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Rh(III)-Catalyzed C−H Bond Activation along with "Rollover" for the Synthesis of 4-Azafluorenes

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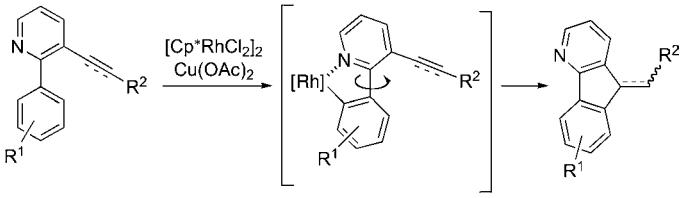
ABSTRACT



An intramolecular reaction of 3-alkynyl and 3-alkenyl-2-arylpyridines selectively gave 4-azafluorene compounds in the presence of a catalytic amount of $[Cp^*RhCl_2]_2$ and $Cu(OAc)_2$. Pyridine-directed C−H bond activation along with "rollover" are likely to be key steps of this transformation.

Transition metal-catalyzed C−H bond activation is currently one of the most active topics in organic chemistry, and C−H bond cleavage using a directing group is a reliable strategy for achieving facile and regioselective C−H bond functionalization.[1] For example, 2-phenylpyridine is a typical substrate, and the reaction with a transition metal complex selectively gives an *ortho*-metalated intermediate with the help of nitrogen coordination to the metal. The subsequent intermolecular reaction with alkyne, alkene and aryl halide leads to carbon−carbon bond formation (Scheme 1a).[2] As a new use for a metalated C−H bond, we were inspired by C−H bond metalation by "rollover": the coordinations of nitrogen to the metal are switched to carbon−metal bonds by rotation of the pyridine ring in 2,2′-bipyridine (Scheme 1b).[3,4] We considered that "rollover" of the *ortho*-metalated intermediate might enable coordination to an alkyne or alkene moiety at the 3-position of the pyridine ring, which follows an intramolecular cyclization (Scheme 1c).[5]

We report here an intramolecular reaction of 3-alkynyl and 3-alkenyl-2-arylpyridines with the use of $[Cp^*RhCl_2]_2$ as a catalyst and $Cu(OAc)_2$ as a catalytic additive. A new carbon skeleton of 4-azafluorene was selectively constructed. A preliminary mechanistic study, which supports the "rollover" step, is also addressed.

We chose 3-(phenylethynyl)-2-(*p*-tolyl)pyridine (**1a**) as a model compound and subjected it to several reaction conditions (Table 1). We have developed cationic Ir(I)-catalyzed reactions initiated by oxidative cleavage of a C−H bond,[6] and used an Ir-BINAP complex for this reaction (entry 1). However, the conventional intermolecular

(1) For recent reviews: (a) Kitamura, T. *Eur. J. Org. Chem.* **2009**, 1111. (b) Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242. (c) Yu, J.-Q., Shi, Z., Eds. *C-H Activation*; Springer-Verlag: Berlin, Germany, 2010. (d) Daugulis, O. *Top. Curr. Chem.* **2010**, *292*, 57. (e) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (f) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (g) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, *46*, 677. (h) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (i) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068.

(2) For selected examples, see: (a) Oi, S.; Fukita, S.; Inoue, Y. *Chem. Commun.* **1998**, 2439. (b) Ackermann, L. *Org. Lett.* **2005**, *7*, 3123. (c) Tobisu, M.; Ano, Y.; Chatani, N. *Chem.—Asian J.* **2008**, *3*, 1585. (d) Gao, K.; Yoshikai, N. *J. Am. Chem. Soc.* **2011**, *133*, 400.

(3) For a review of C−H bond cleavage via "rollover": Butschke, B.; Schwarz, H. *Chem. Sci.* **2012**, *3*, 308.

