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Ru(II)-catalyzed *ortho*-amidation and decarboxylation of aromatic acids: a versatile route to *meta*-substituted *N*-aryl benzamides

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Carboxylate as a promising and valuable directing group has attracted a great deal of attention. However, employing it as a traceless direction group has rarely been reported. We developed the ruthenium-catalyzed amidation of substituted benzoic acids with isocyanates via directed C–H functionalization followed by decarboxylation to afford the corresponding *meta*-substituted *N*-aryl benzamides, in which the carboxylate serves as a unique, removable directing group. Notably, this protocol can provide an efficient alternative to access *meta*-substituted *N*-aryl benzamides, which are much more difficult to prepare than *ortho*-substituted analogues.

amides, decarboxylation, amidation, C–H functionalization, homogeneous catalysis

1 Introduction

Amide represents an important structural motif that is present in many natural products, polymers, pharmaceuticals, and biological systems [1]. They are also important intermediates for the preparation of various useful compounds [2]. Amide bonds are typically formed from amines and preactivated carboxylic acid derivatives such as acid chlorides and anhydrides, or via *in situ* activation of carboxylic acid with coupling reagents such as carbodiimides [3]. Although all of these methods are very effective, they possess considerable drawbacks in terms of the poor overall atom economy and the use of hazardous reactive reagents, both of which can also complicate product purification [4]. Therefore, great efforts have been made recently to develop more efficient processes for amide synthesis [5].

In recent years, the selective functionalization of C–H bonds of directing group-containing arenes has attracted a substantial interest attributable to the potential shortening of synthetic steps [6]. Employing functional group-directed C–H functionalization reactions, several methods were also developed to construct amide motifs. For example, Chang *et al.* [7] described the selective C–C amidation under thermal rhodium catalysis. Cheng *et al.* [8a] and Ellman *et al.* [8b] successively demonstrated the amidation of 2-arylpyridines with isocyanates via C–H bond activation catalyzed by rhodium or ruthenium. However, in all of these reports, the amide group was introduced into the *ortho* position of the directing group (Scheme 1, Route (a)) and the directing group stayed in the original place.

Transition-metal-catalyzed decarboxylative coupling reactions are receiving increasing attention for their use in C–C bond formation reactions [9]. In this context, Larrosa *et al*. [10] displayed carboxylic acids as traceless directing group for a formal meta-selective direct arylation: namely, carboxyl group-directed *ortho* C–H activation followed by decarboxylation. However, the application of this concept to the synthesis of *meta*-substituted compounds has not been as closely investigated [11]. In our study on the insertion of

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C–H to polarized C–N double bonds, we observed unexpectedly that 3-methyl-*N*-phenylbenzamide was generated under a ruthenium catalyst (Scheme 1, Route (b)). This result demonstrates that carboxylic acids act as a unique, removable directing group. Motivated by this finding, we envisioned that *meta*-substituted *N*-aryl benzamides, which are much more difficult to prepare than *ortho*-substituted analogues, could be readily synthetized using this strategy. Moreover, although ruthenium complexes have been considered to be versatile [12], less-expensive alternative catalysts to commonly used transition metals in C–H activation chemistry, few studies have employed them in carboxylate-directed C–H activation and decarboxylation cross-coupling reactions. Herein, we present a convenient synthesis of *meta*-substituted *N*-aryl benzamides via a ruthenium-catalyzed *ortho*-amidation and decarboxylation of benzoic acids.

