

Rhodium-Catalyzed Highly Regioselective C-H Arylation of Imidazo[1,2-*a*]pyridines with Aryl Halides and Triflates

Yi Liu,^{†,*} Lin He,[‡] Guoqiang Yin,[§] Guojie Wu,[§] and Yingde Cui^{§,*}

[†]School of Materials Science and Engineering, Northwestern Polytechnical University, Xi'an 710072, P.R. China

[‡]Lab Center of Zhongshan Campus, Guangdong Pharmaceutical University, Zhongshan, 528458, P.R. China

*E-mail: Andy_Poly@hotmail.com

[§]Department of Chemical Engineering, Zhongkai University of Agriculture and Engineering, Guangzhou, Guangdong 510225, P.R. China. *E-mail: cuigdut@yahoo.com.cn

Received April 8, 2013, Accepted May 13, 2013

A convenient Rh-catalyzed C-H arylation of imidazo[1,2-*a*]pyridines with a variety of aryl halides or triflates has been reported. This process afforded a range of biaryl compounds in excellent yields and showed high activity and broad scope.

Key Words : Rhodium catalyst, Aryl halides, Regioselective arylation, Imidazo[1,2-*a*]pyridines, Triflates

Introduction

Heteroaromatics bearing aryl-heteroaryl bond are always as one of the most important structural units frequently found in biological compounds, natural products, materials chemistry, ligands.¹ As a pharmacophore, those compounds exhibit a wide range of biological activities such as antibiotics, anti-inflammatories, anticancer and antifungal.² Due to their wide range of practical applications, many synthetic organic chemists have focused much of their attention on the coupling reaction to prepare heteroaromatics for the construction of new carbon-carbon bonds.³

Transition-metal-catalyzed coupling reactions play a crucial role in synthetic organic chemistry and have revolutionized the way to form carbon-carbon bonds.⁴ The fields of transition-metal-catalyzed coupling reactions have attracted attention because of their synthetic efficiency. Over the past few decades, many elegant transition-metal-catalyzed coupling reactions have been reported to form this kind of bis(hetero)aryl products, including the classical Suzuki-Miyaura,⁵ Negishi,⁶ Stille,⁷ and Kumada reactions.⁸ In addition, transition-metal-catalyzed arylation has been reported to successfully construct bis(hetero)aryl products and most of them included transition-metal catalysts such as Pd,⁹ Cu,¹⁰ Rh¹¹ and Ru.¹² Therefore, to develop novel transformations for the formation of carbon-carbon bonds *via* rhodium-catalyzed arylation reactions remains a continuing challenge reflecting organic chemistry.

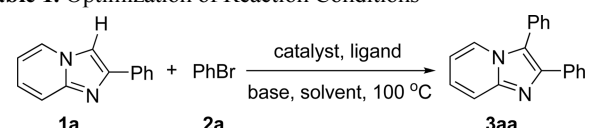
Herein, an convenient rhodium-catalyzed arylation of various imidazo[1,2-*a*]pyridines with aryl halides and triflates has been described to form bis(hetero)aryl products.

Results and Discussion

2,3-Diphenylimidazo[1,2-*a*]pyridine (**1a**) and bromobenzene (**2a**) was chosen as model system to identify and optimize potential catalysts. The critical reaction parameters and

the results were summarized in Table 1. The rhodium catalysts were firstly tested for the direct arylation process. The results indicated that [Rh(cod)OH]₂, Rh(cod)BF₄, Rh(PPh₃)₃Cl afforded **3aa** in moderate yields (entries 1-3) in the presence of K₂CO₃ without ligand at 100 for 20 h. However, using [Rh(cod)Cl]₂ as the catalyst provided **3aa** in 43% yield under the same conditions (entry 4). Among the base surveyed, K₂CO₃ was superior to Na₂CO₃, Cs₂CO₃, NaO*t*-Bu, KOAc (entries 5-8). A variety of ligands were next examined to

