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Ruthenium-Catalyzed C−H Alkynylation of Aromatic Amides with Hypervalent Iodine−Alkyne Reagents

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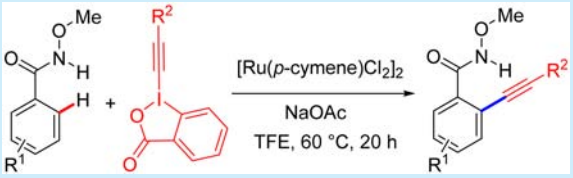
Supporting Information

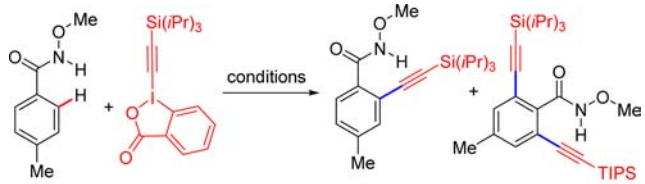
ABSTRACT: An efficient C−H activation method for the *ortho* alkynylation of aromatic *N*-methoxyamides with hypervalent iodine−alkyne reagent using a ruthenium catalyst is described. The reaction proceeds under mild reaction conditions with broad substrate scope. A possible catalytic cycle involving a ruthenium carboxylate assisted C−H bond cleavage is proposed from the preliminary mechanistic evidence.



Organic synthesis relies on the construction of carbon−carbon (C−C) and C−heteroatom (C−X) bonds. The traditional cross-coupling reactions to construct these bonds are environmentally and economically less attractive owing to their requirement of prefunctionalized starting compounds.[1] Recently, the functionalization of carbon−hydrogen (C−H) bonds has become a powerful tool for the straightforward, atom-, and step-economical synthesis of complex molecules.[2,3] In the past two decades, there has been significant progress in the arylation and alkenation of unactivated C−H bonds.[4,5] However, an equally important C−H alkynylation reaction is less explored. Very recently, a few reports appeared on the C−H alkynylation reactions.[6] The known methods mostly involve expensive Rh, Pd, Ir, and Au catalysts and are limited to a few substrates. Our continuous interest in the C−H functionalization reactions leads us to think that the development of a C−H alkynylation reaction using less expensive Ru catalyst should be a significant improvement in this research area.[7,8] In 2012, Tobisu and Chatani reported a nitrogen heterocycle directed C−H alkynylation by alkynyl bromides using a Ru catalyst[6r] at 100−130 °C. Very recently, Hong has demonstrated a Ru(II)-catalyzed C_2-selective alkynylation of *N*-pyrimidyl-4-quinolone with hypervalent iodine−alkyne reagents.[6s] The known reactions worked with substrates containing non-removable directing groups (DGs) or specific substrates. Direct Ru-catalyzed C−H alkynylation of substrates bearing a simple, highly useful, and easily transformable functional group is highly sought after. In this report, we disclose the *ortho* C−H alkynylation of aromatic amides using a $[RuCl_2(p\text{-cymene})]_2$ catalyst system.

We began our investigations using *N*-methoxy-4-methylbenzamide (**1a**) and 1-[(triisopropylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (**2a**) as the substrates. After screening a large number of reaction conditions, we found that the reaction of **1a** (0.20 mmol) and **2a** (0.22 mmol) in the presence of $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %) and NaOAc (1 equiv) in 2,2,2-trifluoroethanol (TFE) at 60 °C for 20 h gave product **3aa** in 75% isolated yield along with dialkynylation product **4aa** in 10% yield (Table 1, entry 7). Our efforts to further reduce **4aa** formation failed. Among the solvents tested, TFE is most effective to give **3aa** in the highest yield. Similarly, NaOAc was found to be a more suitable additive tested to promote the present reaction. Controlled experiments revealed that no product was formed in the absence of $[RuCl_2(p\text{-cymene})]_2$ or NaOAc (entries 15 and 16).

