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A Strategy for Amide C−N Bond Activation with Ruthenium Catalyst: Selective Aromatic Acylation

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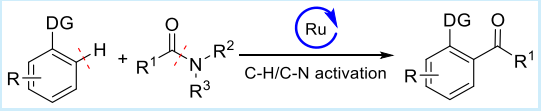
ABSTRACT: A strategy for amide C−N bond activation with ruthenium catalyst is described for the first time. The in situ formed bis-cycloruthenated complexes were demonstrated to be the key active species with superior oxidative addition ability to an inert amide C−N bond. The direct C−H bond activation of 2-arylpyridines followed by the amide C−N bond activation took place in the presence of a ruthenium precatalyst to produce monoacylation products in moderate to good yields. Synthetically useful functional groups, such as halogen atoms (F and Cl), ester, acetyl, and vinyl, remained intact during tandem C−H/C−N bond activation reactions.



Transition metal (TM)-catalyzed amide C−N bond activation has recently become an interesting topic in organic synthesis.[1] After the pioneering works of Garg[2] and Szostak[3] in 2015, many contributions have been made in this field by other researchers, including Rueping,[4] Stanley,[5] Shi,[6] Zou,[7] Zeng,[8] and Han.[9] Hong and co-workers recently reported a dual-photoredox nickel catalytic system for amide C−N bond activation.[10] The readily available and inexpensive but inert amides have been successfully employed as electrophilic reagents in an acylation or alkylation reaction via the release of carbon monoxide through ground state destabilization achieved by modifying the stereoelectronic characters of amides.[11] To the best of our knowledge, only three TMs, namely, palladium (Pd), nickel (Ni), and rhodium (Rh), can be used as catalysts in amide C−N bond activation (Figure 1a). Although ruthenium (Ru) catalysts usually have cost-effectiveness, good compatibility with commonly used oxidants, and stability in air and moisture,[12] no successful example of using Ru catalysts has been reported to date. The reason may be ascribed to the weak capacity of Ru catalysts in oxidative addition reactions with an electrophile.

In comparison, Ru-catalyzed C−H bond activation has been well-studied,[13] and $[RuCl_2(p\text{-cymene})]_2$ has been proven to be a versatile precatalyst for direct C−H functionalization.[14] Among the substrates used, 2-arylpyridines are more frequently utilized as the starting materials in Ru-catalyzed C−H functionalization.[15] Importantly, it was clearly demonstrated that cyclometalated Ru catalysts possess superior catalytic activity compared to commonly employed Ru species.[16] On the basis of previous work, we hypothesized that the cycloruthenated species generated in situ from 2-arylpyridines may undergo oxidative addition reaction with amides because of their enhanced activities and ultimately offer acylation products through reductive elimination. As expected, the desired C−H acylation products were obtained when 2-arylpyridines were treated with amides as acylating reagents in the presence of a Ru catalyst (Figure 1b). The first C−H bond functionalization with amides by double C−H/C−N bond activation using Rh catalyst has recently been reported by Meng and Szostak.[17] Unlike previous reported precious catalytic systems, this is the first example of Ru-catalyzed amide C−N bond activation. The results are reported in this paper.

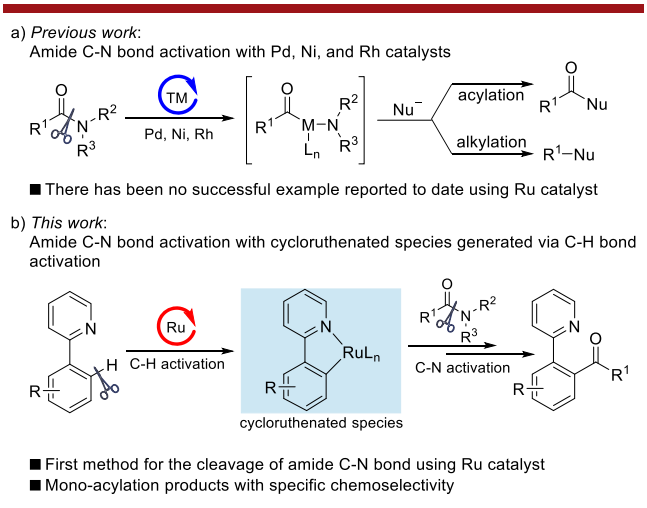


Figure 1. Amide C−N bond activation with TM catalysts.

