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Meta-Selective C_{Ar}–H Nitration of Arenes through a $Ru_3(CO)_{12}$-Catalyzed Ortho-Metalation Strategy

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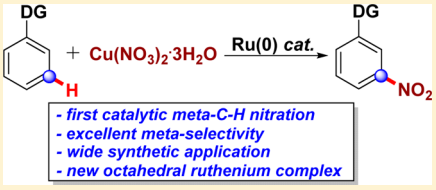
Supporting Information

ABSTRACT: The first example of transition metal-catalyzed meta-selective C_{Ar}–H nitration of arenes is described. With the use of $Ru_3(CO)_{12}$ as the catalyst and $Cu(NO_3)_2{\cdot}3H_2O$ as the nitro source, a wide spectrum of arenes bearing diversified *N*-heterocycles or oximido as the directing groups were nitrated with meta-selectivity exclusively. Mechanism studies have demonstrated the formation of a new 18e-octahedral ruthenium species as a key *ortho*-C_{Ar}–H metalated intermediate, which may be responsible for the subsequent meta-selective electrophilic aromatic substitution (S_EAr). Moreover, this approach provides a fast-track strategy for atom/step economical synthesis of many useful pharmaceutical molecules.



1. INTRODUCTION

The direct transformation of C–H bonds to C–C or C–X (heteroatom) bonds provides a quick access to many natural and synthetic complex molecules.[1] During the past decades, the *ortho* C–C or C–X bond formation has achieved great success via transition-metal-catalyzed directing group (DG)-assisted *ortho*-C_{Ar}–H functionalization.[2] However, the *meta*-C_{Ar}–H functionalization remains a major challenge because of the target *meta*-C_{Ar}–H bond aloof from the DG.[3] At the onset, meta-selective C–B and C–C bond formations were realized by taking advantage of the steric[4] and/or electronic effects[5] of specific substrates under Ir or Pd catalytic systems. Recently, the Yu,[6] Tan,[7] Maiti,[8] and Li[9] groups have developed a series of nitrile- or pyridine-templates as the remote DGs to assist Pd-catalyzed *meta*-C_{Ar}–H activation in the formation of various *meta* C–C, C–O, and C–I bonds. Meanwhile, Pd- or Rh-catalyzed direct *meta*-C_{Ar}–H functionalization mediated by norbornene[10] or induced by a traceless carboxylic acid[11] was also reported to form new C–C bonds. In these approaches, specific substrates, unusual directing groups, or precious metal catalysts (Pd, Rh, or Ir) were generally needed. The cheap Cu catalyst was previously employed by Gaunt and co-workers,[12] but regrettably, only meta-arylation of arenes was accomplished. Very recently, significant progress in *meta*-C_{Ar}–H functionalization has been achieved by using the ortho-metalation strategy, in which the cheap metal Ru catalyst and common *ortho*-DG were used. Representatives included meta-sulfonation and alkylation developed by Frost[13] and Ackermann,[14] and bromination described by Greaney[15] and Huang,[16] respectively. Notably, all of these approaches were limited to construct C–C or a few C–X (O, S, B, halogen) bonds; the methods of DG-assisted direct *meta*-C–H functionalization to form C–N bonds have not been established.

Nitroarenes are an important class of C–N bond-containing compounds in medicinal chemistry and material science either used directly[17] or as precursors.[18] Traditional synthetic methods of nitroarenes are mainly dependent on the Friedel–Crafts type nitration to generate the major compounds bearing nitro groups on the para positions. These reactions generally suffer from the use of strong acids, intolerance of diverse functional groups, and low ortho/meta site-selectivity.[17,19] Though a few examples of DG-assisted C_{Ar}–H nitration were reported recently under the Cu, Pd, or Rh catalysis (Figure 1a),[20] these approaches are only limited to ortho-

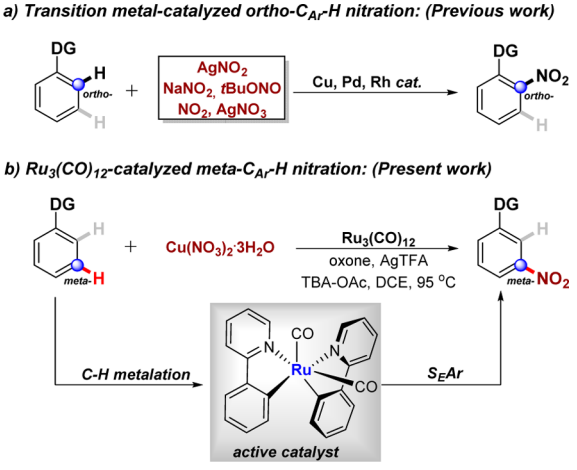


Figure 1. DG-assisted transition-metal-catalyzed *ortho*- and *meta*-C_{Ar}–H nitrations of arenes.

