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Rhodium-Catalyzed Direct Oxidative C–H Acylation of 2-Arylpyridines with Terminal Alkynes: A Synthesis of Pyrido[2,1-*a*]isoindoles

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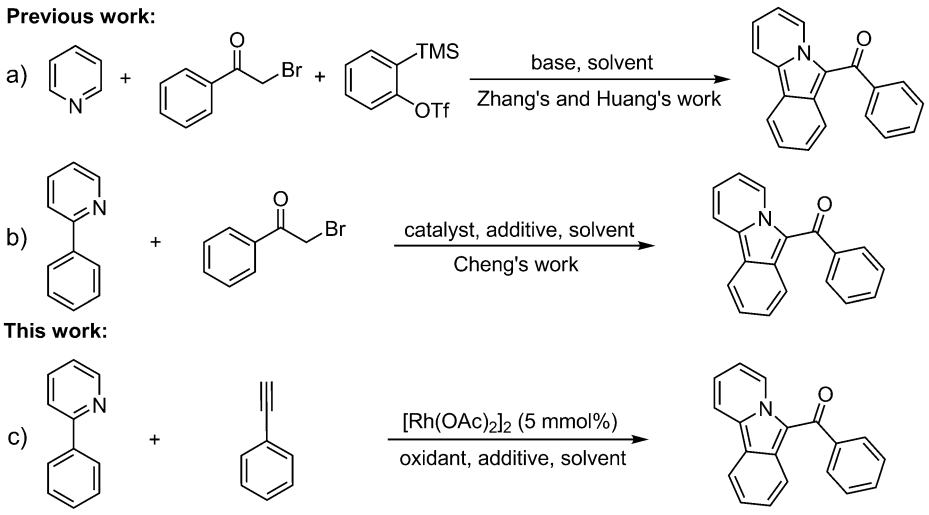
Abstract: A synthesis of pyrido[2,1-*a*]isoindoles is reported by the rhodium-catalyzed direct oxidative C–H acylation of 2-aryl pyridines with terminal alkynes. The desired products were obtained in moderate to excellent yields. This is an efficient and clean method to construct C–C/C–N bonds in one step. In addition, the effective rhodium(III) catalyst was isolated and characterized by X-ray crystallography.

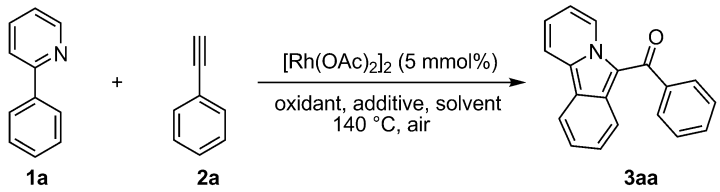
Keywords: acylation; 2-arylpyridines; C–H/C–H functionalization; rhodium; terminal alkynes

Pyrido[2,1-*a*]isoindoles are very important structural motifs in many pharmaceuticals,[1] dyes,[2] and functional materials.[3] In the traditional manner, the free radical cyclization is used frequently to construct these motifs as a powerful strategy. In 2008, Zhang and Huang reported the synthesis of pyrido[2,1-*a*]isoindoles *via* multicomponent reaction assembly involving benzynes, respectively.[4,5] Recently, Cheng developed a new strategy using 2-arylpyridine and 2-bromoacetophenone catalyzed by iron (Scheme 1).[6] In the past decades, many chemists have been interested in selective oxidative C–H functionalization reactions of alkynes employing Ag,[7] Fe,[8] Rh,[9] Ru,[10] Pd,[11] Cu,[12] Au,[13] Zn,[14] Ni,[15] In,[16] Mn,[17] and Re.[18] In most cases, extra ligands are necessary to enhance the high activities of the catalysis. It was shown that rhodium(III) chelated by many ligands such as pentamethylcyclopentadiene (Cp*),[19] cyclo-1,5-octadiene (cod),[9b,d,20] and PCy_3[21] provide effective catalysts in rhodium-catalyzed direct coupling reactions. In con-



Scheme 1. Different pathways for the synthesis of pyrido[2,1-*a*]isoindoles.

