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Rhodium-Catalyzed Regioselective C−H Functionalization via Decarbonylation of Acid Chlorides and C−H Bond Activation under Phosphine-Free Conditions

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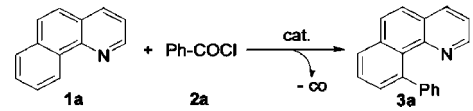
Transition metal catalyzed activation of aromatic C−H bonds followed by new C−C bond formation is of considerable attraction in organic synthesis because of no requirement for prefunctionalization of the arene or heteroaromatic substrates by metalation or halogenation.[1] *o*-Arylation, alkenylation, or alkylation of sp^2 C−H bonds involving subsequent regioselective formation of C−C bonds assisted by various functional groups under palladium, ruthenium, or rhodium catalysis have received much attention.[1,2] Arenes and heterocycles usually undergo chelation-assisted C−H functionalization with organic or organometallic coupling partners such as Ar−X (X = I, Br, Cl, OTs, OTf),[3] organotin,[4a] organoboron,[4b–e] and arylzinc,[4f] reagents, arylsilanes,[5] alkenyl acetates,[6] Ar_2IBF_4,[7] haloolefins,[8] olefins,[9] alkynes,[10] or some unactivated aromatic rings,[11] producing the cross-coupling products. Peroxides and diethyl azodicarboxylate have also been used as the coupling partners for this purpose.[12] Although a variety of coupling partner compounds have been successfully explored, the need to develop readily available coupling partners as well as the corresponding effective catalyst systems is still strongly desired in this area. Acid chlorides are usually cheap and readily derived from their mother acids. Aroyl chlorides can be decarbonylated to undergo Heck-type reactions or decarbonylative addition to alkynes by means of palladium or rhodium catalysts.[13,14] Herein, we report the first protocol for regioselective functionalization of aromatic C−H bonds using acid chlorides as the coupling partners via C−H bond activation by rhodium(I) catalysis under phosphine-free conditions.

Palladium-catalyzed ligand-directed aromatic C−H activation to form C−C bonds has been well documented.[1] Subsequently, we initially tested the coupling reaction of benzo[*h*]quinoline (**1a**) and benzoyl chloride (**2a**) with a base in refluxing toluene using palladium acetate as the catalyst. However, the arylation aimed at forming the coupling product **3a** via decarbonylation of **2a** and C−H bond activation did not occur even if an oxidant such as benzoquinone was added to the reaction system. Using 3 mol % rhodium(I) complex $[Rh(COD)Cl]_2$ as the catalyst, the expected arylation did not take place either (Table 1, entries 1−2). When 4 A molecular sieves were added to the reaction mixture, the coupling was remarkably improved to form the desired decarbonylative coupling product **3a** (entry 3). The CO-retentive coupling product, that is, 10-benzoyl benzoquinoline, was not observed in the reaction. After the reaction conditions were screened and optimized, the decarbonylative coupling product **3a** was afforded in 94% isolated yield using 5 mol% $[Rh(COD)Cl]_2$ as the catalyst, Na_2CO_3 as the base, and 4 A MS as the additive in refluxing xylene at 145 °C for 16 h (entry 7). With KF or K_3PO_4 as the base, **1a** was also efficiently transformed to the desired product (entries 8−9), while an organic base such as Et^iPr_2N did not promote the reaction so much. Carbonyl rhodium(I) complex $[Rh(CO)_2Cl]_2$ was also efficient for the coupling (entry 10), while the ionic rhodium(I) salt $Rh(COD)_2BF_4$ and Wilkinson's catalyst only showed poor catalytic activity (entries 11−13). In contrast to the reported Rh(I)/phosphine-catalyzed C−H activation,[4a,e,9] a phosphine ligand, for example, PPh_3, present in the reaction system dramatically retarded the coupling reaction (entry 14).

