Synthetic Methods

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Ruthenium-Catalyzed Carbonylative C–C Coupling in Water by Directed C–H Bond Activation**

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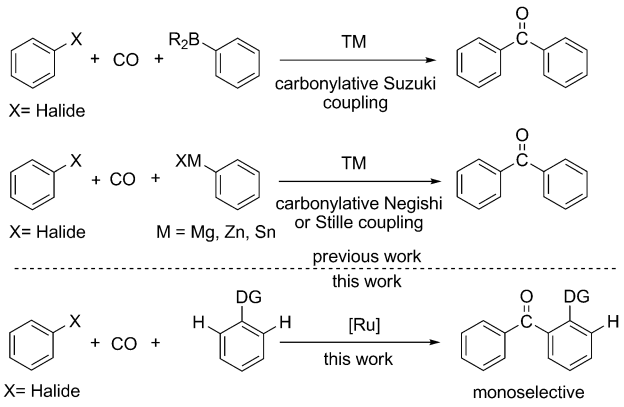
Benzophenones constitute attractive targets for the fine-chemical industry, life sciences, and organic synthesis. Especially, those with heterocyclic substituents exhibit a plethora of biological activities including cholesterol regulation (Tricor), anti-inflammatory effects (Sector), and selective estrogen receptor modulation (Evista). Hence, it is not surprising that several benzophenone derivatives were classified worldwide to be among the top 200 most-sold pharmaceutical compounds in 2009.[1]

Regarding their synthesis, carbon monoxide represents an inexpensive and atom efficient C1 building block, which allows the introduction of a carbonyl group into the desired target molecule by various carbonylation reactions. These transformations are typically catalyzed by palladium complexes. Representative examples include the carbonylative Suzuki, Negishi, Stille, and Hiyama reactions (Scheme 1).[2,3] It is worth noting that a few reports also make use of organoaluminum and organoindium compounds.[2b] Although these transformations have become powerful tools in organic chemistry, the necessity to use (over)stoichiometric amounts of organometallic coupling reagents as well as the need to prepare these in a separate manner lowers their synthetic value.



Scheme 1. Carbonylative three component C–C coupling reactions. TM = transition metal.

In general, direct transition metal catalyzed C–H[4] bond functionalization reactions of arenes and heteroarenes offer an attractive benign alternative to the aforementioned processes. In fact, transition-metal catalysts are often used for selective C–H functionalizations in the preparation of various chemical building blocks.[5,6] With respect to catalysts, in addition to rhodium and palladium salts, ruthenium complexes have evolved as effective systems for C–H bond activation in recent years.[7] More specifically, important progress in the direct $C(sp^2)$–$C(sp^2)$ bond formation between arenes bearing a directing group and aryl halides has been reported by the groups of Inoue,[8] Ackermann,[9] and Dixneuf.[10]

In contrast to the commonly developed arylations and vinylations, carbonylative C–H bond functionalizations have been investigated to a lesser extent.[11] To the best of our knowledge, there exists no examples of carbonylative coupling reactions of aryl halides by directed C–H bond activation.[12]

Based on our continuous interest to discover novel and improve existing carbonylative processes,[13] we report herein a general and selective ruthenium-catalyzed aroylation with carbon monoxide of (hetero)arenes bearing *ortho*-directing groups (Scheme 1).

Initial experiments were carried out using 2-phenylpyridine as a model substrate, phenyl iodide, and 5 mol% of a $[Ru(cod)Cl_2]$ polymer at medium pressure (30 bar of carbon monoxide). Different bases, solvents, and several additives were tested under these reaction conditions. When DMSO was employed as a solvent in the presence of potassium carbonate (2 equiv) and potassium acetate (0.2 equiv) as additives, no conversion of the starting materials was observed (Table 1, entry 1). In the presence of other organic solvents the desired carbonylative product was observed in disappointing yields (Table 1, entries 1–6). However, similar to the recent work of Dixneuf and co-workers, changing the organic solvent to water increased the reactivity of the carbonylative reaction dramatically and 56% of the desired product was obtained. This improvement is also in agreement with the positive effect of water in several classical organic reactions.[14]