Table 1. Optimization of the Rh-catalyzed direct oxidative C–H acylation.[a]



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

Entry	Oxidant (equiv.)	Additive (equiv.)	Solvent	Yield [%][b]
1	$Cu(OAc)_2$ (3)	CuI (1)	DMA	45
2	$Cu(OAc)_2$ (3)	CuI (1)	DMF	37
3	$Cu(OAc)_2$ (3)	CuI (1)	DMSO	30
4	$Cu(OAc)_2$ (3)	CuI (1)	*o*-dichlorobenzene	80
5	$Cu(OAc)_2$ (3)	CuI (1)	*o*-xylene	83
6	$Cu(OAc)_2$ (3)	CuI (1)	toluene	0[c]
7	$Cu(OAc)_2$ (3)	CuI (1)	*o*-xylene/DMA = 1:3	91
8	$PhI(OAc)_2$ (3)	CuI (1)	*o*-xylene/DMA = 1:3	72
9	DDQ[d] (3)	CuI (1)	*o*-xylene/DMA = 1:3	0
10	O_2	CuI (1)	*o*-xylene/DMA = 1:3	72
11	air	CuI (1)	*o*-xylene/DMA = 1:3	62
12	$Cu(OAc)_2$ (1)	CuI (1)	*o*-xylene/DMA = 1:3	93
13	$Cu(OAc)_2$ (0.5)	CuI (1)	*o*-xylene/DMA = 1:3	69
14	$Cu(OAc)_2$ (1)	CuI (0.5)	*o*-xylene/DMA = 1:3	78
15	$Cu(OAc)_2$ (1)	–	*o*-xylene/DMA = 1:3	49
16	–	–	*o*-xylene/DMA = 1:3	0
17	$Cu(OAc)_2$ (1)	CuI (1)	*o*-xylene/DMA = 1:3	0[e]

[a] *Reaction conditions:* **1a** (0.1 mmol), **2a** (0.3 mmol), catalyst, oxidant, additive, in solvent (2.0 mL), 140 °C, air.
[b] Yield after purification.
[c] The reaction was carried out at 100 °C.
[d] DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.
[e] The reaction was carried out under argon.

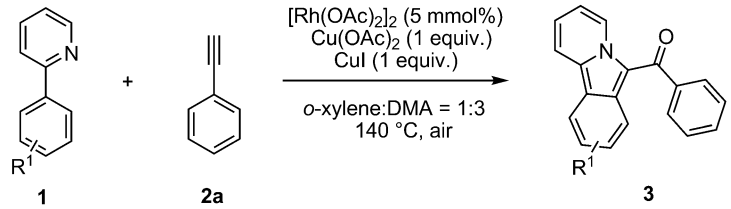
tinuation of our efforts in transition metal-catalyzed C–H functionalization,[22] herein, we report the synthesis of pyrido[2,1-*a*]isoindoles based on the rhodium-catalyzed direct oxidative C–H acylation reaction of 2-arylpyridines with terminal alkynes in the presence of copper salts under air *via* oxidative coupling.

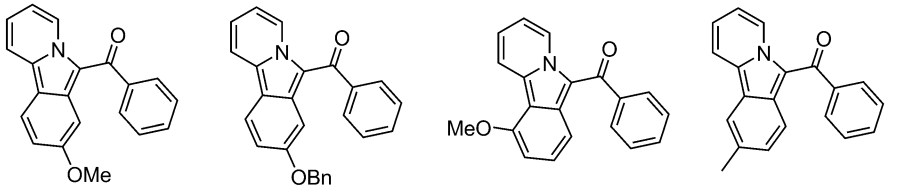
Our initial efforts focused on the reaction of 2-phenylpyridine (**1a**) and phenylacetylene (**2a**) catalyzed by rhodium(II) acetate dimer in *N*,*N*-dimethylacetamide (DMA) at 140 °C under air in the presence of $Cu(OAc)_2$ (3 equiv.) and CuI (1 equiv.). It was observed that the reaction afforded pyrido[2,1-*a*]isoindole (**3aa**) in 45% yield (Table 1, entry 1). Inspired by this result, further studies were continued in order to find suitable reaction conditions to accomplish this transformation. Screening of the solvents revealed that *o*-xylene was a good candidate which induced an increase in yield to 83% (Table 1, entries 2–7), whereas the best solvent was the mixture of *o*-xylene and DMA (1:3) due to the good solubility of the reagents in DMA (Table 1, entry 7). It was found that the other oxidants could also give the desired products in good yields with the exception of DDQ (Table 1, entries 8–11). While the amount of $Cu(OAc)_2$ was dropped to 1 equiv., a 93% yield of **3aa** could be formed (Table 1, entry 12). However, the yield dropped to 69% when the amount of $Cu(OAc)_2$ decreased to 0.5 equiv. (Table 1, entry 13). Moreover it was important for high yield to add 1 equiv. of CuI in the reaction because Cu(I) readily coordinated with terminal alkynes to generate a copper-alkyne complex.[23] Notably, no reaction occurred when the atmosphere was changed from air to argon (Table 1, entry 17).