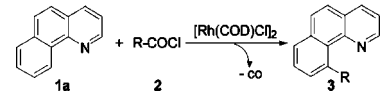
Table 1. Screening of Reaction Conditions[a]



entry	solvent	cat. mol %	additive	base	temp (°C)	time (h)	conversion (%)[b]
1	toluene	$[Rh(COD)Cl]_2$/3	-	Na_2CO_3	110	24	
2	toluene	$[Rh(COD)Cl]_2$/3	-	K_2CO_3	110	24	
3	toluene	$[Rh(COD)Cl]_2$/3	4A MS	K_2CO_3	110	24	45
4	xylene	$[Rh(COD)Cl]_2$/3	4A MS	K_2CO_3	135	24	76
5	xylene	$[Rh(COD)Cl]_2$/3	4A MS	Na_2CO_3	135	24	81
6	xylene	$[Rh(COD)Cl]_2$/5	4A MS	Na_2CO_3	135	16	92
7	xylene	$[Rh(COD)Cl]_2$/5	4A MS	Na_2CO_3	145	16	>99(94)[c]
8	xylene	$[Rh(COD)Cl]_2$/5	4A MS	KF	145	16	98
9	xylene	$[Rh(COD)Cl]_2$/5	4A MS	K_3PO_4	145	16	>99
10	xylene	$[Rh(COD)Cl]_2$/5	4A MS	K_2CO_3	145	16	93
11	xylene	$[Rh(CO)_2Cl]_2$/5	4A MS	Na_2CO_3	145	16	>99
12	xylene	$Rh(COD)_2BF_4$/5	4A MS	Na_2CO_3	145	16	27
13	xylene	$RhCl(PPh_3)_3$/5	4A MS	Na_2CO_3	145	16	15
14[d]	xylene	$[Rh(COD)Cl]_2$/5	4A MS	Na_2CO_3	145	16	15

[a] Reaction conditions: **1a**, 0.3 mmol; **2a**, 1.5 equiv; base, 2 equiv; solvent, 3 mL. [b] Conversion of **1a** determined by GC analysis. [c] Isolated yield of **3a** in parenthesis. [d] PPh_3 (20 mol %) was added.

Table 2. C−H Functionalization of **1a** via Decarbonylation and C−H Bond Activation[a]



entry	R	2	product	yield (%)[b]
1	Ph	**2a**	**3a**	93
2	4-MeC_6H_4	**2b**	**3b**	86
3	4-$MeOC_6H_4$	**2c**	**3c**	90
4	4-ClC_6H_4	**2d**	**3d**	95
5	4-$NO_2C_6H_4$	**2e**	**3e**	87
6	3-$NO_2C_6H_4$	**2f**	**3f**	71
7	1-naphthalyl	**2g**	**3g**	68
8	$C_6H_5CH{=}CH$	**2h**	**3h** (E/Z = 23/1)[c]	74
9	$PhCH_2$	**2i**	**3i**	37
10	—[d]	**2j**	**3a**	94

[a] Reaction conditions: **1a**, 0.5 mmol; **2**, 1.5 equiv; $[Rh(COD)Cl]_2$, 5 mol %; Na_2CO_3, 2 equiv; 4A MS; xylene, 3 mL; 145 °C, 16 h. [b] Isolated yields. [c] Ratio determined by ^1H NMR. [d] **2j**, PhCOCOCl.

Under the optimized conditions, reaction of **1a** (0.5 mmol) with **2a** afforded the functionalization product **3a** in 93% isolated yield (Table 2, entry 1). Other aroyl chlorides also efficiently underwent the coupling reactions with **1a** to form the desired products (**3a**−**h**) (entries 2−7).

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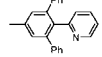
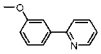
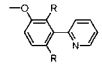
Table 3. C−H Functionalization of **1** via Decarbonylation of **2a** or **2c** and C−H Bond Activation[a]

entry	substrate		condition	product		yield (%)[b]
1		**1b**	A		**3j**	72
2		**1c**	A		**3k**	76
3[c]		**1d**	A		**3l**	68
4[d]					**3m**	66
5		**1e**	B		**3n**	70
6		**1f**	B		**3o**	61
7		**1g**	B		**3p**	60
8		**1h**	B		**3q**	34(54)[e]
9		**1i**	B		**3r**	33