Table 1. Reaction Optimization Studies[a]



1a **2a** **3aa** **4aa**

entry	solvent	additive (equiv)	temp (°C)/time (h)	yield[b] (%) 3aa	4aa
1	TFE	NaOAc (1)	80/24	50	8
2	MeOH	NaOAc (1)	80/24	44	12
3	DCE	NaOAc (1)	80/24	27	5
4	ACN	NaOAc (1)	80/24	trace	
5	EtOH	NaOAc (1)	80/24	27	5
6	TAA	NaOAc (1)	80/24	trace	
7	**TFE**	**NaOAc (1)**	**60/20**	**75**[c]	**10**[c]
8	TFE	NaOAc (1.5)	60/20	67	8
8	TFE	NaOAc (0.5)	60/20	46	trace
9	TFE	NaOAc (0.2)	60/20	41	trace
10	TFE	NaOAc (1)	50/20	55	8
11	TFE	Na_2CO_3 (1.5)	60/20	72	10
12	TFE	$NaHCO_3$ (1)	60/20	60	5
13	TFE	K_2CO_3	60/20	20	trace
14	TFE	Na_2CO_3 (1.0)	60/20	64	10
15	TFE		60/20		
16	TFE	NaOAc (1)	60/20		*d*

[a]Reactions were performed using **1a** (33 mg, 0.20 mmol), **2a** (94 mg, 0.22 mmol), and $[Ru(p\text{-cymene})Cl_2]_2$ (3.0 mg, 2.5 mol %) under the above-mentioned conditions. [b]The yields were determined by ^1H NMR integration method using mesitylene as the internal standard. [c]Isolated yield. [d]No $[Ru(p\text{-cymene})Cl_2]_2$ was used.

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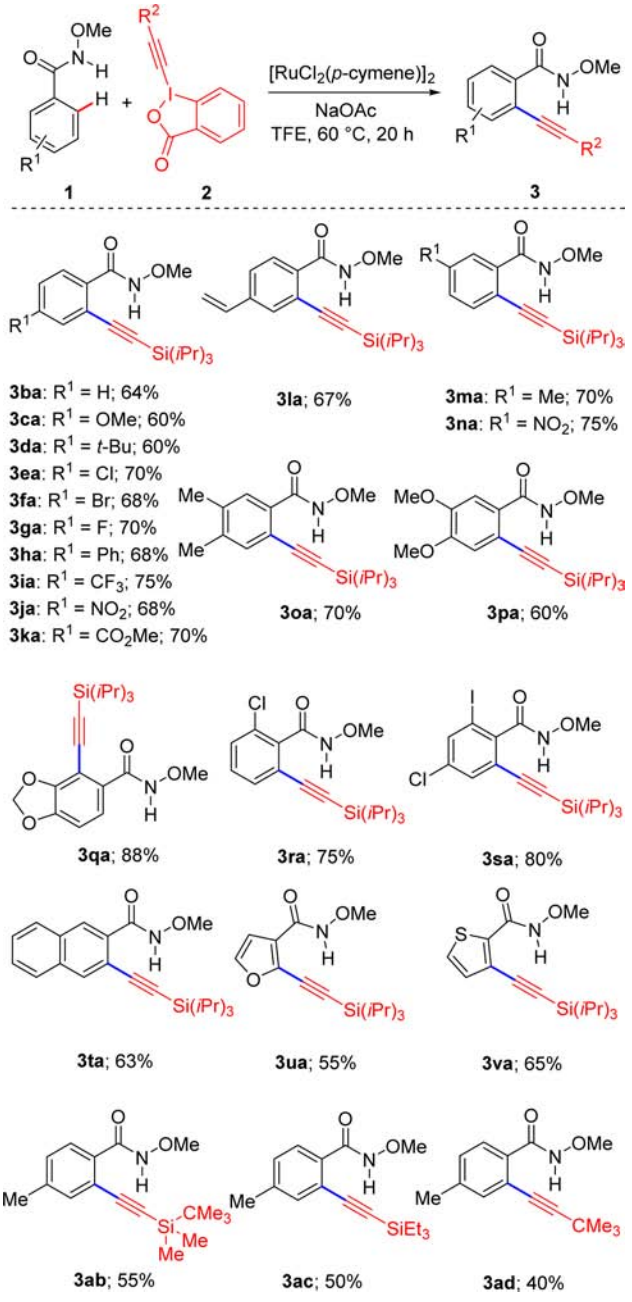
Scheme 1. Scope of the Ru-Catalyzed C−H Alkynylation of Aromatic Amides[a]



[a]Reaction conditions: **1** (0.35 mmol), **2** (0.38 mmol), [$RuCl_2$(*p*-cymene)]$_2$ (2.5 mol %), and NaOAc (0.35 mmol) in TFE (2.5 mL) at 60 °C for 20 h. Isolated yields were given. In all cases, 0−7% dialkynylation products were seen on the crude NMR and could not be isolated in a pure form.