Under the optimized conditions, the scope of the oxidative acylation reaction was expanded to a variety of 2-arylpyridines (**1**) with phenylacetylene (**2a**). As shown in Table 2, all reactions afforded the desired products in moderate to good yields. Substrates with electron-donating groups on the aryl ring of 2-arylpyridines underwent the reaction smoothly to give the corresponding products in good yields (Table 2, **3ba–ea**). Product **3ba** was characterized by single X-ray crystallography[24] (Figure 1). *ortho*- and *meta*-substituents on the aryl ring showed no obvious influence on the reaction outcome (Table 2, **3da** and **3ea**).

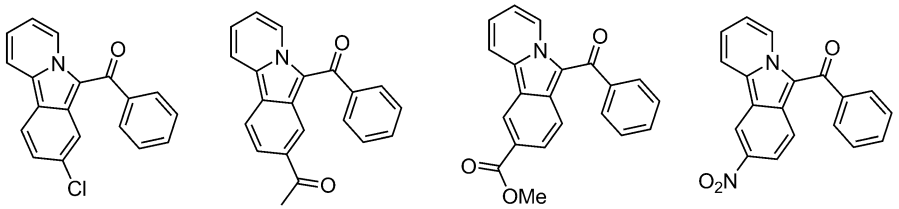
Meanwhile, the electron-withdrawing groups on the aryl ring of 2-arylpyridines hindered the reaction, and the pyrido[2,1-*a*]isoindole derivatives were formed in moderate yields (Table 2, **3fa–ia**). Functional groups such as chloro, acetyl, ester, nitro group on the aryl

Table 2. Rh-catalyzed direct oxidative C–H acylation with different 2-arylpyridines.[a]





3ba, 91% **3ca**, 88% **3da**, 92% **3ea**, 89%



3fa, 73%[c] **3ga**, 65%[c] **3ha**, 67%[c] **3ia**, 78%

[a] *Reaction conditions:* **1** (0.1 mmol), **2a** (0.3 mmol), $[Rh(OAc)_2]_2$ (5 mmol%), $Cu(OAc)_2$ (0.1 mmol), CuI (0.1 mmol), in solvent (2.0 mL), 140 °C, air.
[b] Yield after purification.
[c] 0.5 mmol of phenylacetylene.