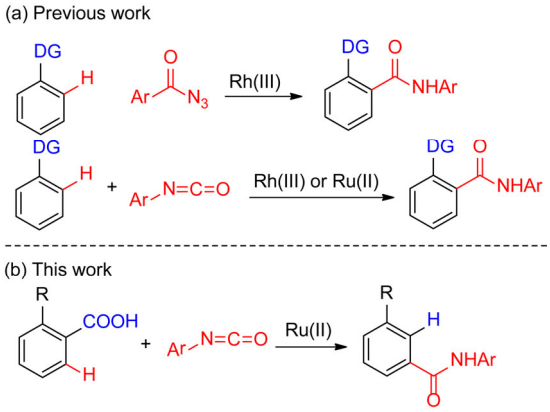
2 Experimental

2.1 General information

All commercial chemicals were used as received, without further purification. ^{1}H NMR spectra were measured on a 300, 400, or 500 MHz spectrometer; ^{13}C NMR spectra were measured on a 300 or 600 MHz spectrometer (^{13}C NMR 75 or 150 MHz), with tetramethylsilane (TMS) as the internal standard at room temperature. Chemical shifts are given in δ relative to TMS; the coupling constants J are given in Hz. High-resolution mass spectra (HRMS) were obtained from a Bruker Compass-Maxis instrument (ESI, Germany).

2.2 General experimental procedure for the synthesis of *N*-aryl benzamides

An oven-dried reaction vessel was charged with [$RuCl_2$(*p*-cymene)]$_2$ (Ru*, 6.1 mg, 0.01 mmol, 5 mol%), acids (0.2 mmol), isocyanates (0.5 mmol), K_2HPO_4 (17.4 mg, 0.1 mmol), and KH_2PO_4 (13.6 mg, 0.1 mmol). After the vessel was evacuated and purged with argon three times, 1,4-dioxane (0.5 mL) was added to the system by syringe. The mixture was stirred at 130 °C for 24 h. When the reaction was complete, the resulting mixture was cooled to room temperature and filtered through a short silica-gel pad. The mixture was then concentrated *in vacuo* to give a residue, which was purified by preparative thin layer chromatography (TLC) to afford the corresponding product.



Scheme 1 Synthesis of *N*-aryl benzamides via C–H functionalization.

3 Results and discussion

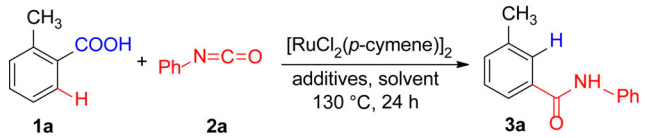
In the preliminary experiments, *o*-toluic acid was treated with [$RuCl_2$(*p*-cymene)]$_2$ (5 mol%), phenyl isocyanate (2.5 equiv.), and K_2HPO_4 (2.0 equiv.) in 1,4-dioxane (0.5 mL) at 130 °C for 24 h. To our delight, the desired product **3a** was obtained in 62% yield. In view of the importance of solvent effect in catalytic reactions, different solvents were tested first to optimize the reaction conditions; of these, 1,4-dioxane appeared to be the best choice. Other solvents such as THF, toluene, xylene, C_6H_5Cl, and DCE can also be used in this reaction to furnish a lower yield of **3a** (Table 1, Entries 3–7). DMF, however, failed to give **3a** (Entry 8).

No desired product was observed without K_2HPO_4 (Entry 1), which suggested that the choice of salt is crucial for the success of the present catalytic reaction. Therefore, a series of salts was examined. Replacing K_2HPO_4 with other alkali metal salts such as Na_2HPO_4, KOAc, LiOAc, Li_2CO_3, and Na_2CO_3 led to decrease in reaction yield (Entries 9–13). Only trace amounts of the desired product were detected with CsOAc, AgOAc, and Ag_2CO_3 (Entries 14–16). The presence of $Cu(OAc)_2$, $Cu(OAc)_2 \cdot H_2O$, K_2CO_3, and Cs_2CO_3 failed to produce any desired product (Entries 17–20).

Subsequently, various conditions related to the amount of K_2HPO_4, phenyl isocyanate, reaction time, and other additives were examined to optimize the formation of **3a**. A slightly higher yield was obtained when 0.5 equiv. of K_2HPO_4 was employed (Entry 21). Eventually, the combination of 0.5 equiv. K_2HPO_4 and 0.5 equiv. KH_2PO_4 increased the product yield to 76% (Entry 22).

