Efficient Synthesis of Isoquinolines via Rh(III)-Catalyzed Oxidative Annulation of Picolinamides with Alkynes

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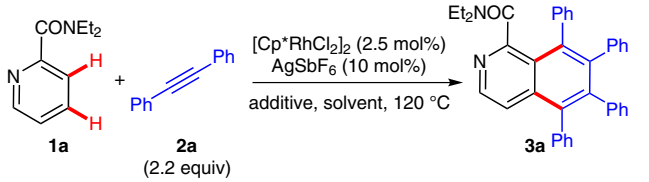
Abstract: An efficient synthesis of isoquinolines via Rh(III)-catalyzed oxidative annulation of picolinamides with alkynes using $Cu(OAc)_2$ as an oxidant has been developed. The scope of the reaction was studied with a selection of various picolinamides and alkynes, and the desired isoquinolines were obtained in good to excellent yields.

Key words: isoquinoline, rhodium(III), C–H activation, pyridine, oxidative annulation

Isoquinolines are valuable and prevalent structural motifs in natural products, pharmaceuticals, materials and agrochemicals.[1] Consequently, a variety of methods have been developed for the synthesis of these scaffolds. Although traditional methods such as Pomeranz–Fritsch, Bischler–Napieralski, and Pictet–Spengler reactions have been frequently applied in the synthesis of isoquinolines, these methods often employ intramolecular cyclization of highly functionalized substrates with strong acids and elevated temperatures.[2] Therefore, various transition-metal-catalyzed methods have been developed to address these drawbacks. In this case, the intermolecular cyclization of *o*-haloaldimines and alkynes catalyzed by Pd[3] and Ni[4] has proved its success. Shortly afterwards, highly prefunctionalized substrates, such as *o*-alkynylaryl aldimines, aldoximes and azides, were employed in the intramolecular cyclization process.[5] However, many of these methods still suffer from limited substrate scope, require multistep sequences to prepare the starting materials, encouraging the development of new methodology with high efficiency and economy.

Recently, Rh(III)-catalyzed C–H activation has become a powerful tool in organic synthesis, partly owing to the lower catalytic loading and high functional group tolerance.[6–8] Especially, Rh(III)-catalyzed oxidative annulation using alkynes has emerged as a valuable and versatile tool for the synthesis of *N*-hetereocycles,[7] such as isoquinolines.[9] Fagnou[9a] and Miura[9b] have independently demonstrated the Rh(III)-catalyzed oxidative coupling of aromatic imines with alkynes towards isoquinolines. Shortly after that, Chiba,[9c] Li,[9d] Rovis[9e] and Hua[9f] employed internal oxidants such as *O*-acetyl oximes and oximes to synthesize isoquinolines under Rh(III)-catalyzed systems.

Table 1 Optimization of Reaction Conditions[a]



Entry	Additive	Solvent	Yield (%)
1	$Cu(OAc)_2$ (2 equiv)	DCE	92
2[b]	$Cu(OAc)_2$ (2 equiv)	DCE	0
3[c]	$Cu(OAc)_2$ (2 equiv)	DCE	31
4	$Cu(OAc)_2$ (2 equiv)	1,4-dioxane	22
5	$Cu(OAc)_2$ (2 equiv)	DMF	0
6	$Cu(OAc)_2$ (2 equiv)	*t*-AmOH	16
7	$Cu(OAc)_2$ (2 equiv)	toluene	trace
8	AgOAc (2 equiv)	DCE	24
9	Ag_2CO_3 (1 equiv)	DCE	0

[a] Conditions: **1a** (0.2 mmol), **2a** (0.44 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol%), $AgSbF_6$ (10 mol%), additive in solvent (2 mL), sealed tube under nitrogen, 120 °C, 24 h, isolated yield.
[b] The reaction was carried out without $[Cp^*RhCl_2]_2$.
[c] The reaction was carried out without $AgSbF_6$.

The above mentioned synthetic methods employed prefunctionalized arenes as substrates to construct heterocycles. Inspired by our continuous studies of Rh(III)-catalyzed C–H functionalization of pyridine derivatives,[10] we envisioned that the use of pyridine derivatives as substrates might be an efficient and straightforward strategy, considering the widespread availability of these substrates. Takahashi has developed a stoichiometric coupling of zirconacyclopentadienes with dihalopyridines for the preparation of quinolines and isoquinolines.[11a] Sato demonstrated the Ni-catalyzed [2+2+2] cycloaddition of diynes and 3,4-pyridynes for the synthesis of isoquinoline.[11b] Miura reported one isolated example of synthesis of isoquinoline from pyridin-4-ylboronate catalyzed by