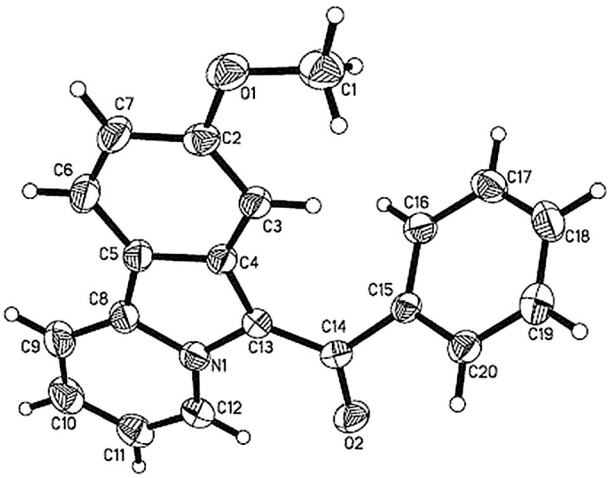


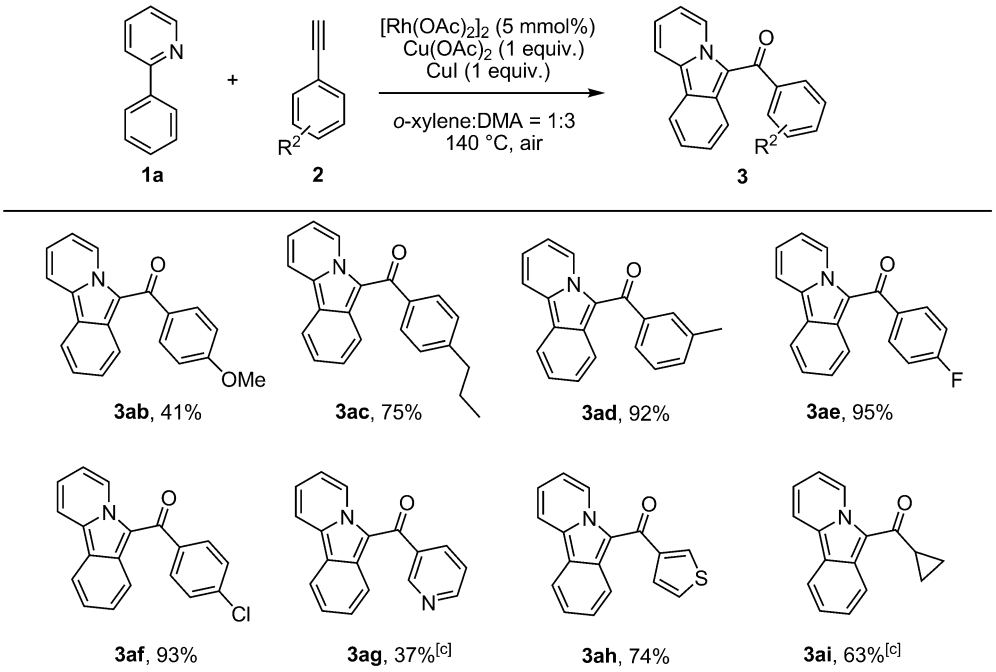
Figure 1. X-ray crystal structure of product **3ba**.

rings were compatible with the reaction conditions (Table 2, **3fa–ia**). The corresponding products could be applied in the additional transformations in organic synthesis.

Next, the reactions of 2-phenylpyridine (**1a**) with different terminal acetylenes (**2**) were examined. In contrast to the substituted 2-arylpyridines, the *para*-substituted electron-donating groups on the aryl ring of acetylenes exhibited low reactivities and only moderate yields were obtained (Table 3, **3ab** and **3ac**). It was thought that the electron-donating groups hindered the activity of the alkynes. The *meta*-substituted methyl group on the aryl ring was compatible with the optimized reaction system, and the desired product was obtained in excellent yield (Table 3, **3ad**). The electron-withdrawing substituted phenylacetylenes were beneficial to the reaction (Table 3, **3ae** and **3af**). Moreover, 3-ethynylpyridine (**2g**) and 3-ethynylthiophene (**2h**) could also react with 2-phenylpyridine smoothly to form the desired products in moderate yields (Table 3, **3ag** and **3ah**). Interestingly, aliphatic acetylene (**2i**) took part in the reaction readily, and was transformed to the corresponding product in 63% yield (Table 3, **3ai**).

To gain some insights into the mechanism, we observed that no product was formed under an atmosphere of argon (Table 1, entry 17). This indicated that oxygen in the air is necessary for the reaction. Firstly, rhodium(II) acetate dimer coordinated with 2-phenylpyridine in DMA at 140 °C to afford the rhodium(III) complex **A** in 71% yield under an air atmosphere. It was found that the complex **A** could not be generated in the absence of oxygen, which showed that Rh(II)

Table 3. Rh-catalyzed direct oxidative C–H acylation with different terminal alkynes.[a]



