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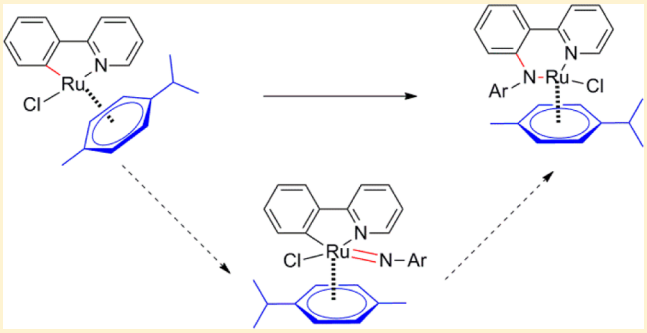
Ruthenium-Catalyzed Direct C−H Amidation of Arenes: A Mechanistic Study

Lu−Lu Zhang, Lian-Hua Li, Yu-Qi Wang, Yan-Fang Yang, Xue-Yuan Liu, and Yong-Min Liang*

State Key Laboratory of Applied Organic Chemistry, lanzhou University, Lanzhou, People's Republic of China

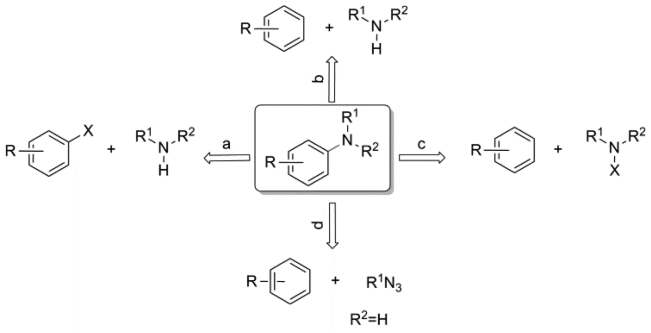
Supporting Information

ABSTRACT: We report mechanistic studies of C−H activitation/amidation reactions using azides as the amino source catalyzed by $[RuCl_2(p\text{-cymene})]_2$. We have achieved two intermediates in the catalytic cycle $(C_5H_4NC_6H_4)Ru(p\text{-cymene})Cl$ and $(C_5H_4NC_6H_4)NArRu(p\text{-cymene})Cl$ (Ar = $NO_2C_6H_4SO_2$). Furthermore, the process from $(C_5H_4NC_6H_4)Ru(p\text{-cymene})Cl$ to $(C_5H_4NC_6H_4)NArRu(p\text{-cymene})Cl$ was monitored by ^{19}F NMR and a ruthenium−imido species was proposed to explain the formation of the azacyclopropane analogue.



Particular attention has been paid to C(sp^2)−N bond formation[1] because aryl amines are key components in numerous natural products and synthetic compounds.[2] As a result, there have long been extensive efforts toward the development of efficient reactions to introduce nitrogen-containing groups into arene molecules. Buchwald−Hartwig amidation, for instance, allows for C−N bond induction in arenes using readily available prefunctionalized haloarenes (Scheme 1a).[3] As palladium or copper catalysts were used in

Scheme 1. Strategies for C−N Bond Formation



combination with suitable ligands under basic conditions, stoichiometric amounts of byproducts such as hydrogen halides or their base salts were generated in this procedure. Direct C−H amidation reactions of (hetero)arenes were developed to avoid the prefunctionalization of arenes (Scheme 1b).[4] However, hydrogen (H_2) is not usually the byproduct, because the thermodynamics of creating a C−N bond with loss of H_2 is unfavorable.[5] Stoichiometric amounts of oxidant were required to change H_2 into H_2O. Stoichiometric byproducts were always generated when a preactivated amine was used as an alternative strategy in the direct amidation reaction (Scheme 1c). Although significant progress has been made in this field, the development of environmentally friendly and atom-economical methods of arene C−N bond formation under mild reaction conditions remains highly desirable. Recently, organic azides have attracted much attention in organic synthesis, due to their unique reactivity as versatile intermediates.[6] The Chang group reported a rhodium-catalyzed direct amidation of arenes using sulfonyl azides as the amine source, which required no external oxidants and released N_2 as the single byproduct (Scheme 1d).[7] A range of arene substrates were selectively amidated in high yields with excellent functional group tolerance. $[RuCl_2(p\text{-cymene})]_2$ could also catalyze the direct amidation of arenes;[8] the mechanistic blueprint of this ruthenium-catalyzed direct amidation reaction was developed, but there was not enough evidence to support the catalytic cycle.[9] Thus, we report herein a mechanistic study of C−H activation/amidation reactions using azides as the amino source catalyzed by$[RuCl_2(p\text{-cymene})]_2$. The mechanistic understanding of this process will help us to design rational catalysts, optimize reaction conditions, and find new transformations.