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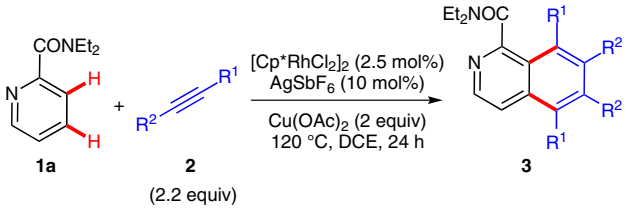
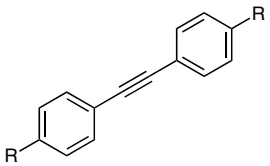
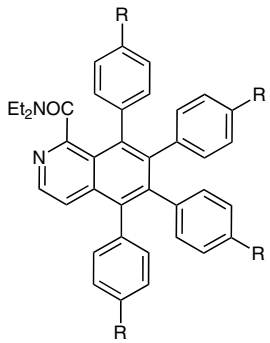
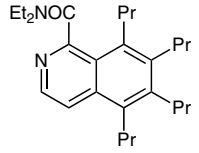
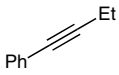
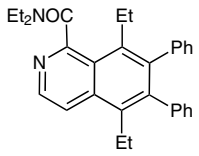
rhodium.[11c] Recently, Li realized the Rh(III)-catalyzed synthesis of quinolines using pyridines and alkynes.[11d] We now report a Rh(III)-catalyzed synthesis of isoquinolines via oxidative annulation of functionalized pyridines with alkynes using $Cu(OAc)_2$ as an oxidant.

Our work started with the oxidative annulation of *N*,*N*-diethylpicolinamide (**1a**) with diphenylacetylene (**2a**) under $[Cp^*RhCl_2]_2/AgSbF_6$ catalytic system (Table 1). We were delighted to find that isoquinoline **3a** was isolated in 92% yield when DCE was used as solvent and $Cu(OAc)_2$ was used as oxidant (entry 1). We further confirmed that both $[Cp^*RhCl_2]_2$ and $AgSbF_6$ are crucial for the present reaction (entries 2 and 3). DCE was found to be the ideal solvent, while other solvents resulted in low yields (entries 4–7). $Cu(OAc)_2$ is essential to the success of this transformation, while other additives such as AgOAc and Ag_2CO_3 led to reduced yields (entries 8 and 9).

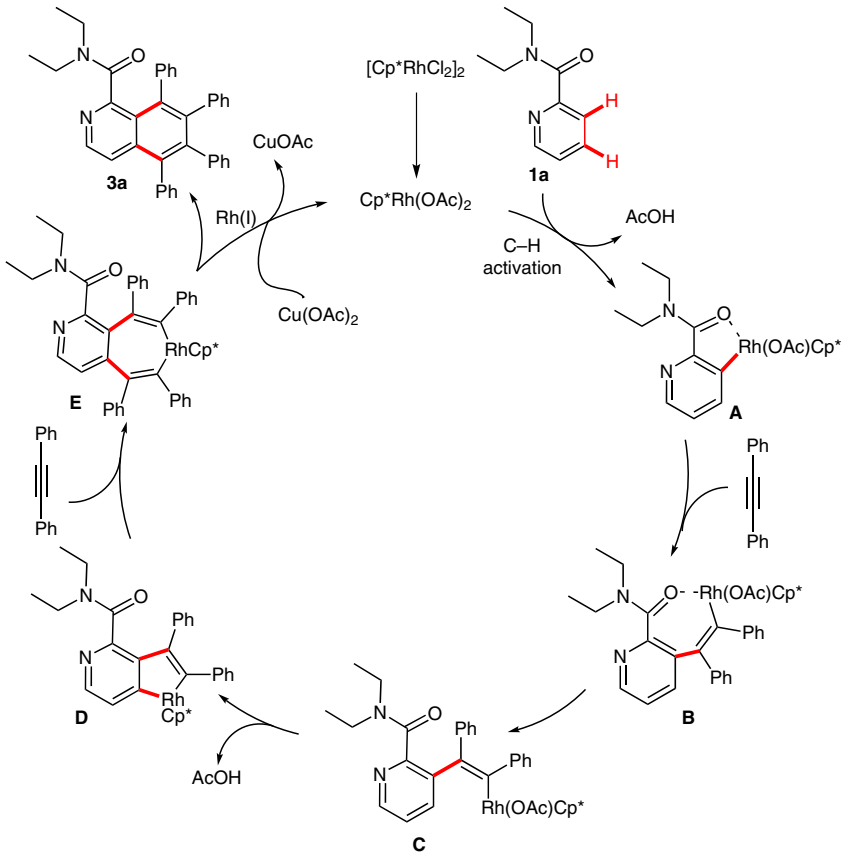
With the optimized conditions in hand, we then examined the scope of various alkynes and the reaction shows broad substrate tolerance among internal alkynes (Table 2). The reactions of **1a** with different diarylacetylenes **2b–d** proceeded efficiently to produce quinolines **3b–d** in excellent yields (Table 2, entries 2–4). Symmetrical dialkyl alkyne, 4-octyne (**2e**) also reacted with **1a** to give **3e** in moderate yield (entry 5). When unsymmetrical alkyne, 1-phenyl-1-butyne (**2f**) was employed, isoquinoline **3f** was obtained predominantly with phenyl group distal to the amide group (entry 6).

