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Ruthenium-Catalyzed Amino- and Alkoxycarbonylations with Carbamoyl Chlorides and Alkyl Chloroformates via Aromatic C−H Bond Cleavage

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Transition metal catalyzed C−C bond formation, particularly, alkylation, alkenylation, and arylation, via aromatic C−H bond cleavage has extensively been studied in the past decade.[1] Although direct introduction of carbonyl groups such as amide and ester groups, which can be easily transformed into a wide range of functionalities, should be highly valuable, such transformations via transition metal catalyzed C−H bond cleavage are still relatively unexplored.[1−5] To date, several methods for direct, catalytic introduction of carbonyl functionalities such as acyl,[2] carboxy,[3] amide,[2a,4] and ester[5] groups have been developed. However, the generality of the applicable carbonyl functionalities is still limited. We envisioned that the use of compounds containing a chlorocarbonyl group for catalytic C−H functionalization by transition metals may allow for the introduction of a variety of amide and ester functionalities because Friedel−Crafts acylation using acyl chlorides is considered to be a general method for direct incorporation of carbonyl groups onto aromatic rings.[6,7]

Here we report ruthenium-catalyzed regioselective amino- and alkoxycarbonylations at aromatic C−H bonds using carbamoyl chlorides and alkyl chloroformates, respectively. This is the first study of transition metal catalyzed introduction of amide and ester groups via C−H bond cleavage using chlorocarbonyl compounds. In addition, oxidants are unnecessary to conduct catalytic C−H amino- and alkoxycarbonylation by our protocol.[8]

When benzo[*h*]quinoline (**1**) was reacted with *N*,*N*-dimethylcarbamoyl chloride using $RuCl_2(PPh_3)_3$ as a catalyst in the presence of K_2CO_3 in toluene at 120 °C, aminocarbonylation proceeded at the 10-position of **1** and amide **2a** was isolated in 94% yield (Table 1, entry 1). Similarly, *N*,*N*-diphenylamide **2b** and morpholine amide **2c** were obtained in 97% and 90% yields, respectively (entries 2 and 3). X-ray crystallographic analysis of **2b** clearly showed the presence of the amide group at the 10-position. Morpholine amide **2c** was obtained in 75% isolated yield with only 1 mol% of $RuCl_2(PPh_3)_3$ at 150 °C in xylene (entry 4).[9] Our aminocarbonylation protocol enables catalytic introduction of a *N*,*N*-disubstituted amide group at the C−H bond, while precedent methods using arylisocyanates only provided *N*-monoarylamides[2a] and their derivatives.[4]

The use of alkyl chloroformates instead of carbamoyl chlorides led to the introduction of ester groups. The reaction of **1** with ethyl and *n*-butyl chloroformates afforded the corresponding esters **3a** and **3b** in 66% and 70% yields, respectively (entries 5 and 6). Isopropyl ester **3c** was similarly obtained in 70% yield (entry 7). It is worth noting that Friedel−Crafts methods are inapplicable for the reaction with alkyl chloroformates due to their rapid decarboxylation.[10] The present alkoxycarbonylation is the first application of alkyl chloroformates for direct catalytic introduction of ester groups on aromatic rings. Very recently, Yu and co-workers reported catalytic alkoxycarbonylation of the C−H bond using diethyl azodicarboxylate. This method has been effectively used only for ethoxycarbonylation.[5]

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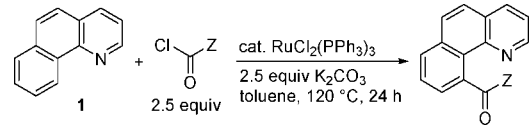
Table 1. Amino- and Alkoxycarbonylation of Benzo[*h*]quinoline[a]