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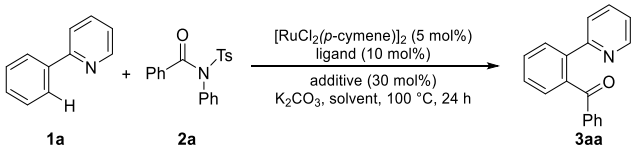
In our initial studies, the reaction of 2-phenylpyridine (**1a**) and *N*-phenyl-*N*-tosylbenzamide (**2a**) was chosen as the model to optimize the reaction conditions for amide C−N bond activation using $[RuCl_2(p\text{-cymene})]_2$ and K_2CO_3 as the precatalyst and base, respectively. The results are summarized in Table 1. The desired *ortho*-acylated product **3aa** was obtained along with 4-methyl-*N*-phenylbenzenesulfonamide as byproduct. The solvent was screened using sodium acetate (NaOAc) as the additive and $P^tBu_3{\cdot}HBF_4$ as the ligand at 100 °C under a nitrogen atmosphere for 24 h. Among the solvents examined [toluene, 1,2-dichloroethane (DCE), tetrahydrofuran (THF), 1,4-dioxane, *N*,*N*-dimethylformamide (DMF), tertiary butanol (^{t}BuOH), and acetone], acetone proved to be the best solvent (entries 1−7). Usually, an additive which will react with a precatalyst to produce active species is necessary in TM-catalyzed C−H bond activation reactions.[18] Therefore, the additives were subsequently screened using acetone as the solvent. The efficiency of salt (NaOAc) and acids [acetic acid (AcOH), trifluoroacetic acid (TFA), pivalic acid (PivOH), 1-adamantane carboxylic acid (1-$AdCO_2H$), benzoic acid ($PhCO_2H$), and 2,4,6-trimethylbenzoic acid ($MesCO_2H$)] was investigated. A relatively high yield (64%) was obtained when $MesCO_2H$ was utilized as the additive (entry 13 vs entries 7−12). The ligands were finally screened using acetone and $MesCO_2H$ as the solvent and additive, respectively. Among the phosphine ligands [tri-*tert*-butylphosphine tetrafluoroborate ($P^tBu_3{\cdot}HBF_4$), triphenylphosphine (PPh_3), tri-*n*-butylphosphine (P^nBu_3), and tricyclohexylphosphine (PCy_3)] examined, the use of PCy_3 led to the formation of acylation product **3aa** in higher yield than those obtained using other ligands (entry 16 vs entries 13 and 14). Although the yield of **3aa** was successfully increased to 70% by the combined use of $MesCO_2H$ and PCy_3 in acetone, the generation of a trace amount of byproduct mesityl(2-(pyridin-2-yl)phenyl)methanone was also detected. To our delight, the formation of a byproduct can be completely suppressed by utilizing a sterically hindered acid, such as 2,4,6-triisopropylbenzoic acid (TIPBA), as the additive instead of $MesCO_2H$ (entry 17, 72% yield). Further investigation revealed that the ligand tri-*p*-tolylphosphane [$P(p\text{-Tol})_3$] gave the same effect as PCy_3 (entry 17 vs entry 18). The reactivities of other activated amides, such as *N*-(*tert*-butyloxycarbonyl)-*N*-benzylbenzamide (**2ab**), *N*,*N*-di(*tert*-butyloxycarbonyl) benzamide (**2ac**), and 1-benzoylpiperidine-2,6-dione (**2ad**), were also investigated. Diminished or no reactivity was observed under the optimal reaction conditions (Scheme 1).

