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Ru(II)-Catalyzed Amidation of 2-Arylpyridines with Isocyanates via C−H Activation

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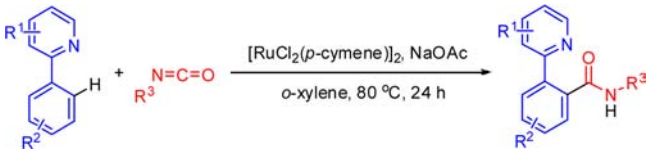
ABSTRACT



An efficient Ru(II)-catalyzed amidation of 2-arylpyridines with isocyanates via C−H bond activation is described.

In recent decades, chelation-assisted C−H bond activation and subsequent addition to alkynes, alkenes, and allenes has attracted increasing attention in metal-catalyzed organic synthesis.[1a−e] These methods have been broadly applied in the syntheses of natural products, drugs, and materials.[1f−h] Previously, a number of direct C−H additions to various polar bonds have been demonstrated.[2] Recently, *ortho* aromatic C−H bond activation and additions across polar unsaturated bonds has been studied considerably for the construction of substituted amides and amines at the *ortho*-position. In this context, Kuninobu and Takai initially observed a rhenium-catalyzed addition of aromatic and heteroaromatic aldimine C−H to isocyanates leading to the formation of phthalimidine[3a] and amidated[3b,c] derivatives. In 2011, Shi, Bergman, and Ellman et al. independently developed a Rh(III)-catalyzed selective C−H activation and subsequent addition to *N*-sulfonyl arylaldimines[4] and boc-imines[5a] respectively. Very recently, Bergman and Ellman reported a synthesis of *N*-acyl anthranilamides and *β*-enamine amides via Rh(III)-catalyzed amidation of aryl and vinyl C−H bonds with isocyanates.[5b] However, these methods required an expensive catalyst or harsh reaction conditions. Recently, the use of Ru(II) complexes as inexpensive, readily available, and environmentally friendly catalysts

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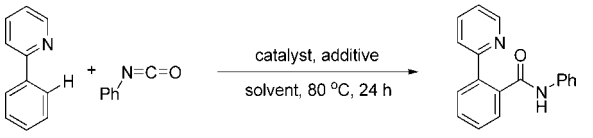
for C−H activation reactions has attracted considerable attention.[6] Our continuous interest in the metal-catalyzed C−H bond activation reactions[7] prompted us to explore the reaction of 2-arylpyridines with isocyanates. Herein, we wish to report a convenient and mild method for *ortho* amidation of 2-arylpyridines via ruthenium-catalyzed C−H bond activation. The use of ruthenium(0)[8] and recently $[RuCl_2(p\text{-cymene})]_2$-catalyzed[6] chelation-assisted C−H bond activation reactions have been reported.

We started the amidation reaction using 2-phenylpyridine **1a** and phenylisocyanate **2a** as the substrates and $[RuCl_2(p\text{-cymene})]_2$ (5 mol %) as the catalyst. The reaction proceeded in the presence of NaOAc (30 mol %) in *o*-xylene at 80 °C for 24 h to give amidation product **3a** in 90% isolated yield (Table 2, entry 1). The structure of **3a** was confirmed by its ^1H, ^{13}C NMR and mass data.

To understand the nature of this reaction and to find the optimal reaction conditions, different additives and solvents were examined. In the absence of any additive, the $[RuCl_2(p\text{-cymene})]_2$-catalyzed reaction gave only a trace of **3a** (Table 1, entry 1). The catalytic reaction appears to require the presence of a base in order to proceed smoothly. Several bases were tested for the reaction. Among them, NaOAc gave the best result and afforded **3a** in 93% yield determined by an NMR integration method (Table 1, entry 2) or 90% isolated yield (Table 2, entry 1). Other metal acetates including KOAc, CsOAc, $Cu(OAc)_2$, and AgOAc are less effective giving **3a** in 41, 36, 7, and 5% yield, respectively (Table 1, entries 3−6). The effect of solvents is also vital to the catalytic reaction. *o*-Xylene was found to be the ideal solvent affording **3a** in 90% isolated yield. Other solvents such as benzene, toluene, THF, and DCE were less effective for the catalytic reaction giving **3a** in 48, 28, 32, and 21% yield, respectively (Table 1, entries 7−10). Alcoholic solvents are not suitable for the catalytic reaction (entries 11−12). Ruthenium complex $[RuCl_2(p\text{-cymene})]_2$ is the most effective giving product **3a** in 90% yield. $[RuCl_2(benzene)]_2$ is also active forming **3a** in 53% yield (entry 13). Other ruthenium complexes including $[RuCl_2(COD)]_n$, $RuCl_2(PPh_3)_3$, and $RuCl_3 \cdot xH_2O$ were totally inactive (entries 14−16).