(4) For examples of C−H bond cleavage via "rollover": (a) Minghetti, G.; Stoccoro, S.; Cinellu, M. A.; Soro, B.; Zucca, A. *Organometallics* **2003**, *22*, 4770. (b) Butschke, B.; Schröder, D.; Schwarz, H. *Organometallics* **2009**, *28*, 4340. (c) Zucca, A.; Petretto, G. L.; Cabras, M. L.; Stoccoro, S.; Cinellu, M. A.; Manassero, M.; Minghetti, G. *J. Organomet. Chem.* **2009**, *694*, 3753. (d) Tyo, E. C.; Castleman, A. W., Jr.; Schröder, D.; Milko, P.; Roithova, J.; Ortega, J. M.; Cinellu, M. A.; Cocco, F.; Minghetti, G. *J. Am. Chem. Soc.* **2009**, *131*, 13009. (e) Butschke, B.; Schwarz, H. *Organometallics* **2010**, *29*, 6002. (f) Petretto, G. L.; Rourke, J. P.; Maidich, L.; Stoccoro, S.; Cinellu, M. A.; Minghetti, G.; Clarkson, G. J.; Zucca, A. *Organometallics* **2012**, *31*, 2971.

(5) Rh(III)-catalyzed oxidative coupling, which involved C-H bond cleavage via C−N bond rotation of 1-phenylpyrazole, is reported: Umeda, N.; Hirano, K.; Satoh, T.; Shibata, N.; Sato, H.; Miura, M. *J. Org. Chem.* **2011**, *76*, 13.

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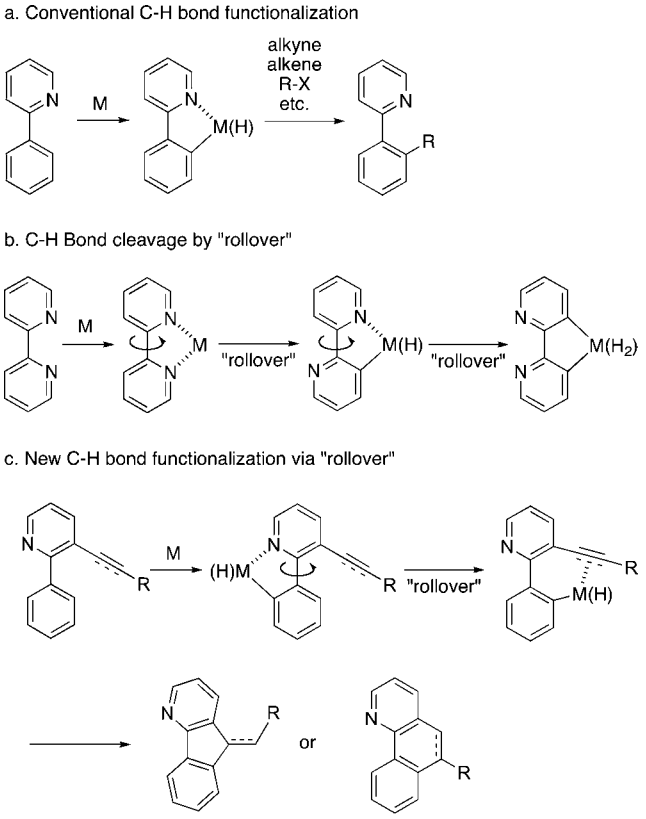
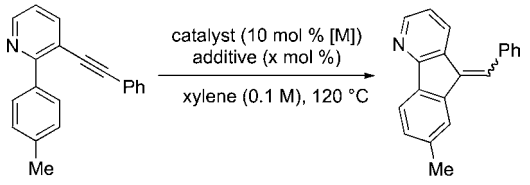
Scheme 1. Concept of C−H Bond Functionalization via "Rollover" in 2-Arylpyridine



alkenylation proceeded to give a dimer of **1a**,[7] and intramolecular adducts including **2a** could not be detected. The rhodium counterpart gave the same results (entry 2). We next examined the catalysis of the electrophilic metalation of C−H bond by using Ir(III) or Rh(III) complex along with a stoichiometric amount of copper acetate (entries 3 and 4).[8] As a result, we were pleased to detect the formation of 4-azafluorene **2a** as a 5-exo-dig-type cycloadduct