Notably, the reaction is highly selective towards the monoaroylation of 2-phenyl pyridine as no traces of the direct mono or the double C–C bond formation have been detected under these reaction conditions. With respect to the conversion of phenyl iodide, traces of benzaldehyde, benzyl alcohol, and the reduction of iodobenzene to benzene caused by a ruthenium-catalyzed water gas shift reaction were

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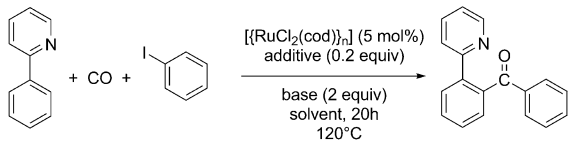
Table 1: Ruthenium-catalyzed carbonylative C–H activation of 2-phenylpyridine: Variation of reaction conditions.[a]



Entry	Solvent (1 mL)	Base (2 equiv)	Additive (0.2 equiv)	Yield[b] [%]
1	DMSO	K_2CO_3	KOAc	0
2	DMF	K_2CO_3	KOAc	4
3	NMP	K_2CO_3	KOAc	13
4	PhMe	K_2CO_3	KOAc	5
5	MeCN	K_2CO_3	KOAc	12
6	*t*AmOH	K_2CO_3	KOAc	8
7	H_2O	K_2CO_3	KOAc	56, 44,[c] 54[d]
8	H_2O	K_2CO_3	NaOAc	54
9	H_2O	K_2CO_3	CsOPiv	36
10	H_2O	K_2CO_3	MesCOOH	28
11	H_2O	K_2CO_3	Cl_3COOH	54
12	H_2O	Cs_2CO_3	KOAc	54
13	H_2O	K_3PO_4	KOAc	44
14	H_2O	KOH	KOAc	44
15	H_2O	NaO*t*Bu	KOAc	<1
16	H_2O	KOAc	–	<1
17	H_2O	$NaHCO_3$	KOAc	65

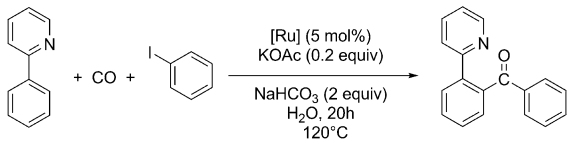
[a] Reactions were performed with 1 mmol of iodobenzene, 0.5 mmol of 2-phenylpyridine, 0.05 equiv of ruthenium complex, 0.2 equiv of additive, and 1 mmol of base under 30 bar of carbon monoxide, at 120°C for 20 h unless otherwise noted. [b] GC yields with hexadecane as an internal standard; average of two runs. [c] Reaction was performed under 20 bar of CO. [d] Reaction was performed under 40 bar of CO. cod = cyclo-1,5-octadiene, DMF = *N*,*N*-dimethylformamide, DMSO = dimethylsulfoxide, NMP = *N*-methylpyrrolidone.

observed in minor amounts.[15] A change of the carbon monoxide pressure to 20 bar decreased the yield slightly to 44% (Table 1, entry 7). However, at higher CO pressure (40 bar) a similar yield was obtained.

Next, we examined the influence of different additives on the reaction (Table 1, entries 8–11). Here, several acids and bases were tested, but none of them improved the product yield. Finally, the base effect was studied in more detail. Cesium carbonate and potassium phosphate were effective and the product was formed in 54 and 44% yield, respectively (Table 1, entries 12 and 13). Strong bases like potassium hydroxide or sodium *tert*-butoxide were ineffective under our reaction conditions (Table 1, entries 14 and 15). Interestingly, the best yield (65% of the product) was achieved in the presence of inexpensive sodium bicarbonate (Table 1, entry 17). It is worth noting that running the reaction exclusively with potassium acetate (2 equiv) gives less than 1% of the product (Table 1, entry 16).