Table 1. Optimization of Reaction Conditions^a



Entry	Catalyst	Base	Ligand	Solvent	Yield (%) ^b
1	[Rh(cod)OH] ₂	K ₂ CO ₃	-	NMP	26
2	Rh(PPh ₃) ₃ Cl	K ₂ CO ₃	-	NMP	23
3	Rh(cod)BF ₄	K ₂ CO ₃	-	NMP	11
4	[Rh(cod)Cl] ₂	K ₂ CO ₃	-	NMP	43
5	[Rh(cod)Cl] ₂	Na ₂ CO ₃	-	NMP	32
6	[Rh(cod)Cl] ₂	Cs ₂ CO ₃	-	NMP	38
7	[Rh(cod)Cl] ₂	NaO <i>t</i> -Bu	-	NMP	10
8	[Rh(cod)Cl] ₂	KOAc	-	NMP	3
9	[Rh(cod)Cl] ₂	K ₂ CO ₃	PPh ₃	NMP	92
10	[Rh(cod)Cl] ₂	K ₂ CO ₃	PBu ₃	NMP	81
11 ^c	[Rh(cod)Cl] ₂	K ₂ CO ₃	Bpy	NMP	52
12 ^c	[Rh(cod)Cl] ₂	K ₂ CO ₃	Phen	NMP	58
13	[Rh(cod)Cl] ₂	K ₂ CO ₃	PPh ₃	DMSO	71
14	[Rh(cod)Cl] ₂	K ₂ CO ₃	PPh ₃	DMA	81
15	[Rh(cod)Cl] ₂	K ₂ CO ₃	PPh ₃	DMF	83
16	[Rh(cod)Cl] ₂	K ₂ CO ₃	PPh ₃	Toluene	78

^aReaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), catalysts 2.5 mol %, base (1.0 mmol), ligands (8 mol %), solvent (3 mL), 20 h. ^bYield determined by GC. ^cBpy = 2,2'-bipyridine; Phen = 1,10-phenanthroline.

improve the yields in the presence of $[\text{Rh}(\text{cod})\text{Cl}]_2$ and K_2CO_3 at $100\text{ }^\circ\text{C}$ for 20 h, such as PPh_3 , PBU_3 , Bpy, Phen (entries 9-12). The results showed the yield of **3aa** was dramatically increased to 92% (entry 9) by using PPh_3 as ligands. Effects of solvents were also investigated in the following tests. It was found that arylation product **3aa** were obtained in very good yields in NMP (entry 9), but when DMSO, DMA, DMF and toluene were employed, the product **3aa** was obtained in lower yield (entries 13-16).

With these sets of optimized conditions in hand, we began to look at arylation of imidazo[1,2-*a*]pyridines **1** and a variety of aryl bromides **2**, and the results are shown in Table 2. A series of imidazo[1,2-*a*]pyridines **1a-f** were subjected to the optimized reaction conditions and the desired products were obtained in good yields. We next investigated whether different types of substituents at C-1, C-5 and C-6 have impact on the yields. The results indicated that different

Table 2. Rhodium-catalyzed Direct Arylation of Substituted Imidazo[1,2-*a*]pyridines with Aryl Bromides^a