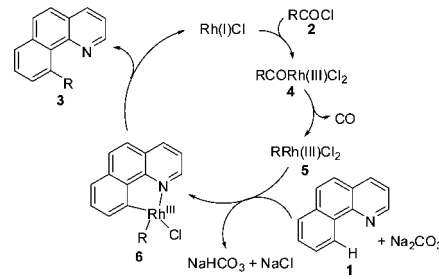
[a] Reaction conditions: **1**, 0.5 mmol; 4A MS; xylene, 3 mL; 145 °C, 16 h. (A) $[Rh(COD)Cl]_2$, 10 mol %; Na_2CO_3, 3 equiv; **2a** or **2c**, 4.0 equiv. (B) $[Rh(COD)Cl]_2$, 5 mol%; Na_2CO_3, 2 equiv; **2a**, 1.5 equiv. [b] isolated yields. [c] R = Ph (**2a**). [d] R = 4-$MeOC_6H_4$ (**2c**). [e] $[Rh(COD)Cl]_2$, 10 mol %.

Styryl-functionalized product **3h** was obtained in 74% yield through the decarbonylation of *trans*-cinnamoyl chloride **2h** and C−H bond activation (entry 8). It is worth noting that arene **1a** was decarbonylatively benzylated by phenylacetyl chloride **2i** in 37% yield (entry 9). Interestingly, acid chloride PhCOCOCl (**2j**) was efficiently coupled with **1a**, producing **3a** in 94% yield through double carbonyl elimination (entry 10).

The scope of *N*-heteroaromatic substrates was explored. In an initial study, treatment of 2-phenylpyridine (**1b**) with 1.5 equiv of **2a** produced the mixture of monoarylated and double arylated products under the same conditions as shown in Table 2, and the molar ratio of double to monoarylation products was increased as the amount of **2a** was increased. Thus, **1b** was reacted with 4 equiv of **2a** in the presence of 3 equiv of Na_2CO_3 at 145 °C for 20 h; a mixture of double and monoarylation products (86:14) was obtained with 93% conversion for **1b**. Presumably, the catalyst was decomposed during the reaction, leading to the incomplete conversion of **1b**. With an increase of the catalyst loading to 10 mol %, as expected, >99% conversion was reached for **1b** and the 97:3 mixture of double and monoarylation products were formed. Eventually, the double arylation product **3j** was isolated in 72% yield (Table 3, entry 1). The methodology was applied to the C−H functionalization of **1c** and **1d**, affording the corresponding double arylation products **3k**−**m** in 66−76% yields (entries 2−4). It should be noted that the monoarylation product, that is, **3n**, was always generated as the major product from the arylation of **1e** with **2a** even if 4 equiv of **2a** was used in the reaction (entry 5), which is attributed to the steric hindrance from the 3-methyl substituent. There is only one reactive site available in **1f** or **1g** that their C−H functionalization with **2a** only afforded the monoarylation products **3o** and **3p** (entries 6 and 7). Less reactive *N*-heterocycles **1h** and **1i** also underwent the arylation reactions with **2a** to afford the desired products (entries 8 and 9), respectively.

A posssible mechanism is proposed in Scheme 1. Acid chloride **2** is oxidatively added to the Rh(I) species to form an aroyl-chlorometal complex $[RCORh(III)Cl_2]$ (**4**) which undergoes decarbonylation to form aryl-chlororhodium(III) intermediate **5** at elevated temperature. Intermediate **5** reacts with arene **1** to form intermediate complex **6** by

Scheme 1. Proposed Mechanism



C−H activation via intramolecular ortho-chelating assistance in the presence of a base. The desired product **3** is then produced by reductive elimination of **6**. Such a proton abstraction mechanism is plausible to explain functionalization of the aromatic C−H bonds by acid chlorides.[3e,15]

In summary, efficient regioselective functionalization of aromatic C−H bonds has been realized by Rh(I) catalysis using acid chlorides as the coupling partners via decarbonylative C−H activation with arene or N-heteroaromatic substrates under phosphine-free conditions. Exploration of the substrate scope and reaction mechanism will be further investigated.

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Supporting Information Available: Experimental procedures, analytical data, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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