Having determined these optimized reaction conditions, we next sought to investigate the substrate scope with respect to benzoic acid derivatives and phenyl isocyanate (Table 2). Significant electronic effects of the substituents on the reactivity were observed. A strong electron-withdrawing group such as NO_2, obviously inhibited the reaction and could not give the desired product under the optimized reaction conditions. On the contrary, benzoic acids-bearing electron-donating substituents, in general, afforded better yields. For example, 2-methyl, 4-methyl, 2-methoxyl, and 4-methoxyl benzoic acids generated the desired products in moderate to good yields (**3a**, **3b**, **3d**, **3e**). This reaction is also compatible with chloro-substituted benzoic acids, which furnished the respective products in

Table 1 Selected results for optimizing reaction conditions [a]



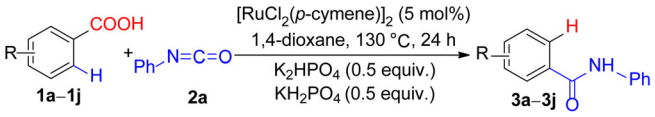
Entry	Additive (equiv.)	Solvent	Yield (%) [b]
1	–	1,4-dioxane	0
2	K_2HPO_4 (2.0)	1,4-dioxane	62
3	K_2HPO_4 (2.0)	THF	42
4	K_2HPO_4 (2.0)	Toluene	46
5	K_2HPO_4 (2.0)	Xylene	54
6	K_2HPO_4 (2.0)	C_6H_5Cl	55
7	K_2HPO_4 (2.0)	DCE	36
8	K_2HPO_4 (2.0)	DMF	ND [c]
9	Na_2HPO_4 (2.0)	1,4-dioxane	49
10	KOAc (2.0)	1,4-dioxane	32
11	LiOAc (2.0)	1,4-dioxane	34
12	Li_2CO_3 (2.0)	1,4-dioxane	22
13	Na_2CO_3 (2.0)	1,4-dioxane	34
14	CsOAc (2.0)	1,4-dioxane	trace
15	AgOAc (2.0)	1,4-dioxane	trace
16	Ag_2CO_3 (2.0)	1,4-dioxane	trace
17	$Cu(OAc)_2$ (2.0)	1,4-dioxane	ND
18	$Cu(OAc)_2{\cdot}H_2O$ (2.0)	1,4-dioxane	ND
19	K_2CO_3 (2.0)	1,4-dioxane	ND
20	Cs_2CO_3 (2.0)	1,4-dioxane	ND
21	K_2HPO_4 (0.5)	1,4-dioxane	67
22	K_2HPO_4 (0.5), KH_2PO_4 (0.5)	1,4-dioxane	76

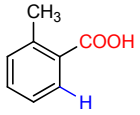
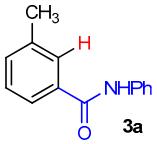
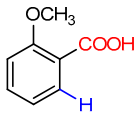
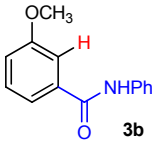
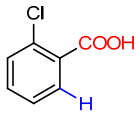
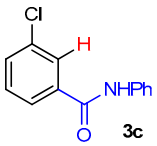
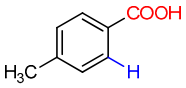
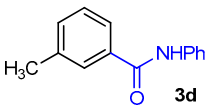
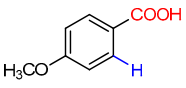
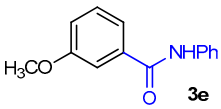
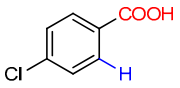
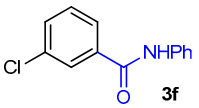
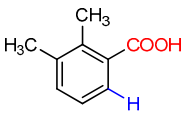
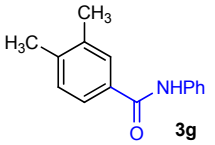
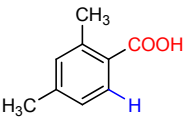
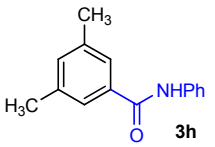
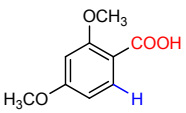
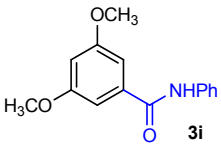
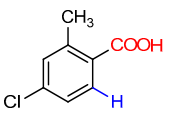
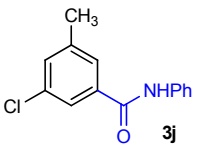
a) Reaction conditions: **1a** (0.1 mmol), **2a** (0.25 mmol), [$RuCl_2$(*p*-cymene)]$_2$ (5 mol%), additive, solvent (0.5 mL), 130 °C for 24 h, under argon in pressure tubes; b) determined by ^{1}H NMR analysis of the crude reaction mixture using mesitylene as internal standard; c) ND=not detected.