Table 2 Reaction of *N*,*N*-Diethylpicolinamide **1a** with Alkynes **2**[a]



Entry	Alkyne **2**	Product **3**	Yield (%)
			
1	**2a**, R = H	**3a**, R = H	92
2	**2b**, R = Me	**3b**, R = Me	88
3	**2c**, R = Cl	**3c**, R = Cl	95
4	**2d**, R = F	**3d**, R = F	87
5	 **2e**	 **3e**	41
6	 **2f**	 **3f**	56

[a] Conditions: **1a** (0.2 mmol), **2** (0.44 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol%), $AgSbF_6$ (10 mol%), $Cu(OAc)_2$ (0.4 mmol), DCE (2 mL), sealed tube under nitrogen, 120 °C, 24 h, isolated yield.



Scheme 1 Plausible mechanism for the reaction of **1a** with alkyne

The scope of picolinamides was also investigated, as given in Table 3. Picolinamides bearing substitutions at the 6-position were generally more reactive and afforded higher yields than those carrying substitutions at the 5-position, because of the steric congestion (Table 3, entries 1–6). Halogenated picolinamides, such as chloride and fluoride, were also tolerated, giving moderate to high yields (entries 2 and 3). Electron-withdrawing group, such as carboxylic ester, survived under the standard conditions, affording isoquinoline **1g** in excellent yield (entry 6). Other *N*,*N*-dialkyl-substituted picolinamides reacted with diphenylacetylene (**2a**) under current conditions to afford the desired products in good yields (entries 7 and 8).

A plausible mechanism for the reaction of **1a** with diphenylacetylene (**2a**) is illustrated in Scheme 1, according to previous studies.[7d,e] The active catalyst Cp*Rh(OAc)$_2$ is coordinated by **1a** via the Lewis basic amide oxygen and subsequent *ortho* C–H activation leads to the five-membered rhodacyclic intermediate **A**. Alkyne then coordinates **A**, followed by regioselective insertion of the alkyne to yield the seven-membered intermediate **B**. Dissociation of rhodium from the oxygen, followed by a second *ortho* C–H activation, gives rhodacyclic intermediate **D**. A second coordination of alkyne and regioselective insertion affords intermediate **E**. Subsequently, isoquinoline **3a** and Rh(I) species are generated by reductive elimination. This Rh(I) species is then reoxidized to Rh(III) by Cu(OAc)$_2$ to accomplish the catalytic cycle.

In summary, we have demonstrated that isoquinolines can be synthesized efficiently by the oxidative annulations of picolinamides with internal alkynes in the presence of a rhodium catalyst and Cu(OAc)$_2$.[12] Further investigations to study the mechanism of this reaction are under way.

Acknowledgment

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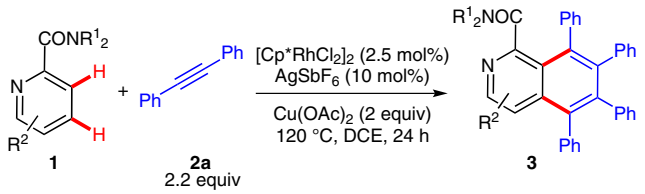
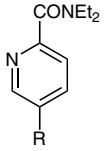
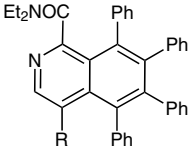
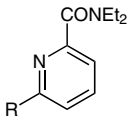
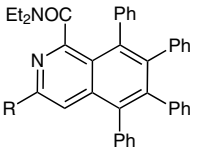
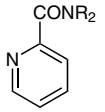
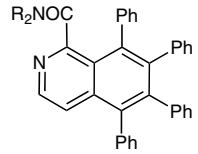
Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