To evaluate the scope of the present catalytic reaction, we examined the reactions of several substituted 2-arylpyridines (**1b**−**l**) with phenyl isocyanate (**2a**) under the optimized reaction conditions (Table 2). Thus, 4-methyl, 4-methoxy, 4-bromo-, 4-fluoro-, and 4-cyanophenylpyridines (**1b**−**f**) underwent C−H activation and an addition reaction effectively with isocyanate **2a** affording the corresponding amidation products **3b**−**f** in 63−83% yields

Table 1. Optimization Studies for the Ru-Catalyzed Amidation of 2-Arylpyridines with Isocyanates[a]



1a **2a** **3a**

entry	catalyst	additive	solvent	yield (%)[b]
1	$[RuCl_2(p\text{-cymene})]_2$	–	*o*-xylene	trace
2	**$[RuCl_2(p\text{-cymene})]_2$**	**NaOAc**	***o*-xylene**	**93(90)**
3	$[RuCl_2(p\text{-cymene})]_2$	KOAc	*o*-xylene	41
4	$[RuCl_2(p\text{-cymene})]_2$	CsOAc	*o*-xylene	36
5	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2$	*o*-xylene	7
6	$[RuCl_2(p\text{-cymene})]_2$	AgOAc	*o*-xylene	5
7	$[RuCl_2(p\text{-cymene})]_2$	NaOAc	benzene	48
8	$[RuCl_2(p\text{-cymene})]_2$	NaOAc	toluene	28
9	$[RuCl_2(p\text{-cymene})]_2$	NaOAc	THF	32
10	$[RuCl_2(p\text{-cymene})]_2$	NaOAc	DCE	21
11	$[RuCl_2(p\text{-cymene})]_2$	NaOAc	MeOH	0
12	$[RuCl_2(p\text{-cymene})]_2$	NaOAc	EtOH	0
13	$[RuCl_2(benzene)]_2$	NaOAc	*o*-xylene	53
14	$[RuCl_2(COD)]_n$	NaOAc	*o*-xylene	0
15	$RuCl_2(PPh_3)_3$	NaOAc	*o*-xylene	0
16	$RuCl_3 \cdot xH_2O$	NaOAc	*o*-xylene	0

[a] Unless otherwise mentioned, all reactions were carried out using 2-phenylpyridine **1a** (1 mmol), **2a** (1.8 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), NaOAc (30 mol %), and solvent (2 mL) at 80 °C for 24 h under N_2. [b] Yields were determined by the ^1H NMR integration method; the value in the parentheses was isolated yield.

(entries 2−6). The above results indicate that both electron-withdrawing and -donating arylpyridines work well. Interestingly, 4-formyl- and 4-phenylarylpyridines (**1g**−**h**) also reacted efficiently with **2a** to afford the corresponding amidation derivatives **3g** and **3h** in 61 and 76% yield respectively (entries 7,8). Similarly, the reaction of 2-(2-methylphenyl)pyridine **1i** with **2a** proceeded smoothly to give **3i** in 84% yield (entry 9). In addition, 2-(3-methoxyphenyl)pyridine **1j** reacted nicely with **2a** to give **3j** in 78% yields (entry 10). In the reaction of 3-methoxyarylpyridine, there are two possible C−H bond activation sites at C2 and C6 of **1j**, but the C−H activation occurs only at C6 likely due to the steric effect of the methoxy group at C3. In a similar manner, 3-fluoro- and 3-chlorophenylpyridines **1k** and **1l** gave amidation derivatives **3k** and **3l** in 72 and 74% yield, respectively (entries 11,12).