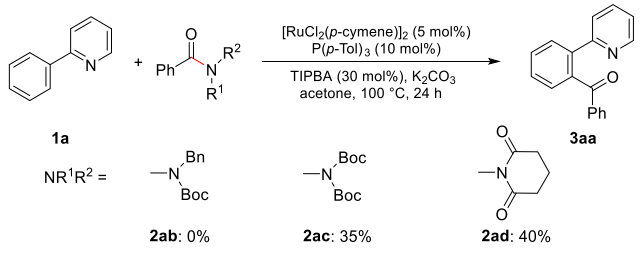
Table 1. Optimization of Reaction Conditions for Ru-Catalyzed C−H/C−N Activation[a]



Entry	Solvent	Additive	Ligand	Yield (%)[b]
1	toluene	NaOAc	$P^tBu_3{\cdot}HBF_4$	25
2	DCE	NaOAc	$P^tBu_3{\cdot}HBF_4$	NR[c]
3	THF	NaOAc	$P^tBu_3{\cdot}HBF_4$	15
4	dioxane	NaOAc	$P^tBu_3{\cdot}HBF_4$	32
5	DMF	NaOAc	$P^tBu_3{\cdot}HBF_4$	trace
6	^{t}BuOH	NaOAc	$P^tBu_3{\cdot}HBF_4$	35
7	acetone	NaOAc	$P^tBu_3{\cdot}HBF_4$	39
8	acetone	AcOH	$P^tBu_3{\cdot}HBF_4$	40
9	acetone	TFA	$P^tBu_3{\cdot}HBF_4$	24
10	acetone	PivOH	$P^tBu_3{\cdot}HBF_4$	45
11	acetone	1-$AdCO_2H$	$P^tBu_3{\cdot}HBF_4$	45
12	acetone	$PhCO_2H$	$P^tBu_3{\cdot}HBF_4$	47
13	acetone	$MesCO_2H$	$P^tBu_3{\cdot}HBF_4$	64
14	acetone	$MesCO_2H$	PPh_3	51
15	acetone	$MesCO_2H$	P^nBu_3	36
16	acetone	$MesCO_2H$	PCy_3	70
17	acetone	TIPBA	PCy_3	72
18	acetone	TIPBA	$P(p\text{-Tol})_3$	72

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (1.5 equiv), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), ligand (10 mol %), and additive (30 mol %) in solvent (1.5 mL) at 100 °C under a N_2 atmosphere for 24 h. [b]Isolated yield. [c]No reaction was observed; the starting materials were recovered.

Scheme 1. Reactivities of Different Activated Amides



The scope and limitation of this type of aromatic C−H bond direct acylation reaction were determined under the optimal reaction conditions. First, the scope of 2-arylpyridines was investigated using **2a** as the reaction partner. The results are shown in Table 2. Similarly, the reactions of *para*-substituted 2-phenylpyridines (**1b**−**1l**) proceeded as smoothly as the reaction of **1a** to produce the *ortho*-acylated products **3ab**−**3al** in satisfactory to good yields (60%−84%). These results revealed that the electronic property (electron-donating or electron-withdrawing) of the substituent linked to the benzene ring did not exert a remarkable influence on the reactivity of 2-arylpyridines. Synthetically useful functional groups, such as vinyl, fluorine, methoxycarbonyl, and acetyl, linked to the benzene rings of substrates **1i**−**1l** were maintained in the structures of products **3ai**−**3al**. This finding suggests that further manipulation may produce additional useful compounds. Interestingly, acylation and aldol condensation simultaneously occurred to produce unexpected product **3am** when the substrate **1m**, which bears a formyl group on the *para*-position, was examined in acetone. No reaction was observed when a 2-arylpyridine substrate with an *ortho*-substituent on the benzene ring was tested under the optimal reaction conditions; the reason may be attributed to the steric hindrance caused by the *ortho*-substituent. The results obtained by further investigation indicated that a substituent linked on the pyridine ring of 2-arylpyridine also did not influence reactivity. The desired products **3an**−**3ar** were obtained in high to good yields (69%−85%). As expected, the reaction of naphthalene ring-containing substrate **1s** also proceeded smoothly to furnish the corresponding product **3as** in 65% yield. Although the desired product **3at** was collected in relatively low yield (52%), the result obtained indicated that the pyrazole ring can be employed as a directing group in this type of C−H/C−N bond activation. In addition, no reaction