[a] *Reaction conditions:* **1a** (0.1 mmol), **2** (0.3 mmol), $[Rh(OAc)_2]_2$ (5 mmol%), $Cu(OAc)_2$ (0.1 mmol), CuI (0.1 mmol), in solvent (2.0 mL), 140 °C, air.
[b] Yield after purification.
[c] 0.5 mmol of phenylacetylene.

was oxidized to Rh(III). Fortunately, the structure of complex **A** was characterized by X-ray crystallography[25] (Figure 2) and NMR spectroscopy. It was observed that two molecules of **1a** coordinated with one rhodium atom and water acted as a ligand. The water was mainly generated from the air atmosphere because complex **A** could be formed in 87% yield when the reaction was carried out under an oxygen atmosphere with 5 equiv. of H_2O. Meanwhile only a trace amount of complex **A** was detected under anhydrous conditions (Scheme 2, a). Interestingly, the reaction performed smoothly and the product (**3aa**) could be obtained in 94% yield when rhodium(III) complex **A** and phenylacetylene reacted under the optimized conditions (91% yield under an anhydrous oxygen atmosphere). Moreover, the yield was decreased when employing one kind of copper salt. However, no desired reaction occurred when air or copper salts were absent in the system. Meanwhile, no product was observed under argon with addition of extra water (Scheme 2, b). It was shown that oxygen took part in the formation of the product and water in complex **A** merely acted as ligand. Then 10 mmol% complex **A** was tested as the catalyst in the reaction of 2-phenylpyridine with phenylacetylene under the optimal conditions to afford desired product in 62% yield. Fortunately, the yield was increased to 88% along with the increase of complex **A** to 15 mmol% (Scheme 2, c). Furthermore, the copper-alkyne complex which was generated from Cu(I) and alkyne[23d] could react with complex **A** smoothly to get **3aa** in 85% yield (82% yield under anhydrous oxygen) (Scheme 2, d). Therefore, rhodium(III) complex **A** is the real active species in this reaction and oxygen and copper salts participated in the formation of the product.