References and Notes

(1) Bentley, K. W. *In The Isoquinoline Alkaloids*; Vol. 1; Hardwood Academic: Amsterdam, **1998**.
(2) *Organic Reactions*; Vol. 6; Adams, R., Ed.; Wiley: New York, **1951**, 74–206.
(3) (a) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 5306. (b) Roesch, K. R.; Larock, R. C. *Org. Lett.* **1999**, *1*, 553.
(4) Korivi, R. P.; Cheng, C.-H. *Org. Lett.* **2005**, *7*, 5179.
(5) (a) Huang, Q.; Larock, R. C. *Tetrahedron Lett.* **2002**, *43*, 3557. (b) Huang, Q.; Hunter, J. A.; Larock, R. C. *J. Org.*

Table 3 Reaction of Picolinamides **1** with Diphenylacetylene **2a**[a]



Entry	Picolinamide **1**	Product **3**	Yield (%)
			
1	**1b**, R = Me	**3g**, R = Me	48
2	**1c**, R = F	**3h**, R = F	88
3	**1d**, R = Cl	**3i**, R = Cl	67
4	**1e**, R = OAc	**3j**, R = OAc	40
5	 **1f**, R = Me	 **3k**, R = Me	90
6	**1g**, R = CO_2Me	**3l**, R = CO_2Me	98
7	 **1h**, R = Cy	 **3m**, R = Cy	94
8	**1i**, R = Bn	**3n**, R = Bn	71

[a] Conditions: **1** (0.2 mmol), **2a** (0.44 mmol), $[Cp^*RhCl_2]_2$(2.5 mol%), $AgSbF_6$ (10 mol%), $Cu(OAc)_2$ (0.4 mmol), DCE (2 mL), sealed tube under nitrogen, 120 °C, 24 h, isolated yield.

Chem. **2002**, *67*, 3437. (c) Su, S.; Porco, J. A. Jr. *J. Am. Chem. Soc.* **2007**, *129*, 7744. (d) Niu, Y. N.; Yan, Z. Y.; Gao, G. L.; Wang, H. L.; Shu, X. Z.; Ji, K. G.; Liang, Y. M. *J. Org. Chem.* **2009**, *74*, 2893.

(6) For selected reviews on Rh(III)-catalyzed C–H functionalization, see: (a) Satoh, T.; Miura, M. *Chem. Eur. J.* **2010**, *16*, 11212. (b) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2012**, *45*, 814. (c) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651. (d) Patureau, F. W.; Wencel-Delord, J.; Glorius, F. *Aldrichimica Acta* **2012**, *45*, 31. (e) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624.

(7) For selected examples of Rh(III)-catalyzed coupling between arenes and alkynes, see: (a) Umeda, N.; Tsurugi, H.; Satoh, T.; Miura, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 4019. (b) Yamashita, M.; Horiguchi, H.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2009**, *74*, 7481. (c) Guimond, N.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 12050. (d) Stuart, D. R.; Alsabeh, P.; Kuhn, M.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 18326. (e) Hyster, T. K.; Rovis, T. *J. Am. Chem. Soc.* **2010**, *132*, 10565. (f) Rakshit, S.; Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9585. (g) Patureau, F. W.; Besset, T.; Kuhl, N.; Glorius, F. *J. Am. Chem. Soc.* **2011**, *133*, 2154. (h) Muralirajan, K.; Parthasarathy, K.; Cheng, C.-H. *Angew. Chem. Int. Ed.* **2011**, *50*, 4169. (i) Song, G.; Chen, D.; Pan, C.-L.; Crabtree, R. H.; Li, X. *J. Org. Chem.* **2010**, *75*, 7487. (j) Chen, J.; Song, G.; Pan, C.-L.; Li, X. *Org. Lett.* **2010**, *12*, 5426. (k) Chuang, S.-C.; Gandeepan, P.; Cheng, C.-H. *Org. Lett.* **2013**, *15*, 5750. (l) Shi, Z.; Tang, C.; Jiao, N. *Adv. Synth. Catal.* **2012**, *354*, 2695. (m) Zhang, G.; Yang, L.; Wang, Y.; Xie, Y.; Huang, H. *J. Am. Chem. Soc.* **2013**, *135*, 8850.