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selective nitration. Therefore, a practical and catalytic approach for the meta-selective C_{Ar}–H nitration of arenes is highly needed.

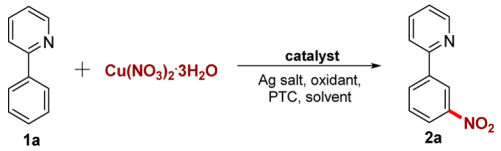
Inspired by the stoichiometric meta-nitration of 2-phenylpyridine organometallic complexes[21] and the pioneering work of $[RuCl_2(p\text{-cymene})]_2$-catalyzed *meta*–C–C, C–S, and C–Br bond formations,[13−16] we recently developed the first catalytic version of $Ru_3(CO)_{12}$-catalyzed meta-selective C_{Ar}–H nitration of arenes with $Cu(NO_3)_2{\cdot}3H_2O$ as the nitro source (Figure 1b). In this approach, the C_{Ar}–H nitration occurs with exclusive selectivity at the *meta*- rather than the common ortho-position and an 18 e-octahedral ruthenium intermediate was identified as the active catalyst. Moreover, diversified transformations of the nitration products have been demonstrated.

2. RESULTS AND DISCUSSION

Our initial investigation was carried out by using 2-phenylpyridine as the model substrate and $Cu(NO_3)_2{\cdot}3H_2O$ as the nitrating agent.[21a] The reaction proceeded under the commonly used Ru(II) catalytic system ($[RuCl_2(p\text{-cymene})]_2/Ac_2O$); unfortunately, the desired meta-nitration product **2a** was not obtained (Table 1, entry 1). Investigations on other ruthenium catalysts in this reaction indicated that $Ru_3(CO)_{12}$ performed better than others, affording the desired product **2a** in 10% yield (Table 1, entry 3). Alternative solvents were also examined, and DCE was found to give the best result (18% yield for **2a**) (Table 1, entry 5). Since transition-metal-catalyzed nitration generally proceeds through a radical process, we decided to screen silver salts as the radical initiators.[20a,i] It was found that AgTFA gave a higher yield of 37% (Table 1, entry 9). Meanwhile, different oxidants were also tested. With the use of combinations of $K_2S_2O_8$/AgTFA and oxone/AgTFA, the yield of **2a** was increased to 48% and 62%, respectively (Table 1, entries 11 and 12). In addition, a phase transfer catalyst (PTC) was added to increase the solubility of the reaction mixture in DCE. To our delight, 0.5 equiv of tetrabutylammonium acetate (TBA-OAc) led to an excellent substrate conversion and the highest isolated yield (78% yield for **2a**) (Table 1, entry 15). The amount of $Ru_3(CO)_{12}$ and $Cu(NO_3)_2{\cdot}3H_2O$ was examined as well; however, no significant improvement was obtained. Meanwhile, other nitrates or nitrites were tested as the alternative nitro sources, and the meta-nitration product **2a** was detected in low yield (<15%, see Supporting Information). A control reaction without $Ru_3(CO)_{12}$ was also conducted, but no product **2a** was produced (Table 1, entry 17). Therefore, the condition of entry 15 was elected as the optimized reaction condition.

With the optimized reaction conditions established, we first examined the scope of substituted 2-arylpyridine substrates (Scheme 1). The para-substituted arylpyridines were found to proceed smoothly under the standard nitration conditions, and the corresponding meta-nitration products **2b–g** were obtained in 54–76% isolated yields. When one of the two meta-positions on the phenyl was occupied, the nitration on the other meta-position occurred and the corresponding products **2h–j** were