We began our study by finding the general conditions for the C−H amidation reaction. At the outset of our studies, we chose 2-phenylpyridine (**1a**) and 4-methylbenzenesulfonyl azide (**2a**) as model substrates to optimize the reaction conditions (Table 1). Initially, the reaction was carried out with NaOAc (1.0 equiv) and KPF_6 (10 mol %) as additives in the presence of 5 mol % of $[RuCl_2(p\text{-cymene})]_2$ in CH_3OH at 80 °C for 12 h. Gratifyingly, the desired amidation product **3aa** was isolated in 32% yield (Table 1, entry 1). When we tried other metal catalysts, such as $RuCl_2(PPh_3)_3$, $RuCl_2(COD)$, and $Pd(OAc)_2$,

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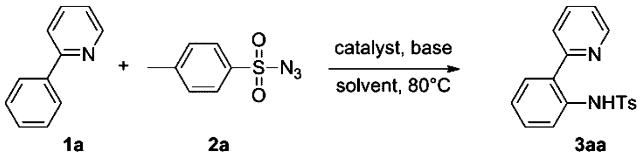
Table 1. Optimization of Reaction Conditions[a]



1a 2a 3aa

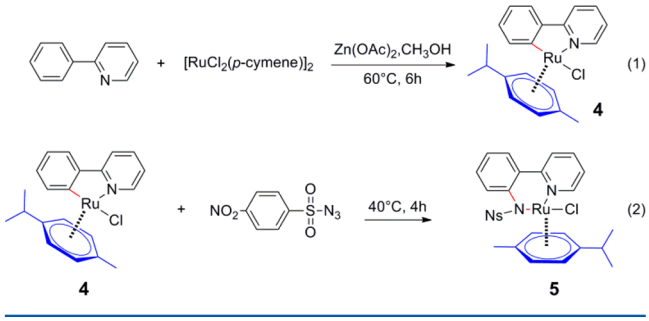
	catalyst	solvent	base	yield (%)[b]
1	$[RuCl_2(p\text{-cymene})]_2$	CH_3OH	NaOAc	32
2	$RuCl_2(PPh_3)_3$	CH_3OH	NaOAc	NR
3[c]	$RuCl_2(COD)$	CH_3OH	NaOAc	NR
4	$Pd(OAc)_2$	CH_3OH	NaOAc	NR
5	$[RuCl_2(p\text{-cymene})]_2$	DCE	NaOAc	30
6	$[RuCl_2(p\text{-cymene})]_2$	1,4-dioxane	NaOAc	trace
7	$[RuCl_2(p\text{-cymene})]_2$	DMF	NaOAc	trace
8	$[RuCl_2(p\text{-cymene})]_2$	THF	NaOAc	trace
9[d]	$[RuCl_2(p\text{-cymene})]_2$	CH_3OH	NaOAc	61
10[d]	$[RuCl_2(p\text{-cymene})]_2$	CH_3OH	K_2CO_3	71
11[d]	$[RuCl_2(p\text{-cymene})]_2$	CH_3OH	NaH_2PO_4	69
12[d]	$[RuCl_2(p\text{-cymene})]_2$	CH_3OH	$Zn(OAc)_2{\cdot}2H_2O$	82
13[d]		CH_3OH	$Zn(OAc)_2{\cdot}2H_2O$	NR
14[d]	$[RuCl_2(p\text{-cymene})]_2$	CH_3OH		trace
15[e]	$[RuCl_2(p\text{-cymene})]_2$	CH_3OH	$Zn(OAc)_2{\cdot}2H_2O$	76