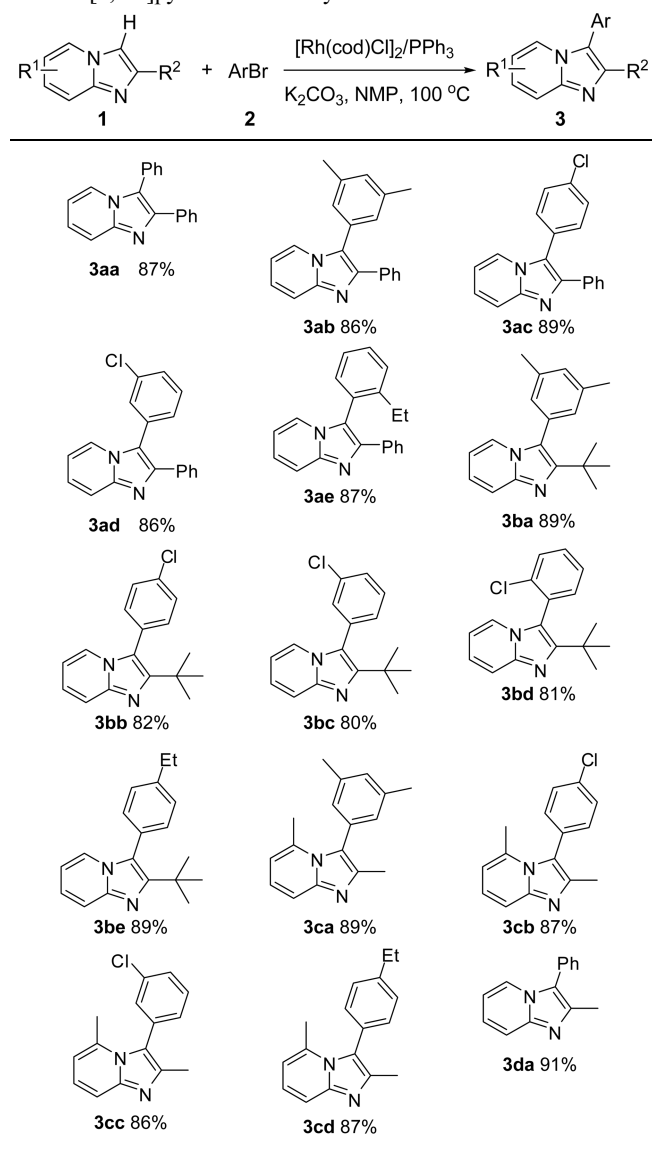
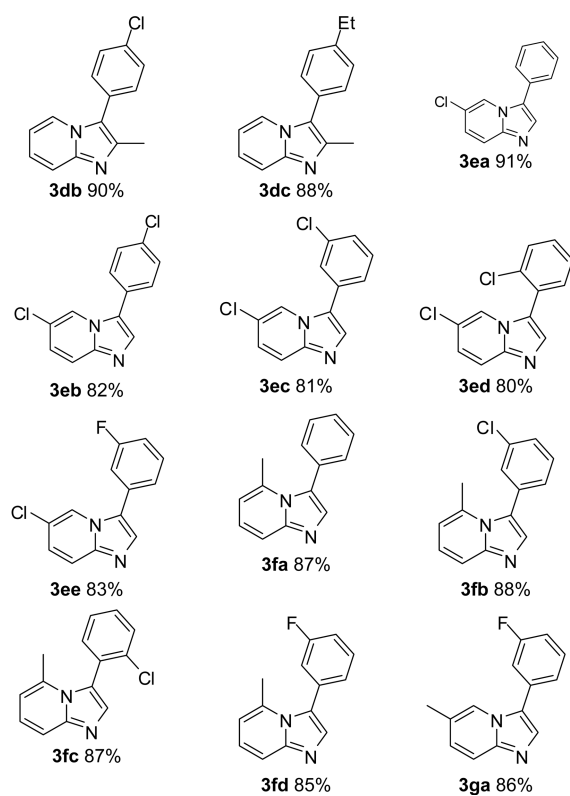


Table 2. Continued



^aIsolated Yield.