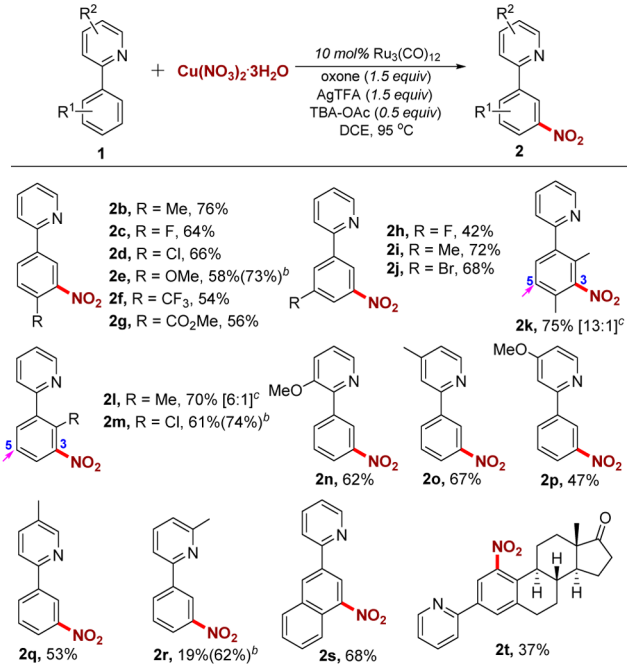
Table 1. Condition Optimization of Meta-Selective C_{Ar}–H Nitration[a]



entry	catalyst (10 mol %)	Ag salt/oxidant	solvent	yield, %[b] (2a/1a)
1	$[RuCl_2(p\text{-cymene})]_2$	−/−	Ac_2O	0/58
2	$RuCl_2(PPh_3)_4$	−/−	Ac_2O	7/46
3	$Ru_3(CO)_{12}$	−/−	Ac_2O	10/45
4	$Ru_3(CO)_{12}$	−/−	MeCN	0/63
5	$Ru_3(CO)_{12}$	−/−	DCE	18/50
6	$Ru_3(CO)_{12}$	−/−	dioxane	0/38
7	$Ru_3(CO)_{12}$	AgOAc	DCE	23/17
8	$Ru_3(CO)_{12}$	$AgNO_3$	DCE	25/19
9	$Ru_3(CO)_{12}$	AgTFA	DCE	37/14
10	$Ru_3(CO)_{12}$	Ag_2O	DCE	12/31
11	$Ru_3(CO)_{12}$	$K_2S_2O_8$/AgTFA	DCE	48/18
12	$Ru_3(CO)_{12}$	oxone/AgTFA	DCE	62/21
13	$Ru_3(CO)_{12}$	BQ/AgTFA	DCE	18/15
14	$Ru_3(CO)_{12}$	$Cu(OAc)_2$/AgTFA	DCE	10/19
15[c]	$Ru_3(CO)_{12}$	oxone/AgTFA	DCE	81(78)[e]/0
16[d]	$Ru_3(CO)_{12}$	oxone/AgTFA	DCE	65/<5
17[c]	-	oxone/AgTFA	DCE	0/91

[a]Reaction conditions: **1a** (0.1 mmol), $Cu(NO_3)_2.3H_2O$ (0.3 mmol), catalyst (10 mol %), Ag salt (1.5 equiv), oxidant (1.5 equiv) and phase transfer catalyst (PTC) (0.5 equiv) in DCE (1.5 mL) for 24 h at 95 °C in a sealed tube. [b]Yield was determined by ^1H NMR analysis using dibromomethane as an internal standard. [c]TBA-OAc (0.5 equiv) was used as a PTC. [d]TBA-HSO_4 (0.5 equiv) was added as a PTC. [e]Isolated yield on 0.4 mmol scale. TBA-OAc = tetrabutylammonium acetate, TBA-HSO_4 = tetrabutylammonium hydrogen sulfate, BQ = *p*-benzoquinone.

Scheme 1. Substrate Scope of Pyridine as the DG[a]



[a]Reaction conditions: **1** (0.4 mmol), $Cu(NO_3)_2{\cdot}3H_2O$ (1.2 mmol), $Ru_3(CO)_{12}$ (10 mol %), oxone (1.5 equiv), AgTFA (1.5 equiv), and TBA-OAc (0.5 equiv) in DCE (3 mL) for 36 h at 95 °C in a sealed tube. Isolated yields. [b]Yield based on the recovered starting material are listed in parentheses. [c]Ratio of C3- and C5-H nitration products is listed in square brackets.