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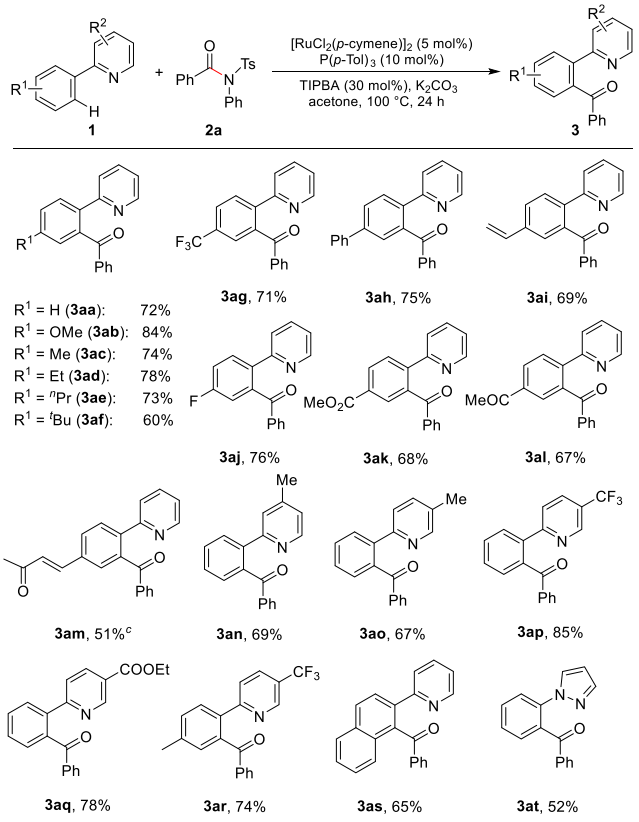
Table 2. Ru-Catalyzed C−H/C−N Activation: Scope of 2-Phenylpyridines[a]



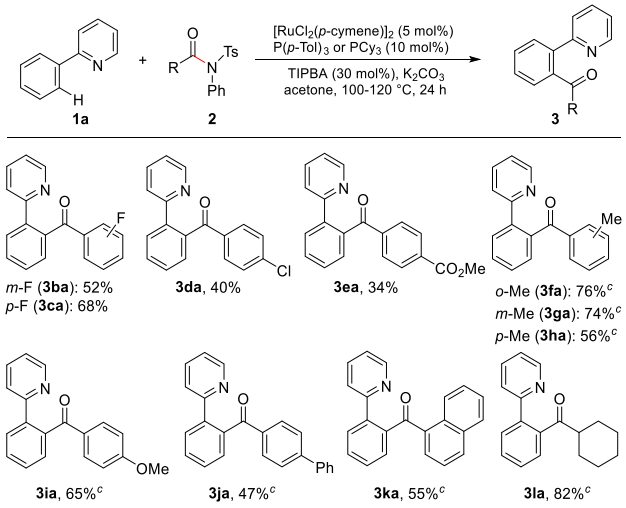
[a]Reaction conditions: **1** (0.2 mmol), **2** (1.5 equiv), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), $P(p\text{-Tol})_3$ (10 mol %), TIPBA (30 mol %), and K_2CO_3 (1.1 equiv) in acetone (1.5 mL) at 100 °C under a N_2 atmosphere for 24 h. [b]Isolated yield. [c]Aldol condensation between product and acetone was occurred.

or decomposition of starting material was observed when the starting materials **1u**, **1v**, and **1w** containing oxazoline or imine directing groups were examined (for details, see SI).

The scope of the amides was then investigated using **1a** as the reaction partner. The results are shown in Table 3. The *meta*- and *para*-fluorinated benzamides **2b** and **2c** smoothly underwent the target acylation reaction to offer products **3ba** and **3ca** in satisfactory yields (52% and 68%, respectively). However, the *para*-chlorinated analog **2d** gave the desired product **3da** in low yield (40%) owing to the side reaction that occurred on the C−Cl bond. A low yield (34%) was observed again when the amide **2e**, which bears a methoxycarbonyl group on the *para*-position, was examined; the reason is attributed to the instability of **2e**. Consistent with literature reports,[3a,5] an electron-donating group linked to the benzene ring of amide might reduce the reactivity of amide. The reactions of amides bearing an electron-donating group at the *ortho*-, *meta*-, or *para*-position were performed in the presence of electron-rich phosphine ligand PCy_3 at enhanced temperature to obtain satisfactory yields. The acylation products **3fa**−**3ka** were obtained with 47%−76% yields. The aliphatic amide **2l** was also examined, and product **3la** was obtained in 82% yield.