Table 1. Optimization of the Reaction Conditions



1a **2a**

entry	catalyst	additive (x)	time (h)	yield (%)[a]
1[b]	$[IrCl(cod)_2]BF_4$	*rac*-BINAP (10)	14	ND[c]
2[b]	$[RhCl(cod)_2]BF_4$	*rac*-BINAP (10)	14	ND[c]
3	$[Cp^*IrCl_2]_2$	$Cu(OAc)_2\cdot H_2O$ (100)	24	30
4	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2\cdot H_2O$ (100)	24	36
5	$[Cp^*RhCl_2]_2$	none	24	trace
6	none	$Cu(OAc)_2\cdot H_2O$ (100)	24	ND
7	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2\cdot H_2O$ (20)	24	37
8[d]	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2\cdot H_2O$ (20)	8	67
9[d]	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$ (20)	6	70
10[d]	$[Cp^*RhCl_2]_2$	NaOAc (20)	24	27
11[d]	$[Cp^*RhCl_2]_2$	KOAc (20)	24	52
12[d]	$[Cp^*RhCl_2]_2$	NaOPiv (20)	24	33
13[d]	$[Cp^*RhCl_2]_2$	KOPiv (20)	24	30
14[d]	$[Cp^*RhCl_2]_2$	CsOPiv (20)	24	49

[a] Z/E ratio of obtained **2a** was from 2/1 to 1/1. [b] Reaction was examined in chlorobenzene at 100 °C. [c] No intramolecular adduct was detected, but a dimer of **1a** was obtained by intermolecular reaction. [d] Concentration of **1a** was 0.05 M.

by intramolecular hydroarylation to alkyne.[9−11] Neither $[Cp^*RhCl_2]_2$ nor $Cu(OAc)_2\cdot H_2O$ was effective by itself (entries 5 and 6), but the combination of a catalytic amount of $[Cp^*RhCl_2]_2$ and $Cu(OAc)_2\cdot H_2O$ gave the same yield as in entry 4, which means that the copper salt acts as a catalytic additive for the promotion of hydrogen abstraction, rather than as an oxidant (entry 7).[6e,12] The yield of the present intramolecular reaction drastically improved under more dilute conditions (entry 8)[13] and anhydrous copper salt gave slightly better results (entry 9). A few alkali metal acetates and pivalates were examined as alternatives

(6) (a) Tsuchikama, K.; Kasagawa, M.; Hashimoto, Y.; Endo, K.; Shibata, T. *J. Organomet. Chem.* **2008**, *693*, 3939. (b) Tsuchikama, K.; Hashimoto, Y.; Endo, K.; Shibata, T. *Adv. Synth. Catal.* **2009**, *351*, 2850. (c) Tsuchikama, K.; Kasagawa, M.; Endo, K.; Shibata, T. *Org. Lett.* **2009**, *11*, 1821. (d) Tsuchikama, K.; Kasagawa, M.; Endo, K.; Shibata, T. *Synlett* **2010**, 97. (e) Shibata, T.; Hashimoto, Y.; Otsuka, M.; Tsuchikama, K.; Endo, K. *Synlett* **2011**, 2075. (f) Shibata, T.; Hirashima, H.; Kasagawa, M.; Tsuchikama, K.; Endo, K. *Synlett* **2011**, 2171. (g) Pan, S.; Endo, K.; Shibata, T. *Org. Lett.* **2011**, *13*, 4692. (h) Takebayashi, S.; Shibata, T. *Organometallics* **2012**, *31*, 4114.