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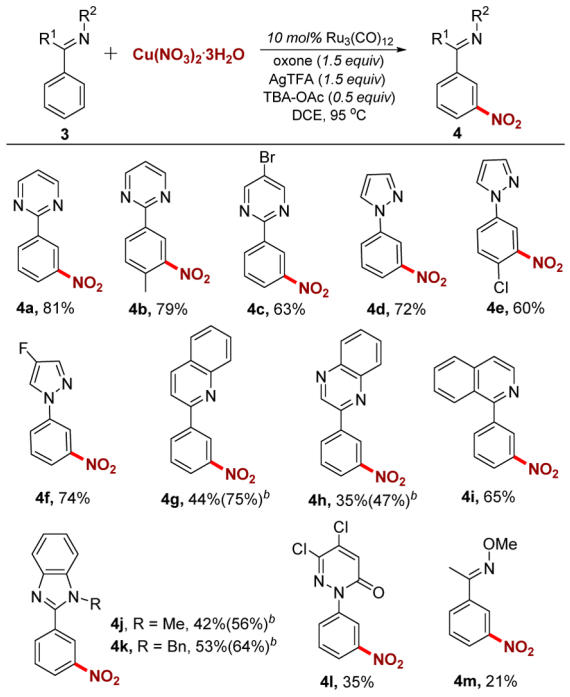
produced in 42−72% yields. Interestingly, in the case of 2-(2,4-dimethylphenyl)pyridine as the substrate, *meta*-C_{Ar}−H nitration was found to prefer the sterically bulkier position (C3), whereas the nitration on the less steric position (C5) was negligible (**2k**, C3/C5 = 13:1). The same preference was observed as well in the case of *ortho*-methyloxy substituted arylpyridine as the substrate (**2l**). Furthermore, arylpyridine substrates bearing an ortho-, meta-, or para-substituent on the pyridine moiety were also tested, and most transformations gave good results (**2n−q**, 47−67% yield), except for 2-methyl-6-phenylpyridine that gave the corresponding nitration product **2r** in 19% isolated yield. The low yield of **2r** is apparently due to the existence of the *ortho*-methyl on the pyridine moiety that may affect the generation of the key ruthenium intermediate. In addition, 2-(naphthalen-2-yl)pyridine also participated in the reaction very well, and the corresponding product **2s** was obtained in 68% yield. Moreover, an example of late-stage meta-selective C_{Ar}−H nitration succeeded using pyridine-containing estrone derivative as the substrate (**2t**).

To survey the scope and limitation of the *N*-heterocyclic directing groups, various phenyl-substituted *N*-heterocycles were employed as the substrates. As shown in Scheme 2,

Scheme 2. Scope of Various *N*-Heterocycles as the DGs[a]

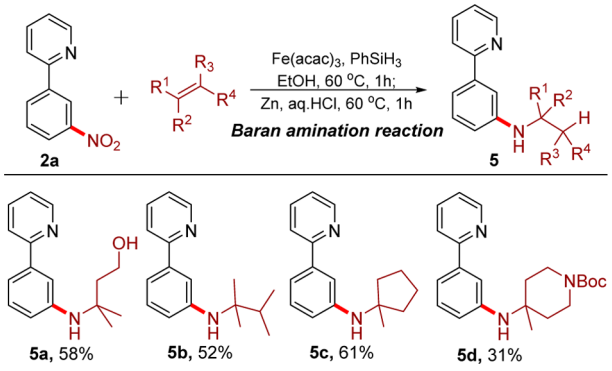


[a]Reaction conditions: **3** (0.4 mmol), $Cu(NO_3)_2{\cdot}3H_2O$ (1.2 mmol), $Ru_3(CO)_{12}$ (10 mol %), oxone (1.5 equiv), AgTFA (1.5 equiv), and TBA-OAc (0.5 equiv) in DCE (3 mL) for 36 h at 95 °C in a sealed tube. Isolated yields. [b]Yield based on the recovered starting material is listed in parentheses.

pyrimidine, pyrazole, and isoquinoline were well tolerant in the standard catalytic conditions and the corresponding meta-nitration products **4a−f** and **4i** were obtained in 60−81% yields. In the case of 2-phenyl-substituted quinoline, quinoxaline, and benzimidazole substrates, the corresponding nitration reactions were incomplete and the desired products were obtained in lower yields (**4g**, **4h** and **4j**,**k**). To our surprise, 4,5-dichloro-2-phenylpyridazinone was also tolerant to the nitration condition and afforded the meta-product **4l** in 35% yield without loss of the chloro atoms. It should be noted that our nitration protocol is also suitable to acetophenone *O*-methyl oxime, a precursor of the widely used ketone, though the yield of product **4m** was somewhat lower.