To evaluate the scope of the present catalytic reaction, we examined the reaction of substrates **1** bearing substituents on the pyridine ring (**1m**−**p**) with **2a** under the optimized reaction conditions. Thus, 6-methyl (**1m**), 5-methyl (**1n**), methoxy (**1o**), and phenyl (**1p**) substituted pyridines underwent C−H activation and addition reaction effectively with isocyanate **2a** affording amidation products **3m**−**p** in 82, 87, 82 and 81% yield, respectively (entries 13−16). 1-Phenylpyrazole (**1q**) also worked well with **2a** to give **3q** in 79% yield (entry 17). In addition to **2a**,

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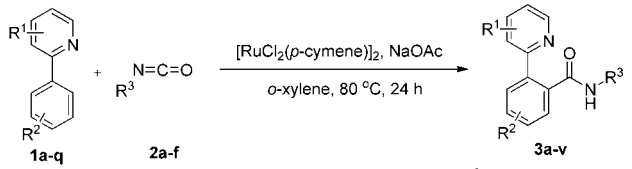
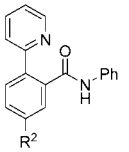
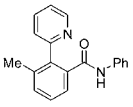
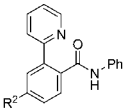
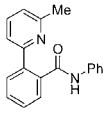
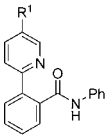
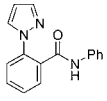
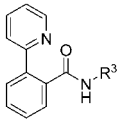
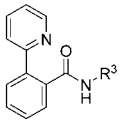
Table 2. Results of the Reaction of 2-Arylpyridines with Isocyanates[a]



1a: R^1, R^2 = H
1b: R^1 = H, R^2 = 4-Me
1c: R^1 = H, R^2 = 4-OMe
1d: R^1 = H, R^2 = 4-Br
1e: R^1 = H, R^2 = 4-F
1f: R^1 = H, R^2 = 4-CN
1g: R^1 = H, R^2 = 4-CHO
1h: R^1 = H, R^2 = 4-Ph
1i: R^1 = H, R^2 = 2-Me
1j: R^1 = H, R^2 = 3-OMe
1k: R^1 = H, R^2 = 3-F
1l: R^1 = H, R^2 = 3-Cl
1m: R^1 = 6-Me, R^2 = H
1n: R^1 = 5-Me, R^2 = H
1o: R^1 = 5-OMe, R^2 = H
1p: R^1 = 5-Ph, R^2 = H
1q: 
2a: R^3 = C_6H_5
2b: R^3 = 4-MeC_6H_4
2c: R^3 = 4-$OMeC_6H_4$
2d: R^3 = 4-BrC_6H_4
2e: R^3 = 4-ClC_6H_4
2f: R^3 = cyclohexyl

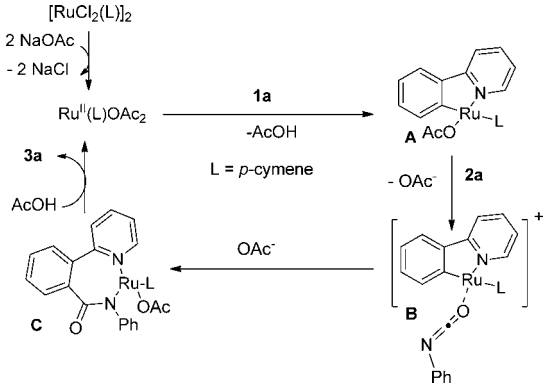
entry	1	2	product 3		yield (%)[b]
1	**1a**	**2a**		**3a**: R^2 = H	90
2	**1b**	**2a**		**3b**: R^2 = Me	81
3	**1c**	**2a**		**3c**: R^2 = OMe	79
4	**1d**	**2a**		**3d**: R^2 = Br	83
5	**1e**	**2a**		**3e**: R^2 = F	78
6	**1f**	**2a**		**3f**: R^2 = CN	63
7	**1g**	**2a**		**3g**: R^2 = CHO	61
8	**1h**	**2a**		**3h**: R^2 = Ph	76
9	**1i**	**2a**		**3i**	84
10	**1j**	**2a**		**3j**: R^2 = OMe	78
11	**1k**	**2a**		**3k**: R^2 = F	72
12	**1l**	**2a**		**3l**: R^2 = Cl	74
13	**1m**	**2a**		**3m**	82
14	**1n**	**2a**		**3n**: R^1 = Me	87
15	**1o**	**2a**		**3o**: R^1 = OMe	82
16	**1p**	**2a**		**3p**: R^1 = Ph	81
17	**1q**	**2a**		**3q**	79
18	**1a**	**2b**		**3r**: R^3 = 4-MeC_6H_4	86
19	**1a**	**2c**		**3s**: R^3 = 4-$OMeC_6H_4$	82
20	**1a**	**2d**		**3t**: R^3 = 4-BrC_6H_4	76
21	**1a**	**2e**		**3u**: R^3 = 4-ClC_6H_4	81
22	**1a**	**2f**		**3v**: R^3 = cyclohexyl	72