(7) For examples of directed C−H alkenylation of 2-phenylpyridine with alkynes: (a) Lim, Y.-G.; Lee, K.-H.; Koo, B. T.; Kang, J.-B. *Tetrahedron Lett.* **2001**, *42*, 7609. (b) Volpe, E. C.; Chadeayne, A. R.; Wolczanski, P. T.; Lobkovsky, E. B. *J. Organomet. Chem.* **2007**, *692*, 4774. (c) Li, L.; Brennessel, W. W.; Jones, W. D. *J. Am. Chem. Soc.* **2008**, *130*, 12414. (d) Cheng, K.; Yao, B.; Zhao, J.; Zhang, Y. *Org. Lett.* **2008**, *10*, 5309. (e) Zhang, Z.; Ferrence, G. M.; Lash, T. D. *Org. Lett.* **2009**, *11*, 101. (f) Katagiri, T.; Mukai, T.; Satoh, T.; Hirano, K.; Miura, M. *Chem. Lett.* **2009**, *38*, 118. (g) Xie, M.-H.; Wang, M.; Wu, C.-D. *Inorg. Chem.* **2009**, *48*, 10477. (h) Gao, K.; Lee, P.-S.; Fujita, T.; Yoshikai, N. *J. Am. Chem. Soc.* **2010**, *132*, 12249.

(8) For reviews of Rh(III)-catalyzed C−H bond activation using a stoichiometric amount of oxidants: (a) Satoh, T.; Miura, M. *Chem.—Eur. J.* **2010**, *16*, 11212. (b) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651.

(9) For pioneering examples of Pd-catalyzed intramolecular hydroarylation to alkyne, (a) Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992. (b) Jia, C.; Piao, D.; Kitamura, T.; Fujiwara, Y. *J. Org. Chem.* **2000**, *65*, 7516. For a review of intramolecular hydroarylation to alkyne (c) Nevedo, C.; Echavarren, A. M. *Synthesis* **2005**, 167.

(10) For Friedel−Crafts type cyclizations of *o*-alkynyl biphenyls in a 6-endo-dig fashion: (a) Mamane, V.; Hannen, P.; Fürstner, A. *Chem.—Eur. J.* **2004**, *10*, 4556. (b) Nevado, C.; Echavarren, A. M. *Chem.—Eur. J.* **2005**, *11*, 3155. (c) Soriano, E.; Marco-Contelles, J. *Organometallics* **2006**, *25*, 4542.

(11) For Pd-catalyzed cyclization of *o*-alkynyl biphenyls in a 5-exo-dig fashion for the synthesis of 9-alkylidene-9*H*-fluorenes: (a) Chernyak, N.; Gevorgyan, V. *J. Am. Chem. Soc.* **2008**, *130*, 5636. (b) Chernyak, N.; Gevorgyan, V. *Adv. Syn. Catal.* **2009**, *351*, 1101.

(12) (a) Davies, D. L.; Al-Duaij, O.; Fawcett, J.; Giardiello, M.; Hilton, S. T.; Russell, D. R. *Dalton Trans.* **2003**, 4132. (b) Davies, D. L.; Donald, S. M. A.; Al-Duaij, O.; Macgregor, S. A.; Pölleth, M. *J. Am. Chem. Soc.* **2006**, *128*, 4210. (c) Li, L.; Brennessel, W. W.; Jones, W. D. *Organometallics* **2009**, *28*, 3492. (d) Boutadla, Y.; Davies, D. L.; Macgregor, S. A.; Poblador-Bahamonde, A. I. *Dalton Trans.* **2009**, 5887.

(13) Under further dilute conditions (0.025 M), the yield of **2a** decreased because of low conversion.