For further optimization we decided to investigate the effect of different ruthenium complexes on the carbonylative C–H functionalization. In the related direct coupling reaction, it is well known that the addition of silver salts had a positive effect on the generation of the active species.[16a] However, in the present model reaction adding silver acetate or silver hexafluoroantimonate inhibited the reactivity of our

Table 2: Ruthenium-catalyzed carbonylative C–H activation of 2-phenylpyridine: Variation of ruthenium complexes.[a]



Entry	[Ru]	Yield [%][b]
1	$[\{RuCl_2(cod)\}_n]$	65
2	$[\{RuCl_2(cod)\}_n]$ + 0.1 equiv $Ag(OAc)_2$	<1
3	$[\{RuCl_2(cod)\}_n]$ + 0.1 equiv $AgSbF_6$	<1
4	$[Ru(OAc)_2(cod)]$	24
5	$[\{RuCl_2(p\text{-cymene})\}_2]$	16
6	$[CpRuCl(PPh_3)_2]$	0
7	$[Ru(CO)_3Cl_2]$	<1
8	$[Ru(acac)_3]$	<1
9	$[Ru_3(CO)_{12}]$	<1

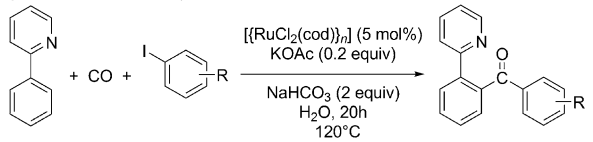
[a] Reactions were performed with 1 mmol of iodobenzene, 0.5 mmol of 2-phenylpyridine, 0.05 equiv of ruthenium complex, 0.2 equiv of KOAc and 1 mmol of base under 30 bar of carbon monoxide at 120°C for 20 h. [b] GC yields with hexadecane as an internal standard; average of two runs. acac = acetylacetonate.

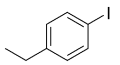
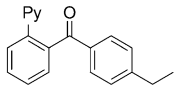
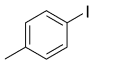
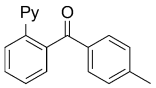
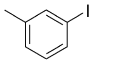
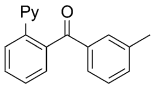
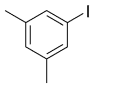
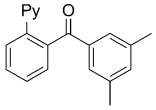
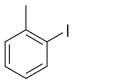
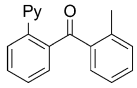
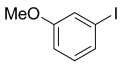
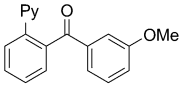
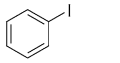
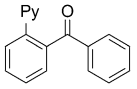
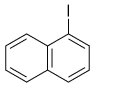
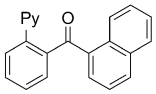
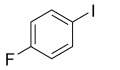
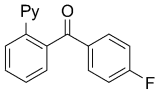
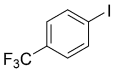
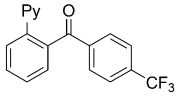
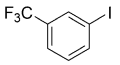
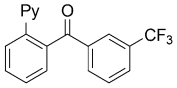
catalyst system completely (Table 2, entries 2 and 3). Furthermore, lower conversion and yield was observed when starting from the presumed active species and only 24 mol% of the product was formed (Table 2, entry 4). A low product yield was also observed when the ruthenium dimer dichloro-(*p*-cymene)ruthenium(II) was used (Table 2, entry 5). Employing other ruthenium catalysts with different oxidation states (0, II, and III) gave marginal product formation (Table 2, entries 7–9).