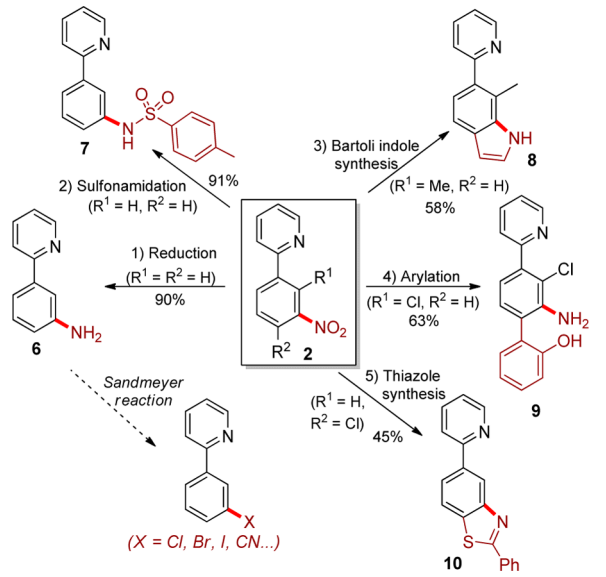
To demonstrate the utility of this methodology, we carried out a few of transformations using the nitration products as the starting materials. As shown in Scheme 3, 2-(3-nitrophenyl)-

Scheme 3. Synthesis of Secondary Amines



pyridine **2a** was treated with various olefins under the Baran amination conditions[18d] leading to the formation of corresponding secondary amines **5a−d** in 31−61% yields. More universal transformations were listed in Scheme 4. Hydro-

Scheme 4. Nitroarenes Diversified Transformations[a]



[a]Reaction conditions: (1) Pd/C, H_2; (2) *p*-$MeC_6H_4SO_2Na$ (1.5 equiv), $FeCl_2$ (10 mol %), $NaHSO_3$ (3 equiv), DMEDA (0.2 equiv), DMSO, 60 °C, 12 h; (3) vinylmagnesium bromide (3 equiv), THF, −70 °C, 2 h; (4) PhMgBr (3 equiv), THF, 0 °C, 30 min; (5) S (1.5 equiv), benzylamine (2.5 equiv), pyridine, 100 °C, 24 h.

genation of **2a** under Pd/C and H_2 condition provided aniline **6** in 90% yield, which could be conveniently converted to other functional groups (e.g., Cl, Br, I, CN...) via Sandmeyer reaction. Meanwhile, sulfonamide **7** was prepared in 91% yield from **2a** in one step.[18e] Moreover, various pyridines bearing diversified aryl substituents were prepared as well from nitroarenes **2**, such as indole **8**, biarylamine **9**,[18a] and benzothiazole **10**.[18c]

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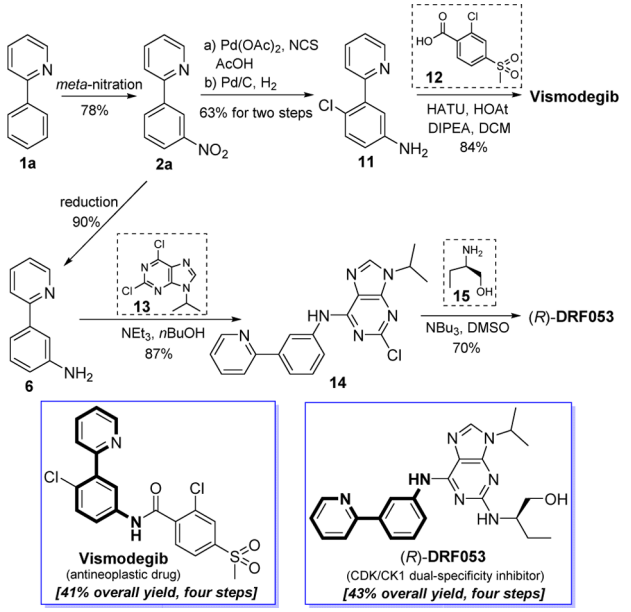
In addition, the current protocol also provided synthetic shortcuts to the marked drug or clinical candidate. As shown in Scheme 5, *meta*-C_{Ar}–H activation/nitration of **1a** followed by