Next, we tested the scope of the C−H alkynylation under the optimized reaction conditions, and the results are presented in Scheme 1. The reaction proceeded well with a variety of aromatic *N*-methoxyamides having both electron-donating and electron-withdrawing groups on the aromatic rings. Thus, treatment of *p*-OMe- and *p*-*t*Bu-substituted amides gave products **3ca** and **3da** in 60% yield in both cases. Under the reaction conditions, halogen-substituted amides were also compatible to afford the expected alkynylated products, **3ea**−**ga**, in good yields. Amides with strong electron-withdrawing groups such as CF_3, NO_2, and CO_2Me on the aromatic ring were also alkynylated smoothly to give the expected products, **3ia**−**ka**, in high yields. Substrate **1l** contains a vinyl group at the para position of the ring also proceeded to give product **3la** in 67% yield. The *meta*-substituted amides, **1m**−**p**, regioselectively underwent C−H activation at the less hindered site to give the respective alkynylated products **3ma**−**pa** in 60−75% yields. Interestingly, the methylenedioxy group substituted amide **1q** underwent C−H activation at the sterically hindered ortho position to give **3qa** as the sole product in 88% yield owing to the strong directing effect of the methylenedioxy substituent.[9] The catalytic *ortho* C−H alkynylation was not affected by the steric hindrance of another *ortho* substitution. Amides **1r** and **1s** having chloro and iodo substituents at the *ortho* position of the aromatic rings gave alkynylated products **3ra** and **3sa** in 75% and 80% yields, respectively. 2-Naphthylamide also underwent C−H activation selectively at the C3 position instead of C1 to give product **3ta** because of the steric hindrance by the fused aromatic ring. Heterocycle amides such as furan and thiophene substrates were also compatible under the reaction conditions to give C−H alkynylation products **3ua** and **3va** in good yields. We also examined the tolerance of different *N*-substituted amides under the reaction conditions. Unluckily, *N*-OPiv-, *N*-OH-, and *N*-OAc-substituted benzamides failed to give the corresponding alkynylated products. In addition to the amide substrates, we also examined different silyl substitutions in place of the Si(*i*Pr)$_3$ group. The reaction also worked well with $SiMe_2$(*t*Bu) and $SiEt_3$ groups on the alkyne moiety. Fortunately, *tert*-butylethyne (**2d**) without a silyl group also proceeded to give **3ad** in moderate yield. However, the phenyl-substituted alkyne did not lead to the desired alkynylation product. The structures of products **3oa** and **3ra** were further confirmed by single-crystal X-ray structure analysis.[10]

To further explore the scope of the Ru-catalyzed C−H alkynylation reaction, we tested 2-phenylpyridine **4** with **2a** under the standard reaction conditions to give expected products **5a** and **5b** in moderate yields (Scheme 2).

Scheme 2. Ru-Catalyzed C−H Alkynylation of 2-Phenylpyridine

To understand the mode of action of the present C−H alkynylation reaction, we performed a series of competition experiments (Scheme 3). The intermolecular competition reactions of **1a** and **1b** and **1a** and **1i** with **2a** revealed that the amide substrates with neutral or electron-withdrawing substitution showed higher reactivity than the electron-donating group substituted amides. In addition, treatment of **D$_5$-1b** in the presence and absence of **2a** under the standard conditions showed a considerable D/H exchange at the *ortho* positions of the amide directing group, suggesting that the initial cycloruthenation via C−H bond cleavage is reversible. Finally, the observed intermolecular kinetic isotope effects (KIE) k_H/k_D = 1.8 for the reaction of **1b** and **D$_5$-1b** with **2a** and intramolecular KIE k_H/k_D = 3.7 for the reaction of **D$_1$-1b** with **2a** suggest that the C−H cleavage step is possibly the rate-limiting step.[11]