With the best reaction conditions in hand ($[\{RuCl_2(cod)\}_n]$/$NaHCO_3$/KOAc), we turned our attention to the evaluation of the substrate scope of ruthenium-catalyzed carbonylative C–C bond formation by direct C–H activation. Using aryl iodides with either electron-donating (Table 3, entries 1–6) or electron-withdrawing groups (Table 3, entries 9–11) led to the formation of the corresponding benzophenone derivatives in moderate to good yields in all the cases. Aryl iodides substituted with alkyl groups in *para*-, *meta*-, or *ortho*-positions were all effective under our reaction conditions (Table 3, entries 2–5). It is important to note that in the case of 4-iodotoluene the optimum yield was obtained with potassium carbonate as a base. The use of 2-iodotoluene as a coupling partner generated the corresponding ketone with the best yield of the isolated product being 74% (Table 3, entry 5). Aryl halides bearing a methoxy group showed slightly slower reactivity (Table 3, entry 6). In general, aryl iodides with an electron-withdrawing group were less reactive than the ones with donating groups. Nevertheless, no position effect between *meta* or *para* substitution was observed for the synthetically interesting fluorinated aryl halides employed in the reaction (Table 3, entries 9–11).

After having observed the general activity with several aryl iodides, we turned our attention to study the reactivity with different directing groups (Table 4). To our delight, phenyl derivatives bearing pyrazole as a directing group were also effective. Hence, 3,5-dimethyl-1-phenyl-1*H*-pyrazole was

Table 3: Ruthenium-catalyzed carbonylative C–H activation: Substrate scope with different aryl iodides.[a]



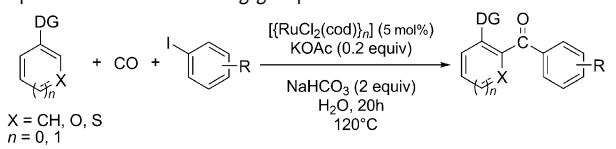
Entries	Aryl iodide	Product		Yield [%][b]
1			**1a**	61
2			**1b**	54[c]
3			**1c**	52
4			**1d**	55
5			**1e**	74
6			**1f**	41
7			**1g**	62
8			**1h**	56
9			**1i**	40
10			**1j**	46
11			**1k**	54

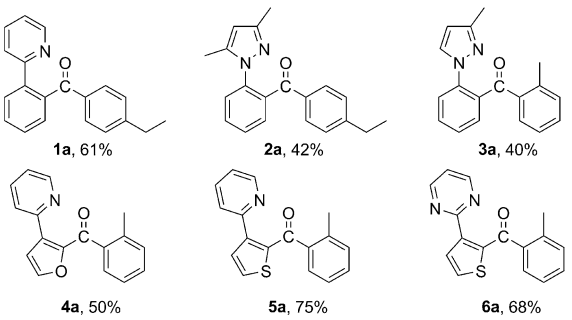
[a] Reactions were performed with 1 mmol of aryl iodide, 0.5 mmol of 2-phenylpyridine, 0.05 equiv of ruthenium complex, 0.2 equiv of KOAc, and 1 mmol of $NaHCO_3$ under 30 bar of carbon monoxide at 120°C for 20 h unless otherwise noted. [b] Yields of isolated products. [c] Reaction performed with K_2CO_3 as base.

successfully converted with 4-ethyliodobenzene as well as with 2-iodotoluene.

When 2-iodotoluene was reacted with the monomethyl-substituted pyrazole under carbon monoxide pressure the corresponding ketone was observed. Furthermore, other heterocycles bearing a directing group have been tested. Reaction of 3-phenylfuran gave **4a** in 50% yield upon isolation. Moreover, thiophene derivatives bearing pyridine or pyrimidine directing groups gave good yields of **5a** (75%) and **6a** (68%), respectively. Interestingly, the C–H carbonylation occurred exclusively on the C2 position of the heterocyclic moiety.