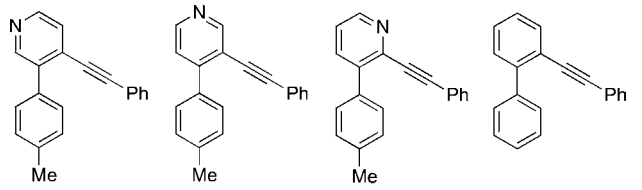
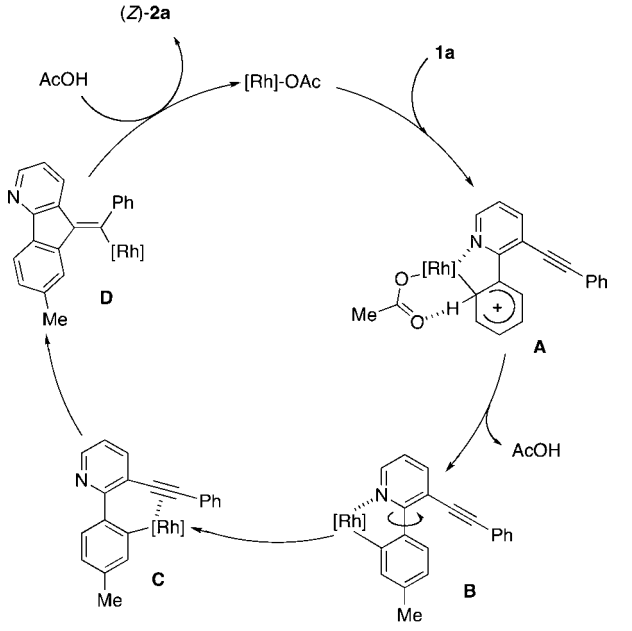


Figure 1. Inappropriate substrates for the present Rh(III)-catalyzed intramolecular reaction.

Scheme 2. Proposed Mechanism Including "Rollover"



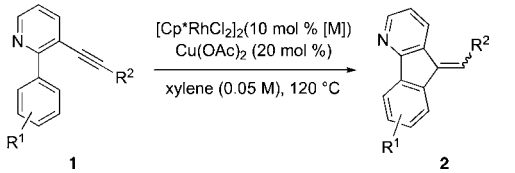
to $Cu(OAc)_2$, but the yield was not improved (entries 10–14).[14]

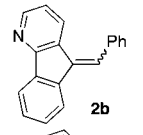
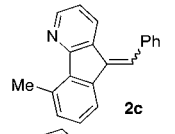
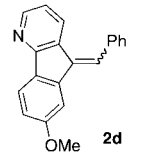
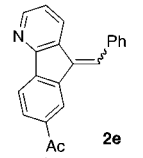
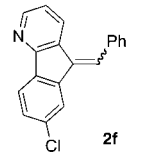
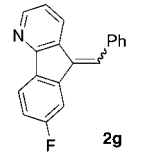
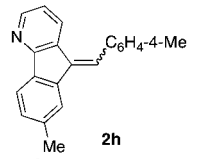
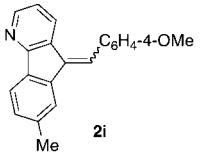
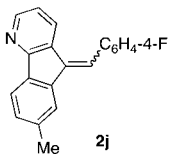
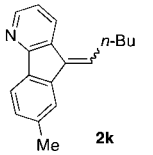
As a preliminary mechanistic study, we performed control experiments using regioisomeric alkynylarylpyridines **3**–**5** and nitrogen-free substrate **6** under the optimal reaction conditions listed in entry 9 of Table 1 (Figure 1). The reaction of these four substrates did not proceed at all, as expected. These results imply that the coordination of nitrogen atom to a metal center assists sp^2 C–H bond cleavage on the benzene ring. Moreover, the present intramolecular reaction is not an electrophilic substitution using an alkyne moiety activated by π-coordination of the metal.

Based on the above results, we can propose a mechanism depicted in Scheme 2. Rhodium acetate is the true catalyst, and acetate facilitates hydrogen abstraction in pyridine-directed C–H bond cleavage. "Rollover" from intermediate

(14) The formation of azafluorene **2a** could not be detected under the heating conditions by using $PtCl_2$, $InCl_3$, or $AuCl(PPh_3)$ along with $AgBF_4$, which is typical catalyst for Friedel–Crafts type intramolecular hydroarylation to alkyne (ref 9c).