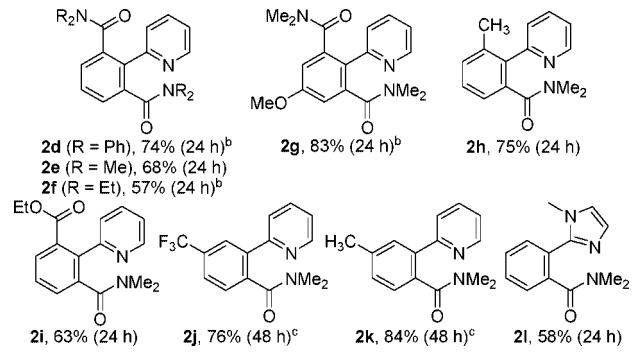


1 2.5 equiv

entry	Z	$RuCl_2(PPh_3)_3$ (mol%)	product	isolated yield (%)
1	NMe_2	10	**2a**	94
2	NPh_2	10	**2b**	97
3		10	**2c**	90
4[b]		1	**2c**	75
5	OEt	10	**3a**	66
6	O^{n}Bu	10	**3b**	70
7	O^{i}Pr	10	**3c**	70

[a] Reaction conditions: benzo[*h*]quinoline (1 mmol), carbamoyl chloride or alkyl chloroformate (2.5 mmol), K_2CO_3 (2.5 mmol), $RuCl_2(PPh_3)_3$, toluene (6 mL), 120 °C, 24 h. [b] Performed in xylene (1 mL) at 150 °C.

Table 2. Aminocarbonylation of Aromatic Compounds[a]



2d (R = Ph), 74% (24 h)[b]
2e (R = Me), 68% (24 h)
2f (R = Et), 57% (24 h)[b]
2g, 83% (24 h)[b]
2h, 75% (24 h)
2i, 63% (24 h)
2j, 76% (48 h)[c]
2k, 84% (48 h)[c]
2l, 58% (24 h)

[a] Reaction conditions: aromatic compound (1 mmol), carbamoyl chloride (2.5 mmol), K_2CO_3 (2.5 mmol), $RuCl_2(PPh_3)_3$ (10 mol%), toluene (3 mL), 120 °C, 24 h. [b] Performed with 5.0 mmol of carbamoyl chloride and K_2CO_3. [c] Reaction conditions: arylpyridine (0.5 mmol), carbamoyl chloride (5.0 mmol), K_2CO_3 (5.0 mmol), $RuCl_2(PPh_3)_3$ (10 mol%), toluene (1 mL), 120 °C, 48 h.

Other aromatic compounds were also examined for the aminocarbonylation (Table 2). The reaction of 2-phenylpyridine with 2.5 equiv of *N*,*N*-diphenylcarbamoyl chloride afforded both monoamide and diamide products, and the use of 5 equiv of the carbamoyl chloride increased the yield of diester **2d** to 74%. *N*,*N*-Dimethyl amide **2e** and *N*,*N*-diethyl amide **2f** were also obtained in 68% and 57% yields, respectively. Arylpyridines bearing a functional group were examined, and the reaction tolerated the presence of functionalities such as OMe, C(O)OEt, and CF_3 groups. While diamide product **2g** was obtained from *p*-methoxyphenylpyridine, *o*- and *m*-substituted arylpyridines

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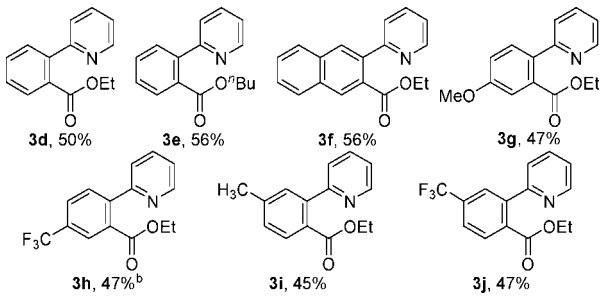
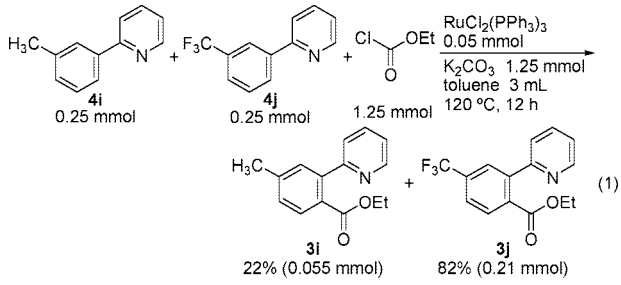
Table 3. Alkoxycarbonylation of Arylpyridines[a]