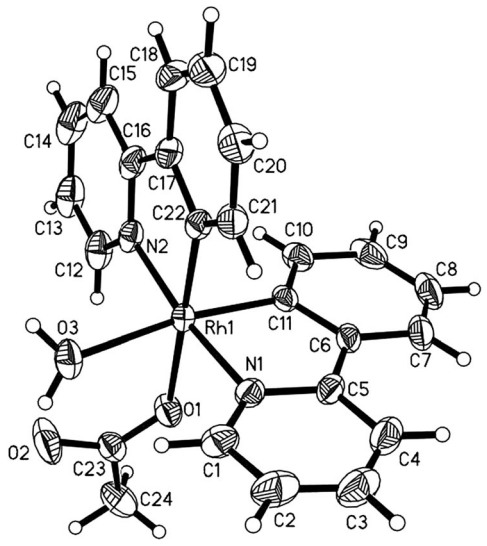
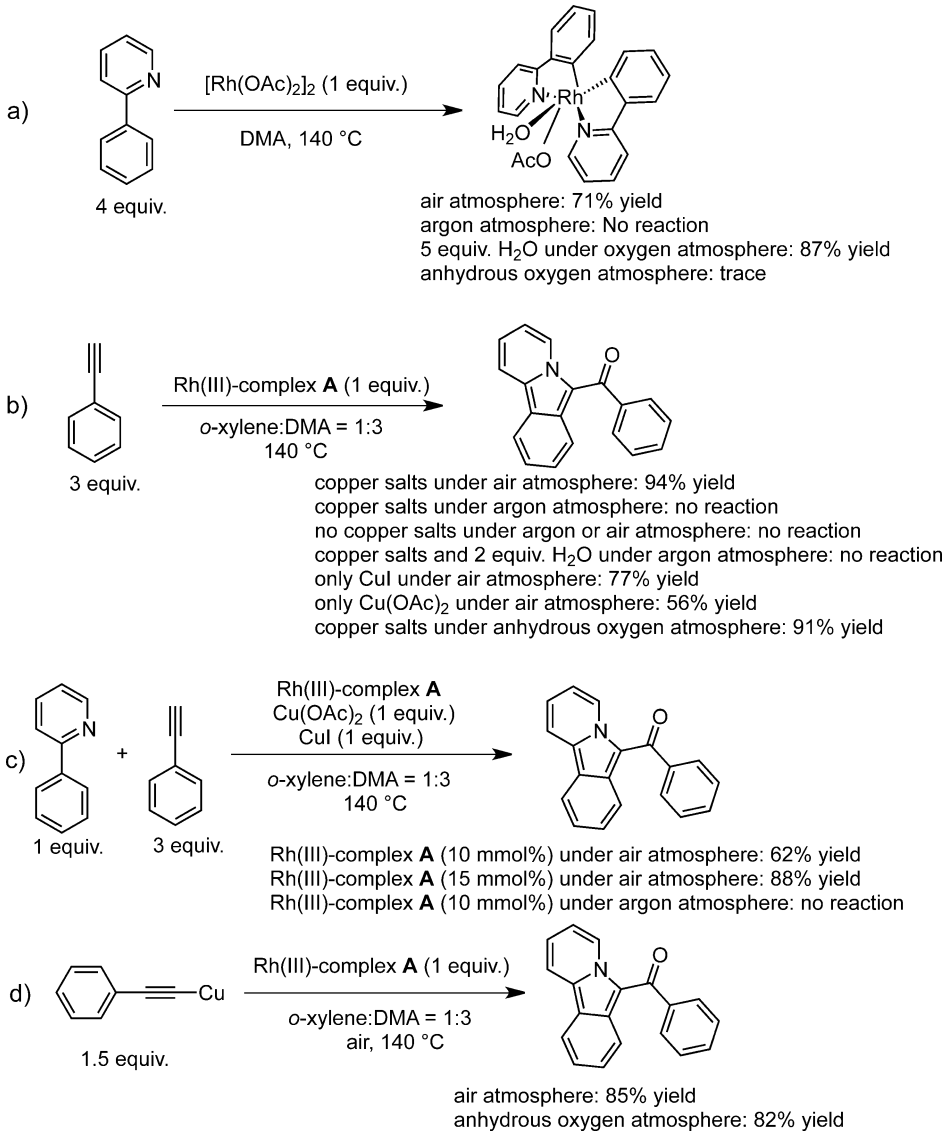


Figure 2. X-ray crystal structure of rhodium(III) complex **A**.



Scheme 2. Synthesis of Rh(III) complex **A** and a study of its activity.

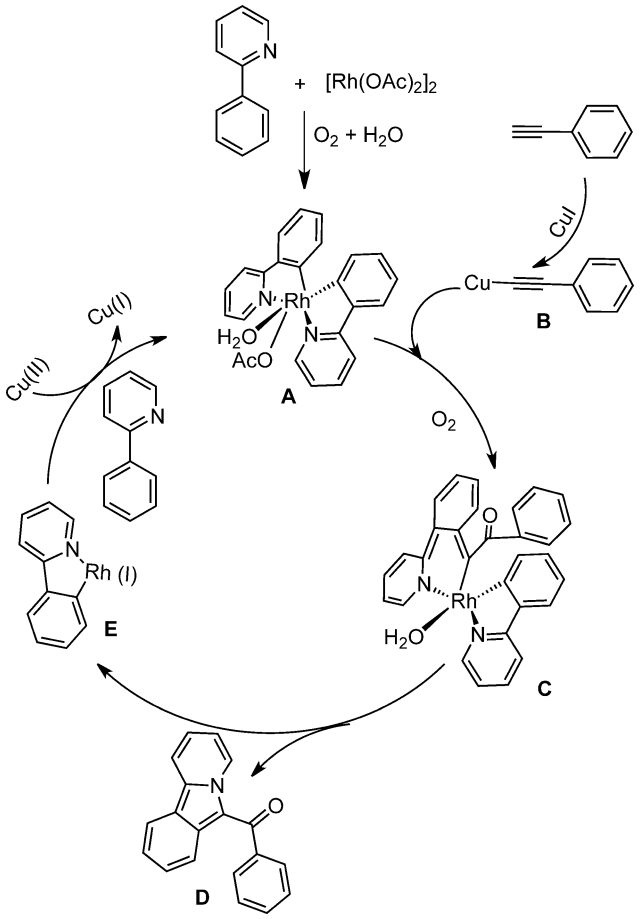
On the basis of the real active species and the previous literature reports,[12g,19e,23,26] a plausible mechanism of the catalytic C–H acylation reaction of 2-arylpyridines with terminal alkynes is described in Scheme 3. Rhodium(II) acetate dimer reacted with 2-phenylpyridine and water to generate the active catalyst **A** under air. Then rhodium(III) complex **A** reacted with copper complex **B**, which was formed from the reaction of alkyne with Cu(I),[12g,23] to produce complex **C** in the presence of oxygen according to our experiments (Scheme 2). The target product was obtained with the release of a Rh(I) species. Finally, the formed Rh(I) species was oxidized by $Cu(OAc)_2$ to regenerate Rh(III) to fulfill the catalytic cycle.[19e,26]