moderate yields (**3c**, **3f**). Several disubstituted benzoic acids could proceed smoothly and generate the corresponding products in moderate to good yields (**3g–3j**). The 2,4-dimethylbenzoic acid gave the highest yield of the desired product (**3h**).

A variety of isocyanates were reacted with 2,4-dimethylbenzoic acid under the optimized reaction conditions to further explore the substrate scope and limitations of this transformation (Table 3). A screening of isocyanates indicated that apart from phenyl isocyanate, phenyl isocyanates with methyl, methoxyl, and chloro are also effective in the reaction. Compared with *meta*-substituted phenyl isocyanate, the ones bearing substituents at the *para* position were readily converted into the corresponding products in higher yields (**3k** vs. **3l**, **3o** vs. **3p**). Particularly noteworthy is that chloro on the aromatic ring of the isocyanate remained intact in the product, which provides the possibility for further useful transformations through common cross-coupling strategies. This transformation also tolerated disubstituents; for example, 3,5-dimethylphenyl isocyanate and 3,4-dichlorophenyl isocyanate proceeded smoothly to afford products in 62% and 49% respective yields (**3n**, **3q**).

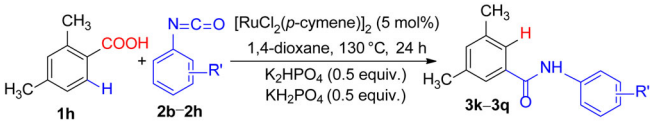
Table 2 Substrate scope for substituted benzoic acids [a]

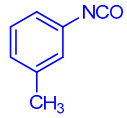
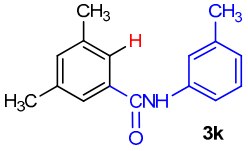
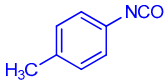
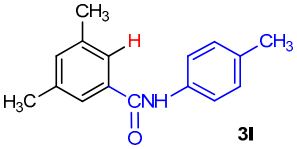
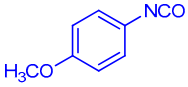
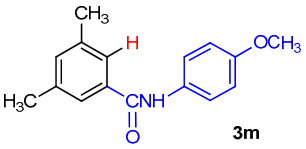
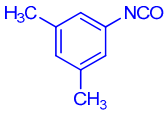
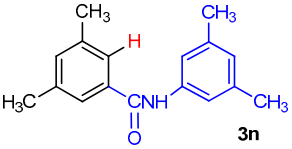
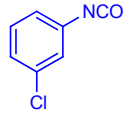
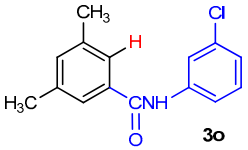
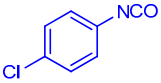
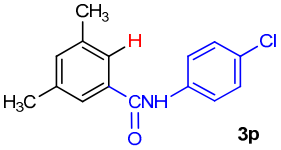
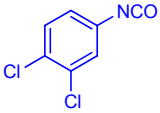
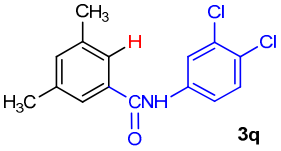


Entry	Substrate	Product	Yield (%) [b]
1		 **3a**	70
2		 **3b**	49
3		 **3c**	37
4		 **3d**	35
5		 **3e**	64
6		 **3f**	31
7		 **3g**	59
8		 **3h**	80
9		 **3i**	56
10		 **3j**	68

a) Reactions were carried out with acids (0.2 mmol), isocyanates (0.5 mmol), [$RuCl_2$(*p*-cymene)]$_2$ (5 mol%), 0.5 mL dioxane, K_2HPO_4 (0.5 equiv.), KH_2PO_4 (0.5 equiv.), 130 °C, 24 h; b) yield of isolated product was reported.