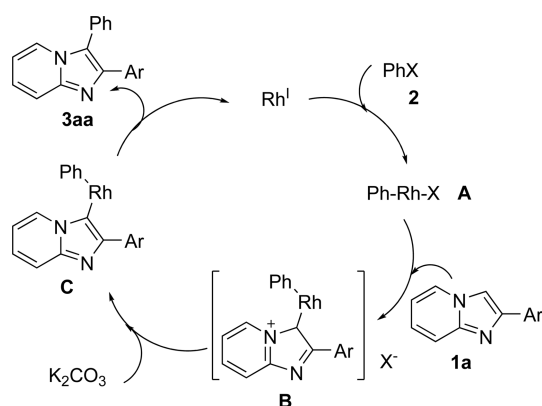
substituents at C-1, C-5 and C-6, including H, CH_3 , Cl, $\text{C}(\text{CH}_3)_3$, Ph, had little impact on the yields of the products. Interestingly, when 6-methylimidazo[1,2-*a*]pyridine, 5-methylimidazo[1,2-*a*]pyridine, 6-methylimidazo[1,2-*a*]pyridine were used as substrates, the corresponding products were also obtained in good yields. As expected, a series of functional groups on the phenyl ring of aryl bromides, such as *p*-Cl, *o*-Cl, *m*-Cl, *m*-F, *p*-Et, *o*-Et, 3,4- $(\text{CH}_3)_2$ were compatible under optimal condition and the products were isolated in high yields.

Table 3. Rhodium-catalyzed Direct Arylation of Substituted Imidazo[1,2-*a*]pyridines with Triflates^a

Reaction scheme for Table 3: Imidazo[1,2-*a*]pyridine **1** + Aryl Triflate **2** with $[\text{Rh}(\text{cod})\text{Cl}]_2/\text{PPh}_3$, K_2CO_3 , NMP, $100\text{ }^\circ\text{C}$ yields product **3**.

Entry	1	Ar	Product	Yield (%)
1	1a	Ph	3aa	84
2	1d	Ph	3da	85
3	1e	Ph	3ea	85
4	1f	Ph	3fa	82
5	1a	4-ClC ₆ H ₄	3ac	78
6	1e	4-ClC ₆ H ₄	3eb	76
7	1b	4-EtC ₆ H ₄	3be	85
8	1d	4-EtC ₆ H ₄	3dc	83

^aIsolated yields



Scheme 1. Plausible mechanism.

After an extensively scope of imidazo[1,2-*a*]pyridines and aryl bromides was established, we were particularly interested in extending the arylation to triflates (Table 3). The arylation of **1a**, **1d**, **1e** and **1f** with phenyl trifluoromethanesulfonate was tested and the corresponding products were formed with good yields (entries 1-4). Other triflates, such as *p*-tolyl trifluoromethanesulfonate and 4-ethylphenyl trifluoromethanesulfonate were also employed and the arylation products were obtained in good yields (entries 4-8).

A possible mechanism of arylation has been described in Scheme 1. A mechanism similar to arylation of heterocycles has been involved in previous reports. It involves an electrophilic attack by the aryl-rhodium halide species **A** to the **1a** to give intermediate **B**. Abstraction of the hydrogen atom in **B** with the help of K_2CO_3 would form intermediate **C**, which would then undergo reductive elimination to give the products **3aa** and release the rhodium catalyst.

Conclusions

In conclusion, we have described an efficient rhodium-catalyzed highly regioselective arylation of imidazo[1,2-*a*]pyridine with excellent yields. This arylation of imidazo[1,2-*a*]pyridines can be used broadly applicable for the synthesis of biologically active molecules.

Experiment

General Information. The reactions were performed at 100 °C under air atmosphere. 1H NMR spectra and ^{13}C NMR spectra were recorded with a Bruker 300 or 400 spectrometer in a $CDCl_3$ solution with TMS as internal standard. **1a-1c** were purchased from Aldrich Chemicals. All products were isolated by short chromatography on silica gel (200-300 mesh) column and the 1H NMR and ^{13}C NMR data have been provided in supporting information.

Synthesis of 3aa: A mixture of **1a** (0.5 mmol), **2a** (0.6 mmol), $[Rh(cod)Cl]_2$ (2.5 mol %), PPh_3 (8 mol %), K_2CO_3 (1.0 mmol) in NMP (3 mL) is stirred for 20 h at 100 °C. After completion of the reaction (monitored by TLC), 10

mL water was added. The aqueous solution was extracted with diethyl ether (3 × 10 mL) and the combined extract was dried with anhydrous $MgSO_4$. The solvent was removed and the crude product was separated by column chromatography (eluted with petroleum ether : ethyl acetate = 2:1) to give a pure sample of **3aa**.

