketones in good to excellent yields (Scheme 2, see **1h**–**5h**). The best product yield was obtained if the arene ring was substituted with a strong donating group (e.g., OMe, see **4h**). Notably, phenyl derivatives bearing a pyrazole as directing group were also effective in this coupling process without further optimization, albeit with lower reactivity. Hence, 3,5-dimethyl-1-phenyl-1*H*-pyrazole and 3-methyl-1-phenyl-1*H*-pyrazole were successfully converted into the corresponding products **7h** and **8h**, respectively (Scheme 2). Furthermore, thiophene-based heterocyclic compounds were examined; thereby, 2-(thiophen-3-yl)pyridine gave **8h** in 74% yield. Notably, small amounts (<10%) of the double hydroaroylation (C2 and C5 positions) product were observed in this case. Moreover, C3-directed carbonylative hydroaroylation was successfully demonstrated, and product **9h** was isolated in an excellent 87% yield.

In addition to heteroarenes, 2-styrylpyridine was shown to undergo a novel tandem reaction involving hydroaroylation and subsequent selective reduction of the C=C bond (Scheme 3).[14] Product **10h** was isolated in 42% yield. Remarkably, the recovered starting materials were not reduced under these conditions.

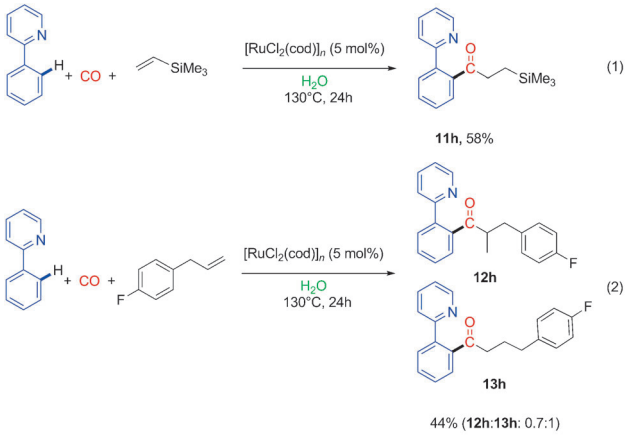
Furthermore, we investigated the application of other vinyl compounds. Thereby, vinyltrimethylsilane was successfully converted into product **11h** and isolated in 58% yield [Scheme 4, Eq. (1)]. Starting the reaction with 1-allyl-4-fluorobenzene was also effective under the standard reaction conditions and led to the isolation of two regioisomers, **12h** and **13h**, in moderate yields [Scheme 4, Eq. (2)].

To shed some light on the mechanism of our hydroaroylation reaction,[15] H/D exchange experiments were performed. If the carbonylative reaction was performed either starting from deuterated 2-phenylpyridine or with the use of deuterated water as the solvent, H/D exchange was observed after 24 h [Scheme 5, Eqs. (1) and (2)]. These results confirm the reversibility of the metalation step. Interestingly, a second H/D exchange in the β-position of the carbonyl group was detected to a significant extend (54%) by ^{1}H NMR spectroscopy if the reaction of 2-phenylpyridine with the corresponding styrene was performed in D_2O [Scheme 2, Eq. (2)]. This observation is explained by concurrent insertion of styrene into the Ru–D species and subsequent β-hydride elimination prior to carbon monoxide insertion and reductive elimination.

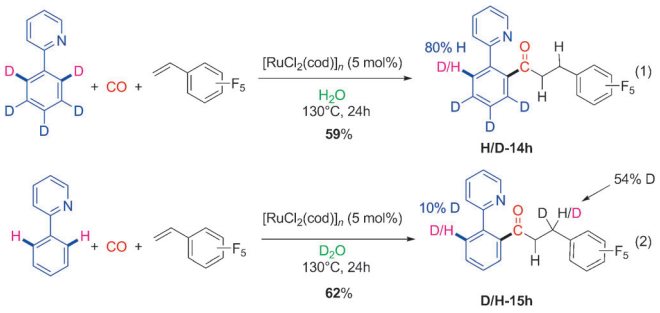
In conclusion, we developed a general protocol for the ruthenium(II)-catalyzed carbonylative hydroarylation of alkenes through directed C–H functionalization. This three-component coupling process of 2-ar-



Scheme 3. Ruthenium-catalyzed tandem hydroaroylation and selective reduction.



Scheme 4. Experiments with different vinyl compounds (reactions performed under standard conditions).



Scheme 5. Deuteration experiments.

yl(heteroaryl)pyridines and related derivatives proceeds selectively in water as the solvent with high atom efficiency.

Experimental Section

Synthesis of 3-phenyl-1-[2-(pyridin-2-yl)phenyl]propan-1-one: Standard catalytic experiments were performed in a Parr Instruments 4560 series 300 mL autoclave containing an alloy plate with wells for six 4 mL Wheaton vials. [{(cod)$RuCl_2$}$_n$] (5 mol%) and a magnetic stirring bar were placed in each of the vials, which were then capped with a septum, equipped with an inlet needle, and flushed with argon. Then, styrene (5 mmol), 2-phenylpyridine (0.5 mmol), and H_2O (1 mL) were added to each vial with a syringe. The vials were placed in an alloy plate, which was then placed in the autoclave. Once sealed, the autoclave was purged with CO several times, then pressurized to 3 MPa at room temperature and heated at 130 °C for 24 h. Afterwards, it was cooled to room temperature and vented to discharge the excess amount of CO. The product was extracted with ethyl acetate (5×3 mL). The organic layer was washed with brine, dried with Na_2SO_4, and evaporated to yield the crude product. Purification by flash chromatography on alumina gel (pH 9.5, heptane/EtOAc = 80:20) gave the product (64%) as a colorless oil.

Acknowledgements

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Keywords: carbonylation · C–H activation · hydroaroylation · ruthenium · water

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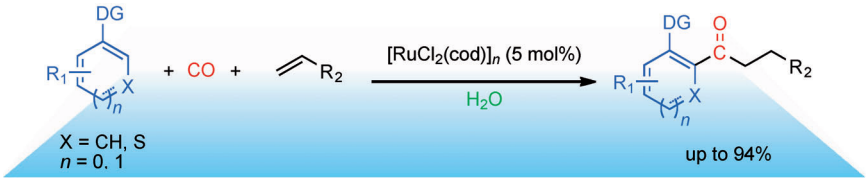
Ruthenium-Catalyzed Hydroaroylation of Styrenes in Water through Directed C–H Bond Activation



Three-Component Hydroaroylation: Hydroaroylation through C–H activation of (hetero)arenes bearing *ortho*-directing groups (DGs) proceeds in the presence of a ruthenium catalyst, carbon monoxide, and styrenes. The shown coupling process provides selective and atom-economic access to (hetero)-aromatic ketones.