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.22 mmol), KPF_6 (0.02 mmol), catalyst (0.01 mmol), base (0.2 mmol) solvent (2.0 mL), 80 °C, 12 h. [b]Isolated yield. [c]COD = 1,5-cyclooctadiene. [d]KPF_6 (0.2 mmol) was used. [e]$AgSbF_6$ (0.2 mmol) was used.

they could not catalyze the reaction (Table 1, entries 2−4). Meanwhile, screening of the solvents revealed that DCE and CH_3OH have comparable results for the reaction (Table 1, entries 5−8). The additive loading of KPF_6 was evaluated as well; adding 1 equiv of KPF_6 increased the yield up to 61% (Table 1, entry 9). After screening of bases, we got the best result of 82% yield by using 5 mol % of $[RuCl_2(p\text{-cymene})]_2$, azide (1.1 equiv), KPF_6 (1.0 equiv), and $Zn(OAc)_2{\cdot}2H_2O$ (1.0 equiv) in CH_3OH at 80 °C for 12 h (Table 1, entry 12). The control experiments indicated that the ruthenium reagent was essential in catalyzing the reaction (Table 1, entry 13), and only a trace of **3aa** was observed without use of any base (Table 1, entry 14). When $AgSbF_6$ was used as an additive, the result was no better (Table 1, entry 15).

With the optimized conditions in hand, we next attempted to uncover the detailed mechanism of this reaction. After a stoichiometric reaction of 2-phenylpyridine (**1a**) with $[RuCl_2(p\text{-cymene})]_2$, the solvent was completely removed to afford a crude orange solid.[10] The crude product was purified by column chromatography and then recrystallized from petroleum ether/ethyl acetate to give orange crystals of **4** (Scheme 2, eq 1) in 60% isolated yield (based on $[RuCl_2(p\text{-cymene})]_2$). The structure of the resulting mononuclear ruthenium complex **4** was unambiguously confirmed by ^1H NMR and ^{13}C NMR spectroscopy and X-ray crystallographic analysis (Figure 1). The X-ray crystal structure showed that the ruthenium atom is in a three-legged piano-stool configuration surrounded by a carbon atom, a nitrogen atom, and a *p*-cymene group. Most importantly, without use of any silver cation source, chloride ion was also coordinated with ruthenium. Encouraged by this result, we next attempted the reaction of ruthenium complex **4** with 4-nitrobenzenesulfonyl azide. The reaction proceeded smoothly, and orange crystals of the ruthenium complex **5** could be isolated in near-quantitative

Scheme 2. Syntheses of 4 and 5



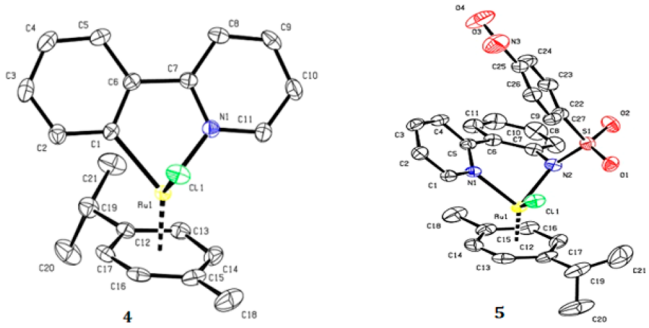


Figure 1. ORTEP view of the ruthenium intermediates **4** and **5**. Hydrogen atoms have been omitted for clarity. Thermal ellipsoids are drawn at the 50% probability level. Selected distances (Å) and angles (deg) for **4**: Ru1−C1 2.057(2), Ru1−N1 2.082(2), Ru1−Cl1 2.4162(7), Ru1−C12 2.180(3), Ru1−C13 2.157(3); C1−Ru1−Cl1 86.95(7), C1−Ru1−N1 77.72(9), N1−Ru1−Cl1 86.05(6), N1−C7−C6−C1 3.3(3). Selected distances (Å) and angles (deg) for **5**: Ru1−N1 2.112(2), Ru1−N2 2.132(2), Ru1−Cl1 2.3997(6), N2−C7 1.425(3), Ru1−C13 2.175(3), Ru1−C14 2.181(3); N1−Ru1−Cl1 85.02(6), N1−Ru1−N2 82.06(9), C7−N2−Ru1 110.40(16), C4−C5−C6−C11 −38.3(4).