Acknowledgments. The work was financially supported by the Chinese Natural Science Foundation (21176269) and the Natural Science Foundation of Guangdong Province (10151022501000033). And the publication cost of this paper was supported by the Korean Chemical Society.

References

- (a) Daugulis, O.; Do, H. Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074-1086. (b) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174-238. (c) Ackermann, L.; Vicente, R. *Top. Curr. Chem.* **2010**, *292*, 211-229.
- Corbet, J. P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651-2710.
- (a) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 3850-3850. (b) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211-241.
- (a) Mori, A.; Sekiguchi, A.; Masui, K.; Shimada, T.; Horie, M.; Osakada, K.; Kawamoto, M.; Ikeda, T. *J. Am. Chem. Soc.* **2003**, *125*, 1700-1701. (b) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050-8057. (c) Campeau, L. C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020-18021.
- (a) Suzuki, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 6722-6737. Marhadour, S.; (b) Bazin, M. A.; Marchand, P. *Tetrahedron Lett.* **2012**, *53*, 297-300.
- Negishi, E. I. *Angew. Chem., Int. Ed.* **2011**, *50*, 6738-6764.
- Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4992-4998.
- Murahashi, S. I. *J. Organomet. Chem.* **2002**, *653*, 27-33.
- (a) Nadres, E. T.; Lazareva, A.; Daugulis, O. *J. Org. Chem.* **2011**, *76*, 471-483. (b) Ioannidou, H. A.; Koutentis, P. A. *Org. Lett.* **2011**, *13*, 1510-1513. (c) Tamba, S.; Okubo, Y.; Tanaka, S.; Monguchi, D.; Mori, A. *J. Org. Chem.* **2010**, *75*, 6998-7001. (d) Kirchberg, S.; Tani, S.; Ueda, K.; Yamaguchi, J.; Studer, A.; Itami, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 2387-2391. (e) Daugulis, O.; Zaitsev, V. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4046-4048. (f) Leclerc, J. P.; Fagnou, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 7781-7786. (g) Cao, H.; Lin, Y. G.; Zhan, H. Y.; Du, Z. D.; Lin, X. L.; Liang, Q. M.; Zhang, H. *RSC Advances* **2012**, *2*, 5972-5975. (h) Cao, H.; Shen, D. S.; Zhan, H. Y.; Yang, L. Q. *Synlett* **2011**, *10*, 1472-1476.
- Cao, H.; Zhan, H. Y.; Lin, Y. G.; Lin, X. L.; Du, Z. D.; Jiang, H. F. *Org. Lett.* **2012**, *14*, 1688-1691.
- (a) Lewis, J. C.; Berman, A. M.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 2493-2500. (b) Lewis, J. C.; Wu, J. Y.; Bergman, R. G.; Ellman, J. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1589-1591. (c) Proch, S.; Kempe, R. *Angew. Chem., Int. Ed.* **2007**, *46*, 3135-3138. (d) Berman, A. M.; Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 14926-14927.
- (a) Arockiam, P.; Poirier, V.; Fischmeister, C.; Bruneau, C.; Dixneuf, P. H. *Green Chem.* **2009**, *11*, 1871-1875. (b) Ackermann, L.; Althammer, A.; Born, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 2619-2622. (c) Özdemir, I.; Demir, S.; Cetinkaya, B.; Gourlaouen, C.; Maseras, F.; Bruneau, C.; Dixneuf, P. H. *J. Am. Chem. Soc.* **2008**, *130*, 1156-1157. (d) Ackermann, L.; Mulzer, M. *Org. Lett.* **2008**, *10*, 5043-5045. (e) Ackermann, L.; Vicente, R.; Althammer, A. *Org. Lett.* **2008**, *10*, 2299-2302. (f) Cao, H.; Zhan, H. Y.; Shen, D. S.; Zhao, H.; Liu, Y. *J. Organomet. Chem.* **2011**, *696*, 3086-3090.