Table 4: Ruthenium-catalyzed carbonylative C–H activation: Substrate scope with different directing groups.[a]

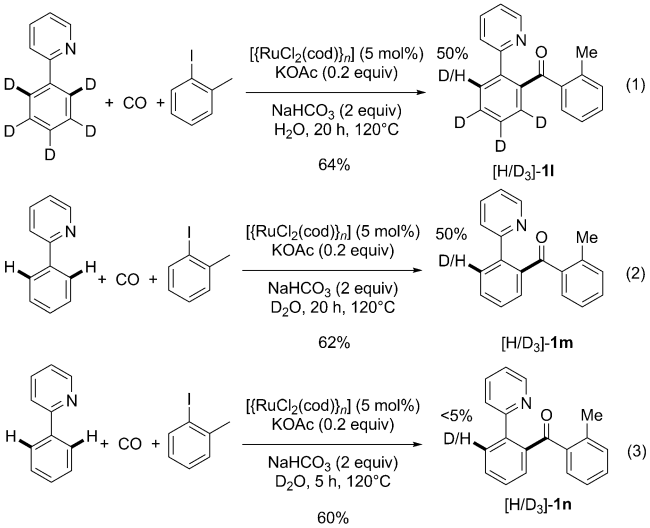




[a] Reactions were performed with 1 mmol of aryliodide, 0.5 mmol of aryl bearing a directing group, 0.05 equiv of ruthenium complex, 0.2 equiv of KOAc, and 1 mmol of base under 30 bar at 120°C for 20 h unless otherwise noted. [b] Yields of isolated products.

Based on previous investigations by the groups of Ackermann, Jutand, and Dixneuf, we propose the following mechanism for this carbonylative coupling process. After initial formation of the cyclometalated ruthenium complex, subsequent carbonylation and oxidative addition of the aryl halide takes place. Finally, reductive elimination gives the product and regenerates the active catalyst.

To understand the selectivity of the process, experiments with labeled starting materials or in deuterated water were undertaken [Eqs. (1), (2), and (3); Scheme 2]. It is worth noting that Ackermann et al. described a D/H exchange for the direct arylation of phenyl pyridine when their reaction



Scheme 2. Deuteration experiments.

was carried out for 18 hours at 120 °C.[16b] More recently, in similar investigations by Jutand, Dixneuf, and co-workers[16a] no H/D exchange was observed when the reaction was carried out at room temperature. Under the carbonylative reaction conditions using deuterated 2-phenylpyridine or deuterated water an H/D exchange was observed after 20 hours [Eqs. (1) and (2)]. More interestingly, when the reaction of 2-phenylpyridine was stopped after five hours less than 5% of H/D exchange was detected [Eq. (3)]. This result can be explained by the reversibility of the second metalation after the product has been formed.[17] Further experiments are under way in our laboratory to elucidate the mechanism of the transformation in more details.

In conclusion, we have developed the first ruthenium-catalyzed carbonylative C–C bond formation by directed C–H functionalization. The aroylation of 2-arylpyridines and related derivatives proceeds highly selective with water as the solvent. Compared to known carbonylative coupling processes stoichiometric amounts of organometallic reagents are avoided. Currently, the effects of different directing groups as well as further mechanistic investigations are under way in our laboratory.

Experimental Section

Synthesis of phenyl(2-(pyridin-2-yl)phenyl)methanone: The reaction was carried out in a Parr Instruments 4560 series 300 mL autoclave containing an alloy plate with wells for six 4 mL Wheaton vials. $[\{RuCl_2(cod)\}_n]$ (5 mol%), KOAc (20 mol%), $NaHCO_3$ (1 mmol), benzoxazole, and a magnetic stir 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, iodobenzene (1 mmol), 2-phenylpyridine (0.5 mmol), and H_2O (1 mL) were added to the 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 several times with CO, then pressurized to 30 bar at room temperature and heated at 120 °C for 20 h. It was then cooled to room temperature and vented to discharge the excess CO. The product was extracted with ethyl acetate (5 × 3 mL). The organic layers were washed with brine, dried over Na_2SO_4, and evaporated to yield the crude reaction mixture. Purification by flash chromatography on silica gel (eluent: heptane/EtOAc 80:20) gave the product (62%) as a white solid.

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Keywords: C–H activation · homogenous catalysis · ruthenium · synthetic methods · water

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