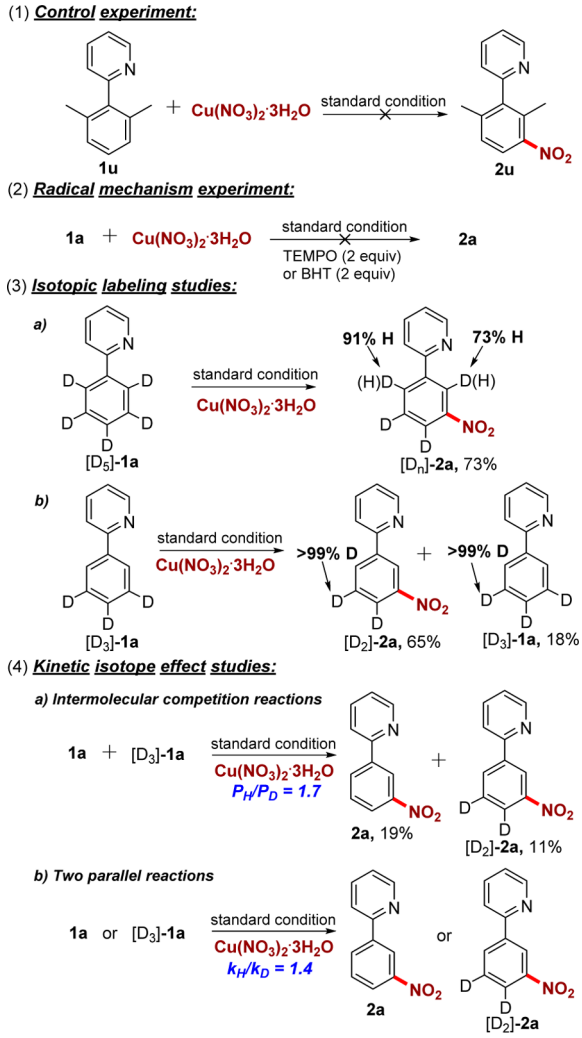
Scheme 5. Concise Synthesis of Vismodegib and (*R*)-DRF053



ortho-C_{Ar}–H activation/chlorination and hydrogenation provided the key intermediate **11**. Subsequent condensation of **11** with acid **12** afforded the first-in-class hedgehog inhibitor Vismodegib[22] in 84% yield. Such a four-step process represents an atom- and step-economical synthesis of this important anticancer drug. Similarly, the CDK/CK1 dual inhibitor (*R*)-**DRF053**[23] was also conveniently prepared through two sequential electrophilic substitution reactions of 2,6-dichloro-9-isopropylpurine **13** and an overall yield (from **1a**) of 43% was obtained.

To gain insights on the reaction pathway, additional experiments were performed. First, substrate **1u** bearing two methyls to block the two ortho positions of the phenyl ring failed to react with $Cu(NO_3)_2{\cdot}3H_2O$ under the standard conditions, supporting the importance of the *ortho*-C_{Ar}–H metalation in the meta-nitration process (Scheme 6-1). Second, no product **2a** was observed when the reaction was performed in the presence of radical scavengers, such as TEMPO and BHT, suggesting that a radical process might be involved (Scheme 6-2). Third, the meta-nitrations of the isotopically labeled substrates were investigated (Scheme 6-3). It was found that treating [D_5]-**1a** with $Cu(NO_3)_2{\cdot}3H_2O$ under the standard condition afforded product [D_n]-**2a** with a significant *ortho*-D/H exchange (see Supporting Information). However, when [D_3]-**1a** was used as the substrate, no *meta*-D/H exchange occurred in both product [D_2]-**2a** and recovered substrate [D_3]-**1a**. The results confirmed that the initial *ortho*-C_{Ar}–H ruthenation was reversible, whereas the *meta*-C_{Ar}–H cleavage was not. These results were consistent with Ackermann's reports on meta-selective C_{Ar}–H alkylation.[14b,c] Finally, the intermolecular competition experiment established a kinetic isotopic effect (KIE) of P_H/P_D was 1.7. The value of k_H/k_D was determined to be 1.4 by two independent reactions using