In conclusion, we have developed a direct and efficient rhodium-catalyzed oxidative acylation of 2-arylpyridines with terminal alkynes to afford the corresponding pyrido[2,1-*a*]isoindoles in moderate to excellent yields in the presence of copper salts. The mechanism was investigated according to the real catalytic species which was derived from the substrates and rhodium acetate. It should give a new strategy for designing some new and efficient Rh-catalyzed oxidative C–H activation reactions. Considering the complex process of this reaction, further investigations on detailed mechanisms are underway in our laboratory.

Experimental Section

Typical Procedure

2-Phenylpyridine **1a** (15.5 mg, 0.1 mmol), $[Rh(OAc)_2]_2$ (2.2 mg, 0.005 mmol), $Cu(OAc)_2$ (18.2 mg, 0.1 mmol), CuI (19.1 mg, 0.1 mmol), *N*,*N*-dimethylacetamide (DMA) (1.5 mL), and *o*-xylene (0.5 mL) were placed into a 10-mL



Scheme 3. Plausible mechanism for the oxidative C–H functionalization of 2-phenylpyridine with a terminal alkyne.

Schlenk tube equipped with a reflux condenser. Then, the temperature was increased to 140 °C. Phenylacetylene **2a** (30.6 mg, 0.3 mmol) was dissolved in DMA (0.5 mL), which was added in batches over five hours. After finishing the addition, the solution was stirred under an air atmosphere at 140 °C for another 1 h and monitored by TLC. After cooling to room temperature, the reaction mixture was quenched with ethyl acetate (15 mL) and washed with water (30 mL). The aqueous phase was extracted twice with EtOAc (3× 10 mL), and the combined organic layer was dried over anhydrous Na_2SO_4. After evaporation of the solvents under vacuum, the crude product was purified by column chromatography on aluminum oxide to give desired product **3aa** as a yellow solid; yield: 25.2 mg (93%); mp 112–115 °C. ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 10.61$ (d, $J = 7.0$ Hz, 1H), 8.19 (d, $J = 8.5$ Hz, 1H), 8.07 (d, $J = 7.9$ Hz, 1H), 7.67 (d, $J = 7.1$ Hz, 2H), 7.55 (t, $J = 7.3$ Hz, 1H), 7.52–7.49 (m, 3H), 7.35 (t, $J = 6.9$ Hz, 1H), 7.25–7.18 (m, 2H), 6.82 (d, $J = 8.3$ Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 182.24$, 141.50, 133.83, 131.48, 129.12, 128.36, 127.53, 127.17, 127.09, 124.20, 120.25, 118.90, 118.67, 118.19, 117.39, 116.20, 113.10; IR (KBr): $\nu = 3059$, 1585, 1562, 1522, 1457, 1434, 1312, 1268, 1218, 1022, 964, 794, 759, 690, 616, 437 cm^{-1}; HR-MS: $m/z =$ 271.1005, calculated for $C_{19}H_{13}NO$: 271.0997.

Acknowledgements

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[24] CCDC 982184 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[25] CCDC 982185 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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8 Rhodium-Catalyzed Direct Oxidative C–H Acylation of 2-Arylpyridines with Terminal Alkynes: A Synthesis of Pyrido[2,1-*a*]isoindoles

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