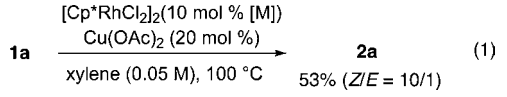
Table 2. Substrate Scope of 3-Alkynyl-2-arylpyridines



entry	product	time (h)	yield (%)[a]
1	 **2b**	8	71 (1.5:1)
2	 **2c**	24	42 (2.5:1)
3	 **2d**	4	69 (5:1)
4[b]	 **2e**	24	70 (1:1)
5	 **2f**	24	59 (3:1)
6	 **2g**	24	44 (5:1)
7	 **2h**	3	63 (1:1)
8	 **2i**	6	50 (1:2)
9	 **2j**	6	68 (1:2)
10	 **2k**	24	58 (1:1)

[a] Z/E ratio of product **2** is listed in parentheses. [b] Reaction was examined at 100 °C.

B gives alkyne-metal complex **C**, and subsequent intramolecular carborhodation affords cyclic adduct **D**. Protonation by acetic acid gives (*Z*)-**2a** along with regeneration of the catalyst. We ascertained that isomerization from the (*Z*)- to (*E*)-isomer of isolated **2a** did not occur under either thermal or Rh-catalyzed conditions. In contrast, the reaction at a lower temperature predominantly gave the (*Z*)-isomer, but in moderate yield due to low conversion (eq 1). These results imply that *Z*/*E* isomerization of intermediate **D** proceeds at a higher temperature (120 °C).

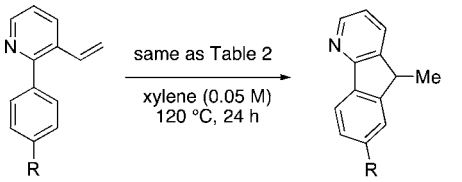


(1)

Under the optimal reaction conditions, we examined the substrate scope of 3-alkynyl-2-arylpyridine for the synthesis of 9-alkylidene-9*H*-4-azafluorenes (Table 2).[15] We first screened the substituents (R^1) on the benzene ring. 2-Phenyl-3-(phenylethynyl)pyridine (**1b**) was efficiently transformed into the corresponding azafluorene (**2b**) (entry 1). The yield of **2c** was moderate, probably because the steric bulkiness of the *ortho* methyl group (entry 2). Electron-donating and -withdrawing groups including a fluoro group can be installed at the para position (entries 3−6). With regard to the substituents (R^2) at the alkyne terminus, either an aryl group possessing an electron-donating or -withdrawing group or an alkyl group is suitable (entries 7−10).

(15) Pd-catalyzed intermolecular coupling of 3-iodopyridine with an alkyne gave regioisomeric mixture of 9-alkylidene-9*H*-2-azafluorenes and 4-azafluorenes: (a) Tian, Q.; Larock, R. C. *Org. Lett.* **2000**, *2*, 3329. (b) Larock, R. C.; Tian, Q. *J. Org. Chem.* **2001**, *66*, 7372.

We next investigated 2-aryl-3-vinylpyridines as substrates (eq 2). The reactions of **7a** and **7b** proceeded under the same reaction conditions to give methyl-substituted azafluorenes **8a** and **8b** in moderate yield.



(2)

7a (R = H)
7b (R = Me)

8a (R = H): 52%
8b (R = Me): 44%

In summary, we have described a Rh(III)-catalyzed transformation from 3-alkynyl and 3-alkenyl-2-arylpyridines into 4-azafluorene compounds using $Cu(OAc)_2$ as a catalytic additive. Pyridine-directed C−H bond cleavage along with "rollover" realizes an intramolecular reaction for the new construction of a nitrogen-containing multicyclic skeleton. Further studies on C−H bond functionalization via "rollover" in synthetic chemistry and the further mechanistic study are in progress in our laboratory.

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Supporting Information Available. Experimental procedure and physical property of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.