(8) For selected examples, see: (a) Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2007**, *9*, 1407. (b) Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9982. (c) Tsai, A. S.; Brasse, M.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2011**, *13*, 540. (d) Tan, X.; Liu, B.; Li, X.; Li, B.; Xu, S.; Song, H.; Wang, B. *J. Am. Chem. Soc.* **2012**, *134*, 16163. (e) Gong, T.-J.; Xiao, B.; Liu, Z.-J.; Wan, J.; Xu, J.; Luo, D.-F.; Fu, Y.; Liu, L. *Org. Lett.* **2011**, *13*, 3235. (f) Park, S. H.; Kim, J. Y.; Chang, S. *Org. Lett.* **2011**, *13*, 2372. (g) Li, B.-J.; Wang, H.-Y.; Zhu, Q.-L.; Shi, Z.-J. *Angew. Chem. Int. Ed.* **2012**, *51*, 3948. (h) Qin, X.; Liu, H.; Qin, D.; Wu, Q.; You, J.; Zhao, D.; Guo, Q.; Huang, X.; Lan, J. *Chem. Sci.* **2013**, *4*, 1964. (i) Zhou, B.; Du, J.; Yang, Y.; Li, Y. *Org. Lett.* **2013**, *15*, 2934. (j) Dong, J.; Long, Z.; Song, F.; Wu, N.; Guo, Q.; Lan, J.; You, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 580. (k) Shang, Y.; Jie, X.; Zhao, H.; Hu, P.; Su, W. *Org. Lett.* **2014**, *16*, 416; and references therein.

(9) (a) Stuart, D. R.; Bertrand-Laperle, M.; Burgess, K. M. N.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 16474. (b) Fukutani, T.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Commun.* **2009**, 5141. (c) Too, P. C.; Wang, Y.-F.; Chiba, S. *Org. Lett.* **2010**, *12*, 5688. (d) Zhang, X.; Chen, D.; Zhao, M.; Zhao, J.; Jia, A.; Li, X. *Adv. Synth. Catal.* **2011**, *353*, 719. (e) Hyster, T. K.; Rovis, T. *Chem. Commun.* **2011**, *47*, 11846. (f) Zheng, L.; Ju, J.; Bin, Y.; Hua, R. *J. Org. Chem.* **2012**, *77*, 5794.

(10) Zhou, J.; Li, B.; Hu, F.; Shi, B.-F. *Org. Lett.* **2013**, *15*, 3460.

(11) (a) Takahashi, T.; Li, Y.; Stepnicka, P.; Kitamura, M.; Liu, Y.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **2002**, *124*, 576. (b) Iwayama, T.; Sato, Y. *Chem. Commun.* **2009**, 5245. (c) Fukutani, T.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2011**, *76*, 2867. (d) Song, G.; Gong, X.; Li, X. *J. Org. Chem.* **2011**, *76*, 7583.

(12) **General Procedure for the Synthesis of Isoquinolines 3 via Oxidative Annulation of Picolinamides 1 with 2**: *N*,*N*-Diethylpicolinamide (**1**; 0.2 mmol, 1.0 equiv), $[Cp^*RhCl_2]_2$ (0.005 mmol, 2.5 mol%), $AgSbF_6$ (0.02 mmol, 10 mol%), $Cu(OAc)_2$ (0.4 mmol, 2.0 equiv), alkyne **2** (0.44 mmol, 2.2 equiv) and DCE (2 mL) were added to a 20-mL Schlenk tube. After being purged with nitrogen, the mixture was stirred at 120 °C for 24 h. Then concd aq NH_3 (2 mL) was added and stirred for 5 min. The resulting mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4, concentrated under reduced pressure and purified by chromatography on silica gel to afford isoquinoline **3**. **5,6,7,8-Tetraphenylisoquinoline-1-carboxylic Acid Diethylamide (3a)**: Compound **3a** was prepared in 92% yield according to the general procedure as a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7.2 Hz, 3 H), 1.21 (t, *J* = 6.8 Hz, 3 H), 2.60–2.69 (m, 1 H), 2.72–2.81 (m, 1 H), 2.95–3.04 (m, 1 H), 3.36–3.44 (m, 1 H), 6.59 (d, *J* = 6.8 Hz, 1 H), 6.75–6.86 (m, 9 H), 7.04–7.13 (m, 5 H), 7.20–7.27 (m, 5 H), 7.43 (d, *J* = 5.6 Hz, 1 H), 8.40 (d, *J* = 5.6 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.9, 156.5, 143.3, 142.5,

141.4, 139.7, 139.6, 138.3, 138.2, 138.1, 136.5, 133.5, 131.4, 131.3, 130.9, 130.8, 130.7, 130.6 (2 × C), 127.9, 127.2 (2 × C), 127.0, 126.9, 126.7, 126.5, 125.9, 125.7, 125.6, 124.0, 120.1, 77.5, 77.2, 76.8, 45.3, 40.1, 13.8, 13.7. HRMS (EI–TOF): *m*/*z* [M^+] calcd for $C_{38}H_{32}N_2O$: 532.2515; found: 532.2511.