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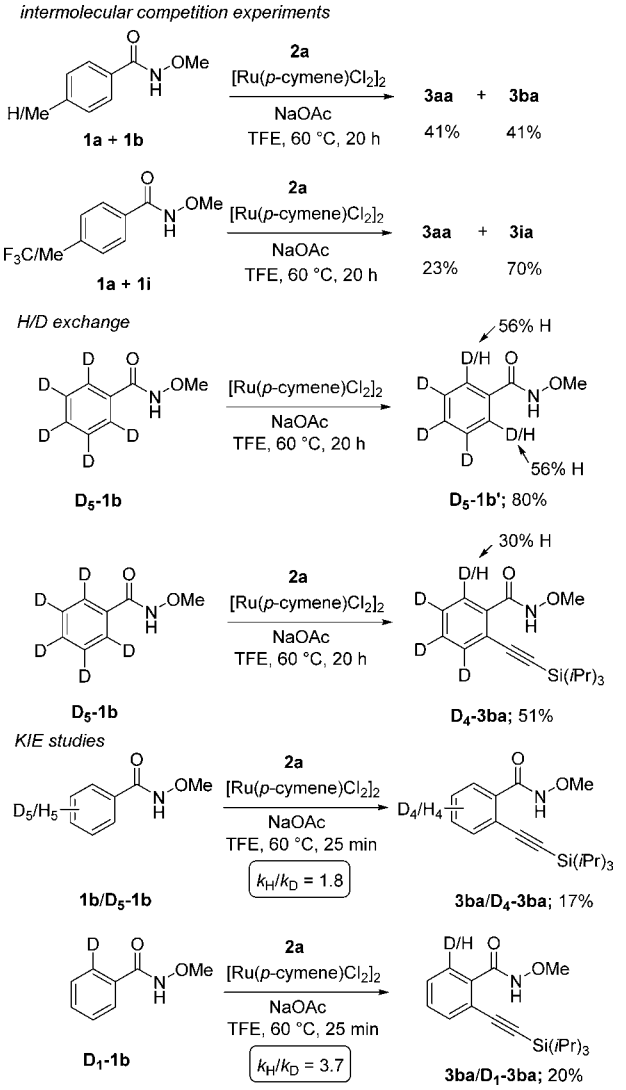
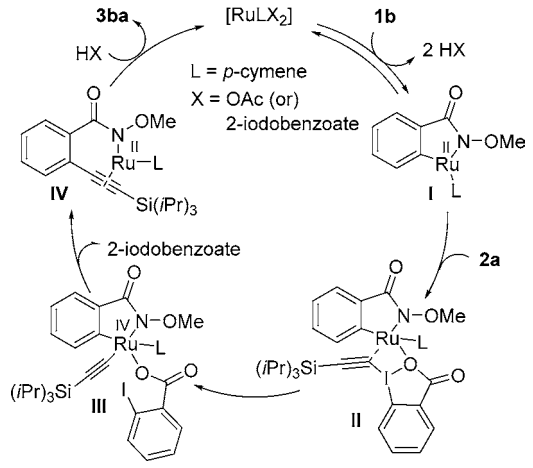
Scheme 3. Mechanistic Studies



Scheme 4. Plausible Catalytic Cycle



A plausible catalytic cycle for the Ru-catalyzed C−H alkynylation of amides is shown in Scheme 4. The ruthenium carboxylate complex undergoes ligand exchange with an amide group followed by an *ortho* C−H bond cleavage to give ruthenacycle **I**. Oxidative addition of **2a** to **I** via intermediate **II** affords ruthenium **III** intermediate. Dissociation of 2-iodobenzoate followed by reductive elimination affords Ru(II) complex **IV**. Protonation and alkyne dissociation from **IV** through ligand exchange delivers the final product **3ba**. An alternative mechanism that involves insertion of the C−C triple bond of **2a** into the Ru−C bond of intermediate **I** as a key step cannot be ruled out at this moment.

In summary, we have developed a ruthenium-catalyzed mild C−H activation method for the alkynylation of aromatic amides. A wide range of substituents on the amide moiety was tolerated and gave good yields. The preliminary mechanistic studies suggested that the initial C−H ruthenacycle formation is reversible.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01281.

General experimental procedures, characterization details, and ^{1}H and ^{13}C NMR spectra of new compounds (PDF)
Crystallographic data for **3oa** (CIF)
Crystallographic data for **3ra** (CIF)

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Notes

The authors declare no competing financial interest.

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