[a] Reaction conditions: arylpyridine (1.0 mmol), alkyl chloroformate (2.5 mmol), K_2CO_3 (2.5 mmol), $RuCl_2(PPh_3)_3$ (10 mol%), toluene (6 mL), 120 °C, 12 h. [b] Formation of the corresponding diester product (8% isolated yield) was observed.

were transformed into monoamides (**2h**−**k**). For *m*-substituted substrates, the reaction took place at less congested *o*-positions (**2j**,**k**). Besides the pyridyl group, a *N*-methylimidazolyl group also functioned as a directing group (**2l**).[11]

Alkoxycarbonylation was also performed with arylpyridines (Table 3). In sharp contrast to the aminocarbonylation, the alkoxycarbonylation of phenyl- and *p*-methoxyphenylpyridines afforded the corresponding monoesters predominantly, with the exception of **3h**, which was formed with 8% yield of the diester product. Alkoxycarbonylation of *m*-methyl- and *m*-trifluoromethylphenylpyridines (**4i** and **4j**, respectively) afforded monoesters **3i** and **3j** in similar yields. Interestingly, however, a competition reaction between **4i** and **4j** with ethyl chloroformate preferentially afforded the product with the more electron-withdrawing CF_3 group (**3j**) in a ca. 4:1 ratio (eq 1).



Precedent studies of several palladium-[12,13] and ruthenium-catalyzed[14] C−H arylations using aryl halides revealed that C−H bond cleavage may proceed via a base-assisted proton abstraction mechanism, and in this case, electron-deficient arenes react faster in the competition experiments. On the basis of these studies, we proposed a mechanism of our reaction as shown in Figure 1.[15] Cleavage of the ortho C−H bond of arylpyridine occurs to form five-membered ruthenacycle **B** from catalyst **A**, most likely via proton abstraction by a coordinating carbonate. Oxidative addition of a C−Cl bond of the chlorocarbonyl group (**B**→**C**) and reductive elimination affords the product with regeneration of catalyst **A**.

In summary, we developed ruthenium-catalyzed regioselective direct amino- and alkoxycarbonylations of aromatic rings via C−H bond cleavage using chlorocarbonyl compounds. A broad generality of amide and ester groups was achieved, taking advantage of the wide availability of carbonylating agents. Alkyl chloroformates, inapplicable to usual Friedel−Crafts methods, can be used for the direct catalytic alkoxycarbonylation.

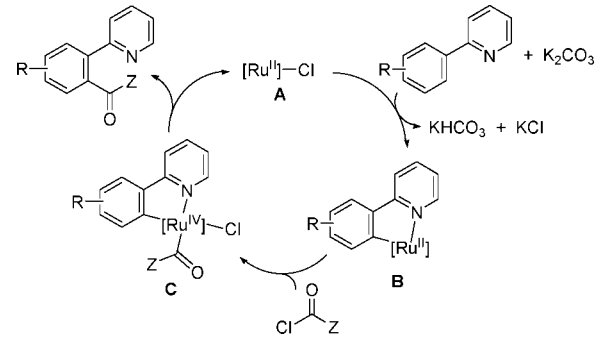


Figure 1. A possible catalytic cycle for the amino- and alkoxycarbonylation.

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Supporting Information Available: Experimental procedures and characterization (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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