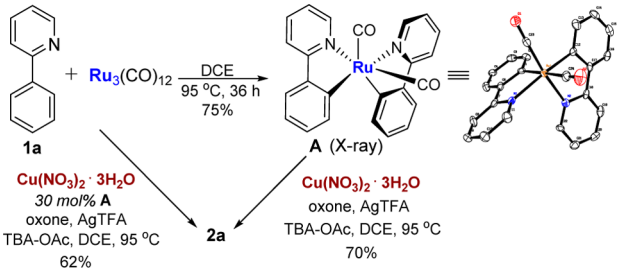
Scheme 6. Preliminary Mechanistic Studies



substrates **1a** and [D_3]-**1a**, indicating that the *meta*-C–H cleavage was likely kinetically relevant (Scheme 6-4).

Next, we examined the active catalyst in our *meta*-C_{Ar}–H nitration reaction. Interestingly, the octahedral ruthenium complex **A** was isolated by mixing **1a** with 1 equiv of $Ru_3(CO)_{12}$ in DCE at 95 °C for 36 h and the structure was confirmed by the X-ray diffraction analysis (Scheme 7). It was found that the complex **A** could catalyze the nitration of **1a** and produced the product **2a** in 62% yield. Furthermore, direct nitration of the isolated complex **A** with $Cu(NO_3)_2{\cdot}3H_2O$ afforded **2a** as well in 70% yield. These results implied that the

Scheme 7. Synthesis and Verification of Ruthenium(II) Intermediate



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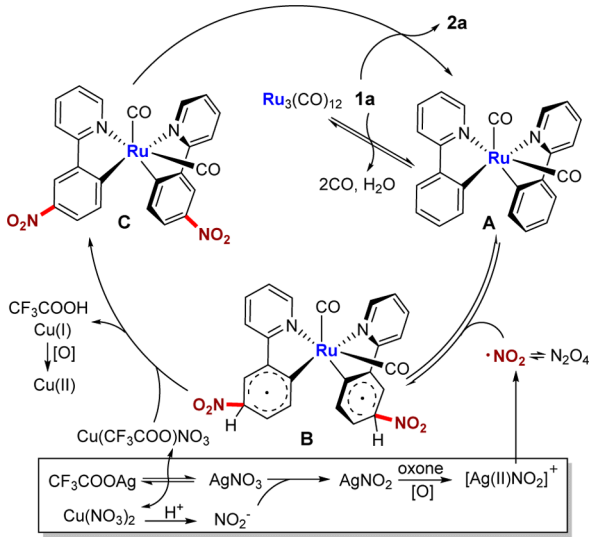
complex **A** might be the active catalyst in the current catalytic nitration reaction.

On the basis of the experiments above and literature precedents,[20a,b,i,21] a plausible catalytic cycle is proposed in Scheme 8. The active Ru complex **A** is first formed from

Scheme 8. Proposed Mechanism



substrate **1a** with $Ru_3(CO)_{12}$ via C_{Ar}–H activation step. Subsequent electrophilic attack of the *para*-carbon relative to the Ru–C_{Ar} σ-bond occurs to generate species **B**.[21b] In this process, nitrogen dioxide radical (NO_2·) is originated through a silver-mediated radical process.[20a,i] An anion exchange between $Cu(NO_3)_2$ and CF_3COOAg gave a new copper(II) salt, $Cu(CF_3COO)NO_3$,[20b] which may assist the deprotonation of species **B** to generate a more stable complex **C**. Subsequent ligand exchange of complex **C** with **1a** releases the nitration product **2a**, and complex **A** is regenerated for recycling.

3. CONCLUSION

In conclusion, we have reported the first example of catalytic meta-selective C_{Ar}–H nitration of a wide range of 2-aryl *N*-aromatics using $Ru_3(CO)_{12}$ as the catalyst, and $Cu(NO_3)_2 \cdot 3H_2O$ as the nitro source. The generated nitration products represent a class of super useful intermediates for further transformations and a shortcut synthesis to a number of pharmaceutical intermediates, clinical candidates, as well as marketed drugs. Furthermore, a novel octahedral ruthenated intermediate is crystallized and confirmed as the active catalyst.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b03402.

Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra for all new compounds (PDF)
X-ray for complex **A** (CCDC 1456692) (CIF)

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Notes

The authors declare no competing financial interest.

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