[a] Unless otherwise mentioned, all reactions were carried out with 2-phenylpyridine **1a** (1 mmol), **2a** (1.8 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), NaOAc (30 mol %), and *o*-xylene (2 mL) at 80 °C for 24 h under N_2. [b] Isolated yields.

other isocyanates (**2b**−**e**) were also tested for the reaction. Thus, treatment of 4-methyl- and 4-methoxyphenyl isocyanates **2b**−**c** with **1a** gave **3r** and **3s** in 86 and 82% yield, respectively (entries 18−19). In a similar manner, 4-bromo- and 4-chlorophenyl isocyanates **2d**−**e** gave products **3t**−**u** in 76 and 81% yield, respectively (entries 20−21). The present catalytic reaction can be further extended to alkyl isocyanates. Thus, cyclohexyl isocyanate **2f** reacted with **1a** to afford amidation derivative **3v** in 72% yield (entry 22).

Based on the known chemistry of metal-catalyzed C−H bond activation and addition reactions,[1,4−9] a possible mechanism to account for the present catalytic reaction is proposed (Scheme 1). The catalytic cycle is likely initiated by the dissociation of the $[RuCl_2(p\text{-cymene})]_2$ dimer into the coordinatively unsaturated monomer and the exchange of acetate with the coordinated chloro ligand to form an acetate-ligated species.[10] Then, the coordination of the 2-phenylpyridine nitrogen to the ruthenium center and subsequent *ortho* C−H bond activation form a five-membered ruthenacycle **A** and the release of an acetic acid. Selective insertion of isocyanate **2a** into the ruthenium−carbon bond of intermediate **B** gives the seven-membered ruthenacycle **C**. Protonation of **C** by acetic acid affords final product **3a** and regenerates the active Ru(II) species for the next cycle.

Scheme 1. Proposed Mechanism for the Amidation of 2-Arylpyridines with Isocyanates



To support the proposed mechanism, we tried to isolate the ruthenium catalyst intermediate. Thus, heating **1a** in the presence of 0.10 equiv of $[RuCl_2(p\text{-cymene})]_2$ and 0.30 equiv of NaOAc in *o*-xylene at 80 °C for 10 h led to the isolation of five-membered ruthenacycle **A-OAc** in 78% yield which is characterized by its ^1H, ^{13}C NMR and IR

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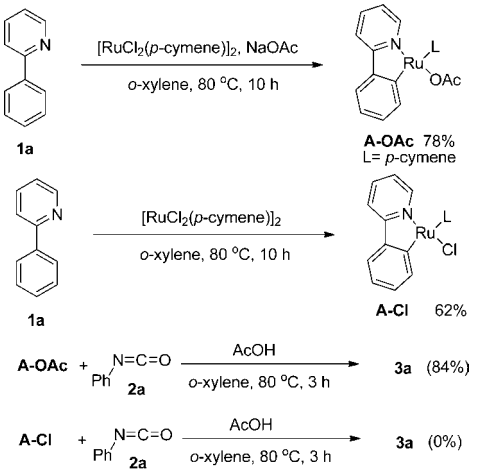
Scheme 2. Structure and Reactivity of Intermediate **A**



data (Scheme 2). The spectral data are in agreement with those reported previously.[11] As expected, the reaction of **A-OAc** with phenylisocyanate **2a** in the presence of HOAc (proton source) in *o*-xylene at 80 °C for 3 h gave amidation product **3a** in 84% yield (Scheme 2). It is interesting to note that the reaction of **A-OAc** with **2a** under slightly different conditions, either in the absence of HOAc or in the presence of NaOAc, gave product **3a** in only a trace amount. We also successfully isolated **A-Cl** from $[RuCl_2(p\text{-cymene})]_2$ and **1a**. However, **A-Cl** did not react with **2a** to give amidation product **3a** under any of the conditions shown above for **A-OAc**.

In conclusion, we have demonstrated an easy and convenient Ru(II)-catalyzed amidation of 2-arylpyridines with isocyanates via C−H bond activation. This method provides an opportunity for the synthesis of various amidated 2-arylpyridines under mild reaction conditions. Further applications of this methodology in natural product synthesis are in progress.

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Supporting Information Available. General experimental procedure, characterization details, and crystallographic data (CIF) for **3r**. This material is available free of charge via the Internet at http://pubs.acs.org

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The authors declare no competing financial interest.