yield without further purification (Scheme 2, eq 2).[11] The structure of ruthenium complex **5** was fully characterized, including ^1H NMR and ^{13}C NMR and X-ray crystallography. The ruthenium atom is also in a three-legged piano-stool configuration surrounded by two nitrogen atoms, chloride ion, and a *p*-cymene group in complex **5**. Ruthenium complexes **4** and **5** are almost the same, except for the release of nitrogen gas from 4-nitrobenzenesulfonyl azide and the insertion of a nitrogen atom into the Ru−C bond.

As a part of our studies investigating the reactivity of ruthenium complexes **4** and **5**, we then attempted to use **4** and **5** as a catalyst (precursor) in the amidation reaction, respectively (Scheme 3, eqs 1 and 2). Importantly, ruthenium complexes **4** and **5** catalyzed the amidation reaction of 2-phenylpyridine to give **3aa** in high yield under the standard conditions, suggesting the plausible intermediacy of a cyclometalated complex in the catalytic cycle. Furthermore, a notable primary kinetic isotope effect (KIE, k_H/k_D = 2.4) was observed for two competition reactions with **1a** and **1a**-d_5 (Scheme 3, eq 3), suggesting that C−H bond cleavage likely precedes the rate-limiting step.[12]

The progress of organic azide coordination with the transition metal and release of nitrogen gas has been studied;[13] Meyer successfully isolated some terminal cobalt(III) imido complexes and revealed an intramolecular imido insertion reaction for the first time.[14] With **4** and **5** in hand, we were eager to understand the details of this progress. We tried our

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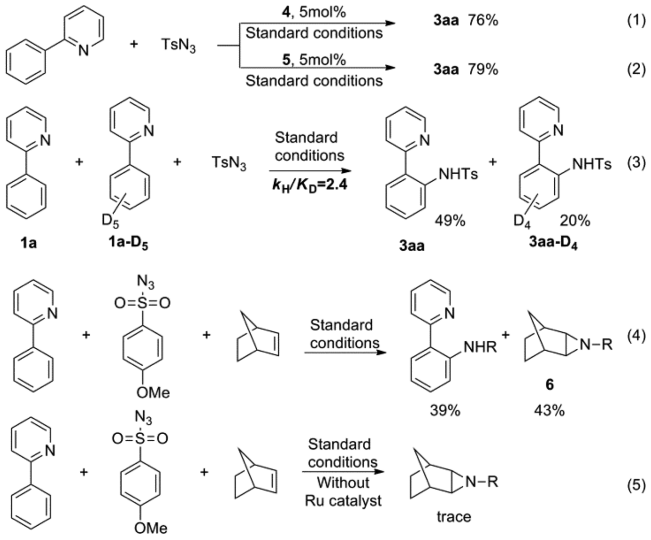
Scheme 3. Preliminary Mechanistic Studies



best to isolate a ruthenium−imido species but failed. Then, we monitored the reaction of **4** with 1-azido-2-fluorobenzene by ^{19}F NMR spectroscopy, as shown in Figure 2.[15] When the

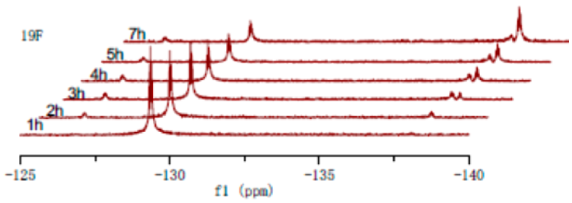
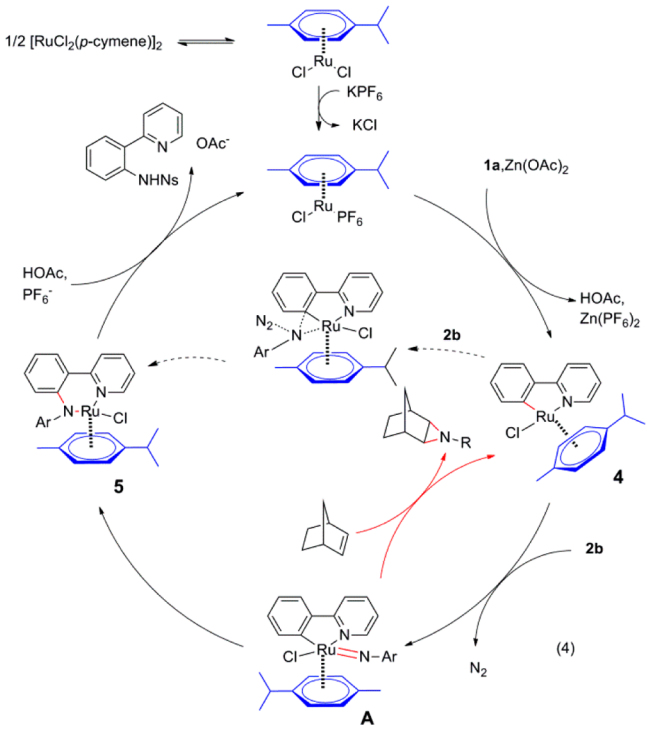