The substrate **1a** was finally scaled-up to 6 mmol to verify the usefulness of the current Ru-catalyzed C−H/C−N activation reaction. The *ortho*-C−H bond benzoylation

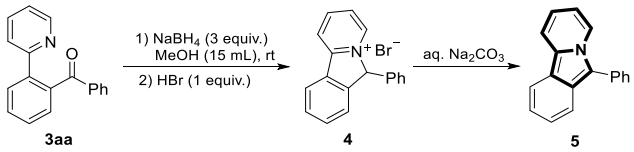
Table 3. Ru-Catalyzed C−H/C−N Activation: Scope of Amides[a,b]



[a]Reaction conditions: **1** (0.2 mmol), **2** (1.5 equiv), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), $P(p\text{-Tol})_3$ (10 mol %), TIPBA (30 mol %), and K_2CO_3 (1.1 equiv) in acetone (1.5 mL) at 100 °C under N_2 atmosphere for 24 h. [b]Isolated yield. [c]The reaction was carried out at 120 °C using PCy_3 (10 mol %) as the ligand instead of $P(p\text{-Tol})_3$.

reaction of **1a** proceeded smoothly even though the loadings of precatalyst, ligand, and additive were decreased. This finding suggests that this protocol opens up an opportunity for the large-scale acylation of 2-arylpyridines (see the Supporting Information). The C−H acylation product **3aa** was then transformed to a cyclic pyridinium bromide **4** through sequential reduction using $NaBH_4$ and cyclization under acidic conditions (Scheme 2).[19] The cyclic pyridinium bromide **4** was quantitatively transformed to an indolizine product **5** when it was treated with sodium carbonate (Na_2CO_3) in aqueous medium.

Scheme 2. Transformation of C−H Acylation Product 3aa to Indolizine 5



Control experiments were conducted to gain insights into the underlying mechanism of Ru-catalyzed aromatic C−H and amide C−N bond activation (Scheme 3). A 11:14 ratio of **3ab** to **3ag** was observed in the intermolecular competition reaction between **1b** and **1g**, indicating that the electronic property (electron-donating or electron-withdrawing) of the substituent linked to the benzene ring did not exert a remarkable influence on the reactivity of 2-arylpyridines. The deuterium kinetic isotope effect was investigated by conducting an intermolecular competition reaction between **1a** and **1a**-d_5. The 1:1 ratio of **3aa** to **3aa**-d_4 demonstrated that the cleavage of the aromatic C−H bond in **1a** was not the rate-determining step (see the Supporting Information). This observation suggests that the cleavage of the amide C−N bond should be the rate-determining step. The ruthenium carboxylate complex **6** was considered to be an active catalyst species in the

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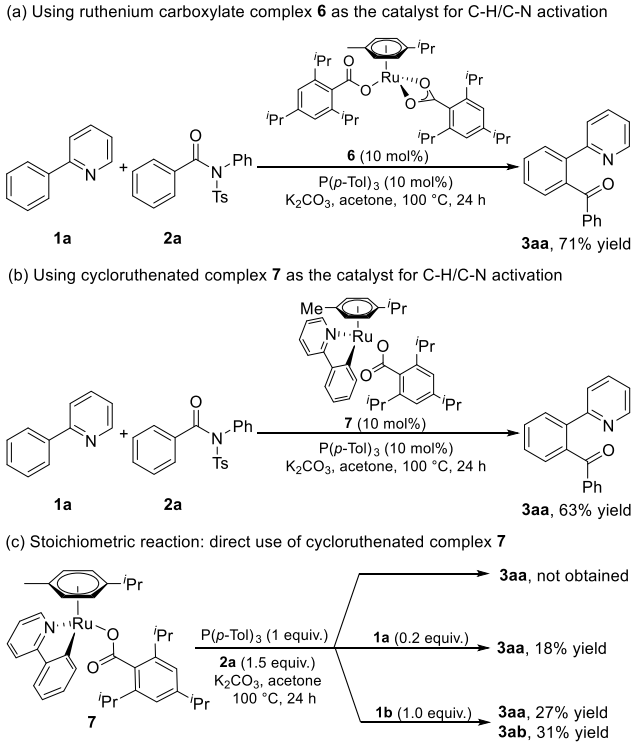
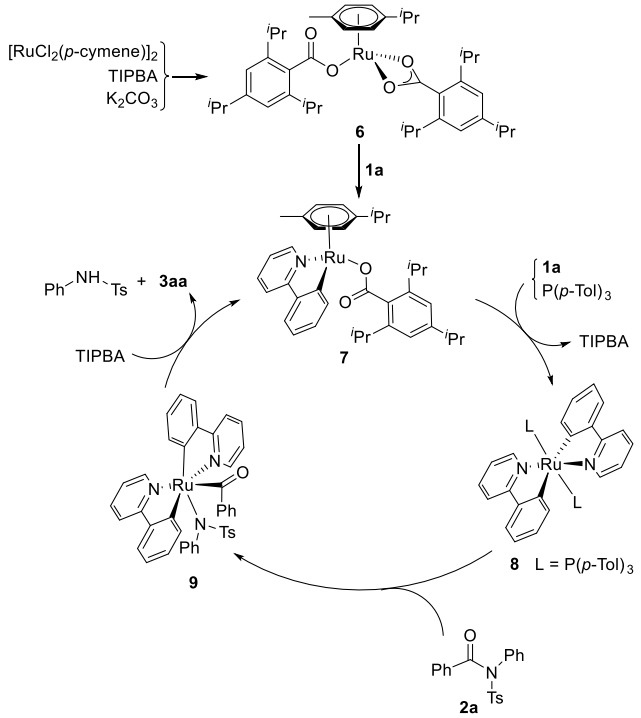
Scheme 3. Control Experiments of Ru-Catalyzed C−H/C−N Activation