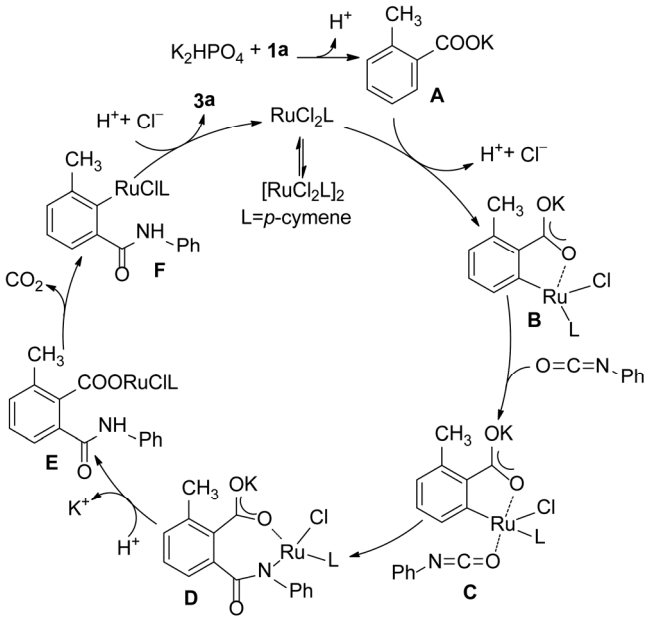
Table 3 Substrate scope for isocyanates [a)]



Entry	Substrate	Product	Yield (%) [b)]
1		 **3k**	74
2		 **3l**	90
3		 **3m**	69
4		 **3n**	62
5		 **3o**	75
6		 **3p**	92
7		 **3q**	49

a) Reactions were carried out with acids (0.2 mmol), isocyanates (0.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), 0.5 mL dioxane, K_2HPO_4 (0.5 equiv.), KH_2PO_4 (0.5 equiv.), 130 °C, 24 h; b) yield of isolated product was reported.

Based on the known chemistry of Ru-catalyzed directing-group-assisted C–H bond activation reaction and metal-mediated decarboxylation reactions [13,14], a possible mechanism to account for the present catalytic reaction was proposed (Scheme 2). The catalytic cycle is likely initiated by the dissociation of the dimer precatalyst $[RuCl_2(p\text{-cymene})]_2$ into the coordinatively unsaturated monomer. With the help of K_2HPO_4, the coordination of a carboxylic oxygen atom to the ruthenium center and subsequent *ortho*



Scheme 2 Proposed catalytic cycle for the *ortho*-selective decarboxylative C–H amidation of aromatic acids with isocyanates.

C–H activation affords a five-membered ruthenium-cyclic intermediate **B** and releases a proton at the same time. Subsequently, Complex **B** was proposed to undergo coordination and migratory insertion with isocyanate to furnish the key intermediate **D**. It is noteworthy that such additions to C-heteroatom multiple bonds are scarce in ruthenium (II)-catalyzed C–H activation. Protonation of **D** gives intermediate **E**. Then, decarboxylation of **E** followed by protonation affords the final product and regenerates the active Ru(II) species.

4 Conclusions

We have succeeded in developing a ruthenium-catalyzed regiospecific *ortho* amidation of aromatic acid with concomitant decarboxylation. This protocol, which provides a convenient access to the synthesis of *meta*-substituted *N*-aryl benzamides derivatives, allows to use a less-expensive precious metal Ru(II) as catalyst and readily available acids and isocyanates as starting materials. In these reactions, the carboxyl functions effectively serve as a unique, removable directing group. More important is that this protocol can provide an efficient alternative to access *meta*-substituted *N*-aryl benzamides, which are much more difficult to prepare than *ortho*-substituted analogues.

Supporting information

The supporting information is available online at chem.scichina.com and link.springer.com/journal/11426. The supporting materials are published as submitted, without typesetting or editing. The responsibility for scientific accuracy and content remains entirely with the authors.

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