Figure 2. Monitoring of the reaction of **4** with 1-azido-2-fluorobenzene using ^{19}F NMR spectroscopy. Conditions: CD_3OD, 40 °C.

mixture was kept at 40 °C for 2 h, two new downfield peaks (δ −126.3 and −138.2) appeared alongside the signal for 1-azido-2-fluorobenzene itself (δ −129.2). Additionally, the NMR spectra were displayed with clarity, which suggests that the process from **4** to **5** may be through an unstable state. Inspired by Meyer's great work, we tried to capture the ruthenium carbine with an alkene.[16] After addition of norbornylene (2 equiv), we got azacyclopropane analogue **6** in 43% yield (Scheme 3, eq 4). Without Ru catalyst, almost no azacyclopropane analogue **6** could be isolated (Scheme 3, eq 5). We proposed the ruthenium imido complex **A** to explain this phenomenon.[17] Ruthenium imido complex **A** goes through an intramolecular imido insertion reaction to reach **5**; at the same time the cycloaddition reaction of carbene **5** is inevitable. Due to the mismatched reactivity of the hard imido ligand and the soft electron-rich metal center,[18] there is no distinct kinetic difference between the formation of ruthenium complex **5** and the formation of cycloaddition product **6**.

On the basis of the data observed above, a mechanism using 2-phenylpyridine (**1a**) and 4-nitrobenzenesulfonyl azide (**2b**; NsN_3) is proposed in Scheme 4. First, treatment of $[RuCl_2(p\text{-cymene})]_2$ with KPF_6 generates a cationic Ru(III) species,[19] which facilitates the key C−H bond activation to afford the five-membered ruthenium intermediate **4**. Intermediate **4** was fully characterized by X-ray crystallography. The azide coordinates with **4** to give ruthenium−imido complex **A** by releasing nitrogen gas. Then, ruthenium−imido complex **A** rearranges to

Scheme 4. Proposed Reaction Pathway



afford the six-membered ruthenium intermediate **5**. However, an amido insertion can proceed via a transition state of a three-centered interaction between the ruthenium, phenyl carbon, and azide nitrogen atoms.[20] In addition, ruthenium−imido complex **A** can also be captured by norbornylene. Finally, intermediate **5** undergoes reductive elimination to give rise to the final product.

In summary, we have studied the mechanism of a ruthenium-catalyzed protocol for the synthesis of benzenesulfonamides from arenes and sulfonyl azides through C−H bond activation/amidation reactions. Notably, two ruthenium intermediates (**4** and **5**) were isolated and fully characterized, including by ^{1}H NMR, ^{13}C NMR, and X-ray crystallography. The process from **4** to **5** was monitored by ^{19}F NMR, and a ruthenium−imido species was proposed to explain the formation of the azacyclopropane analogue. Further investigations on the detailed mechanism from **4** to **5** and the isolation of the ruthenium−imido species **A** are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Text, figures, and CIF files giving general synthetic remarks, detailed synthetic procedures, characterization data, and NMR spectra for all new compounds as well as crystallographic data for compounds **4** and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail for Y.-M.L.: liangym@lzu.edu.cn.

Notes

The authors declare no competing financial interest.

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