Scheme 4. Proposed Mechanism of Ru-Catalyzed C−H/C−N Activation



current tandem C−H/C−N activation reaction. Therefore, the reaction of **1a** with **2a** was investigated in the presence of complex **6** as the catalyst to confirm our conjecture. As expected, the target reaction proceeded smoothly to furnish the desired acylation product **3aa** in high yield (Scheme 3a, 71%). The desired product **3aa** was also obtained in 63% yield by using cycloruthenated complex **7** as the catalyst, indicating that the complex **7** was another active catalyst species in the current tandem C−H/C−N activation reaction (Scheme 3b). The desired product **3aa** could not be obtained by direct treatment of cycloruthenated complex **7** with **2a** in the absence of **1a**, whereas the product **3aa** was obtained in 18% yield when 0.2 equiv of **1a** was added into the above-mentioned reaction mixture (Scheme 3c). The acylation products **3aa** and **3ab** were obtained in 27% and 31% yields, respectively, when the substrate **1b** was added into the above-mentioned reaction mixture instead of substrate **1a** (Scheme 3c). These findings are consistent with the literature report[16a] that a bis-cycloruthenated intermediate generated from complex **7** is the key intermediate that activates the amide C−N bond.

Based on the previous reports[16] and our experimental outcomes, a plausible mechanism for ruthenium-catalyzed C−H/C−N activation is shown in Scheme 4. Initially, the Ru(II) biscarboxylate complex **6**, an active catalyst species, is generated in situ from the reaction of precatalyst $[RuCl_2(p\text{-cymene})]_2$ with 2,4,6-triisopropylbenzoicacid (TIPBA) in the presence of base K_2CO_3. Then five-membered cyclometalated complex **7** is formed through the *ortho*-ruthenation of **1a** with complex **6**. Subsequently, a bis-cycloruthenated intermediate **8** would form through the *ortho*-ruthenation of another **1a** with complex **7**. Oxidative addition of intermediate **8** to the amide C−N bond takes place to generate the acylruthenium(IV) intermediate **9**, which then undergoes reductive elimination to produce the desired *ortho*-acylation product **3aa** and regenerate the cycloruthenated species **7**.

In summary, we described a new strategy for amide C−N bond activation with a Ru catalyst. The Ru-catalyzed tandem C−H and C−N bond activation reaction proceeded smoothly at mild conditions to produce monoacylation products in moderate to good yields. Notable features of our approach include the following: (a) the use of air stable and inexpensive Ru(II) catalyst; (b) the reaction shows specific monoacylation selectivity; (c) no alkylation reaction via the release of carbon monoxide takes place; (d) broad substrate scope and good functional group tolerance. Further study on the theoretical explanation of the reaction mechanism is currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00464.

Experimental details and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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